Psyadon Pharmaceuticals, Inc.

TO: Richard E. Chipkin, Phd

FROM: Harold Amkraut, DrPH

SUBJECT: PSY302 Statistical Analysis Plan (SAP)

DATE: December 21, 2016

This is the SAP for the final analysis of study PSY302 (Ecopipam for the Treatment of Tourette Syndrome in Children 7-17 years) anticipated to be conducted in December 2016.

An interim analysis was conducted in January 2016 by an independent Drug Safety Monitoring Board (DSMB) after the first 16 subjects completed the protocol. The DSMB reviewed unblinded data and determined that the study should continue to completion. The SAP for the interim analysis is attached as an appendix.

Per the protocol, all the subjects who have been treated under the protocol will be analyzed in this final analysis (N = 40). Although this SAP identified the 16 interim subjects from the Interim Analysis and the 24 subjects enrolled after the interim, it is notable that no data in the database for the 16 subjects involved in the interim analysis has been changed, and data decisions made prior to their analysis have not been altered.

Blinded data listings and tabulations were prepared by a contract research organization (CRO) employed by Psyadon based on the final database for all 40 subjects. Members from Psyadon and the statistician from the DSMB reviewed the data listings/tabulations only for the 24 subjects enrolled after the interim analysis. The CRO confirmed that the data for the 16 subjects were unchanged in the final database. The intent of this BLINDED review was to (i) determine the evaluability of the subjects in the database; (ii) review the data structure and (iii) identify any data issues.

The following table lists the subjects (16) who were included in the interim analysis database and the 24 newly enrolled subjects:

Site #	Subjects Enrolled at Interim Analysis	Subject Enrolled Since Interim Analysis
Site 1	01-01, 01-03, 01-04	01-06
Site 2	02-01, 02-02, 02-03, 02-04, 02-05, 02-06	02-07, 02-08, 02-09, 02-10 02-11, 02-12
Site 3	03-01	03-02, 03-03
Site 4	(none)	04-01, 04-03
Site 5	05-01, 05-02	(none)
Site 6	06-01, 06-02, 06-03, 06-04	06-05, 06-06, 06-07, 06-09, 06-10, 06-11, 06-13

Site 9	(none)	09-01
Site 10	(none)	10-01
Site 11	(none	11-01, 11-02
Site 12	(none)	12-01, 12-02

Sites 7 and 8 did not any enroll subjects. The following subjects were assigned study numbers but never treated under the protocol: 01-02, 01-05, 04-02, 06-08, 06-12.

The following data issues were noted:

- Subject 06-02 (interim analysis subject) - During Treatment Period 2 this subject prematurely dropped out of the study due to worsening symptoms. Although the reported data on the case report form for week 4 was actually done at week 3 (i.e., when the subject discontinued), for the purpose of this final analysis this score will be carried forward and used for the week 4 score.
- Subject 06-11(final analysis subject) discontinued immediately after the first dose of Treatment Period 2. For the purposes of the intent to treat (ITT) analysis, the Treatment Period 2 Baseline will be carried forward and used for all subsequent visits in Period 2.
- Subject 06-06 (final analysis subject) was missing two items on the ADHD scale at day 16 of Treatment Period 2 which will be imputed as the average of the items from visits just before and just afterwards (values of 3 and 2 thus will be filled in for the two items currently listed as ND)
- Subject 01-06 Period 1 Day 16 and subject 03-02 Period 2 Day 30 have CGI improvement and severity recorded as "Not Done". Last treatment values will be used, i.e. subject 01-06 Period 1 Day 30 and subject 03-02 Period 2 Day 16 will be used to replace the "Not Done" values.

Two populations will be analyzed: Intent to Treat (ITT): All subjects in the study (n=40) and Evaluable: (n= 32)

1. The ITT Population includes all subjects who took at least one dose of study medication.

2. The Evaluable Population includes all subjects who took at least one dose of study medication but excludes the following subjects:

    a. Subjects failing to meet the baseline comparability criterion, i.e., the Baseline 2 YGTSS total motor and phonic tic scores must be within 20% of the Baseline 1 YGTSS total motor and phonic scores.

Subjects Enrolled At Interim Analysis Failing to Meet Baseline Comparability	Subjects Enrolled Since Interim Analysis Failing to Meet Baseline Comparability
01-04, 06-02	02-11, 06-05, 06-06, 11-01

b. Subject 03-02 is non-evaluable for two reasons: 1) The subject incorrectly entered with a Treatment Period 2 score below the disease severity criterion, i.e., subjects needed to have a total motor + phonic tic score of >20. This subject's score was 16. 2) This subject also failed to meet the baseline comparability criterion above, i.e. Baseline 2 YGTSS total motor and phonic tic scores must be within 20% of the Baseline 1 YGTSS total motor and phonic score.
c. Subject 06-11 started Treatment Period 2 but was immediately discontinued when a rash was seen after the first dose of study medicine.

In the interim analysis because of the smaller sample size, two subjects with extreme responses relative to other subjects were identified and separately analyzed so as not to impact the interim analysis population's overall standard deviation (see interim SAP attached). However, due to the increased sample size in the final analysis an analysis excluding such subjects will not be done.

Once the database is locked with the subjects identified as not evaluable, the random code will be loaded onto the final database for the analysis.

The primary parameter specified in the protocol is the sum of the motor and phonic subscales of the Yale Global Tic Severity Score (YGTSS). This is a well-validated scale used in clinical trials of drugs for the treatment of Tourette's. It is a ten-item scale evaluating the subject's symptoms (rated 0-5) and includes a separate item relating to the impairment experienced by the subject due to their symptoms. The endpoint for this analysis is the sum of the motor and phonic tic severity scores at week 4/endpoint (see below) versus Baseline.

Since this is a crossover study, there are two baseline scores (Baseline 1 and Baseline 2) and four efficacy scores (Treatment Period 1, weeks 2 and 4; Treatment Period 2, weeks 2 and 4).

The following statistical analyses will be done:

1. The baselines of each period will be compared.
2. The endpoint (last value carried forward) change from the relevant baseline in each period will be compared.

Baseline and change from baseline to Endpoint will be analyzed using the model pre-specified in the protocol, i.e., sequence, subject (within sequence), period and treatment using an ANOVA. As per agreement with the DSMB, a McNemar's test based on whether a subject had at least a 5-point improvement in score at endpoint compared to baseline will be added as a secondary method of analysis.

The secondary efficacy parameter is the Clinical Global Impression - Improvement score (CGI-I). These data will be tabulated by each sequence by period and for the treatments. A Wilcoxon signed rank test will be used to assess treatment differences.

Other measures include the following endpoints each of which will be analyzed using the ANOVA specified above using the change from baseline to last observation carried forward (LOCF):

- Motor YGTSS
- Phonic YGTSS
- Impairment YGTSS
- Motor+Phonic+Impairment total YGTSS
- Child Depression Scores
- ADHD
- CGI Severity will be tabulated by treatment and sequence
- Data for all parameters for Week 2 will also be analyzed.

Subgroup analysis by demographic (e.g., sex, age, site) may be explored to further understand treatment differences.

Concomitant medications pretreatment and added during the study will be tabulated by sequence and treatment.

Adverse reactions will be tabulated by sequence, treatment and treatment within sequence displaying the worst severity within a period; events reported during the washout between periods will be attributed to the treatment taken in Period 1 while events reported during the follow-up will be attributed to the treatment taken in Period 2.

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