TITLE PAGE

Protocol Number:	810P304
Title:	Open-Label Extension Study to Evaluate the Long-Term Safety of Molindone Hydrochloride Extended-Release Tablets for the Treatment of Impulsive Aggression in Pediatric and Adolescent Subjects with Attention Deficit/Hyperactivity Disorder (ADHD) in Conjunction with Standard ADHD Treatment
Sponsor:	Supernus Pharmaceuticals, Inc. [redacted]
IND number:	106,515
Investigational Medicinal Product:	Molindone Hydrochloride Extended-Release Tablets (SPN-810)
Indication:	Treatment of Impulsive Aggression in subjects with Attention Deficit/Hyperactivity Disorder (ADHD) in conjunction with standard ADHD treatment
Medical Monitor	[redacted]
Phase:	3
Protocol Version:	5.0
Release Date:	22 Feb 2019
Good Clinical Practice (GCP) Statement:	This study is to be performed in full compliance with International Conference on Harmonization (ICH) GCP and all applicable local regulations. All required study documentation will be archived as required by regulatory authorities.

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PROTOCOL SIGNATURE PAGE

I, the undersigned, have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with ICH GCP and all applicable local guidelines, including the Declaration of Helsinki and all its accepted amendments to date.

Principal Investigator's Signature	Date
Print Name	
Site Number	

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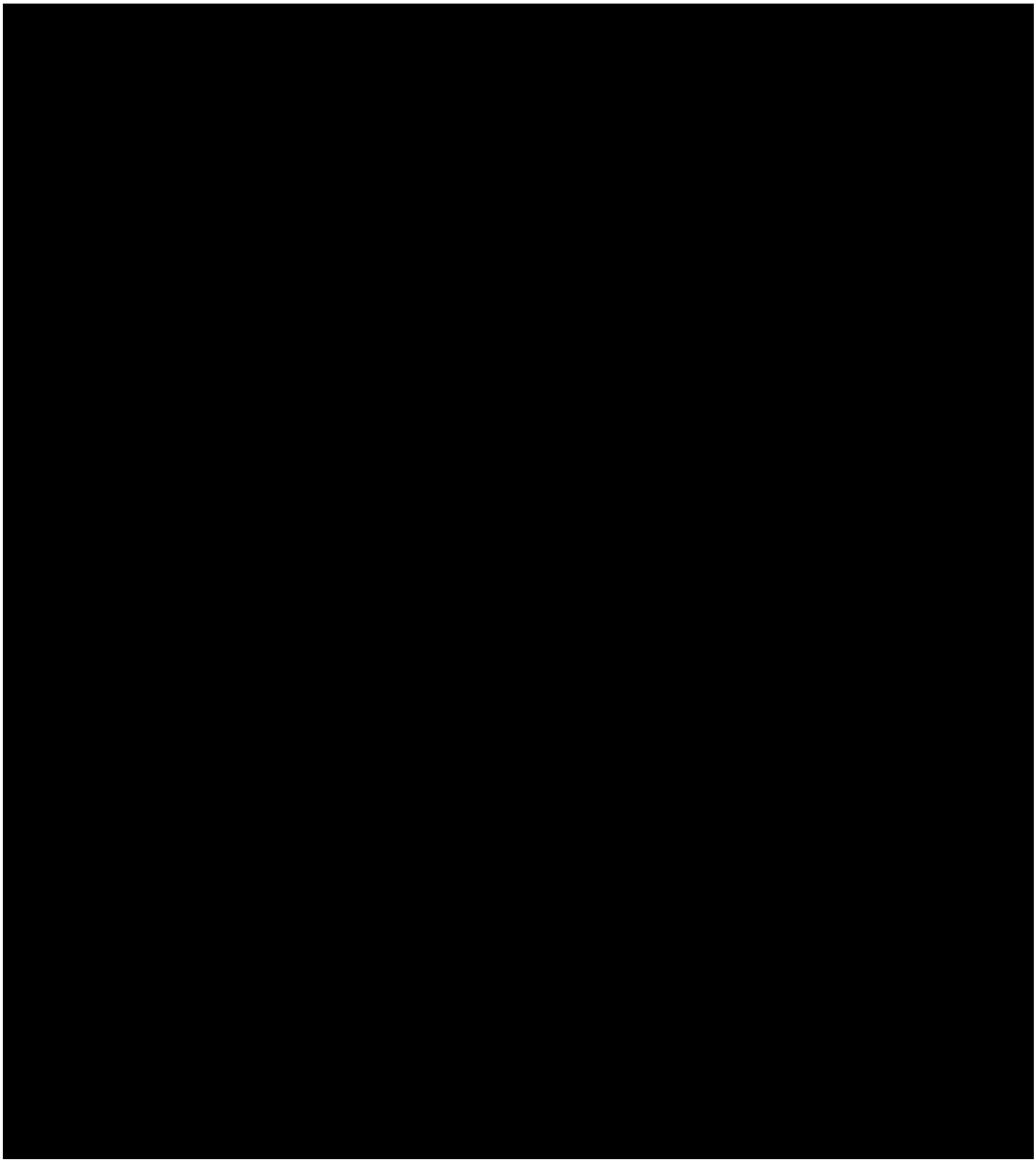
PROTOCOL APPROVAL PAGE



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SUMMARY OF CHANGES

This summary table lists all clarifications, administrative changes, or amendments to Supernus protocol 812P304. Additions are denoted by bold letters, and deletions by strikethrough.

Section	Page	Description of Change	Rationale
Changes to 810P304 V1.0 Dated 21 Jan 2015			
Title Page	1	Protocol version and date was updated	Administrative
List of Abbreviations	14	List of Abbreviations was updated to include Adverse Event of Special Interest (AESI)	For clarification
Table 1	25, 26	Table 1 was updated to include drug compliance during Visit 2, 3 and 4, visit windows and footnotes.	For Clarification
4.2.1-4.2.7	27-30	Each of these sections was updated to include: Administer Investigator **and Caregiver** CGI-I	For Clarification
4.4	33	The following was added: **4.4 Prohibited Medications:** **Subjects may not be on any prohibited medication. These medications include:** • **α 2- adrenergic agonists (e.g. clonidine and guanfacine) used for any other reason except for monotherapy treatment for ADHD** • **Anti-psychotics including aripiprazole, risperidone, quetiapine, and ziprasidone** • **Anticonvulsants including carbamazepine and valproic acid, antidepressants, mood stabilizers including lithium, benzodiazepines, cholinesterase inhibitors or any drug known to inhibit [redacted] activity** • **Herbal supplements**	For Clarification
5.1.3.1	37	The following was changed: All SAEs must be reported to the Drug Safety Contact within 24 hours of first becoming aware of the SAE. The Investigator must complete an SAE **eCRF in EDC** ~~**Form**~~ and include a detailed description of the SAE, as well as other available information pertinent to the case (e.g., hospital records, autopsy reports and other relevant documents). **Should the site be unable to access EDC, a paper SAE form must be completed and sent to [redacted] Drug Safety by email or fax.** The investigator will keep a copy of this SAE Report form on file at the study site. **Once EDC becomes available, the site must complete the SAE eCRF in EDC.**	For Clarification

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5.1.3.1	37	The E-mail address for drug safety contact was updated: [redacted]	Administrative
5.1.3.2.	37, 38	The following was added: **The Investigator must complete a Pregnancy Outcome Form as a follow up.**	For Clarification
5.1.3.2	38	The following was changed: Treatment-emerging EPS (e.g. akathisia, dystonia, Parkinsonism, tardive dyskinesia) and neuroleptic malignant syndrome should be reported to the Drug Safety Contact person(s) by **completing the Adverse Event Special Interest (AESI) eCRF in EDC. Should the site be unable to access EDC, a paper AESI form must be completed and sent to [redacted] Drug Safety by email or fax** ~~faxing or scanning the appropriate source documentation~~ within 24 hours of first becoming aware of the event. **Once EDC becomes available the site must complete AESI eCRF in EDC.** EPS incidence will be summarized and shared with study Investigators throughout the trial.	For Clarification
5.1.5	39	The following was added: **Any repeat laboratory testing will be conducted under fasting condition.**	For Clarification
5.2.2	40	The following was changed: CGI-I, relative to the condition at baseline **(Visit 3 in the double-blind study 810P301 or 810P302)**, will be evaluated by the caregiver and by the Investigator at each post-baseline visit on a 7-point scale with 1=Very much improved, 2=Much improved, 3=Minimally improved, 4=No change, 5=Minimally worse, 6=Much worse, and 7=Very much worse	For Clarification
6.4	43	The following was added: Only one **(primary)** reason for study discontinuation will be recorded for each subject**.**	For Clarification
6.9	46	The following was added: The quality of life endpoints ~~(~~CHQ-PF28 and PSI-4-SF~~)~~ **subscales (Parental Distress, Parent-Child Dysfunctional Interaction and Difficult Child),** will be listed and summarized by group of the optimized dose.	For Clarification
Changes to 810P304 V2.0 Dated 16 Dec 2016 Protocol version 2.0 was amended to allow adolescents (subjects 13-17 years of age) inclusion in the open-label study.			

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Title Page	1	Protocol version and date was updated	Administrative
Signature Page	3	The signature page was updated	Administrative
Signature Page	3	Authorship updated One of the was changed: [redacted]	Administrative
Synopsis	8	The following was added: 5. Weight of at least 20 kg **for 6-12 year old subjects**.	Procedural
Synopsis	8	The following was changed: Criteria for Exclusion: 1. Body Mass Index (BMI) ~~in~~ **less than 25th and above** 99th percentile **for 13-17 year old subjects only.** ~~3~~ **4. Criminal arrest or report at least 6 months prior to Visit 2.**	Procedural
List of Abbreviation	16	The following was changed: FOCP changed to FOC**B**P	To Clarify
3.1	23	The following was changed: The present study is designed to collect long-term safety data for the use of SPN-810 in the treatment of IA in subjects aged 6 to ~~12~~ **17**	Procedural
3.1	23	The following was added: SPN-810 was used in Phase 2 and Phase 3 studies for the treatment of IA in children **and adolescents** with ADHD	Procedural
3.2	23	The following was changed: Study 810P304 is a multicenter, open-label, extension study aimed to assess safety of SPN-810 in the treatment of IA in patients aged 6-~~12~~ **17** years with ADHD	Procedural
4.1.1	25	The following was changed: Inclusion Criteria: 5. Weight of at least 20 kg **for 6-12 year old subjects**.	Procedural
4.1.2	25	The following was changed: Exclusion Criteria 1. Body Mass Index (BMI) ~~in~~ **less than 25th and above** 99th percentile ~~or above~~ **for 13-17 year old subjects only**.	Procedural

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		~~3~~. **4. Criminal arrest or report at least 6 months prior to Visit 2.**	
Table 1	28	The following was added: d To be performed for female subjects of childbearing potential **prior to administration of first dose of SM and will have to be tested as negative for the subject to continue in the study**.	Procedural
4.2.1. 4.2.5, 4.2.6, 4.2.7 and 4.2.8	29,30,31,32	The following was changed: FOCP changed to FOC**B**P	To Clarify
Table 3	41	The following was changed: FOCP changed to FOC**B**P	To Clarify
Changes to 810P304 V3.0 Dated 17 August 2017 **The protocol Version 3.0 was submitted to the IRB but the submission was withdraw before approval.** <u>Summary of revisions in addition to administrative changes made to Version 3.0</u> • Allow inclusion of additional studies (i.e 810P503 and 810P204) • Increase study medication dose-range due to adolescents inclusion • Explore Molindone pharmacogenomics • Socio-demographic characteristics addition as a quality of life variable • Home urine pregnancy test at each visit during maintenance phase • Urine sample for drug screen at each visit during maintenance phase • Preferred Akathisia treatment			
Title Page	1	The following was added: Open-Label Extension Study to Evaluate the **Long-Term** Safety of Molindone Hydrochloride Extended-Release Tablets for the Treatment of Impulsive Aggression in Pediatric **and Adolescent** Subjects with Attention Deficit/Hyperactivity Disorder (ADHD) in Conjunction with Standard ADHD Treatment [redacted] Protocol version and date was updated	Administrative
Approval Page	3	The signature page was updated : [redacted]	Administrative

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		[redacted]	
Synopsis	26	The following was added: **Full Title of Study:** Open-Label Extension Study to Evaluate the **Long-Term** Safety Molindone Hydrochloride Extended-Release Tablets for the Treatment of Impulsive Aggression in Pediatric **and Adolescent** Subjects with Attention Deficit/Hyperactivity Disorder (ADHD) in Conjunction with Standard ADHD Treatment.	To Clarify
Synopsis	26	The following was changed: The objective of this Phase 3 Open-Label Extension (OLE) study is to collect additional long-term safety data on the use of SPN-810 as a treatment for impulsive aggression (IA) in pediatric **and adolescents** subjects with ADHD when taken in conjunction with standard ADHD treatment These subjects would have completed a satisfactory participation in the double-blind studies 810P301**,** ~~or~~ 810P302, **810P503 or 810P204**.	To clarify the inclusion of additional studies
Synopsis	26	The following was changed: Approximately **600** subjects who have completed a satisfactory participation in 810P301 ~~study or~~, 810P302**, 810P503 or 810P204** stud~~y~~**ies** and/or converted after discontinuation from one of these previous double-blind randomized studies.	To clarify the inclusion of additional studies
Synopsis	26	The following was changed: **Criteria for Inclusion:** 1. Completed and converted from a satisfactory participation in the stud~~y~~**ies** 810P301**,** ~~or~~ 810P302, **810P503 or 810P204**, or discontinued early during the maintenance phase from one of these previous studies and allowed to enroll only after consultation between the Investigator, the Medical Monitor and the Sponsor, 3. Existing diagnosis of ADHD, as described by DSM-5 and confirmed by the K-SADS PL 2013 from study	To account for the inclusion of additional studies

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		810P301 or 810P302 **or by the MINI-KID from study 810P503 or 810P204.** 5. Weight of at least 20 kg ~~for 6-12 year old subjects~~.	
Synopsis	26, 27	The following was changed: **Criteria for Exclusion:** 1**.** Body Mass Index (BMI) **in the** ~~less than 25th and above~~ 99th percentile **or above** ~~for 13-17 year old subjects only~~. 3. Pregnancy, **breastfeeding** or refusal to practice contraception during the study (for female subjects of childbearing potential and sexually active males). ~~4. Criminal arrest or report at least 6 months prior to Visit 2.~~ 5. Suicidal thoughts or behaviors confirmed at Visit 7 ~~from~~ **for** 810P301 or 810P302, **Visit 8 for 810P503 or Visit 6 for 810P204 studies.**	To Clarify
Synopsis	27	The following was changed: **Treatment, Dose, and Mode of Administration:** [redacted]	To account for the inclusion of additional studies

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Synopsis	27	The following was added: Just prior to the End of Study (EOS) visit, subjects who complete at least one maintenance **phase** will be instructed to taper off study medication over a period of 2 weeks.	To Clarify
Synopsis	27	The following was added: Once treatment on the previous clinical study is complete and consent obtained for this study, the Investigator will initiate the subjects at [redacted]	To account for the inclusion of additional studies
Synopsis	28	The Following was added: **2.** Parenting Stress Index (PSI-4-SF) **or Stress Index for Parents of Adolescents (SIPA)** **3. Socio-demographics**	For the inclusions of adolescents
Synopsis	28	The following was added: **Pharmacogenomic (PGx):** **For subjects already enrolled in this study a blood sample for PGx analysis will be collected at the next visit following this amendment. For newly enrolled subjects, the blood sample for PGx analysis will be obtained at screening. Prior to testing all subjects will be consented for PGx testing.** **The DNA will be extracted and tested for any genetic variations associated with [redacted] enzyme. This enzyme is involved in the metabolism of molindone and genetic variation may affect the pharmacokinetics of the drug. The residual DNA will be stored for possible testing of genes involved in the efficacy and possible association with particular adverse events of the drug (e.g., understand the non-responders to treatment and/or individuals who show unusual safety profile). The DNA analysis will not be used for individual genetic characterization and the subject identity will be kept confidential. The PGx report may be a stand-alone document.**	To explore the pharmacogenomics of the study medication
List of Abbreviations	36	List of Abbreviations was updated to include MINI-KID (Mini International Neuropsychiatric Interview for	Administrative

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		Children and Adolescents) and PGx (Pharmacogenomic) and SIPA (Stress Index for Parents of Adolescents)	
Sec. 1.4	40, 41	The following was added: The Sponsor is conducting two Phase 3 multicenter, randomized, double-blind, placebo controlled trials in a pediatric population of subjects 6-12 years of age **and one in adolescents (12-17 years old)** diagnosed with ADHD and IA (810P301**,** ~~and~~ 810P302 **and 810P503, respectively**). The primary objective of ~~both~~ **these** studies is to assess the efficacy and safety of SPN-810 in reducing the frequency of IA behaviors in pediatric **and adolescent** patients with ADHD when taken in conjunction with standard ADHD treatment. Additional secondary endpoints include the assessment of subjects and caregivers quality of life using the Child Health Questionnaire Parent Form 28-item (CHQ-PF28) and the Parenting Stress Index-Short Form (PSI-4-SF) **or the Stress Index for Parents of Adolescents (SIPA).** Children 6 to 12 years of age with ADHD and **the associated feature of** IA are randomized, with 97 subjects in each treatment arm [redacted]). **For the 810P503 study, 93 patients diagnosed with ADHD and the associated feature of IA are randomized to placebo or a flexible dose of SPN-810. After two weeks of titration, the dose will be maintained at [redacted] during the first week of maintenance and then increased up to [redacted] the discretion of the Investigator during the following two weeks. After the completion of the maintenance phase, subjects will enter a taper down period if they decide to discontinue, or will be given the option to enroll in the OLE (810P304 study). Subjects who choose to enroll in the OLE will receive a blinded conversion card and enter the OLE study at [redacted].**	To account for the inclusion of additional studies
Sec. 1.5	41, 42	The following was changed: This Phase 3 study, 810P304, is available to eligible subjects who complete the randomized, double blind portion of one of the t**hree**~~wo~~ Phase 3 studies, 810P301**,** ~~or~~ 810P302, **810P503 or the additional Phase 2 study, 810P204**. Subjects who discontinue during the maintenance phase ~~prior to Visit 6~~ may be allowed to	To account for the inclusion of additional studies

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		participate in the OLE on a case-by-case basis only after consultation between the Investigator, the Medical Monitor and the Sponsor. In addition to safety, we will assess the ~~frequency and~~ severity of aggressive behaviors using the R-MOAS scale, and the severity and improvement of IA using the CGI scales. Changes in CHQ-PF28 and PSI-4-SF **or SIPA** scores will be used to evaluate improvement of quality of life of both the subject and the caregiver.	
Sec. 2.1	42	The following was added: The objective of this Phase 3 OLE study is to collect long-term safety data on the use of SPN-810 as a treatment for IA in ~~pediatric~~ subjects **(6-17 years of age)** with ADHD when taken in conjunction with standard ADHD treatment only after satisfactory participation in a preceding double-blind study (810P301**,** ~~or~~ 810P302**, 810P503 or 810P204**).	To account for the inclusion of additional studies
Sec 3.1	42	The following was changed: The present study is designed to collect long-term safety data for the use of SPN-810 in the treatment of IA in subjects aged 6 to 17 years ~~comorbid~~ **diagnosed** with ADHD. SPN-810 was used in Phase 2 and **currently** in Phase 3 studies for the treatment of IA in children and adolescents with ADHD who experienced IA behaviors despite monotherapy treatment with an FDA-approved ADHD medication. The **subjects** ~~patient population~~ will be eligible to **enroll** ~~enter~~ in this study after the completion of the double-blind studies 810P301 **or** 810P302**, 810P503 or 810P204**. At Visit 6 of 810P301 **and** 810P302 studies~~,~~ **or at Visit 4 of 810P204**, subjects are invited to convert from their randomized dose in a blinded fashion to a dose of 18 mg/day [redacted] the initial total daily dose for this OLE study. **Subjects participating in the 810P503 study will receive a blinded conversion card at Visit 7 and will initiate the OLE study at** [redacted] Additionally, subjects are eligible to enroll in this study on a case-by-case basis only after consultation between the Investigator, the Medical Monitor and the Sponsor if they discontinue from one of the double-blind studies ~~810P301 or 810P302~~ during the maintenance phase prior to Visit 6 **(810P301 or 810P302) or Visit 5 (810P204**). Subjects will be converted from their randomized dose to the initial total daily dose of [redacted] in a blinded fashion.	To account for the inclusion of additional studies

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		If subjects discontinued from the 810P503 study prior to Visit 7 during the maintenance phase, they will be converted in a blinded fashion from the randomized dose to [redacted]	
Sec. 3.2	43	The following was changed: All subjects who complete the randomized, double-blind portion of study 810P301**,** ~~or~~ 810P302, **810P503 or 810P204** will have the option to participate in the OLE study in which all subjects will receive active Study Medication (SM) treatment. Subjects **who choose** ~~choosing~~ to participate **in the OLE** will receive blinded conversion medication kits at Visit 6 of the previous SPN-810 double-blind randomization study **(810P301, 810P302) or at Visit 4 for subjects completing the 810P204 study**. **Subjects, who have completed the 810P503 study and, chose to participate in this study, will receive the blinded conversion card at Visit 7.** Visit 7 of 810P301 ~~or~~, 810P302 **or Visit 8 for 810P503** will be Visit 1 of 810P304. **Visit 6 of the 810P204 will be Visit 1 of the 810P304**. The initial total daily dose for the OLE is 18 mg**/day except for subjects who participated in the 810P503 study, their initial dose in the OLE is** [redacted] **The Investigator may gradually increase the dose of SPN-810 up to** [redacted] **for subjects with body weight ≥ 30 kg.**	Procedural and to account for the inclusion of additional studies
Sec. 3.2.1	43, 44	The following was added: Subjects may enter the study upon completion **of one of the following double-blind studies:** 810P301, or 810P302, **810P503 or 810P204.** • Subjects who have completed one of the double-blind **randomized** ~~Phase 3~~ studies **(810P301, 810P302, 810P204 or 810P503)** will be converted during their last week of participation and will initiate dosing at [redacted], **respectively.** • On a case-by-case basis, subjects who discontinued early during the maintenance phase of 810P301 ~~or~~**,** 810P302, **810P204 or 810P503 studies** and are approved for participation in this study will ~~be converted and will~~ initiate at [redacted] **respectively**. • In rare occasions, subjects who have discontinued early from the maintenance phase of 810P301 ~~or~~**,** 810P302, **810P204 or 810P503 studies** and have	To account for the inclusion of additional studies

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		washed out from the study medication for at least 2 days may be approved to enroll in the OLE. • These subjects will enter the study at a ~~dose~~ and ~~will be~~ gradually titrated up to an optimized dose.	
Sec. 3.2.2	44	The following was added: **For subjects already enrolled in this study, a blood sample will be collected at the next visit following this amendment. For newly enrolled subjects (from 810P301, 810P302 or 810P204 study), the blood samples for PGx analysis will be obtained at Visit 1/Baseline. Prior to testing all subjects will be consented for PGx testing. The DNA will be extracted and tested for any genetic variations associated with enzyme. Test results in this study will identify the subject's metabolizer phenotype.** **The residual DNA will be stored for possible testing of genes involved in the efficacy and possible association with particular adverse events of the drug (e.g., understand the non-responders to treatment and/or individuals who show unusual safety profile). The DNA analysis will not be used for individual genetic characterization and the subject identity will be kept confidential.**	To explore the pharmacogenomics of the study medication
Sec. 3.2.3	44	The following was changed: During the optimization phase, the study medication dose should be optimized between 6 mg/day and 36 **or 54** mg/day given as divided dose**s** BID **in children (6-12 years of age) or adolescents (12-17 years of age), respectively**.	To account for the inclusion of adolescent study
Sec. 3.2.4	44,45	The following was added: **For subjects whose body weight is ≥ 30 kg, the Investigator may gradually increase the dose of SPN-810 up to 54 mg/day based on safety and tolerability.** **During the maintenance phase, a urine pregnancy test will be requested for all Females of Child Bearing Potential (FOCBP). At each visit during Maintenance (Visit 5-Visit 16), FOCBP subjects will receive a urine pregnancy test to take at home and will be asked to complete the testing approximately 6 weeks following each visit. The site will call the caregiver as a reminder and follow-up to obtain the pregnancy test results. Sites**	To account for the inclusion of adolescent study

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		are encouraged to educate the caregivers and the subjects on the importance of preventing pregnancies during participation in the study. **The distribution of the home pregnancy test as well as the results of the test will be recorded on paper source, at the clinical trial sites.** **If a positive result is reported, the subject will be brought to the clinic for an unscheduled visit to confirm through a serum pregnancy test. If pregnancy is confirmed, the subject will be withdrawn from the study. The Investigator will report the pregnancy and complete the follow-up procedures as outlined in Sec. 5.1.3.2.**	
Sec. 4.1	45	The following was added: Approximately **60**~~400~~ subjects will be enrolled in this clinical investigation. The population will be male and female subjects with IA and diagnosed with ADHD, currently treated with an FDA-approved standard ADHD treatment and who have completed a satisfactory participation in one of the double-blind randomized studies, 810P301 ~~or~~, 810P302, **810P503 or 810P204**. Subjects who discontinued early from ~~810P301 or 810P302~~ **the above double-blind randomized studies** during the maintenance phase will be allowed to enroll in this study after consultation between the Investigator, the Medical Monitor and the Sponsor on a case-by case basis.	To account for the inclusion of additional studies
Sec. 4.1.1	45	The following was changed: **Inclusion Criteria:** 1. Healthy male or female subjects, who completed and converted from a satisfactory participation in the stud~~y~~**ies** 810P301 ~~or~~**,** 810P302**, 810P503 or 810P204** or discontinued early from the previous study during the maintenance phase and allowed to enroll only after consultation between the Investigator, the Medical Monitor and the Sponsor. 3. Existing diagnosis of ADHD, as described by DSM-5 and confirmed by the K-SADS PL 2013 from study 810P301 or 810P302 **and by the MINI-KID from the 810P503 or 810P204 studies.** 5. Weight of at least 20 kg ~~for 6-12 year old subjects~~.	To account for the inclusion of additional studies
Sec. 4.1.2	45, 46	The following was changed: **Exclusion Criteria:**	Procedural

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		1. Body Mass Index (BMI) **in the** ~~less than 25th and above~~ 99th percentile **or above** ~~for 13-17 year old subjects only~~. 3. Pregnancy**, breastfeeding** or refusal to practice contraception during the study (for female subjects of childbearing potential and sexually active males). ~~4. Criminal arrest or report at least 6 months prior to Visit 2.~~	
Table 1	47, 48	Table 1 was updated to include: • **EOS** Visit ~~7~~/Visit 1 • **Socio-demographic Information at Baseline** • **Urine Drug Screen at Baseline and at Visit 5, 7, 9, 11, 13 and 15** • **Urine Pregnancy Test at Visit 2, Visit 3 and Visit 4** • **Home urine pregnancy test at Visits 5-16** • **Blood Collection for Pharmacogenomic (PGx) Testings.** • **SIPA for Adolescents**	Procedural
Table 1	48	The following was added in the footnote: a. Assessment is completed as the EOS visit in the ~~SPN-810~~ **preceding-**double-blind randomized study: Visit 7 (810P301 and 810P302), Visit 8 (810P503) and Visit 6 (810P204). **b. At each visit, a home urine pregnancy test will be distributed to female subjects of childbearing potential. Subjects are required to complete testing 6 weeks after each visit. The site will follow up with a call to record the results.** **h. PGx Testing will be performed in subjects enrolling from the following studies: 810P301, 810P302 or 810P204. Subjects already enrolled, will provide a blood sample during the next visit following this amendment is effective**. **i. The SIPA scale will be administered <u>only</u> to subjects 13 and 17 years of age.**	For the adolescents inclusion
Sec. 4.2.1	49	The following was added: <u>Visit 7 of 810P301 or 810P302, **Visit 8 of 810P503** ~~will serve as Visit 1 of the OLE~~ **and Visit 6 of 810P204 will be Visit 1 of the OLE.**</u> Subjects who meet the requirements for study participation will begin titration at Visit 6 of 810P301 or 810P302 stud~~y~~**ies and at Visit 5 for the 810P204 study** to the dose level of 18 mg/day. **Subjects who have completed 810P503 study participation will**	Procedural

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		start titration at Visit 7 to the initial dose of 36 mg/day in this study. ~~1. Confirm Interactive Web Response System (IWRS) subject number~~ **5. Record socio-demographic information** 8. Collect blood samples for hematology, chemistry **and pharmacogenomic testing (when applicable)** 9. **Collect urine sample for drug screen**	
Sec. 4.2.2	49, 50	The following was added: **3. Collect urine sample for pregnancy test (Females of Child Bearing Potential (FOCBP) only)** **11. Assess treatment compliance**	For the adolescents inclusion
Sec. 4.2.3	50	The following was added: **3. Collect urine sample for pregnancy test (Females of Child Bearing Potential (FOCBP) only)** **11. Assess treatment compliance**	For the adolescents inclusion
Sec. 4.2.4	50	The following was added: **4. Collect urine sample for pregnancy test (Females of Child Bearing Potential (FOCBP) only)** **12. Assess treatment compliance**	For the adolescents inclusion
Sec. 4.2.5	51	The following was added: **4.** Collect urine sample for pregnancy test (FOCBP only) **and dispense home pregnancy test kit** **5. Collect urine sample for drug screen** 6. Administer quality life scales (CHQ-PF28, PSI-4-SF **or SIPA**)	For the adolescents inclusion
Sec. 4.2.6	51	The following was added: **4. Dispense home pregnancy test kit** 12. Administer quality life scales (CHQ-PF28, PSI-4-SF **or SIPA**)	For the adolescents inclusion

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Sec. 4.2.7	51, 52	The following was added: After completion of the initial 6-month period (at Visit 6), subjects will be offered the option to continue participation for another 6-month maintenance period for up to a total of 36 months (3 years) **or until market availability .** At Visits 7, 9, 11, 13 and 15, the following procedures will be conducted: 4. Collect urine sample for pregnancy test (FOCBP only) **and dispense home pregnancy test kit** **5. Collect urine sample for drug screen** **10.** Administer quality life scales (CHQ-PF28, PSI-4-SF **or SIPA)** At Visit 8, 10, 12, 14 and 16, the following procedures will be conducted: **4. Dispense home pregnancy test kit** **12.** Administer quality life scales (CHQ-PF28, PSI-4-SF **or SIPA)**	For the adolescents inclusion
Sec. 4.2.8	53	The following was added: 10. Administer quality life scales (CHQ-PF28, PSI-4-SF **or SIPA**, only for subjects who discontinue early)	For the adolescents inclusion
Sec. 4.3.1	53, 54	The following was added: Subjects will enter this study from one of the previous double-blind ~~Phase 3~~ clinical studies **(810P301, 810P302 or 810P204)** and will initiate at [redacted] for a total of [redacted]. **Subjects from the double-blind 810P503 study will initiate this study at [redacted].** Eligible subjects who discontinue early in one of the randomized, double-blind ~~Phase 3~~ studies **(810P301, 810P302 or 810P204)** and are approved for participation in the OLE study will ~~receive blinded conversion medication card and~~ initiate study ~~at the same initial dose~~ [redacted] **s outlined in Sec. 3.2.1.** **For subjects with body weight ≥ 30 kg and not fully responding to [redacted], the Investigator may gradually increase the dose of SPN-810 up to 54 mg/day.** ~~If at some point during the study the measured BMI is above 99th percentile, the Investigator may adjust the dose to the subject's weight.~~ **A combination of extended-and immediate-release formulations of the same ADHD medication are not considered monotherapy.**	To account for the inclusion of additional studies

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Sec. 4.34	55	The following was changed: Each subject who completes or discontinues ~~the study~~ **from** 810P301 ~~or~~**,** 810P302**, 810P503 or 810P204** and is eligible for **enrollment in** the OLE will maintain the same unique subject identification number that was given **to them** in the ~~study 810P301 or 810P302~~ **previousceding** double-blind randomized study**.**	To clarify the inclusion of additional studies
Sec. 4.3.6	55	The following was added: Subjects will initiate dosing at [redacted] in a blinded fashion, ~~which is the starting dose for 810P304~~ and subsequently optimized. At the Investigator's discretion, the dose may be gradually adjusted based upon tolerability and effectiveness between the doses of [redacted] **mg/day for subjects whose body weight is ≥ 30 kg.** ~~given as divided dose BID.~~ **Doses should always remain** BID **and, whenever possible, evenly divided (same number of mg in morning and evening).**	To clarify the adolescents inclusion
Sec. 4.4	55	The following was added: • **Non-FDA approved formulations of FDA for the treatment of ADHD** (**e.g. IR or ER formulations of the same compound)** • **Combination of extended-and immediate-release formulation of the same compound (e.g. IR formulation in the morning and ER formulation in the evening)**	To Clarify
Sec. 4.5	56	The following was added: **3. For the treatment of Akathisia, propranolol is allowed up to 90 mg /day in divided doses three times per day, starting at 10 mg BID and up to 30 mg TID, as needed.** 4. Treatment for AEs other than EPS or minor transient ailments is permitted only in consultation with the Medical Monitor or his/her designee **with the exception of required treatments for acute conditions in the emergency room/hospital and/or office visit as indicated**. All concomitant medications as well as the changes ~~on~~**in** the dosing of the ADHD medication or the changes to any other FDA-approved ADHD treatment will be recorded in the eCRF.	To Clarify

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Sec. 5.1.2.1	58	The following was added: Adverse events occurring in the previous clinical study or ongoing at the end of the 810P301 ~~or~~**,** 810P302, **810P503 or 810P204** will become part of the subject's medical history. • **Serious vs. Non-serious:** Is the event a~~n~~ Serious Adverse Event (SAE)?	To clarify the inclusion of additional studies
Sec. 5.1.4	61	The following was added: **For the treatment of Akathisia, propranolol is recommended up to 90 mg /day in divided doses three times per day, starting at 10 mg BID and up to 30 mg TID, as needed.**	To Clarify
Sec. 5.1.5	61, 62	The following was added: With the exception of urine pregnancy test, clinical laboratory tests will be performed by a central laboratory as specified in the ~~reference~~ **regulatory** binder. Any repeat laboratory testing will be conducted under fasting condition **as indicated.**	To Clarify
Table 2	62	Table 2 was updated to include **HbA1c**[a]lab parameters only for subjects participating in the 810P503 study and to clarify the urine and urinalysis parameters. The following footnote was added: a. **This parameter will be measured only in subjects who participated in the 810P503 study.**	To Clarify
Sec. 5.1.6	62	The following was changed: Vital Sign**s** and Height/Weight Measurements Vital sign**s'** measurements (e.g., blood pressure, heart rate, temperature, and respiratory rate) and height, weight and BMI will be obtained at visits designated on the Schedule of Visits and Procedures (Table 1).	Administrative
Sec. 5.1.8	63	The following was added: **A total of 2 mL blood samples will be collected for [redacted] pharmacogenomic testing.** **For subjects already enrolled into this study (810P304) a blood sample will be collected at the next visit following this amendment. For newly enrolled subjects, the blood sample for PGx analysis will be obtained at screening. Results from individual tests will be used for research purposes only and will not be distributed**. **Samples will be identified only by the study subject number to maintain confidentiality. The DNA will be**	To explore the pharmacogenomics of the study medication

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		extracted and tested for any genetic variations associated with [redacted] enzyme. Collected samples will be stored for up to 10 years for potential future research purposes such as possible testing of genes involved in the efficacy and possible association with particular adverse events of the drug (e.g., understand the non-responders to treatment and/or individuals who show unusual safety profile). **Data from samples will not have diagnostic value and will not be used for individual genetic characterization or development of a commercial product. At the end of testing or 10 years, any remaining samples will be destroyed. The subject may withdraw consent for pharmacogenomic testing at any time; if consent is withdrawn, the subject's sample will be destroyed.**	
Sec. 5.2.2	64	The following was added: • CGI-I, relative to the condition at baseline (Visit 3 in the double-blind stud~~y~~**ies** 810P301**,** ~~or~~ 810P302, **810P503 or 810P204**), will be evaluated by the caregiver and by the Investigator at each post-baseline visit on a 7-point scale with 1=Very much improved, 2=Much improved, 3=Minimally improved, 4=No change, 5=Minimally worse, 6=Much worse, and 7=Very much worse.	To Clarify
Sec. 5.3.2	64	The following was added: The PSI-4-SF will be administered **to the caregivers of subjects 6-12 years of age**, at each visit after the first 6 months (Visits 5 to 17). For subjects who discontinue early, this will be administered at the EOS (Visit 17).	To Clarify
Sec. 5.3.3	65	The following was added: **5.3.3 Stress Index for Parents of Adolescents (SIPA)** T**he Stress Index for Parents of Adolescents (SIPA) is a screening and diagnostic instrument that identifies areas of stress in parent–adolescent interactions, allowing examination of the relationship of parenting stress to adolescent characteristics, parent characteristics, the quality of the adolescent–parent interactions, and stressful life circumstances in parents of adolescents (11-19 years old). The SIPA consists of 90 items divided in three major domains, the Adolescents Domain (AD), the Parent Domain (PD) and the Adolescent-Parent Relationship Domain (APRD), which include the following subscales: moodiness/emotional lability, social isolation/withdrawal, delinquency/antisocial, failure to achieve and**	To take into account the adolescents inclusion

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		persevere, relationship with spouse/partner, social alienation and incompetence/guilt. The SIPA includes 22- item Life Stressors (LS) Scale and the Index of Total Parenting Stress (TS). **Parents respond to the first 90 items using a 5-point rating scale ranging from Strongly Disagree (5) to Strongly Agree (1) and the final 22 items by indicating Yes (Y) or No (N).** **The SIPA will be administered to caregivers of adolescents (13-17 years of age) at each visit after the first 6 months (Visits 5 to 17). For subjects who discontinue early, this will be administered at the EOS (Visit 17).**	
Sec. 5.3.4	65	The following was added: **5.3.4. Socio-demographic Characteristics** **Socio-demographic characteristics are valuable addition information that will be used to correlate with health-related quality of life and clinical measures. The variables include the number of siblings in the study, siblings with IA, caregiver's age and gender, living situation, marital status, household income and education level.** **The socio-demographic characteristics will be recorded at baseline for newly enrolled subjects and, for subjects already enrolled, at the next visit once this protocol amendment is effective.**	To explore an additional variable for correlation
Sec. 5.4	65	The following was added: **Pharmacogenomic Variable** **The extracted DNA will be tested for any genetic variations associated with [redacted] enzyme. [redacted] The residual DNA will be stored for possible testing of genes involved in the efficacy and possible association with particular adverse events of the drug (e.g., understand the non-responders to treatment and/or individuals who show unusual safety profile).** **The DNA analysis will not be used for individual genetic characterization and the subject identity will be kept confidential.** **Blood samples will be collected at Screening (Visit 1) for eligible subjects who have not been previously tested in the blinded studies. Subjects already enrolled in this study, will be tested at the next visit to the clinical site, once this protocol amendment is effective.**	To explore the pharmacogenomics of the study medication

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Sec. 6.1	66	The following was added: All data analyses will be performed by the Clinical Research Organization (CRO) after ~~the~~ study ~~is~~ complet**ioned** and ~~the~~ database ~~is~~ release~~d~~. Statistical programming and analyses will be performed using SAS® **Version 9.3 or above** and/or other validated statistical software as required. In general, the baseline value for a variable is defined as the value observed at Visit 7 of 810P301 ~~or~~ **and** 810P302, **Visit 8 of 810P503 and at Visit 6 of the 810P204 study** or the first value observed before the first dose in the OLE study, i.e. at Visit 1 ~~(see Table 1)~~.	To Clarify the inclusion of additional studies
Sec. 6.2	67	The following was added: The population of "all enrolled subjects" consists of all ~~screened~~ subjects **from any of the preceding**~~who completed~~ ~~the~~ double-blind studies **(**810P301 ~~or~~**,** 810P302**, 810P503 and 810P204)** and meet the eligibility requirements for this study including subjects who discontinued ~~one~~ **from any** of the ~~Phase 3~~ double-blind studies early **and approved for enrollment in this study**. The safety population will include all subjects who have signed Informed Consent/Assent forms and received at least ~~1~~**one** dose of study drug during this study.	To Clarify the inclusion of additional studies
Sec. 6.3	67	The following was added: **Demographics** and Baseline Characteristics Demographic **and baseline** variables include age, sex, ethnicity, race, height, weight, and medical history ~~and~~ will be summarized ~~as in the study 810P301 or, 810P302~~.	To Clarify
Sec. 6.4	67	The following was added: **6.4 Socio-demographics** **Socio-demographic variables include number of siblings in the study, siblings with IA, caregiver's age and gender, living situation, marital status, household income and education level will be summarized.**	To explore an additional variable for correlation
Sec. 6.5	67	The following was moved up from the last paragraph: The number and percentage of subjects who completed and discontinued from the study will be summarized. **Only one (primary) reason for study discontinuation will be recorded for each subject.**	To Clarify
Sec. 6.7	68	The following was changed: Duration of exposure is defined as the total number of days a subject is exposed **to study** treatment. This will be	To clarify the increased dose

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		calculated for each subject by taking the difference between the date of last dose *minus* the date of the first dose, *plus* ~~1~~ **one** (date of last dose – date of first dose +1). {D-R)/**(**~~2~~**T***(D_L- D_F **+ 1))**}*100, where D=number of tablets dispensed, R= number of tablets returned, **T= number of tablets administered per day** , D_L = date of last visit (dose) and D_F= date of first visit (dose) **The number of tablets (T) taken each day may vary during the maintenance phase: subjects can take up five tablets per day to the maximum dose of 54mg/day BID**.	
Sec. 6.8.1	68	The following was changed: TEAE incidence tables will be listed and summarized by the group of the optimized doses (<18 mg/day; 18-24 mg/day, ~~or >~~24-**36** mg/day**, or 36-54 mg/day**) the subject received.	To clarify the increased dose due to the adolescents inclusion
Sec. 6.8.3	69	The following was changed: Vital signs will be summarized by the group of the optimized doses (<18 mg/day; 18-24 mg/day, ~~or >~~24-**36** mg/day**, or 36-54 mg/day**) the subject received using descriptive statistics.	To clarify the increased dose due to the adolescents inclusion
Sec. 6.8.4	69	The following was changed: ECG results will be summarized by visit by group of optimized doses (<18 mg/day; 18-24 mg/day, ~~or >~~24-**36** mg/day**, or 36-54 mg/day**) using descriptive statistics (for quantitative ECG parameters) and frequency tables (for qualitative ECG parameters, including the overall ECG finding).	To clarify the increased dose due to the adolescents inclusion
Sec. 6.8.7	70	The following was changed: The summary will be presented by group of the optimized doses (<18 mg/day; 18-24 mg/day, ~~or >~~24-**36** mg/day **or 36-54 mg/day**) the subject received.	To clarify the increased dose due to the adolescents inclusion
Sec. 6.10	70	The following was added: The quality of life endpoints CHQ-PF28, ~~and~~ PSI-4-SF subscales (Parental Distress, Parent-Child Dysfunctional Interaction and Difficult Child)**, and SIPA subscales (Adolescents Domain, Parent Domain, Adolescent-Parent Relationship Domain, Life Stressors Scale and Index of Total Parenting Stress)** will be listed and summarized by group of the optimized doses **(<18 mg/day; 18-24 mg/day,**	To clarify the inclusion of adolescents

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		~~or >~~24-36 mg/day or 36-54 mg/day) the subject received. Socio-demographic variables will be presented as a listing and summaries will be tabulated using descriptive statistics.	
Sec. 6.11	70	The following was added: **Pharmacogenomic Analysis** **Individual data will be presented as a listing and summaries will be tabulated using descriptive statistics. The pharmacogenomic report may be a stand-alone document.**	To explore the pharmacogenomics of the study medication
Sec. 6.12	70	The following was changed: There is no consideration for power or sample size determination in this open label study. The present study is an extension to the double-blind randomized 801P301**,** ~~or~~ 810P302**, 810P503 and 810P204** studies~~, where the planned samples size in each study is 291 subjects,~~ for the purpose of evaluating long term safety of SPN-810.	To take into account for the inclusion of additional studies
Sec. 8.3	75	The following was changed: This study will be conducted by qualified Investigators under the sponsorship of Supernus Pharmaceuticals, Inc. (Sponsor) at US study sites used in the double-blind Phase 3 studies, 810P301**,** ~~and~~ 810P302**, 81P503 and 810P204**. Contact persons at the Sponsor and the CROs are listed in the **regulatory**~~reference~~ binder provided to each investigational site. ~~The study will be monitored by qualified~~**Qualified personne**l **will monitor the study.**~~from the designated [redacted] The Sponsor will oversee and review the monitoring activities of the~~[redacted] Laboratory tests will be conducted by a central laboratory as designated in the **regulatory** ~~reference~~ binder.	To Clarify
Sec. 10	79	SIPA appendix was added	For the adolescents inclusion
Changes to 810P304 V4.0 Dated 04Sep2018 Protocol Version 4.0 was amended to Version 5.0 to allow subjects who are receiving benefit from SPN-810 to continue to receive the study medication for another 2 years (i.e., a total of 5 years) or until commercial availability of the product. Additional changes made for clarity and correction include: • Clarifying that PGx testing is optional • Correcting the maximum number of study medication tablets that may be taken per day • Other administrative changes as noted			
Title page	1	Protocol version and date were updated. Protocol title was corrected for grammar:	Administrative

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		Open-Label Extension Study to Evaluate the Long-Term Safety of Molindone Hydrochloride Extended-Release Tablets for the Treatment of Impulsive Aggression in Pediatric and ~~Adolescents~~ **Adolescent** Subjects with Attention Deficit/Hyperactivity Disorder (ADHD) in Conjunction with Standard ADHD Treatment	
Protocol Approval page	3	Reviewers: [redacted]	Administrative
Synopsis	28	Study Design: Long-term, flexible-dose, open-label, multi-center, up to ~~36~~ **60-**month study	To extend study duration up to 5 years
Synopsis	29	Duration of Treatment and Study Duration: The subject can continue to receive study medication for up to ~~36~~ **60** months. Treatment Schedule: Once treatment on the previous clinical study is complete and consent obtained for this study, the Investigator will initiate the subjects at 18 mg/day (810P301, 810P302 and 810P204) or 36 mg/day (810P503), and may gradually adjust the dose of SPN-810 between 6 mg/day and 36 mg/day for up to ~~36~~ **60** months. Maximum duration of the study: ~~Approximately~~ ~~36~~ **Up to 60** months **or until market availability**. • Optimization Phase: 8 weeks • Maintenance Phase: **initial period of 6 months, with the option for additional** ~~repeat~~ period**s** of 6 months **each** • Taper Phase: 2 weeks	To extend study duration up to 5 years
Synopsis	30	Pharmacogenomic**s** (PGx): (Added) **Participation in PGx testing is optional.**	Clarification
3.1	44	The duration of the study will continue up to ~~36~~ **60** months or until market availability.	To extend study duration up to 5 years
3.2.2	46	~~Pharmcogenomics (PGX)~~ **Pharmacogenomics (PGx)** (Added) **Participation in PGx testing is optional.**	Clarification
3.2.4	46	At each visit during Maintenance (Visit 5-Visit ~~16~~ **24**), FOCBP subjects will receive a urine pregnancy test to take at home and will be asked to complete the testing approximately 6 weeks following each visit.	To extend study duration up to 5 years
4.2	49	Table 1 Maintenance Phase: Visits 5 (Mo 3), 7, 9, 11,13**,** ~~and~~ 15**, 17, 19, 21, and 23** (Mo ~~33~~ **57**) Maintenance Phase: Visits 6 (Mo 6), 8, 10, 12, 14**,** ~~and~~ 16**, 18, 20, 22 and 24** (Mo ~~36~~ **60**)	To extend study duration up to 5 years

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		Taper Phase: Visit ~~17~~ **25** Footnote b: Visit 7 ~~16~~ **24** will occur 3 months ± 1 week from the previous visit.	
4.2	49	Table 1 Footnote h: (added) **Participation in PGx testing is optional.** Footnote i: The SIPA scale will be administered only to subjects 13 ~~and~~ **to** 17 years of age.	Clarification
4.2.7	53	Subsequent Visits (Visits 7 through ~~16~~ **24**) (approximately every 3 months (+/- 1 week)) After completion of the initial 6-month period (at Visit 6), subjects will be offered the option to continue participation for another 6-month maintenance period for up to a total of ~~36~~ **60** months (~~3~~ **5** years) or until market availability. Each 6-month period will have two visits every 3-months. These will include Visits 7 through ~~16~~ **24**. At Visits 7, 9, 11, 13**,** ~~and~~ 15**, 17, 19, 21, and 23**, the following procedures will be conducted: At Visit 8, 10, 12, 14**,** ~~and~~ 16**, 18, 20, 22 and 24**, the following procedures will be conducted:	To extend study duration up to 5 years
4.2.8	54	Visit ~~17~~ **25** [(End of Study (EOS)] (Month ~~36~~ **60** +/- 2 weeks) Subjects who complete the study (~~36~~ **60** months) will be instructed to down titrate for 2 weeks before returning to the office for the EOS Visit. The following procedures will be performed for ~~patients~~ **subjects** who complete the study (~~36~~ **60** months) or discontinue early.	To extend study duration up to 5 years
5.1.8	65	Added: **Participation in PGx testing is optional.**	Clarification
5.2.1	65	This assessment will be administered at each visit after the first 6 months (Visits 5 to ~~17~~ **25**). For subjects who discontinue early, this will be administered at the EOS (Visit ~~17~~ **25**).	To extend study duration up to 5 years
5.3.1	66	The CHQ-PF28 will be administered at each visit after the first 6 months (Visit 5 to ~~17~~ **25**). For subjects who discontinue early, this will be administered at the EOS (Visit ~~17~~ **25**).	To extend study duration up to 5 years
5.3.2	66	The PSI-4-SF will be administered to the caregivers of subjects 6-12 years of age, at each visit after the first 6 months (Visits 5 to ~~17~~ **25**). For subjects who discontinue early, this will be administered at the EOS (Visit ~~17~~ **25**).	To extend study duration up to 5 years

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5.3.3	67	The SIPA will be administered to caregivers of adolescents (13-17 years of age) at each visit after the first 6 months (Visits 5 to ~~17~~ **25**). For subjects who discontinue early, this will be administered at the EOS (Visit ~~17~~ **25**).	To extend study duration up to 5 years
5.4	67	Added: **Participation in PGx testing is optional.**	Clarification
6.5	69	The reasons for study discontinuation may include one of the following: (added) **Lack of efficacy**	Clarification
6.7	71	The number of tablets (T) taken each day may vary during the maintenance phase: subjects can take up ~~five~~ **six** tablets per day to the maximum dose of 54mg/day BID.	Correction

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CLINICAL PROTOCOL SYNOPSIS

Name of Company: Supernus Pharmaceuticals, Inc.	**IND Number:** 106,515
Name of Product: Molindone Hydrochloride Extended-Release Tablets (SPN-810)	**Name of Active Ingredient:** Molindone Hydrochloride
Protocol Number: 810P304	**Phase of Development:** 3

Full Title of Study: Open-Label Extension Study to Evaluate the Long-term Safety of Molindone Hydrochloride Extended-Release Tablets for the Treatment of Impulsive Aggression in Pediatric and Adolescent Subjects with Attention Deficit/Hyperactivity Disorder (ADHD) in Conjunction with Standard ADHD Treatment.

Investigator(s) / Center(s): Approximately 50 US centers

Objective:

The objective of this Phase 3 Open-Label Extension (OLE) study is to collect additional long-term safety data on the use of SPN-810 as a treatment for impulsive aggression (IA) in pediatric and adolescent subjects with ADHD when taken in conjunction with standard ADHD treatment. These subjects would have completed a satisfactory participation in the double-blind studies: 810P301, 810P302, 810P503 or 810P204.

Study Design: Long-term, flexible-dose, open-label, multi-center, up to 60-month study

Number of Subjects: Approximately 600 subjects who have completed a satisfactory participation in 810P301, 810P302, 810P503 or 810P204 studies and/or converted after discontinuation from one of these previous double-blind randomized studies.

Criteria for Inclusion:

1. Completed and converted from a satisfactory participation in the studies 810P301, 810P302, 810P503 or 810P204, or discontinued early during the maintenance phase from one of these previous studies and allowed to enroll only after consultation between the Investigator, the Medical Monitor and the Sponsor.
2. Continues to be medically healthy and with clinically normal laboratory profiles, vital signs, and electrocardiograms (ECGs).
3. Existing diagnosis of ADHD, as described by DSM-5 and confirmed by the K-SADS PL 2013 from study 810P301 or 810P302 or by the MINI-KID from study 810P503 or 810P204.
4. Currently receiving monotherapy with an optimized dose of FDA-approved ADHD medication (including stimulants and non-stimulants).
5. Weight of at least 20 kg.
6. Written informed consent/assent obtained from the subject's parent or legally authorized representative (LAR), and written informed assent obtained from the subject if required.

Criteria for Exclusion:

1. Body Mass Index (BMI) in the 99th percentile or above.
2. Clinically significant change in health status, safety concern or any other reason, which in the opinion of the Sponsor or the Investigator, would prevent the subject from participating in this study or successfully completing the study.

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3. Pregnancy, breastfeeding or refusal to practice contraception during the study (for female subjects of childbearing potential and sexually active males).
4. Current substance or alcohol use.
5. Suicidal thoughts or behaviors confirmed at Visit 7 for 810P301 or 810P302, Visit 8 for 810P503 or Visit 6 for 810P204 studies.
6. Known allergy or sensitivity to molindone hydrochloride.

Treatment, Dose, and Mode of Administration:

Molindone Hydrochloride Extended-Release (SPN-810) tablet dosage forms of 3 mg, 9 mg and 18 mg are available. Treatment is to be administered orally twice daily with or without food. Subjects who completed one of the following double-blind studies (810P301, 810P302 or 810P204) will have converted during their last week of participation and will initiate dosing [redacted]
Subjects who completed the 810P503 study will initiate [redacted]
Subjects who discontinued early during the maintenance phase of study 810P301, 810P302 or 810P204 and, on a case-by-case basis, are approved for participation in this study will receive a blinded conversion card and will initiate at [redacted] Subjects who discontinued early from 810P503 study and approved to participate in this study will be blind-converted and initiate at [redacted]

However, in rare occasions, if subjects who have discontinued from the maintenance phase of any of the previous double-blind studies and have washed out from the study medication for at least 2 days, may be approved to enroll in the OLE. These subjects will enter the study on a [redacted] and receive instructions to gradually titrate to an optimized dose. Following the optimization phase and throughout the course of the study, the Investigator may gradually adjust the dose based upon tolerability or effectiveness within the limits of [redacted] for subjects with a body weight ≥ 30 kg.

Duration of Treatment and Study Duration:

The subject can continue to receive study medication for up to 60 months. During an initial dose optimization phase, visits will occur at 2, 4 and 8 weeks after study start and every 3 months thereafter to assess safety, perform drug accountability, and to dispense new study medication. Every 6 months, subjects can extend their participation for an additional period of 6 months, during which subjects will visit the office every 3 months. Subjects may discontinue at any time if the subject or LAR withdraws consent or if the treating physician feels it is no longer in the best interest of the subject. Efficacy and quality of life data will be collected during the study. Just prior to the End of Study (EOS) visit, subjects who complete at least one maintenance phase will be instructed to taper off study medication over a period of 2 weeks.

Treatment Schedule:

Once treatment on the previous clinical study is complete and consent obtained for this study, the Investigator will initiate the subjects at [redacted]), and may gradually adjust the dose of SPN-810 between [redacted] for up to 60 months. For subjects with body weight ≥ 30 kg and not fully responding to 36 mg/day doses, the Investigator may gradually increase the dose of SPN-810 up to 54 mg/day. At the end of the maintenance phase, the subject will be tapered off study medication over a period of 2-weeks.

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Maximum duration of the study: Up to 60 months or until market availability.

- Optimization Phase: 8 weeks
- Maintenance Phase: initial period of 6 months, with the option for additional periods of 6 months each
- Taper Phase: 2 weeks

Safety Variables:

1. Adverse Events (AE) and Serious Adverse Events (SAE)
2. Extrapyramidal Symptoms (EPS) scales (Simpson-Angus Scale, Barnes Akathisia Scale, and Abnormal Involuntary Movement Scale)
3. Clinical Laboratory Tests (Hematology, Chemistry (Glucose, LDL, HDL, Triglycerides, Total cholesterol, etc.), Insulin, Prolactin and Urinalysis)
4. Concomitant Medications
5. Vital signs, Standardized BMI, Physical Examination and ECG (12-lead)
6. Columbia Suicide Severity Rating Scale (C-SSRS)

Efficacy Variables:

1. Retrospective-Modified Overt Aggression Scale (R-MOAS)
2. Clinical Global Impression – Improvement Scale (CGI-I)
3. Clinical Global Impression – Severity Scale (CGI-S)

Quality of Life Variables:

1. Child Health Questionnaire (CHQ-PF28)
2. Parenting Stress Index (PSI-4-SF) or Stress Index for Parents of Adolescents (SIPA)
3. Socio-demographics

Pharmacogenomics (PGx):

Participation in PGx testing is optional. For subjects already enrolled in this study, a blood sample for PGx analysis will be collected at the next visit following this amendment. For newly enrolled subjects, the blood sample for PGx analysis will be obtained at screening. Prior to testing, all subjects will be consented for PGx testing.

The DNA will be extracted and tested for any genetic variations associated with [redacted] enzyme. [redacted] The residual DNA will be stored for possible testing of genes involved in the efficacy and possible association with particular adverse events of the drug (e.g., understand the non-responders to treatment and/or individuals who show unusual safety profile). The DNA analysis will not be used for individual genetic characterization and the subject identity will be kept confidential. The PGx report may be a stand-alone document.

Analysis Populations:

All subjects who have documented Informed Consent/Assent and have taken at least one dose of SPN-810 during this study will be in the safety population.

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Statistical Methods:

All statistical analyses will be based on the safety population. Summary statistics for continuous variables will include sample size (N), mean, median, standard deviation, minimum, and maximum. Summary statistics for discrete variables will be presented in terms of frequencies and percentages in the safety population.

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LIST OF ABBREVIATIONS

ADHD	Attention-Deficit Hyperactivity Disorder
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BARS	Barnes Akathisia Rating Scale
BID	Twice a Day
BMI	Body Mass Index
BP	Blood Pressure
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impression – Severity of Illness
CGI-I	Clinical Global Impression – Global Improvement
CHQ-PF28	Child Health Questionnaire Parent Form 28 item
CK	Creatine Kinase
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
C-SSRS	Columbia Suicide Severity Rating Scale
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eOBsRO	Electronic Observer-Reported Outcome
EOS	End of Study
EPS	Extrapyramidal Symptoms
ER	Extended Release
FDA	Food and Drug Administration
FOCBP	Females of Childbearing Potential
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
HCT	Hematocrit
HDL	High Density Lipoprotein
Hgb	Hemoglobin
HR	Heart Rate
IA	Impulsive Aggression
IAF	Informed Assent Form
ICF	Informed Consent Form

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ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IR	Immediate Release
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LAR	Legal Authorized Representative
LDL	Low Density Lipoprotein
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MINI-KID	Mini International Neuropsychiatric Interview for Children and Adolescents
MTA	Multimodal Treatment of Children with ADHD
ODD	Oppositional Defiant Disorder
OLE	Open Label Extension
PGx	Pharmacogenomic
PSI-4-SF	Parenting Stress Index-Short form
RBC	Red Blood Cells
R-MOAS	Retrospective Modified Overt Aggression Scale
RR	Respiratory Rate
SADR	Suspected Adverse Drug Reaction
SAE	Serious Adverse Event
SIPA	Stress Index for Parents of Adolescents
SOP	Standard Operating Protocol
SM	Study Medication
SNAP-IV	Swanson, Nolan and Pelham-IV
TEAE	Treatment Emergent Adverse Event
TEOSS	Treatment of Early-Onset Schizophrenia Spectrum Disorders Study
TID	Three Times a Day
TOSCA	Treatment of Severe Childhood Aggression
WBC	White Blood Cells
[redacted]	[redacted]

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1 INTRODUCTION

1.1 Background

Aggression refers to a behavior that can result in both physical and psychological harm to oneself, others or objects in the environment. The expression of aggression can occur in a number of ways, including verbally, mentally, and physically. Aggressive behavior becomes maladaptive when it persists, occurs outside an acceptable social context, and is of an intensity, frequency, severity and/or duration detrimental to the child's interests (Jensen 2007, Connor 2006).

Aggression can be categorized into two broad subtypes based on the aggressor's motivation – 1) reactive or impulsive and 2) proactive or instrumental (Vitiello, 1997). Impulsive aggression (IA) is angry, retaliatory aggression arising out of frustration, annoyance, or hostility to real or perceived provocations – stressors that non-affected youth of the same age can typically control in a more socially acceptable manner. IA is an unplanned, immediate response and an out-of-control emotional state, reflecting the inability to contain rage in response to apparent threat that usually does not lead to a secondary benefit. In contrast, instrumental aggression is consciously planned, goal-oriented behavior with the specific intent of benefiting the aggressor (Jensen, 2007). IA is then a behavior that implies an immediate action without thinking: this type of impulsivity seems to nurture internalizing behaviors leading to depression and anxiety due to poor parent-child interaction, peer rejection or sensitivity to stress (Vitaro, 2002).

IA is a common symptom in a distinct group of patients such as attention-deficit/hyperactivity disorder (ADHD), although it is not a criterion for diagnosis of ADHD. IA is a behavior, which requires specific pharmacological intervention in children with ADHD. In pre-adolescent children with ADHD Combined subtype participating in the Multimodal Treatment of Children with ADHD (MTA) study, (The MTA Cooperative Group, 1999) 54% displayed clinically significant aggression at baseline. Of these, 44% remained aggressive even after 14 months of multimodal therapy (The MTA Cooperative Group, 1999; Jensen 2007).

Moreover, aggressive behavior had a much greater impact on parents' overall impairment ratings than the core ADHD symptoms themselves. Children with ADHD are an especially vulnerable population that bear the brunt of ADHD-related morbidity, including severe IA, and may therefore benefit from the addition of a drug specifically targeting residual aggressive behaviors refractory to primary ADHD therapy. A stepped care approach with aggression-targeted therapy, such as an antipsychotic added to ADHD therapy has been recommended to treat residual aggressive behaviors (Scotto-Rosato, 2012). IA in the context of ADHD represents a serious clinical and public health concern and requires effective and timely intervention.

IA amplifies the psychological, academic, emotional, and social problems associated with ADHD (Shelton, 1998), markedly increasing the risk of persistent behavioral problems, conduct disorder, encounters with the justice system, deficits in academic achievement, behavioral and disciplinary problems at school, and substance experimentation/abuse. Early-onset, pervasive and unremitting IA in the context of impulsive thoughts, emotional lability, and impulsive behavior is thought to represent a high-risk profile for progression from childhood ADHD to adult antisocial disorders (McKay, 2001).

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1.2 **Current Treatment Options**

Based largely on the beneficial effects of risperidone on disruptive behavior disorders in children of sub-average intelligence, antipsychotics have been recommended as adjunctive therapy for treating aggression in children with ADHD (Pappadopulos at al. 2003; Pliszka et al. 2006; Pliszka et al. 2007). The TOSCA (Treatment of Severe Childhood Aggression) study has provided empirical evidence to support a stepped-care approach in which children with ADHD and severe aggression are initially treated with primary ADHD therapy followed by adjunctive antipsychotic therapy targeting residual aggressive behaviors (Farmer 2011; Aman 2014; Gadow 2014). However, risperidone, had only a limited impact on aggression (effect size, 0.29) in the TOSCA study even though the dosage could be adjusted for optimal effect. Moreover, the TOSCA study confirmed that stimulant co-therapy does not attenuate the long term effects of risperidone or similar agents on body composition, metabolic parameters, prolactin, or sedation (Calarge, 2009: Penzner 2009). Use of the antipsychotics olanzapine, quetiapine, risperidone, and aripiprazole in children were all associated with significant increase in weight and BMI (8.5 kg/3.01 kg/m^2, 6.1 kg/2.12 kg/m^2, 5.3 kg/1.92 kg/m^2, and 4.4 kg/1.67 kg/m^2, respectively) (Correll et al. 2009). Olanzapine and quetiapine produced significant increases in multiple metabolic parameters and risperidone significantly increased triglyceride levels.

Molindone hydrochloride is a first-generation mid-potency compound for which the Sponsor has developed an extended release (ER) formulation (SPN-810), administered orally for the treatment of IA in children with ADHD.

The immediate-release molindone (Moban®) was approved in 1974 for the management of schizophrenia in adults and adolescents but was discontinued due to commercial reasons by the original manufacturer. Its effects relative to the second-generation antipsychotics (olanzapine and risperidone) were evaluated in a pediatric population with early-onset schizophrenia and schizoaffective disorder in the Treatment of Early-Onset Schizophrenia Spectrum Disorders Study (TEOSS) (McClellan et al. 2007). Molindone was selected as the first generation antipsychotic based on its favorable safety profile in comparison with the second generation agents. At the average dose of 60 mg/day molindone was shown to be safe and well tolerated (Sikich 2008). Molindone was also not associated with significant increases in weight/BMI in contrast to olanzapine. Results of randomized controlled trials such as TEOSS stimulated interest in the potential usefulness of molindone as a weight- and metabolically-neutral D2-receptor antagonist in children with ADHD and comorbid IA.

In an open-label study, molindone, at the optimized dose of 0.5 mg/kg/day, improved aggressive behavior in children (N=6, 6-11 years of age) with undersocialized conduct disorder, aggressive type (Greenhill 1981). Molindone was also shown to be effective in treating aggressive behavior in a double-blind, 8-week, inpatient study of 31 children, ages 6 to 11, with undersocialized conduct disorder, aggressive type (Greenhill, 1985). The overall clinical profile of molindone makes it an attractive candidate for the treatment of IA in children with ADHD, especially with the anticipated benefits of an ER formulation.

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1.3 **Sponsor's Phase 2 Studies**

Study 810P201 was a proof-of-principle, open label, parallel-group, randomized, dose-ranging, safety and tolerability study using the investigational immediate-release (IR) formulation of molindone (Molindone IR) dosed three times a day (TID) in children with ADHD and persistent serious conduct problems (Stocks 2012). Target subjects were healthy male or female children aged 6 to 12 years, with a diagnosis of ADHD accompanied by persistent serious conduct problems. A total of 78 subjects (19-20 per treatment group) in ten U.S sites were randomized. The primary objective was to evaluate the safety and tolerability of four weight-based dosages of Molindone IR dosed three times daily in children with ADHD and persistent serious conduct problems [redacted]). The secondary objectives were to 1) explore the relationship between molindone plasma concentration exposure and safety/tolerability endpoints and 2) assess the effect of Molindone IR after 6 weeks of maintenance treatment in reducing persistent serious conduct problems as measured by the Conduct Problem Subscale of the Nisonger Child Behavior Rating Form-Typical Intelligence Quotient (NCBRF-TIQ).

Treatment with Molindone IR three times daily was safe and well tolerated. Preliminary efficacy results suggested that treatment with Molindone IR resulted in behavioral improvements and that those improvements were more marked in higher dose groups than lower dose groups.

Study 810P202 was a Phase 2b multicenter, randomized, double-blind, placebo controlled trial in a pediatric population of subjects 6-12 years of age diagnosed with ADHD and IA that was not controlled by optimal stimulant and behavioral therapy (Sponsor Study 810P202). The primary objective of the study was to assess the effect of an extended-release tablet formulation of molindone hydrochloride (SPN-810) (12 to 54 mg/day) in reducing IA as measured by the Retrospective-Modified Overt Aggression Scale (R-MOAS) after at least three weeks of assigned treatment. Secondary endpoints included the rate of remission of IA and measurement of the effectiveness of SPN-810 on Clinical Global Impression (CGI) and ADHD scales as well as evaluation of the safety and tolerability of the drug. Patients who completed the study could continue into an open-label phase of six months duration.

SPN-810 dose within treatment groups was stratified by weight (below/above 30 kg). Both the Medium (24/36 mg) and Low (12/18 mg) dose groups showed a statistically significant difference from the Placebo group in the change from baseline to final visit (Visit 10) in R-MOAS but the High (36/54 mg) dose group was not significantly different from the Placebo group. Additionally, both the Low dose and Medium dose groups were significantly different from the High dose based on pair-wise comparison among the dose groups.

[redacted]

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Other study results further supported a beneficial treatment effect on IA behaviors. The CGI results (Severity and Improvement) were consistent with the findings for the R-MOAS; notable improvement occurred primarily in the Low dose and Medium dose groups. Scores for Swanson, Nolan and Pelham Questionnaire (SNAP-IV) Hyperactivity and Impulsivity did not exhibit statistically significant differences across groups. Numeral trends in SNAP-IV Oppositional Defiant Disorder (ODD) scores, while not always significant, consistently favored the Low dose- and Medium dose groups over Placebo.

Study 810P203 was the multicenter open label extension (OLE) to the Phase 2b trial in a pediatric population of subjects 6-12 years of age diagnosed with ADHD and IA (Sponsor Study 810P203). The starting dose for this open-label extension study was based on subjects' weight at the end of 810P202. Subjects were initiated at doses of 18 and 36 mg/day, in children weighing less than 30 kg, and more than 30 kg, respectively. The dose was gradually adjusted based on tolerability or effectiveness, regardless of weight group to 9 mg/day, 18 mg/day, 27 mg/day or 36 mg/day. Of the 121 subjects randomized into the double blind Study 810P202, 78 subjects continued on to the OLE study and received SPN-810 for up to 6 months.

SPN-810 was well tolerated when dosages were adjusted according to clinical response. The overall incidence of AEs was dose-related: 9 mg/day, 26.7%; 18 mg/day, 32.7%; 27 mg/day, 39.1%; and 36 mg/day, 55.2%. The most frequently reported AEs with 36 mg/day were abnormal weight gain (12.1%), sedation (10.3%), and increased appetite (8.6%). Other common AEs included somnolence, which occurred in 5.1% of subjects in any dose group. Of all AEs, nervous system disorders were reported with the highest frequency, with similar reporting frequency among all 4 dose groups (8.7-15.5%). The frequency of AEs associated with EPS was low (n=2, 2.6%), as was the frequency of discontinuations due to AEs (n=7, 9.0%). Over the course of 6 months, the average increase was 2.18–3.70 kg in weight and 0.55–1.06 kg/m^2 in BMI across the dose groups, most of this increase was considered to be due to normal growth. A total of seven subjects (9.0%) discontinued due to AEs. No unexpected, life-threatening, or dose-limiting safety issues were observed. The overall frequency of events was relatively low as were discontinuations due to AEs. Treatment effects achieved during the double-blind study 810P202 appeared to be maintained in the OLE study supporting the clinical relevance of SPN-810 as a treatment for IA in children diagnosed (comorbid) with ADHD.

1.4 **Sponsor's Phase 3 Studies**

The Sponsor is conducting two Phase 3 multicenter, randomized, double-blind, placebo controlled trials in a pediatric population of subjects 6-12 years of age and one in adolescents (12-17 years old) diagnosed with ADHD and IA (810P301, 810P302 and 810P503, respectively). The primary objective of these studies is to assess the efficacy and safety of SPN-810 in reducing the frequency of IA behaviors in pediatric and adolescent patients with ADHD when taken in conjunction with standard ADHD treatment. The Sponsor has recently developed a new measurement tool to assess the frequency of the behaviors associated with IA (Sponsor Study 810P501). This instrument is an electronic observer-reported outcome (eOBsRO) diary that monitors the occurrence of IA behaviors. Severity of IA is assessed using the Clinical Global Impression scales completed by both the caregiver and the Investigator.

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Additional secondary endpoints include the assessment of subjects and caregivers quality of life using the Child Health Questionnaire Parent Form 28-item (CHQ-PF28) and the Parenting Stress Index-Short Form (PSI-4-SF) or the Stress Index for Parents of Adolescents (SIPA). The effect of molindone on body composition, metabolic parameters, prolactin and possible drug-drug interaction is also evaluated.

Children 6 to 12 years of age with ADHD and the associated feature of IA are randomized, with 97 subjects in each treatment arm (18 mg, 36 mg and placebo). [redacted]. After completing the two-week titration phase and the three-week maintenance phase, subjects will have the option to enroll in the OLE study (this study 810P304), at which time they will enter either the conversion phase or the tapering phase prior to the completion of the double-blind study. Subjects who choose to participate in this OLE will be converted from their maintenance study dose to a dose of 18 mg/day SPN-810 in a blinded fashion.

For the 810P503 study, 93 patients diagnosed with ADHD and the associated feature of IA are randomized to placebo or a flexible dose of SPN-810. After two weeks of titration, the dose will be maintained at 36 mg/day during the first week of maintenance and then increased up to 54 mg/day at the discretion of the Investigator during the following two weeks. After the completion of the maintenance phase, subjects will enter a taper down period if they decide to discontinue, or will be given the option to enroll in the OLE (810P304 study). Subjects who choose to enroll in the OLE will receive a blinded conversion card and enter the OLE study at 36 mg/day.

1.5 **Study Rationale**

Results from Phase 2 studies and the associated open label study have shown that molindone hydrochloride extended-release (SPN-810) is safe and well tolerated in the target population of children 6-12 years of age. The goal of the phase 3 studies is to support the efficacy, safety and tolerability of SPN-810 in reducing the frequency of IA behaviors. This Phase 3 study, 810P304, is available to eligible subjects who complete the randomized, double-blind portion of one of the three Phase 3 studies, 810P301, 810P302, 810P503 or the additional Phase 2 study, 810P204. Subjects who discontinue during the maintenance phase may be allowed to participate in the OLE on a case-by-case basis only after consultation between the Investigator, the Medical Monitor and the Sponsor.

The objective of this extension study is to collect additional long-term safety data on the use of SPN-810 for the treatment of IA in subjects diagnosed with ADHD in conjunction with a standard ADHD treatment (stimulant or non-stimulant) and to collect additional data on the maintenance of the effect on IA behaviors and quality of life.

Monitoring the occurrence of any treatment emergent AEs, concomitant medications and the frequency of extrapyramidal symptoms are the primary outcome measures for this study.

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In addition to safety, we will assess the severity of aggressive behaviors using the R-MOAS scale, and the severity and improvement of IA using the CGI scales. Changes in CHQ-PF28 and PSI-4-SF or SIPA scores will be used to evaluate improvement of quality of life of both the subject and the caregiver.

2 STUDY OBJECTIVE

2.1 Objective

The objective of this Phase 3 OLE study is to collect long-term safety data on the use of SPN-810 as a treatment for IA in subjects (6-17 years of age) with ADHD when taken in conjunction with standard ADHD treatment only after satisfactory participation in a preceding double-blind study (810P301, 810P302, 810P503 or 810P204).

3 INVESTIGATIONAL PLAN

3.1 Rationale for Study Design, Including Choice of Treatment Groups, Appropriateness of Measurements

The present study is designed to collect long-term safety data for the use of SPN-810 in the treatment of IA in subjects aged 6 to 17 years diagnosed with ADHD. SPN-810 was used in Phase 2 and currently in Phase 3 studies for the treatment of IA in children and adolescents with ADHD who experienced IA behaviors despite monotherapy treatment with an FDA-approved ADHD medication.

The subject will be eligible to enroll in this study after the completion of the double-blind studies 810P301 or 810P302, 810P503 or 810P204. At Visit 6 of 810P301 and 810P302 studies or at Visit 4 of 810P204, subjects are invited to convert from their randomized dose in a blinded fashion to a dose of [redacted] the initial total daily dose for this OLE study. Subjects participating in the 810P503 study will receive a blinded conversion card at Visit 7 and will initiate the OLE study at [redacted]

Additionally, subjects are eligible to enroll in this study on a case-by-case basis only after consultation between the Investigator, the Medical Monitor and the Sponsor if they discontinue from one of the double-blind studies during the maintenance phase prior to Visit 6 (810P301 or 810P302) or Visit 5 (810P204). Subjects will be converted from their randomized dose to the initial total daily dose of [redacted] n a blinded fashion. If subjects discontinued from the 810P503 study prior to Visit 7 during the maintenance phase, they will be converted in a blinded fashion from the randomized dose to [redacted]

The duration of the study will continue up to 60 months or until market availability. After the completion of an initial period of 6 months, subject will have an option to continue the enrollment for additional periods of 6 months each.

Safety will be assessed throughout the study by the monitoring of AEs, concomitant medications, vital signs, clinical laboratory tests, physical examinations, and ECGs. Emergence of extrapyramidal symptoms will be assessed using the Simpson-Angus Scale, the Barnes Akathisia Scale, and the Abnormal Involuntary

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Movement Scale (AIMS). These scales were specifically chosen since youth treated with antipsychotics are at a greater risk for extrapyramidal side effects than adults (Findling, 2005) and they were also utilized in our Phase 2 and Phase 3 studies.

3.2 **Overall Study Design and Plan**

Study 810P304 is a multicenter, open-label, extension study aimed to assess safety of SPN-810 in the treatment of IA in patients aged 6-17 years with ADHD in conjunction with standard ADHD treatment. The study has three phases: Optimization, Maintenance, and Taper.

All subjects who complete the randomized, double-blind portion of study 810P301, 810P302, 810P503 or 810P204 will have the option to participate in the OLE study in which all subjects will receive active Study Medication (SM) treatment. Subjects who choose to participate in the OLE will receive blinded conversion medication kits at Visit 6 of the previous SPN-810 double-blind randomization study (810P301, 810P302) or at Visit 4 for subjects completing the 810P204 study. Subjects, who have completed the 810P503 study and, chose to participate in this study, will receive the blinded conversion card at Visit 7.

Visit 7 of 810P301, 810P302 or Visit 8 for 810P503 will be Visit 1 of 810P304. Visit 6 of the 810P204 will be Visit 1 of the 810P304. The initial total daily dose for the OLE is [redacted]

After enrollment, eligible subjects will enter an optimization phase of two to eight weeks. Subjects will return to the office for visits at weeks 2, 4 and 8 during which the SM dose may be gradually adjusted based upon tolerability or effectiveness within the limits of [redacted]. The Investigator may gradually increase the dose of SPN-810 up to 54 mg/day for subjects with body weight ≥ 30 kg. Following optimization, subjects will return to the office at each visit (every 3 months) during maintenance phase or until the subject discontinues or the study ends. The subject may discontinue at any time if the subject or the LAR withdraws IAF or ICF or if it is no longer in the best interest of the subject, at the investigator's discretion. If the subject discontinues or is removed from the study, he/she will taper off the SM over a period of at least 2 weeks.

3.2.1 **Baseline Phase**

There will be no screening period. Subjects may enter the study upon completion of one of the following double-blind studies: 810P301, 810P302, 810P503 or 810P204. Prior to conducting any procedures, written informed consent/assent must be obtained from the parent or LAR, and subject (when required). Inclusion and exclusion criteria will be re-assessed to confirm the subjects' eligibility. Each eligible subject will be assigned the same subject number used in the previous double-blind randomized study.

- Subjects who have completed one of the double-blind randomized studies (810P301, 810P302, 810P204 or 810P503) will be converted during their last week of participation and will initiate dosing [redacted] respectively.
- On a case-by-case basis, subjects who discontinued early during the maintenance phase of 810P301, 810P302, 810P204 or 810P503 and are approved for participation in this study will initiate at [redacted] respectively.

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- In rare occasions, subjects who have discontinued early from the maintenance phase of 810P301, 810P302, 810P204 or 810P503 and have washed out from the study medication for at least 2 days may be approved to enroll in the OLE. These subjects will enter the study at [redacted] and gradually titrated up to an optimized dose.

3.2.2 **Pharmacogenomics (PGx)**

Participation in PGx testing is optional. For subjects already enrolled in this study, a blood sample will be collected at the next visit following this amendment. For newly enrolled subjects (from 810P301, 810P302 or 810P204 study), the blood samples for PGx analysis will be obtained at Visit 1/Baseline. Prior to testing, all subjects will be consented for PGx testing.

The DNA will be extracted and tested for any genetic variations associated with [redacted] enzyme. [redacted].

The residual DNA will be stored for possible testing of genes involved in the efficacy and possible association with particular adverse events of the drug (e.g., understand the non-responders to treatment and/or individuals who show unusual safety profile). The DNA analysis will not be used for individual genetic characterization and the subject identity will be kept confidential.

3.2.3 **Optimization Phase (2-8 weeks)**

During the optimization phase, the study medication dose should be optimized between [redacted]y given as divided doses BID in children (6-12 years of age) or adolescents (12-17 years of age), respectively.

3.2.4 **Maintenance Phase (repeated 6 month periods)**

During the maintenance phase, subjects will return to the office every 3 months to evaluate safety and efficacy, perform drug accountability and to receive new study medication, as required. The Investigator may continue to adjust the dose as needed between 6 mg/day and 36 mg/day given as a divided dose (BID). For subjects whose body weight is ≥ 30 kg, the Investigator may gradually increase the dose of SPN-810 up to 54 mg/day based on safety and tolerability. After each 6-month period, subjects will be offered the option to extend their participation for an additional period of 6 months.

During the maintenance phase, a urine pregnancy test will be requested for all Females of Child Bearing Potential (FOCBP). At each visit during Maintenance (Visit 5-Visit 24), FOCBP subjects will receive a urine pregnancy test to take at home and will be asked to complete the testing approximately 6 weeks following each visit. The site will call the caregiver as a reminder and follow-up to obtain the pregnancy test results. Sites are encouraged to educate the caregivers and the subjects on the importance of preventing pregnancies during participation in the study.

The distribution of the home pregnancy test as well as the results of the test will be recorded on paper source at the clinical trial sites.

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If a positive result is reported, the subject will be brought to the clinic for an unscheduled visit to confirm through a serum pregnancy test. If pregnancy is confirmed, the subject will be withdrawn from the study. The Investigator will report the pregnancy and complete the follow-up procedures outlined in Sec. 5.1.3.2.

3.2.5 **Taper Phase (2 weeks)**

All subjects who discontinue early or complete the OLE study 810P304 will taper off the study medication over a period of 2 weeks.

3.2.6 **End of Study / Early Termination**

Subjects will return to the study site for a final visit, after completing the 2-weeks Taper Phase. Subjects who discontinue early will return to the study site for a final visit.

4 STUDY METHODS

4.1 Study Population

Approximately 600 subjects will be enrolled in this clinical investigation. The population will be male and female subjects with IA and diagnosed with ADHD, currently treated with an FDA-approved standard ADHD treatment and who have completed a satisfactory participation in one of the double-blind randomized studies 810P301, 810P302, 810P503 or 810P204. Subjects who discontinued early from the above double-blind randomized studies during the maintenance phase will be allowed to enroll in this study after consultation between the Investigator, the Medical Monitor and the Sponsor on a case-by case basis.

4.1.1 **Inclusion Criteria**

1. Healthy male or female subjects, who completed and converted from a satisfactory participation in the studies 810P301, 810P302, 810P503 or 810P204 or discontinued early from the previous study during the maintenance phase and allowed to enroll only after consultation between the Investigator, the Medical Monitor and the Sponsor.
2. Medically healthy and with clinically normal laboratory profiles, vital signs, and electrocardiograms (ECGs).
3. Existing diagnosis of ADHD, as described by DSM-5 and confirmed by the K-SADS PL 2013 from study 810P301 or 810P302 and by the MINI-KID from the 810P503 or 810P204 studies.
4. Currently receiving monotherapy treatment with FDA-approved ADHD medication (stimulants and non-stimulants).
5. Weight of at least 20 kg.
6. Written Informed Consent obtained from the subject's parent or LAR, and written Informed Assent obtained from the subject if appropriate.

4.1.2 **Exclusion Criteria**

1. Body Mass Index (BMI) in the 99th percentile or above.

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2. Clinically significant change in health status, safety concern or any other reason that, in the opinion of the Sponsor or the Investigator, would prevent the subject from participating in this study or successfully completing this study.
3. Pregnancy, breastfeeding or refusal to practice contraception during the study (for female subjects of childbearing potential and sexually active males).
4. Current substance or alcohol use.
5. Suicidal thoughts or behaviors confirmed at last visit in the previous double-blind randomized study.
6. Known allergy or sensitivity to molindone hydrochloride.

4.2 Schedule of Visits and Procedures

All subjects who are enrolled and take the initial dose of SM are required to follow the protocol procedures regardless of the number of doses of SM taken. The Sponsor, or the Sponsor's designee, must be notified of all deviations from the Schedule of Visits and Procedures (Table 1), and these procedures, if applicable, should be performed at the nearest possible time to the original schedule. Subjects will be instructed to call study personnel to report any issues or abnormal reactions during the intervals in between study visits and to return to the study site if medical evaluation is needed especially when urgent. Unscheduled visits may be conducted at the discretion of the Investigator throughout all study periods. The medical monitor must be contacted promptly in the event that any clinically significant findings or information is obtained during the unscheduled visit. For emergency and other unscheduled visits to a medical facility other than the study site, medical records will be obtained by the Investigator or qualified designee as source data for study follow-up by the Investigator.

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Table 1: Schedule of Events and Procedures

		Treatment					EOS
Phase	***Baseline[a]***	***Optimization***			***Maintenance***		***Taper***
Visit Number	**EOS Visit[a]/ Visit 1**	**Visit 2 (Week 2)**	**Visit 3 (Week 4)**	**Visit 4 (Week 8)**	**[b]Visits 5 (Mo 3), 7, 9, 11, 13, 15, 17, 19, 21, and 23 (Mo 57)**	**[b]Visits 6 (Mo 6), 8, 10, 12, 14, 16, 18, 20, 22, and 24 (Mo 60)**	**Visit 25**
Window (Days)		**2 weeks ±1 week from Visit 1**	**2 weeks ±1 week from Visit 2**	**4 weeks ±1 week from Visit 3**	**Visit 5 will occur 4 weeks ±1 week from Visit 4**	**Visit 6 will occur 3 months ± 1 week from Visit 5**	
Informed Consent/Assent[c]	X						
Physical Examination	X					X	X
ECG	X				X	X	X
Inclusion/Exclusion Criteria	X						
Socio-demographic Information	X						
Urine Drug Screen	X				X	X	X
Urine Pregnancy Test[d]	X[a]	X	X	X	X	X	X
Home urine pregnancy follow-up (call)[b]					X	X	
Vital Signs[e]	X[a]	X	X	X	X	X	X
Weight, Height and BMI	X[a]	X	X	X	X	X	X
Blood collection for Pharmacogenomic (PGx) Testings[h]	X						
Hematology/Chemistry/Urinalysis	X[a]			X		X	X
Columbia Suicide Severity Rating Scale (CSSRS)	X[a]	X	X	X	X	X	X
Investigator CGI-S	X	X	X	X	X	X	X[f]
Caregiver and Investigator CGI-I	X	X	X	X	X	X	X[f]
R-MOAS					X	X	X[f]

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		Treatment					EOS
Phase	***Baseline[a]***	***Optimization***			***Maintenance***		***Taper***
Visit Number	**EOS Visit[a]/ Visit 1**	**Visit 2 (Week 2)**	**Visit 3 (Week 4)**	**Visit 4 (Week 8)**	**[b]Visits 5 (Mo 3), 7, 9, 11, 13, 15, 17, 19, 21, and 23 (Mo 57)**	**[b]Visits 6 (Mo 6), 8, 10, 12, 14, 16, 18, 20, 22, and 24 (Mo 60)**	**Visit 25**
Window (Days)		**2 weeks ±1 week from Visit 1**	**2 weeks ±1 week from Visit 2**	**4 weeks ±1 week from Visit 3**	**Visit 5 will occur 4 weeks ±1 week from Visit 4**	**Visit 6 will occur 3 months ± 1 week from Visit 5**	
CHQ-PF28					X	X	X[f]
PSI-4-SF/SIPA[i]					X	X	X[f]
Safety Scales (Simpson-Angus, Barnes, AIMS)	X[a]	X	X	X	X	X	X
Adverse Events	X[a]	X	X	X	X	X	X
Concomitant Medications	X[a]	X	X	X	X	X	X
Drug Dispensation & Return	X[a]	X	X	X	X	X[g]	X
Drug Compliance		X	X	X	X	X	X

a. Assessment is completed as the EOS visit in the preceding double-blind randomized study: Visit 7 (810P301 and 810P302), Visit 8 (810P503) and Visit 6 (810P204).
b. Visit 7-24 will occur 3 months ±1 week from the previous visit. At each visit, a home urine pregnancy test will be distributed to female subjects of child-bearing potential. Subjects are required to complete testing 6 weeks after each visit. The site will follow-up with a call to record the results.
c. Written consent and assent must be obtained prior to performing any 810P304 study-related procedures.
d. To be performed for females subjects or childbearing potential prior administration of first dose of SM and will have to be tested as negative for the subjects to continue in the study.
e. Heart rate (HR), blood pressure (BP), temperature, and respiratory rate (RR) will be measured.
f. Assessments will be performed only for subjects who discontinue prior the end of the study
g. Taper medication and instructions will be dispensed.
h. Participation in PGx testing is optional. PGx Testing will be performed in subjects enrolling from the following studies: 810P301, 810P302 or 810P204. Subjects already enrolled, will provide a blood sample during the next visit after this amendment is effective.
i. The SIPA scale will be administered only to subjects 13 to 17 years of age.

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4.2.1 **Baseline/Visit 1**

Prior to conducting any procedures, written Informed Consent must be obtained from the parent or LAR, and, if appropriate, Informed Assent from the subject. Visit 7 of 810P301 or 810P302, Visit 8 for 810P503 and Visit 6 of 810P204 will be Visit 1 of the OLE. Subjects who meet the requirements for study participation will begin titration at Visit 6 of 810P301 or 810P302 studies and at Visit 5 for the 810P204 study to the dose level of [redacted] Subjects who have completed 810P503 study participation will start titration at Visit 7 to the initial dose of [redacted] in this study. Subjects will receive instructions and begin the study at their designated dose and will then continue on their optimized dose until the subject discontinues. The SM dose may be adjusted throughout the study upon the Investigator's discretion.

The following procedures will be performed at Baseline or Visit 1:

1. Obtain written informed consent and assent.
2. Perform physical examination
3. Perform 12-lead ECG
4. Confirm Inclusion/Exclusion criteria
5. Record socio-demographic information
6. Record vital signs (Heart Rate (HR), Blood Pressure (BP), temperature, and Respiratory Rate (RR))
7. Record height, weight and BMI
8. Collect blood samples for hematology, chemistry and pharmacogenomic testing (when applicable)
9. Collect urine sample for drug screen
10. Administer Investigator CGI-S
11. Administer Investigator and Caregiver CGI-I
12. Dispense SM
13. Administer Columbia Suicide Severity Rating Scale (C-SSRS)
14. Collect urine sample for pregnancy test (Females of Child Bearing Potential (FOCBP) only) and urinalysis
15. Assess and record concomitant medications
16. Collect and assess adverse events
17. Administer safety scales (Simpson-Angus, Barnes Akathisia, AIMS)

4.2.2 **Visit 2**

Visit 2 will occur approximately 2 weeks (±1 week) following Visit 1.

1. Record vital signs (HR, BP, temperature, and RR)
2. Record height, weight and BMI
3. Collect urine sample for pregnancy test (Females of Child Bearing Potential (FOCBP) only)
4. Administer C-SSRS
5. Administer Investigator CGI-S
6. Administer Investigator and Caregiver CGI-I
7. Administer safety scales (Simpson-Angus, Barnes Akathisia, AIMS)

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8. Collect and assess adverse events
9. Dispense SM.
10. Assess and record concomitant medications
11. Assess treatment compliance

4.2.3 **Visit 3**

Visit 3 will occur approximately 2 weeks (±1 week) following Visit 2 according to the Schedule of Visits and Procedures.

1. Record vital signs (HR, BP, temperature, and RR)
2. Record height, weight and BMI
3. Collect urine sample for pregnancy test (Females of Child Bearing Potential (FOCBP) only)
4. Administer C-SSRS
5. Administer Investigator CGI-S
6. Administer Investigator and Caregiver CGI-I
7. Administer safety scales (Simpson-Angus, Barnes Akathisia, AIMS)
8. Collect and assess adverse events
9. Dispense SM.
10. Assess and record concomitant medications
11. Assess treatment compliance

4.2.4 **Visit 4**

Visit 4 will occur approximately 4 weeks (±1 week) following Visit 3 according to the Schedule of Visits and Procedures.

1. Record vital signs (HR, BP, temperature, and RR)
2. Record height, weight and BMI
3. Collect blood samples for hematology, chemistry and urinalysis
4. Collect urine sample for pregnancy test (Females of Child Bearing Potential (FOCBP) only)
5. Administer C-SSRS
6. Administer Investigator CGI-S
7. Administer Investigator and Caregiver CGI-I
8. Administer safety scales (Simpson-Angus, Barnes Akathisia, AIMS)
9. Collect and assess adverse events
10. Dispense SM.
11. Assess and record concomitant medications
12. Assess treatment compliance

4.2.5 **Visit 5**

Visit 5 will occur 4 weeks (±1 week) following Visit 4 according to the Schedule of Visits and Procedures.

1. Perform 12-lead ECG
2. Record vital signs (HR, BP, temperature, and RR)

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3. Record height, weight and BMI
4. Collect urine sample for pregnancy test (FOCBP only) and dispense home pregnancy test kit
5. Collect urine sample for drug screen
6. Administer C-SSRS
7. Administer Investigator CGI-S
8. Administer Investigator and Caregiver CGI-I
9. Administer R-MOAS
10. Administer quality life scales (CHQ-PF28, PSI-4-SF or SIPA)
11. Administer safety scales (Simpson-Angus, Barnes Akathisia, AIMS)
12. Collect and assess adverse events
13. Dispense SM.
14. Assess and record concomitant medications
15. Assess treatment compliance

4.2.6 **Visit 6**

Visit 6 will occur 3 months (±1 week) following Visit 5 according to the Schedule of Visits and Procedures.

1. Perform physical examination
2. Perform 12-lead ECG
3. Collect urine sample for urinalysis and urine drug screen (all subjects), and pregnancy test (FOCBP only)
4. Dispense home pregnancy test kit
5. Record vital signs (HR, BP, temperature, and RR)
6. Record height, weight and BMI
7. Collect blood for samples for hematology and chemistry
8. Administer C-SSRS
9. Administer Investigator CGI-S
10. Administer Investigator and Caregiver CGI-I
11. Administer R-MOAS
12. Administer quality life scales (CHQ-PF28, PSI-4-SF or SIPA)
13. Administer safety scales (Simpson-Angus, Barnes Akathisia, AIMS)
14. Collect and assess adverse events
15. Collect SM and assess treatment compliance
16. Confirm subject's decision to continue or taper
17. Dispense SM (continue or taper)
18. Assess and record concomitant medications

4.2.7 **Subsequent Visits (Visits 7 through 24) (approximately every 3 months (+/- 1 week))**

After completion of the initial 6-month period (at Visit 6), subjects will be offered the option to continue participation for another 6-month maintenance period for up to a total of 60 months (5 years) or until market availability. Each 6-month period will have two visits every 3-months. These will include Visits 7 through 24.

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At Visits 7, 9, 11, 13, 15, 17, 19, 21, and 23, the following procedures will be conducted:

1. Perform 12-lead ECG
2. Record vital signs (HR, BP, temperature, and RR)
3. Record height, weight and BMI
4. Collect urine sample for pregnancy test (FOCBP only) and dispense home pregnancy test kit
5. Collect urine sample for drug screen
6. Administer C-SSRS
7. Administer Investigator CGI-S
8. Administer Investigator and Caregiver CGI-I
9. Administer R-MOAS
10. Administer quality life scales (CHQ-PF28, PSI-4-SF or SIPA)
11. Administer safety scales (Simpson-Angus, Barnes Akathisia, AIMS)
12. Collect and assess adverse events
13. Dispense SM
14. Assess and record concomitant medications
15. Assess treatment compliance

At Visit 8, 10, 12, 14, 16, 18, 20, 22, and 24, the following procedures will be conducted:

1. Perform physical examination
2. Perform 12-lead ECG
3. Collect urine sample for urinalysis and urine drug screen (all subjects), and pregnancy test (FOCBP only)
4. Dispense home pregnancy test kit
5. Record vital signs (HR, BP, temperature, and RR)
6. Record height, weight and BMI
7. Collect blood for samples for hematology and chemistry
8. Administer C-SSRS
9. Administer Investigator CGI-S
10. Administer Investigator and Caregiver CGI-I
11. Administer R-MOAS
12. Administer quality life scales (CHQ-PF28, PSI-4-SF or SIPA)
13. Administer safety scales (Simpson-Angus, Barnes Akathisia, AIMS)
14. Collect and assess adverse events
15. Collect SM and assess treatment compliance
16. Confirm subject's decision to continue or taper
17. Dispense SM (continue or taper)
18. Assess and record concomitant medications

4.2.8 **Visit 25 [(End of Study (EOS)] (Month 60 +/- 2 weeks)**

Subjects who complete the study (60 months) will be instructed to down titrate for 2 weeks before returning to the office for the EOS Visit.

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Subjects may discontinue prior the end of the study if the subject or the LAR withdraws assent and/or consent, or if the Investigator or the Sponsor decide it is no longer in the best interest of the subject. If the decision is made to discontinue early then the subject will be contacted and instructed to down-titrate at least 2 weeks prior to the EOS Visit.

The following procedures will be performed for subjects who complete the study (60 months) or discontinue early.

1. Perform physical examination
2. Perform 12-lead ECG
3. Collect urine sample for urinalysis and urine drug screen (all subjects), and pregnancy test (FOCBP only)
4. Record vital signs (HR, BP, temperature, and RR)
5. Record height, weight and BMI
6. Collect blood samples for hematology and chemistry
7. Administer C-SSRS
8. Administer safety scales (Simpson-Angus, Barnes Akathisia, AIMS)
9. Administer efficacy scales (R-MOAS, CGI-I and CGI-S, only for subjects who discontinue early)
10. Administer quality life scales (CHQ-PF28, PSI-4-SF or SIPA, only for subjects who discontinue early)
11. Collect and assess adverse events
12. Collect SM and assess treatment compliance
13. Assess and record concomitant medications

4.3 Treatments

4.3.1 Treatments Administered

SPN-810

Subjects will enter this study from one of the previous double-blind clinical studies (810P301, 810P302 or 810P204) and will initiate at [redacted]. Subjects from the double-blind 810P503 study will initiate this study at [redacted] Eligible subjects who discontinue early in one of the randomized, double-blind studies (810P301, 810P302 or 810P204) and are approved for participation in the OLE study will initiate study as outlined in Sec. 3.2.1. At the Investigator's discretion, this initial dose may be gradually adjusted based upon tolerability and effectiveness between [redacted] For subjects with body weight ≥ 30 kg and not fully responding to 36 mg/day doses, the Investigator may gradually increase the dose of SPN-810 up to 54 mg/day.

In rare occasions, subjects who discontinue early and have washed out from the SM for at least 2 days may be approved to enroll in the OLE. These subjects will enter the study at [redacted] will be instructed to gradually titrate at the optimized dose.

Subjects will take molindone hydrochloride extended-release tablet (SPN-810) twice each day (BID) with or without food, in the morning and in the evening, in addition to the optimized dose of ADHD medication.

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If dosing starts before noon, the subject should start with the morning dose; if dosing starts after noon, the subject should start with the evening dose.

ADHD medication

The Investigator is allowed to adjust the FDA-approved ADHD monotherapy medication and/or its dose at any time during the course of this study.

A combination of extended-and immediate-release formulations of the same ADHD medication are not considered monotherapy.

4.3.2 Identity of Investigational Product(s)

Study medications are either purple (3 mg) or yellow (9 mg) round tablets or a reddish-brown (18 mg) oval tablet which are all printed on one side with the appropriate dose strength in a black underscored font ("3" "9" or "18"). Sites will dispense a sufficient quantity (60-120 day supply) of medications for the subject to take the designed dose every day until the next visit to the office, according to Table 1.

The SM is supplied to the sites in bottles: the 3 mg and 9 mg (60-120 day supply) is packaged in a 60cc white, square high-density polyethylene bottle with a white child resistant closure. The 18 mg (60-day supply) drug product is packaged in a 60cc, while the 18 mg (120-day supply) drug product is packaged in a 90cc white, square high-density polyethylene bottle with a white child resistant closure.

4.3.3 Study Medication Handling and Accountability

All SM is supplied to the Investigator by the Sponsor. SM must be kept in an appropriate secure area (e.g., locked cabinet) and stored according to the conditions specified on the SM labels. SM must be stored between 68°F – 77°F (20°C – 25°C).

Following Sponsor instructions and in compliance with ICH E6 as well as local, state, and federal regulations, the Investigator and study staff will be responsible for the accountability of all clinical supplies (receiving, shipment, dispensing, inventory, and record keeping) in a SM accountability log, a copy of which will be collected by the Sponsor at the end of the study.

Under no circumstances will the Investigator allow the SM to be used other than as directed by this protocol. Clinical supplies will not be dispensed to any individual who is not enrolled into the study.

An accurate and timely record of the receipt of all clinical supplies; dispensing of SM to the subject; collection of unused supplies returned by the subject; and subsequent return of unused SM to the Sponsor must be maintained with dates. This SM accountability log includes, but may not be limited to: (a) documentation of receipt of clinical supplies, (b) SM inventory log, (c) SM accountability log, and (d) all shipping notifications. All forms will be provided by the Sponsor. Any comparable forms that the study site wishes to use must be approved by the Sponsor.

Supplies and inventory records must be made available, upon request, for inspection by the designated representative of the Sponsor or a representative of the FDA. The assigned CRA will review these documents along with all other study conduct documents at each and every visit to the study site once

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SM has been received by the study site. All used, partly used, and unused clinical supplies, including empty containers, are to be returned to the Investigator by the subject and ultimately to the Sponsor at the conclusion of the study, unless provision is made by the Sponsor for destruction of supplies and containers at the study site. Upon completion of SM accountability and reconciliation procedures by study site personnel and documentation procedures by Sponsor personnel, SM is to be returned to the Sponsor with a copy of the completed SM disposition form as outlined in the Study Medication Manual.

4.3.4 **Method of Assigning Subjects to Treatment Groups**

Each subject who completes or discontinues from 810P301, 810P302, 810P503 or 810P204, and is eligible for enrollment in the OLE, will maintain the same unique subject identification number that was given to them in the preceding double-blind randomized study.

4.3.5 **Treatment Replacement**

In the event that a subjects' original bottle is lost, damaged, or consumed prior to the end of treatment, a new bottle will be dispensed to that subject from the supplies already available at the site. Limited stock of study medication will be maintained at each site.

4.3.6 **Dosing Schedule**

Subjects will initiate dosing at 18 mg/day (9 mg BID) or 36 mg/day (18 mg BID) in a blinded fashion and subsequently optimized. At the Investigator's discretion, the dose may be gradually adjusted based upon tolerability and effectiveness between the doses of 6 mg/day and 36 mg/day or 54 mg/day for subjects whose body weight is ≥ 30 kg. Doses should always remain BID and, whenever possible, evenly divided (same number of mg in morning and evening).

4.3.7 **Method of Administration**

The SM must be swallowed whole. SM must not be crushed, chewed or cut. The SM may be taken with or without food in the morning and in the evening, preferably every 12 hours.

4.3.8 **Blinding**

Blinding is not applicable.

4.4 **Prohibited Medication**

Subjects may not be on any prohibited medication while on study. These medications include:

- α 2- adrenergic agonists (e.g. clonidine and guanfacine) used for any other reason except for monotherapy treatment for ADHD
- Non-FDA approved formulations for the treatment of ADHD (e.g. IR or ER formulations of the same compound)
- Combination of extended-and immediate-release formulation of the same compound(e.g. IR formulation in the morning and ER formulation in the evening)
- Anti-psychotics including aripiprazole, risperidone, quetiapine, and ziprasidone

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- Anticonvulsants including carbamazepine and valproic acid, antidepressants, mood stabilizers including lithium, benzodiazepines, cholinesterase inhibitors or any drug known to inhibit [redacted] activity
- Herbal supplements

4.5 Concomitant Medication

The following concomitant medications are allowed during this study:

1. Current or other FDA-approved monotherapy ADHD medication.
2. Benztropine is permitted for the treatment of emerging EPS at a starting dose of 0.5 mg BID up to a range of 1 to 4 mg/day. Lorazepam (1 to 2 mg per dose not to exceed three times daily) and clonazepam (0.25 to 1 mg per dose not to exceed twice daily) is also permitted to treat extrapyramidal symptoms.
3. For the treatment of Akathisia, propranolol is allowed up to 90 mg /day in divided doses, three times per day, starting at 10 mg BID and up to 30 mg TID, as needed.
4. Treatment for AEs other than EPS or minor transient ailments is permitted only in consultation with the Medical Monitor or his/her designee with the exception of required treatments for acute conditions in the emergency room/hospital and/or office visit as indicated.

All concomitant medications as well as the changes in the dosing of the ADHD medication or the changes to any other FDA-approved ADHD treatment will be recorded in the eCRF.

4.6 Completion of Study and Discontinuation of Subjects

Subjects will be considered to have completed the study if they complete all visits up to and including the end of study visit. All subjects who discontinue early will be contacted by the study staff and instructed to down-titrate gradually over approximately 2 weeks prior to the EOS visit.

The Investigator(s) or subjects themselves may stop SM treatment at any time for safety or personal reasons. A subject is free to withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The Investigator or Sponsor may also withdraw the subject at any time in the interest of subject safety. The withdrawal of a subject from the study should be discussed where possible with the Medical Monitor and/or the Investigator before the subject stops SM. Subjects removed from the study for any reason will not be replaced.

Reasons for withdrawal may include but are not limited to subject withdrawal of consent, occurrence of unmanageable AEs, or at the Investigator's discretion.

The primary reason for withdrawal must be recorded in the subject's medical record and on the eCRF. If a subject is withdrawn for more than one reason, each reason should be documented in the source document and the most medically significant reason should be entered on the eCRF.

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5 ANALYSIS VARIABLES

5.1 Safety Variable

The primary outcome measure will be the safety and tolerability of the SM. At every visit, safety assessment will consist of monitoring and recording of all AEs and concomitant medications, clinical laboratory tests, together with prolactin and insulin plasma levels, vital signs, physical examinations and 12-lead ECG and suicidality thoughts and behaviors.

Assessment of possible neurological side effects and EPS will be performed using the Simpson-Angus scale, the Barnes Akathisia scale and the Abnormal Involuntary Movement scale. A positive rating or finding on any safety scale will be captured as an Adverse Event at the discretion of the Investigator if it satisfied the criteria for Adverse Event.

5.1.1 Adverse Events

As defined by the ICH Guideline for GCP, an **adverse event (AE)** is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with treatment.

An AE can be:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- Any new disease, intercurrent injuries, or exacerbation of an existing disease.
- Any deterioration in a laboratory value or other clinical test (e.g., ECG) that results in symptoms, a change in treatment, or discontinuation from SM.
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline.

Surgical procedures are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required is an AE, if it occurs or is detected during the study period.

5.1.2 Causality

Adverse events may be categorized as either Adverse Drug Reactions or Suspected Adverse Drug Reactions based on their relationship to SM and the degree of certainty about causality.

Suspected Adverse Drug Reactions (SADRs) are a subset of adverse events for which there is evidence to suggest a causal relationship between the SM and the AE, i.e., there is a reasonable possibility that the SM caused the adverse event.

Adverse Drug Reactions (ADRs) are a subset of all SADRs for which there is reason to conclude that the SM caused the event.

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5.1.2.1 **Recording and Evaluation of Adverse Events**

All subjects who are enrolled (starting at Visit 1) will be questioned regarding the occurrence of AEs. Adverse events occurring in the previous clinical study or ongoing at the end of the 810P301, 810P302, 810P503 or 810P204 will become part of the subject's medical history. At each visit, the Investigator must seek information on AEs by specific questioning and, as appropriate, by examination. Information on all AEs should be recorded immediately in the source document and also in the appropriate adverse event module of the electronic Case Report Form (eCRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though they may be grouped under one diagnosis. For example, fever, elevated WBC, cough, abnormal chest X-ray, etc., can all be reported as "pneumonia".

All AEs occurring after enrollment and throughout the study period must be recorded. A treatment-emergent adverse event (TEAE) is defined as an AE with a start date on or after the first dose of study medication, or that worsened following first administration of study medication. TEAEs will be collected starting from the first dose of SM. The clinical course of each AE should be followed until resolution or until, in the medical judgment of the Investigator, the event has stabilized or is assessed as chronic.

An increased score in the C-SSRS, Simpson Angus Scale, Barnes Akathisia Scale, or the Abnormal Involuntary Scale will not necessarily be rated as an AE unless the event meets AE criteria.

The Investigator is responsible for evaluating AEs and determining the following:

- **Serious vs. Non-serious:** Is the event a Serious Adverse Event (SAE)?
- **Causality:** Was AE related or possibly related to the SM?
- **Severity:** How pronounced is the incapacity/discomfort caused by an AE?

5.1.2.2 **Criteria for Assessing Severity**

The Investigator will evaluate the comments of the subject and the response to treatment in order that he or she may judge the true nature and severity of the AE. Severity refers to the accumulated intensity of discomfort/impairment of health since the last recording of AEs and will be assessed according to the following criteria:

- **Mild:** Awareness of sign, symptom, or event, but easily tolerated
- **Moderate:** Discomfort enough to interfere with usual activity and may warrant intervention
- **Severe:** Incapacitating with inability to do usual activities or significantly affects clinical status and warrants intervention

The criteria for assessing severity are different from those used for seriousness.

5.1.2.3 **Criteria for Assessing Causality**

The Investigator is responsible for determining the relationship between the administration of SM and the occurrence of an AE as **not suspected** or as a **suspected** reaction to SM. These are defined as follows:

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Not suspected: The temporal relationship of the AE to SM administration makes a **causal relationship unlikely**, or other drugs, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

- **Not related:** Temporal relationship to SM administration is missing or implausible, or there is an evident other cause.
- **Unlikely related**: Temporal relationship to SM administration makes a causal relationship improbable; and other drugs, chemicals, or underlying disease provide plausible explanations.

Suspected: The temporal relationship of the AE to SM administration makes a **causal relationship possible**, and other drugs, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

- **Possibly related:** Temporal relationship to SM administration is plausible, but concurrent disease or other drugs or chemicals could also explain event. Information on medication withdrawal may be lacking or unclear. This will be reported as a **Suspected Adverse Drug Reaction (SADR)**.
- **Definitely related:** Temporal relationship to SM administration is plausible, and concurrent disease or other drugs or chemicals cannot explain event. The response to withdrawal of the medication (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary. This will be reported as an **Adverse Drug Reaction (ADR)**.

5.1.3 Serious Adverse Events (SAE)

AEs are classified as serious or non-serious. An AE or ADR is considered "**serious**" if, in the view of either the Investigator or Sponsor, it results in one of the following outcomes:

- death
- life-threatening AE (i.e., the subject was at immediate risk of death from the AE as it occurred. This does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death.)
- in-patient hospitalization or prolongation of existing hospitalization
- persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening or result in death or hospitalization, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug dependence or abuse, blood dyscrasias, a seizure that did not result in in-patient hospitalization, or intensive treatment for allergic bronchospasm in an emergency department would typically be considered serious.

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5.1.3.1 **Investigator Responsibilities for Reporting SAEs**

The Investigator must immediately report to the Sponsor all **SAEs**, regardless of whether the Investigator believes they are drug related.

All SAEs must be reported to the Drug Safety Contact person(s) within 24 hours of first becoming aware of the SAE. The Investigator must complete an SAE ECRF in EDC and include a detailed description of the SAE, as well as other available information pertinent to the case (e.g., hospital records, autopsy reports and other relevant documents). Should the site be unable to access EDC, a paper SAE form must be completed and sent to [redacted] Drug Safety by email or fax. The Investigator will keep a copy of this SAE Report Form on file at the study site. Once EDC becomes available, the site must complete the SAE eCRF in EDC.

The Investigator or study physician, after thorough consideration of all facts that are available, must include an assessment of causality of an AE to SM in the report to the Sponsor.

Follow-up information, or new information available after the initial report, should be actively sought and reported to the Sponsor as it becomes available using the SAE Report Form.

The Drug Safety Contact for SAE reporting is:

[redacted]

5.1.3.2 **Other Events Requiring Immediate Reporting**

The Investigator must report a **pregnancy** that occurs in a subject during a clinical study to the Drug Safety Contact within 24 hours of first becoming aware of the event. Pregnancy should be reported on a Pregnancy Report Form. The Investigator should discuss the case with the Medical Monitor also, he/she must follow any pregnant subject for 3 months after the child is born. The Investigator must complete a Pregnancy Outcome Form as follow up. Any AEs concerning the pregnancy of the subject during pregnancy or the child after birth must be documented and reported to the Sponsor.

Treatment-emergent **extrapyramidal symptoms** (e.g. akathisia, dystonia, Parkinsonism, tardive dyskinesia) and neuroleptic malignant syndrome should be reported to the Drug Safety Contact person(s) by completing the Adverse Event Special Interest (AESI) eCRF in EDC. Should the site be unable to access EDC, a paper AESI form must be completed and sent to [redacted] Drug Safety by email or fax within 24 hours of first becoming aware of the event. Once EDC becomes available, the site must complete the AESI eCRF in EDC. EPS incidence will be summarized and shared with study Investigators throughout the clinical trial.

Overdosage of molindone presumably may be manifested by severe EPS and sedation. Coma with respiratory depression and severe hypotension resulting in a shock-like syndrome could occur. In the

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event of a suspected overdose, the parent or LAR should be instructed to call 911 or their local poison control center at 1-800-222-1222.

Symptomatic, supportive therapy should be the rule. Gastric lavage is indicated for the reduction of absorption of molindone which is freely soluble in water. Since the adsorption of molindone by activated charcoal has not been determined, the use of this antidote must be considered of theoretical value.

Emesis in a comatose patient is contraindicated. Additionally, while the emetic effect of apomorphine is blocked by molindone in animals, this blocking effect has not been determined in humans.

5.1.3.3 **Sponsor Responsibilities for Expedited Reporting of SAEs**

The Sponsor will inform Investigators and regulatory authorities of adverse drug reaction (ADRs) that are both serious and unexpected, in compliance with applicable regulatory requirements, on an expedited basis (i.e., within specific timeframes). For this reason, it is imperative that study sites submit SAE information to the Sponsor in the manner described above.

Investigators must comply with the applicable regulatory requirements related to the reporting of SAEs to the IRB/IEC. Investigators must also submit the safety information provided by the Sponsor to the IRB/IEC unless the country legal regulation requires that the Sponsor should be responsible for the safety reporting to the IRB/IEC.

It is the responsibility of the Sponsor to notify all participating Investigators, in a written IND safety report, of any SADR that is both serious and unexpected. The Sponsor will also notify participating Investigators of any findings from other sources (other studies, animal and in vitro testing, etc.) that suggest a significant risk for human subjects. Such findings will typically lead to safety-related changes in the study protocol, Informed Consent, and/or Investigator's Brochure.

5.1.4 **Management of Treatment-Emergent EPS**

If a subject experiences treatment-emergent EPS (including akathisia, dystonia, Parkinsonism, or tardive dyskinesia), benztropine will be permitted at a starting dose of 0.5 mg BID up to a range of 1 to 4 mg/day. Lorazepam (1 to 2 mg per dose not to exceed three times daily) and clonazepam (0.25 to 1 mg per dose not to exceed twice daily) will also be permitted to treat the occurrence of extrapyramidal symptoms.

For the treatment of Akathisia, propranolol is recommended up to 90 mg /day in divided doses, three times per day, starting at 10 mg BID and up to 30 mg TID, as needed.

A positive finding on an EPS safety assessment scale (Barnes Akathisia, Simpson-Angus, AIMS) does not necessarily equate to an EPS event. Investigators should evaluate positive findings on the EPS safety assessment scales and integrate them into a global clinical observation to determine if an AE of EPS should be recorded.

5.1.5 **Laboratory Measurements**

With the exception of urine pregnancy test, clinical laboratory tests will be performed by a central laboratory as specified in the regulatory binder.

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Details for collecting, handling, and shipping samples (including shipment addresses) will be detailed in a separate laboratory manual. The Schedule of Visits and Procedures (Table 1) shows the time points at which urine samples will be collected for urinalysis and blood samples will be collected for clinical laboratory tests and plasma concentration levels.

Table 2 presents the clinical laboratory tests to be performed. Metabolic parameters (including insulin, glucose, triglycerides, and total-cholesterol) and prolactin will be measured.

All laboratory tests will be reviewed in a timely manner by qualified site personnel to ensure safety. Abnormal lab findings may be confirmed if necessary by one repeated testing at the discretion of the Investigator. Any repeat laboratory testing will be conducted under **fasting condition as indicated**. Any laboratory abnormality may qualify as an AE in the Investigator's judgment.

Approximately 5.5 mL of blood per subject will be drawn at specified visits as per the schedule in Table 1.

Table 2: Clinical Laboratory Tests

Category	Parameters
Hematology	RBC, WBC, Hgb, HbA1c[a], HCT, MCH, MCHC, MCV, platelet count, and WBC with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Chemistry	**Electrolytes**: Na^+, K^+, chloride, bicarbonate
	Liver function tests: alkaline phosphatase, AST, ALT, total bilirubin, direct bilirubin, indirect bilirubin
	Renal function parameters: BUN, creatinine
	Other: glucose, Ca^{+2}, albumin, phosphorus, lactate dehydrogenase, total protein, CK/CPK, globulin, uric acid, triglycerides, insulin, prolactin, cholesterol – total, HDL and LDL Amylase, gammaGT (GGT), Iron, Lipase, Magnesium
Urinalysis	Glucose, protein (total), ketones, bilirubin, urobilinogen, hemoglobin, leucocyte esterase, nitrite
Urine Drug Screen	Cocaine, amphetamines, barbiturates, benzodiazepines, cannabinoids, opioids, phencyclidine, propoxyphene, methadone and alcohol
Urine and Serum Pregnancy Test (FOCBP only)	hCG

a. This parameter will be measured **only** in subjects who participated in the 810P503 study.

5.1.6 Vital Signs and Height/Weight Measurements

Vital signs' measurements (e.g., blood pressure, heart rate, temperature, and respiratory rate) and height, weight and BMI will be obtained at visits designated on the Schedule of Visits and Procedures (Table 1). Blood pressure and heart rate will be measured after the subject has been sitting for 5 minutes. Vital signs may be taken at any other time, as deemed necessary by the Investigator.

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5.1.7 **Physical Examinations and Electrocardiograms (ECGs)**

A physical examination and a 12-lead ECG will be obtained at visits designated on the Schedule of Visits and Procedures (Table 1). Additional ECGs may be performed at other times if deemed necessary by the Investigator.

The ECG will be recorded while the subject is resting in a supine position. The ECG will electronically measure the PR, QRS, QT, and QTc intervals, and heart rate.

All ECG tracings will be reviewed within 24 hours by the Investigator or qualified Sub-Investigator. PR intervals will be determined for each of these ECGs from a single reading. Invalid measurements will be repeated. QTc will be reported as QTcF (QT corrected using Fridericia's method).

5.1.8 **Pharmacogenomic Sample Collection**

Participation in PGx testing is optional. A total of 2 mL blood samples will be collected for [redacted] pharmacogenomic testing. For subjects already enrolled into this study (810P304) a blood sample will be collected at the next visit following this amendment. For newly enrolled subjects, the blood sample for PGx analysis will be obtained at screening. Results from individual tests will be used for research purposes only and will not be distributed.

Samples will be identified only by the study subject number to maintain confidentiality. The DNA will be extracted and tested for any genetic variations associated with [redacted] enzyme. Collected samples will be stored for up to 10 years for potential future research purposes such as possible testing of genes involved in the efficacy and possible association with particular adverse events of the drug (e.g., understand the non-responders to treatment and/or individuals who show unusual safety profile).

Data from samples will not have diagnostic value and will not be used for individual genetic characterization or development of a commercial product. At the end of testing or 10 years, any remaining samples will be destroyed. The subject may withdraw consent for pharmacogenomic testing at any time; if consent is withdrawn, the subject's sample will be destroyed.

5.2 **Efficacy Variables**

The following scales will be administered at visits designated in the Schedule of Visits and Procedures (Table 1).

5.2.1 **Retrospective-Modified Overt Aggression Scale (R-MOAS)**

The Retrospective-Modified Overt Aggression Scale (R-MOAS) was developed to gauge the severity of aggressive behavior (Blader, 2010). Parents rate the frequency over the past week of 16 aggressive behaviors in four areas: verbal aggression; physical aggression toward others; aggression toward oneself; and destruction or hostile misuse of property. Numeric weighting amplifies the seriousness of more harmful behaviors in the total score. This assessment will be administered at each visit after the first 6 months (Visits 5 to 25). For subjects who discontinue early, this will be administered at the EOS (Visit 25).

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5.2.2 **Clinical Global Impression (CGI)**

The CGI scale was developed to provide a brief, stand-alone assessment of the clinician's view of a subject's global functioning prior to and after administration of a SM (Guy, 1976). Severity of illness (CGI-S) and global improvement (CGI-I) are both rated on a scale of 1 to 7 with 7 being "extremely ill" or "very much worse", respectively. Successful therapy is indicated by a lower overall score in subsequent testing. Investigators should consider their total clinical experience with children who have IA comorbid with ADHD and rate how severe the subject's condition is at the time.

- CGI-S will be evaluated by the Investigator at each visit on a 7-point scale with 1=Normal, 2=Borderline ill, 3=Mildly ill, 4=Moderately ill, 5=Markedly ill, 6=Severely ill, and 7=Extremely ill.
- CGI-I, relative to the condition at baseline (Visit 3 in the double-blind studies 810P301, 810P302, 810P503 or 810P204), will be evaluated by the caregiver and by the Investigator at each post-baseline visit on a 7-point scale with 1=Very much improved, 2=Much improved, 3=Minimally improved, 4=No change, 5=Minimally worse, 6=Much worse, and 7=Very much worse.

CGI-S and CGI-I will be assessed at each visit.

5.3 **Quality of Life Variables**

5.3.1 **The Child Health Questionnaire Parent Form 28-item (CHQ-PF28)**

The Child Health Questionnaire Parent Form 28-item (CHQ-PF28) is a short generic measure of health status and health related quality of life (Landgraf, 1996). CHQ-PF28 items have four, five, or six response options, divided over eight multi-item scales (physical functioning, general behavior, mental health, self-esteem, general health perceptions, parental impact: emotional, parental impact: time, and family activities) and five single item concepts (role functioning: emotional/behavior, role functioning: physical, bodily pain, family cohesion, and change in health). The CHQ-PF28 should be performed by the primary caregiver.

The CHQ-PF28 will be administered at each visit after the first 6 months (Visit 5 to 25). For subjects who discontinue early, this will be administered at the EOS (Visit 25).

5.3.2 **The Parenting Stress Index – Short Form (PSI-4-SF)**

Reduction in stress is considered important for parents of children with disruptive behavior problems, developmental disabilities, and chronic illness (Haskett, 2006). The Parenting Stress Index – Short Form (PSI-4-SF) is a 36-item self-report measure of parenting stress (Abidin, 1995). Three subscales (Parental Distress, Parent-Child Dysfunctional Interaction, and Difficult Child) consist of 12 items each. Parents use a 5-point scale to indicate the degree to which they agree with each statement.

The PSI-4-SF will be administered to the caregivers of subjects 6-12 years of age, at each visit after the first 6 months (Visits 5 to 25). For subjects who discontinue early, this will be administered at the EOS (Visit 25).

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5.3.3 **Stress Index for Parents of Adolescents (SIPA)**

The Stress Index for Parents of Adolescents (SIPA) is a screening and diagnostic instrument that identifies areas of stress in parent–adolescent interactions, allowing examination of the relationship of parenting stress to adolescent characteristics, parent characteristics, the quality of the adolescent–parent interactions, and stressful life circumstances in parents of adolescents (11-19 years old). The SIPA consists of 90 items divided in three major domains, the Adolescents Domain (AD), the Parent Domain (PD) and the Adolescent-Parent Relationship Domain (APRD), which include the following subscales: moodiness/emotional lability, social isolation/withdrawal, delinquency/antisocial, failure to achieve and persevere, relationship with spouse/partner, social alienation and incompetence/guilt. The SIPA includes 22-item Life Stressors (LS) Scale and the Index of Total Parenting Stress (TS).

Parents respond to the first 90 items using a 5-point rating scale ranging from *Strongly Disagree* (5) to *Strongly Agree* (1) and the final 22 items by indicating *Yes* (Y) or *No* (N).

The SIPA will be administered to caregivers of adolescents (13-17 years of age) at each visit after the first 6 months (Visits 5 to 25). For subjects who discontinue early, this will be administered at the EOS (Visit 25).

5.3.4 **Socio-demographic Characteristics**

Socio-demographic characteristics are valuable information that will be used to correlate with health-related quality of life and clinical measures. The variables include the number of siblings in the study, siblings with IA, caregiver's age and gender, living situation, marital status, household income and education level.

The socio-demographic characteristics will be recorded at baseline for newly enrolled subjects and, for subjects already enrolled, at the next visit once this protocol amendment is effective.

5.4 **Pharmacogenomic Variable**

The extracted DNA will be tested for any genetic variations associated with [redacted] enzyme. [redacted] The residual DNA will be stored for possible testing of genes involved in the efficacy and possible association with particular adverse events of the drug (e.g., understand the non-responders to treatment and/or individuals who show unusual safety profile).

The DNA analysis will not be used for individual genetic characterization and the subject identity will be kept confidential.

Participation in PGx testing is optional. Blood samples will be collected at Screening (Visit 1) for eligible subjects who have not been previously tested in the blinded studies. Subjects already enrolled in this study, will be tested at the next visit to the clinical site, once this protocol amendment is effective.

5.5 **Special Safety Assessments**

The following special scales will be administered in the clinic at visits designated in the Schedule of Visits and Procedures (Table 1).

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5.5.1 **Simpson-Angus Scale**

The Simpson-Angus scale is a 10-item rating scale that is widely used for assessment of neuroleptic-induced Parkinsonism (Simpson 1970). It consists of 1 item measuring gait, 6 items measuring rigidity, and three items measuring glabella tap, tremor and salivation, respectively. This assessment will be administered at each visit.

5.5.2 **Barnes Akathisia Scale**

The Barnes Akathisia scale is a rating scale for drug-induced akathisia and includes components for rating the observable, restless movements characteristic of akathisia, the awareness of restlessness, and any distress associated with the condition (Barnes, 1989). This assessment will be administered at each visit.

5.5.3 **Abnormal Involuntary Movement Scale (AIMS)**

The AIMS test is a rating scale used to measure tardive dyskinesia (Munetz, 1988). There are 12 items that rate involuntary movements of various areas of the subject's body. This assessment will be administered at each visit.

5.5.4 **Columbia Suicide Severity Rating Scale (C-SSRS)**

The C-SSRS is a questionnaire that prospectively assesses suicidal ideation and behavior using a semi-structured interview to probe patient responses (Posner, 2011). The C-SSRS versions applicable to the current study are the Baseline version and the Since Last Visit version.

The Baseline version of the scale assesses lifetime suicidal ideation and behavior. This version is suitable as part of a subject's first interview and will be used at Visit 1 to identify volunteers who must not participate in the trial due to their suicidal tendencies.

The Since Last Visit version of the scale assesses any suicidal thoughts or behaviors the subjects may have had since the last administration of the C-SSRS. This version will be used for the other study visits.

6 STATISTICAL METHODS

6.1 **Statistical and Analytical Plans**

Tabular summaries of the data collected during the study will be presented to provide a general description of the subjects studied and an overview of safety results. Data from all sites will be combined in the computation of these summaries. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, standard deviation [SD], median, and minimum and maximum values). Categorical (nominal) variables will be summarized using frequency tables (number and percentage of subjects in each category).

In addition to tabular summaries, subject data listings, as specified in Sections 16.2 and 16.4 of ICH Guidance E3, will be provided. Additional subject data listings to be provided for this study are listed under the relevant subsections below. All data analyses will be performed by the Clinical Research Organization (CRO) after study completion and database release. Statistical programming and analyses will be performed using SAS® Version 9.3 or above and/or other validated statistical software as required.

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In general, the baseline value for a variable is defined as the value observed at Visit 7 of 810P301 and 810P302, Visit 8 of 810P503 and at Visit 6 of the 810P204 study or the first value observed before the first dose in the OLE study, i.e. at Visit 1.

6.2 Analysis Populations

The population of "all enrolled subjects" consists of all subjects from any of the preceding double-blind studies (810P301, 810P302, 810P503 and 810P204) and meet the eligibility requirements for this study including subjects who discontinued from any of the double-blind studies early and approved for enrollment in this study.

The safety population will include all subjects who have signed Informed Consent/Assent forms and received at least one dose of study drug during this study.

Safety population will be used for all safety, efficacy and quality life variables.

6.3 Demographic and Baseline Characteristics

Demographic and baseline variables include age, sex, ethnicity, race, height, weight, and medical history will be summarized.

6.4 Socio-demographics

Socio-demographic variables include number of siblings in the study, siblings with IA, caregiver's age and gender, living situation, marital status, household income and education level will be summarized.

6.5 Subject Disposition

The number and percentage of subjects who completed and discontinued from the study will be summarized. Only one (primary) reason for study discontinuation will be recorded for each subject.
The reasons for study discontinuation may include one of the following:

- Subject withdrew consent
- Lost to follow-up
- Administrative reason
- Adverse event
- Investigator decision
- Lack of efficacy
- Failure to follow required study procedures

6.6 Other Protocol Deviations

Protocol deviations will be presented in listings. If applicable, the number and percent of subjects within each type of protocol deviation will be presented using discrete summary statistics. Protocol deviations may include, but are not limited to:

- Non-compliance with any scheduled study visit
- Non-compliance with study treatment

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- Disallowed concomitant medications
- Non-compliance with study inclusion or exclusion criteria
- Non-compliance with study assessment procedures

6.7 **Study Medication Exposure and Compliance**

Duration of exposure is defined as the total number of days a subject is exposed to study treatment. This will be calculated for each subject by taking the difference between the date of last dose *minus* the date of the first dose, *plus* one (date of last dose – date of first dose +1).

Duration of Treatment exposure will also be summarized using descriptive statistics (n, mean, SD, median, minimum, and maximum).

Percent of study drug compliance will be calculated as

{(D-R)/(T*(D_L- D_F +1))}*100, where D=number of tablets dispensed, R= number of tablets returned, T= number of tablets administered per day, D_L = date of last visit (dose) and D_F= date of first visit (dose)

The number of tablets (T) taken each day may vary during the maintenance phase: subjects can take up six tablets per day to the maximum dose of 54mg/day BID.

The study medication compliance will be summarized by compliance category (<80%, 80-120%, and >120%) and number of subjects in each compliance category. Study medication compliance will also be summarized as a continuous variable using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum).

6.8 **Safety Analysis**

Evaluation of safety will be performed for the safety population. Safety data that will be evaluated include concomitant medications, AEs, clinical laboratory results, vital signs, ECGs, and findings from the physical examinations. The occurrence of neurological side effects will be assessed by looking at any worsening in scores from Baseline (Visit 1) to each subsequent visit for each of the Simpson-Angus scale, Barnes Akathisia scale, and AIMS. Suicidal ideation and suicidal behavior will be measured by C-SSRS.

All summary tables related to safety analyses will use the safety population.

6.8.1 **Adverse Events**

AEs will be classified into standardized medical terminology from the verbatim description (Investigator term) using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be summarized using discrete summaries at the subject and event level by system organ class and preferred term for each group of doses. Similarly, treatment-emergent AEs will be summarized by severity and relationship separately. Verbatim description and all MedDRA level terms, including the lower level terms, for all AEs will be contained in the subject data listings.

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All AEs occurring throughout the study period will be recorded. Treatment-emergent AEs (TEAEs) will be collected starting after the first dose of SM (Visit 1) to the end of the study. These AEs include those that emerge during treatment or worsen in severity during treatment. These AEs will be tabulated, listed and analyzed.

TEAE incidence tables will be listed and summarized by the group of the optimized doses (<18 mg/day; 18-24 mg/day, 24-36 mg/day or 36-54 mg/day) the subject received. The incidence rates for all SADRs will also be summarized as described for all TEAEs.

Listings (and tabular summaries, if warranted) of deaths, other SAEs, and other significant TEAEs, including TEAEs resulting in treatment discontinuation, will be provided.

6.8.2 **Laboratory Values**

Clinical laboratory values will be summarized by visit using descriptive statistics for hematology and chemistry. For quantitative laboratory parameters, both actual values and change from Baseline values will be summarized.

Laboratory test results will be assigned a low, normal, high (LNH) classification according to whether the values were below (L), within (N), or above (H) the laboratory parameters' reference ranges provided by the central laboratory. By subject-listings of all abnormal laboratory values, i.e., those with L or H classification will be provided.

6.8.3 **Vital Signs, Height, Weight and BMI**

Vital signs will be summarized by the group of the optimized doses (<18 mg/day; 18-24 mg/day, 24-36 mg/day or 36-54 mg/day) the subject received using descriptive statistics. Both actual values and changes from the Baseline to final visit will be summarized. Descriptive summary statistics (mean, SD, median, and range) for vital sign data, height, weight and BMI will be evaluated.

6.8.4 **ECG Results**

Tabular summaries of the quantitative ECG parameters and the overall ECG findings (normal, abnormal not clinically significant, or abnormal clinically significant) will be presented. The QT will be corrected using Fridericia's method.

ECG results will be summarized by visit by group of optimized doses (<18 mg/day; 18-24 mg/day, 24-36 mg/day or 36-54 mg/day) using descriptive statistics (for quantitative ECG parameters) and frequency tables (for qualitative ECG parameters, including the overall ECG finding). For quantitative ECG parameters, both actual values and change from Baseline values will be summarized.

6.8.5 **Physical Examinations**

Findings from the physical examinations will be listed for each system or area examined.

6.8.6 **Concomitant Medications**

Concomitant medications will be assigned an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) drug codes. Concomitant medications will be further coded to the appropriate

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Anatomical-Therapeutic-Chemical (ATC) code indicating therapeutic classification. A tabular summary of concomitant medications by drug class will be presented.

6.8.7 **C-SSRS**

C-SSRS outcomes will be summarized using number and percent of subjects by categories for suicidal ideation only, suicidal behavior only and suicidality (ideation and behavior combined). The summary will be presented by group of the optimized doses (<18 mg/day; 18-24 mg/day, 24-36mg/day or 36-54 mg/day) the subject received.

6.8.8 **Extrapyramidal Symptoms**

The occurrence of neurological side effects will be assessed by looking at the changes in scores from Baseline to each of the post-Baseline visit for each of the Simpson-Angus scale, Barnes Akathisia scale, and AIMS. For each item on each of these scales, the number (and percentage) of subjects with a worse score at any post-Baseline visit, compared to Baseline, will be presented. A listing of these subjects will also be provided.

6.9 **Efficacy Analysis**

Each one of the three efficacy variables (R-MOAS, CGI-I and CGI-S) will be listed and summarized by group of the optimized dose.

6.10 **Quality of Life Analysis**

The quality of life endpoints CHQ-PF28, PSI-4-SF subscales (Parental Distress, Parent-Child Dysfunctional Interaction and Difficult Child), and SIPA subscales (Adolescents Domain, Parent Domain, Adolescent-Parent Relationship Domain, Life Stressors Scale and Index of Total Parenting Stress) will be listed and summarized by group of the optimized doses (<18 mg/day; 18-24 mg/day, 24-36 mg/day or 36-54 mg/day) the subject received.

Socio-demographic variables will be presented as a listing and summaries will be tabulated using descriptive statistics.

6.11 **Pharmacogenomic Analysis**

Individual data will be presented as a listing and summaries will be tabulated using descriptive statistics. The pharmacogenomic report may be a stand-alone document.

6.12 **Sample Size and Power Considerations**

There is no consideration for power or sample size determination in this open label study. The present study is an extension to the double-blind randomized 801P301, 810P302, 810P503 and 810P204 studies for the purpose of evaluating long term safety of SPN-810.

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7 DOCUMENTATION

7.1 Adherence to the Protocol

The Investigator agrees, when signing the protocol, to adhere to the instructions and procedures described within and to the principles of ICH GCP as well as all governing local regulations and principles for medical research.

The protocol, ICF, and appropriate related documents must be reviewed and approved by an IRB constituted and functioning in accordance with ICH E6 and any local regulations. Documentation of IRB compliance with the ICH and any local regulations regarding constitution and review conduct will be provided to the Sponsor.

A signed letter of study approval from the IRB must be sent to the Investigator with a copy to the Sponsor prior to study start and the release of SM to the site by the Sponsor or its designee. If the IRB decides to suspend or terminate the study, the Investigator will immediately send the notice of study suspension or termination by the IRB to the Sponsor.

Study progress is to be reported to IRB annually (or as required) by the Investigator or Sponsor, depending on local regulatory obligations. If the Investigator is required to report to the IRB, he/she will forward a copy to the Sponsor at the time of each periodic report.

7.2 Changes to the Protocol

There are to be no changes to the protocol without written approval from the Sponsor.

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the Sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require additional approval by the applicable IRBs and, in some countries, by the regulatory authority. These requirements should in no way prevent any immediate action from being taken by the Investigator, or by the Sponsor, in the interest of preserving the safety of all subjects included in the study. If an immediate change to the protocol is felt by the Investigator to be necessary for safety reasons, the Medical Monitor and IRB must be notified promptly.

Changes to the protocol, which are administrative in nature do not require formal protocol amendments or IRB approval, but the IRB must be kept informed of such changes. In these cases, the Sponsor will send a letter to the IRB detailing such changes.

7.3 Protocol Deviations

There are to be no Investigator-initiated deviations from the protocol. Any subject whose treatment deviates from the protocol or who is not qualified for study participation may be ineligible for analysis and may compromise the study. The date of and reason for deviations must be documented in all cases. Significant or major protocol deviations impacting the safety of the subject or the integrity of the study must be reported by the Investigator to the IRB immediately. Reporting of all other protocol deviations

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must adhere to the requirements of the governing IRB. Protocol assessments will continue until the end of the study, unless the protocol deviations put the subject at risk or the subject's condition requires that he/she be discontinued from the study.

7.4 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures (SOPs), working practice documents, and applicable regulations and guidelines. Site audits may be made periodically by the Sponsor's Quality Assurance team or qualified designee, as an independent function from the study conduct team.

7.4.1 Data Collection

The primary source document will be the subject's medical record. If separate research records are maintained by the Investigator(s), both the medical record and the research record will be considered the source documents for the purposes of monitoring and auditing the study.

Electronic data collection techniques will be used to collect data directly from the study sites using eCRFs. The electronic data will be stored centrally in a fully validated clinical database.

Data recorded on source documents will be transcribed into the eCRFs in accordance with the eCRF Completion Instructions provided to the study sites. The Investigator is responsible for ensuring that all sections of each eCRF are completed correctly, and that entries can be verified against source documents. The eCRFs will be monitored for completeness and accuracy against the source documents by the CRA(s) on a regular basis. Inconsistencies between the eCRFs and source documents will be resolved in accordance with the principles of Good Clinical Practice (GCP).

At the conclusion of the clinical study, each site's eCRF data will be extracted from the clinical database, stored on a CD-ROM and sent to the respective clinical study site for archiving. A CD-ROM containing all eCRFs will be kept by the Sponsor in the Sponsor's Trial Master File.

7.4.2 Clinical Data Management

Data from eCRFs and other external data sources (e.g., laboratory data) will be entered into and/or merged within a single clinical database as specified in the data management plan. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the data in the clinical database.

7.4.3 Database Quality Assurance

In accordance with the vendor's procedures, the clinical database will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification will be documented and returned to the study site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections will be documented in an audit trail.

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7.5 **Retention of Records**

The Investigator has the responsibility to retain all study "essential documents", as described in ICH E6. Essential documents include but are not limited to the protocol, copies of paper CRFs or eCRFs, source documents, laboratory test results, SM inventory records, Investigator's Brochure, and regulatory agency registration documents (e.g., FDA form 1572, ICFs, and IRB/IEC correspondence). The investigator should take measures to prevent accidental or premature destruction of these documents. Study essential documents should be retained until at least two years after the last approval of a marketing application or after formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. The Investigator must obtain written permission from the Sponsor prior to the destruction of any study document.

It is requested that at the completion of the required retention period, or should the Investigator retire or relocate, the Investigator contact the Sponsor, allowing the Sponsor the option of permanently retaining the study records.

These records must be made available at reasonable times for inspection and duplication, if required, by a properly authorized representative of the US FDA in accordance with the US 21 CFR 312.68 or other national or foreign regulatory authorities in accordance with regulatory requirements.

7.6 **Auditing Procedures**

In addition to the routine monitoring procedures, the Sponsor's Corporate Quality Assurance department or qualified designee may conduct audits of clinical research activities in accordance with the Sponsor's written SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. A government regulatory authority may also wish to conduct an inspection (during the study or after its completion). Any inspections requested by a regulatory authority must be communicated immediately by the Investigator to the Sponsor and the CRO.

All study-related records must be made available at reasonable times for inspection and duplication, if required, by a properly authorized representative of the US FDA in accordance with the US 21 CFR 312.68 or other national or foreign regulatory authorities in accordance with regulatory requirements.

7.7 **Publication of Results**

Any presentation or publication of data collected as a direct or indirect result of this trial will be considered as a joint publication by the Investigator(s) and the appropriate personnel at the Sponsor. Authorship will be determined by mutual agreement. All manuscripts, abstracts or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the Sponsor, prior to submission for publication or presentation. No publication or presentation with respect to the study shall be made until any Sponsor comments on the proposed publication or presentation have been addressed to the Sponsor's satisfaction.

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The detailed obligations regarding the publication of any data, material results, or other information, generated or created in relation to the study shall be outlined in the agreement between each Investigator and the Sponsor or designee.

7.8 Financing and Insurance

Financing and Insurance information will be set forth in a separate document between the Investigator and Sponsor (provided by the Sponsor or designee).

7.9 Disclosure and Confidentiality

The contents of this protocol, any amendments and results obtained during the course of this study will be kept confidential by the Investigator, the Investigator's staff, and the IRB and will not be disclosed in whole or in part to others or used for any purpose other than reviewing or performing the study without the written consent of the Sponsor. No data collected as part of this study will appear in any written work, including publications, without the written consent of Sponsor.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in the Confidentiality Agreement between the Investigator and Sponsor.

7.10 Discontinuation of Study

The Sponsor reserves the right to discontinue the study for medical or administrative reasons at any time. The Investigator will be reimbursed for reasonable expenses covering subjects, use of live-in facilities, laboratory tests, and other professional fees. The Investigator will refund the excess of payments made in advance.

The Investigator reserves the right to discontinue the study should his/her judgment so dictate. The Investigator will notify the IRB in case of study discontinuation. Study records must be retained as noted above.

8 ETHICS

8.1 Institutional Review Boards / Independent Ethics Committees

A list of the Institutional Review Board(s) (IRB) and/or Independent Ethics Committee(s) (IEC) that approved this study and the approval letters will be included in the clinical study report for this protocol.

The protocol, any protocol amendments, and the informed consent form (ICF) will be reviewed and approved by the appropriate IRB before subjects are enrolled. IRB Approval is required and will be acquired prior to the distributing SM to investigational sites". The Investigators or Sponsor will submit, depending on local regulations, periodic reports and inform the IRB of any reportable adverse events (AEs) per International Conference on Harmonization (ICH) guidelines and local IRB standards of practice.

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8.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures (SOPs) from either the Sponsor or [redacted]. These SOPs are designed to ensure adherence to GCP guidelines as required by:

- Declaration of Helsinki, 1964 ("Recommendations Guiding Physicians in Biomedical Research Involving Human Patients"), and all its accepted amendments to date concerning medical research in humans.
- ICH Guideline for GCP (Committee for Proprietary Medicinal Products/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, ICH of Pharmaceuticals for Human Use.
- United States (US) Code of Federal Regulations (CFR) dealing with clinical studies (21 CFR, including parts 50 and 56 concerning Patient Informed Consent and IRB regulations).
- Local, national legal guidelines.

8.3 Investigators and Study Personnel

This study will be conducted by qualified Investigators under the sponsorship of Supernus Pharmaceuticals, Inc. (Sponsor) at US study sites used in the double-blind studies, 810P301, 810P302 81P503 and 810P204.

Contact persons at the Sponsor and the CROs are listed in the regulatory binder provided to each investigational site. Qualified personnel will monitor the study. Medical writing, data management, and statistical analyses will be performed by qualified service partners/CROs. Laboratory tests will be conducted by a central laboratory as designated in the regulatory binder.

8.4 Subject Information and Consent/Assent

The Investigator (or designee) will inform the subject and their parent(s), or legal representative, of all aspects pertaining to the subject's participation in the study and will provide oral and written information describing the nature and duration of the study, the procedures involved, the expected duration, the potential risks and benefits involved, and any potential discomfort.

The process for obtaining informed consent/assent will be in accordance with all applicable regulatory requirements. The Investigator (or designee) and the parent (or legal representative) must sign and date the Informed Consent Form (ICF)/Informed Assent Form (IAF) before the subject can participate in the study. The parent or legal representative and the subject will be given a copy of the signed and dated consent/assent form and the original will be retained in the investigational site study records.

The decision regarding subject participation in the study is entirely voluntary. The Investigator (or designee) must emphasize to the subject and their parent(s) or legal representative that consent regarding study participation may be withdrawn at any time without penalty or loss of benefits to which the subject is otherwise entitled.

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The ICF/IAF should be given by means of a standard written statement, written in non-technical language. The subject should understand the statement before signing and dating it. If written consent is not possible, oral consent may be obtained if witnessed by at least one person not involved in the study. The verbal consent will be documented and signed by the Investigator and the witness(es). No subject can enter the study before his/her ICF has been obtained.

If the ICF/IAF is amended during the study, the Investigator must follow all applicable regulatory requirements pertaining to approval of the amended ICF by the IRB and use the amended informed consent form (including ongoing subjects).

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10 APPENDICES

10.1 Retrospective Modified Overt Aggression Scale (R-MOAS)

Refer to the Investigator Site File

10.2 Clinical Global Impression (CGI) Scale

Refer to the Investigator Site File

10.3 Columbia-Suicide Severity Rating Scales (C-SSRS)

Refer to the Investigator Site File

10.4 Simpson-Angus Rating Scale

Refer to the Investigator Site File

10.5 Barnes Akathisia Rating Scale (BARS)

Refer to the Investigator Site File

10.6 Abnormal Involuntary Movement Scale (AIMS)

Refer to the Investigator Site File

10.7 Child Health Questionnaire Parent Form 28-item (CHQ-PF28)

Refer to the Investigator Site File

10.8 Parenting Stress Index-Short Form (PSI-4-SF)

Refer to the Investigator Site File

10.9 Stress Index for Parents of Adolescents (SIPA)

Refer to the Investigator Site File

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