STATISTICAL ANALYSIS PLAN

Final v1.0

Protocol ENGAGE-E-001(Amendment 6, v7.0, 01FEB2019)

A Double-Blind, Placebo-Controlled, Inpatient, Dose-Ranging Efficacy Study of Staccato Alprazolam (STAP-001) in Subjects with Epilepsy with a Predictable Seizure Pattern

Date: July 8, 2019

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LIST OF ABBREVIATIONS

AE	***adverse events***
AED	***antiepileptic drugs***
ATC	***anatomical-therapeutic-chemical***
AUCinf	***area under the concentration curve from 0 to infinity***
AUClast	***area under the concentration curve from 0 to the last measurable value***
CI	***confidence interval***
Cmax	***maximum concentration***
CRU	***clinical research unit***
CTCAE	***Common Terminology Criteria for Adverse Events***
EMU	***epilepsy monitoring unit***
FDA	***Food and Drug Administration***
ITT	***intend-to-treat***
ICH	***International Committee for Harmonization***
MedDRA	***Medical Dictionary for Drug Regulatory Affairs***
PBRS	***Peachtree BioResearch Solution***
PCS	***potentially clinically significant***
PD	***pharmacodynamic***
PK	***pharmacokinetic***
PI	***principal investigator***
PP	***per-protocol***
SAE	***serious adverse events***
SAP	***statistical analysis plan***
SAS	***statistical analysis system***
SD	***standard deviation***
SOC	***system organ class***
Tmax	***time to maximum***
US	***United States***
VAS	***visual analog scale***
WHODRUG	***World Health Organization Drug Dictionary***

1. INTRODUCTION

1.1 Objectives

The overall objectives of the study are to assess the efficacy and safety of a single administration of STAP-001 in subjects with epilepsy with a predictable seizure pattern.

The primary objectives are:

- To assess the efficacy of STAP-001 (1.0 mg and 2.0 mg) compared to placebo in treating a seizure episode
- To assess the clinical feasibility and safety of the inhalation of STAP-001 (1.0 mg and 2.0 mg) compared to placebo in subjects during a seizure episode
- To assess the sedation associated with administration of STAP-001 (1.0 mg and 2.0 mg) compared to placebo

1.2 Design

This is a multicenter, dose-ranging study to investigate the efficacy, safety, and clinical usability of STAP-001 in adult (18 years of age and older) subjects with epilepsy with a predictable seizure pattern.

This is an in-patient study. Eligible and qualified subjects will be admitted to a Clinical Research Unit (CRU) or Epilepsy Monitoring Unit (EMU) for study participation. The duration of the stay in the in-patient unit during the Treatment phase will be 2-8 days. The study consists of two parts: Part 1- Open-Label Feasibility; Part 2 - Double-Blind.

1.2.1 *Part 1: Open-Label Feasibility*

The first subjects enrolled in the study will participate in an open-label feasibility evaluation. Enrollment in this phase will end when there are data from at least 8 individual subjects with a treated single seizure episode in a CRU/EMU. Eligible subjects will receive a single dose of 1 mg STAP-001 at the onset of their predictable seizure episode. The subjects will undergo all study procedures and evaluations as outlined in this protocol. The feasibility data (with special emphasis on the drug administration and clinical assessment procedures) from these 8 subjects will be analyzed and reviewed by the Sponsor before starting the double-blind part of the study. If deemed necessary based on the feasibility data, the study protocol will be amended (for example, to change the drug administration procedure or to redefine the time frame for primary endpoint assessment), before starting the double-blind part of the study.

1.2.2 *Part 2: Double-Blind*

After admission to the in-patient unit eligible and qualified subjects will be stratified by the use of inducing vs non-inducing AED and the use of chronic daily benzodiazepines (yes or no) and randomly assigned (1:1:1) to one of two doses of STAP-001 (1 mg or 2 mg) or Staccato placebo. A blood sample for PK analysis (pre-dose) will be obtained. For each subject, a single seizure episode will be treated and assessed. Study medication will be self-administered (when feasible) or administered by a Staff Caregiver when a predictable seizure episode starts. Assessment of the seizure activity is based on clinical observation by the Staff Caregiver using a stop watch. In addition, a video EEG will record the occurrence, start time, and duration, of the seizure event. PK samples will be collected 10, 30 and 60

minutes, and 2 and 6 hours after the administration of the study drug. If possible, subjects will signal when they experience a seizure event. Subject will be under video EEG surveillance throughout the Treatment Phase. The Staff Caregiver will signal the event for the video EEG recording, starts the stop watch at the time of drug administration, and mark the occurrence of the seizure event on a seizure diary. If the seizure episode does not stop within 5 minutes of the study drug administration, rescue medication other than alprazolam may be administered at the discretion of the principal investigator per the protocol of the research unit. The study exit procedures will be conducted 24 to 32 hours after the administration of study medication or when the subject discontinues from the study.

After discharge from the in-patient unit there will be a safety-follow-up phone contact 14 ± 2 days after the subject received the study medication.

2. ELABORATION OF STUDY PROTOCOL

2.1 Study Populations

Five analysis populations will be defined and analyzed:

1. The Efficacy Population (ITT population) will include all subjects who have a seizure event and receive study drug during the Treatment Period.
2. Modified Intent to Treat (mITT) population will consist of all subjects who have a seizure event, receive study drug, and have had at least one evaluation after study drug administration. mITT will be used for primary efficacy analysis.
3. The Per Protocol Population will include all subjects in the Efficacy Population who were dosed according to protocol and have no major protocol deviations. Major protocol deviations will be identified by Engage Therapeutics, Inc., before the database is locked and unblinded.
4. The PK Population will include all subjects who receive study drug and have at least one pharmacokinetic data point during the Treatment Period. Subjects who receive placebo will be excluded from the PK Population. PK concentrations will be analyzed using PK population.
5. The Safety Population will include all subjects who receive study drug during the Treatment Period from both Part 1 Open-label Feasibility and Part 2 Double-blind. All safety parameters will be analyzed using safety population.

2.2 Study Endpoints

2.2.1 *Efficacy*

Primary efficacy endpoint:

- The proportion of responders in each treatment group achieving seizure activity cessation within 2 minutes after the administration of the study drug and no recurrence of seizure activity within 2 hours

Secondary endpoints:

- Seizure episode severity assessed by subject and/or Staff Caregiver
- Use of rescue medication

- Secondary generalization (evolution to a complex partial seizure and/or a generalized tonic-clonic seizure)

Exploratory endpoints:

- Number of seizures during the 4, 6, and 12 hour time periods after study drug administration
- Time to next seizure event with start time >2 minutes after study drug administration

2.2.2 *Pharmacokinetic*

Blood samples will be collected for plasma alprazolam concentration measurement pre-dose and then at 10, 30, and 60 minutes, and 2 and 6 hours after the dosing of the study drug.

2.2.3 *Safety*

Safety and tolerability will be assessed by evaluating adverse events (AEs), vital signs, concomitant medications, clinical laboratory, and electrocardiogram (ECG) results, as well as neurological and physical examinations. Sedation will also be assessed using a subject visual analog scale (VAS).

2.3 Sample Size

There are no studies in the literature to provide reliable estimates of active treatment or placebo response rates for this study. Assuming a 10% drop-out/protocol violation rate, approximately 115 subjects will be enrolled in the double-blind part of the study to provide approximately 35 evaluable subjects per treatment arm. Enrollment may be stopped after 105 evaluable subjects have completed the study.

Approximately 30% of the overall study population randomized in the study may be subjects being treated with chronic daily benzodiazepines as part of their epilepsy management. Since the effect of concomitant chronic daily benzodiazepines use on study treatment is unknown, a 50% response rate for chronic benzodiazepines users on active treatment arms is assumed. For subjects who are not chronic benzodiazepines users, a response rate of 60% for active treatment arms is assumed. With up to 30% of study population being chronic benzodiazepines users and these response assumptions, a 57% response for the active treatment arm is targeted.

Power calculations assume a 2-sided test and significance level of 0.05 with 90% power and are based on the assumption that the proportion of responders with STAP-001 is 57% (best active treatment arm) whereas the assumed placebo responder rate is 20%.

3. STATISTICAL METHODS

3.1 General

All data will be analyzed using the Statistical Analysis System (SAS®; Version 9.4).

Safety and efficacy data will be summarized and presented by treatment group and time point in summary tables. Continuous variables will be presented by descriptive statistics: n, mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be tabulated by frequency count and percentage.

When the actual treatment received by a subject is different from the randomized treatment assigned, the subject will be analyzed per the randomized treatment for the efficacy parameters (using the ITT, and mITT populations); while the subject will be analyzed per actual treatment that was taken for the safety parameters (using the safety population).

Unless otherwise stated, all statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance for main effects and all confidence intervals (CIs) will be 2-sided 95% confidence intervals.

For the Treatment Period, data will be summarized by active treatment by dose level versus placebo-treated subjects (i.e., by treatment group). All data for analysis will be listed by subject.

3.2 Subject Disposition, Demographics, Baseline Characters and Study Drug Compliance

- Disposition will be summarized by randomized treatment group. The number and percentage of subjects, who are randomized, treated, prematurely discontinued, and complete the study will be summarized.
- Baseline characteristics will be summarized by treatment group.
- The number of subjects in each cohort's treatment group will be summarized for each investigative site for the Treatment Period.
- Medical history will be listed with reported terms.
- Concomitant medications will be summarized by World Health Organization Drug Dictionary Anatomical-Therapeutic-Chemical (WHODRUG_ATC) classification and preferred term.

3.3 Analysis of Study Endpoints

3.3.1 Efficacy

All statistical tests will be 2-sided with a significance level of 0.05. Testing will be performed only for the Treatment Period.

Data will be summarized by active treatment by dose level versus placebo-treated subjects (i.e., by treatment group). Continuous measures will be summarized descriptively (mean, standard deviation, median, minimum value, and maximum value) and categorical measures will be presented as number and percentage.

The primary efficacy analysis will be conducted following completion of the Treatment Period for the last subject and data base lock.

Primary Efficacy Endpoint

The primary efficacy endpoint will be the proportion of responders in each treatment group achieving seizure activity cessation within 2 minutes after the administration of the study drug and no recurrence of seizure activity within 2 hours. The primary endpoint will be analyzed with a chi-squared test. The overall treatment comparison, as well as pair-wise comparisons between each dose level and placebo will be performed. The estimates of the treatment difference versus placebo and their 95% confidence interval will be presented.

There will be no adjustment for multiple treatment group comparisons in this dose-ranging Phase 2b study. The dose-response relationship will be explored with a regression analysis.

Secondary and Exploratory Efficacy Endpoints

Secondary and exploratory endpoints will be summarized by treatment group and if applicable, by assessment time point. Exploratory statistical testing may be performed if warranted. The Cochran-

Mantel-Haenszel (CMH) test for row-mean score difference will be used to test the treatment difference in the seizure episode severity. The Kruskal-Wallis test will be used to compare seizure frequencies. The time-to-next-seizure data will be summarized and displayed with Kaplan-Meier plots. No multiplicity adjustment will be implemented for exploratory tests.

3.3.2 *Pharmacokinetics*

The collection status of PK samples will be listed for each visit with scheduled pharmacokinetic sampling. Plasma concentrations of study drug and the active metabolites may be summarized separately, as appropriate.

PK parameters including maximum concentration (C_{max}), time to maximum (T_{max}), area under the concentration curve from 0 to the last measurable value (AUC_{last}) will be estimated for each subject using non-compartmental methods. Since the time point range is 0 to 6 hours and the alprazolam half-life is 11 hours, we do not plan to estimate half-life or AUC_{inf}.

3.3.3 *Safety Analysis*

All safety summaries will be descriptive with no statistical hypothesis testing and based on the Safety Population. Subjects will be summarized according to the study drug received. (i.e., as treated), should it differ from the randomized treatment arm. All safety endpoints will be listed in by-subject data listings.

Adverse Events

An adverse event reported after informed consent and occurring before the first dose of study drug in the CRU/EMU will be considered a pre-treatment adverse event. Treatment-emergent adverse events (TEAEs) will be defined as any adverse event that occurs after administration of study drug.

- The number and percentage of subjects who experience TEAEs will be summarized by treatment group for the following:
  - By system organ class and preferred term
  - By severity, system organ class, and preferred term
  - By relationship to study drug, system organ class, and preferred term
  - Serious adverse events by system organ class and preferred term
  - TEAE by preferred term and overall frequency.
- Subjects who report the same preferred term on multiple occasions will be counted once for the preferred term: under the highest severity when summarized by severity and under the closest relationship to study drug when summarized by relationship.
- If a subject reports multiple preferred terms for a system organ class, the subject will be counted only once for that system organ class.
- Subject listings will be provided for any deaths, serious adverse events, and adverse events leading to withdrawal.

Sedation Assessment

- Sedated and alert scale as measured using a 100-mm linear VAS will be summarized by time point.
- Sleepy and Awake scale as measured using a 100-mm linear VAS will be summarized by time point.

Clinical Laboratory

Clinical laboratory variables will be presented in 3 ways.

1. Change from Baseline to each scheduled assessment will be summarized descriptively. Baseline will be defined as the laboratory value obtained before the first dose of study drug on Day 1; if Day 1 values are unavailable, then values obtained at the Screening Visit will be used.

2. The number and percentage of subjects with abnormal laboratory values will be summarized by treatment group for each clinical laboratory variable.

3. The number and percentage of subjects with treatment-emergent potentially clinically significant (PCS) laboratory values will be summarized by treatment group for each clinical laboratory variable. Potentially clinically significant lab values are defined as those that toxicity grade are ≥ 3 from the common terminology criteria for adverse events (CTCAE) criteria (See Section 7 Appendix). Treatment-emergent PCS laboratory values are those in which the baseline value is not PCS and the post-baseline value is PCS.

Vital Signs

The mean change from baseline to each scheduled assessment will be summarized descriptively by treatment group for each vital sign variable specified in this protocol.

Baseline will be defined as the last vital sign value obtained before the first dose of study drug on Day 1; if Day 1 values are unavailable, then values obtained at the Screening Visit will be used.

Electrocardiogram

The change from baseline in ECG intervals (PR, QT, QTcF, QRS, and RR) to each scheduled assessment will be summarized descriptively by treatment group.

Neurological and Physical Examinations

- The number (%) of subjects of baseline neurological and physical examination results will be provided by categories of Normal/Abnormal/Not Done and treatment group for each examination item.
- The number (%) of subjects of post-baseline results will be summarized by categories of Normal/Abnormal/Not Done/No Change and treatment group for each examination item at scheduled assessment.

3.3.4 *Multiplicity Adjustment*

- Multiplicity adjustment will not be applied for multiple testing in this study.

3.4 Handling of Missing Data

3.4.1 *Imputation Rules for AE Records*

For safety analyses, the incomplete date and time for the safety events will not be imputed. However, the following imputation rule will be applied for AEs.

- If the start date of an AE is missing, then the AE will be considered as Treatment-Emergent AE (TEAE).

- If the end date of an AE is missing and the ongoing flag is missing, then the AE status will be considered as ongoing.
- If the severity of an AE is missing, then the AE will be considered as "Severe" (CTCAE grads 3).
- If the relationship to the study agent of an AE is missing, then the AE will be considered as "related" to study agent.

3.4.2 *Imputation Rules for Epilepsy Onset Date*

To calculate duration of seizure history, the incomplete epilepsy onset date will be imputed as following.

- Completely missing epilepsy onset date (UNK-UNK-UNK) will not be imputed, and hence no duration of seizure history will be calculated.
- If epilepsy onset date recoded as yyyy-UNK-UNK, then epilepsy onset date will be imputed as yyyy-07-01. July 1 will be used for unknown month and date.
- If epilepsy onset date recoded as yyyy-MM-UNK, then epilepsy onset date will be imputed as yyyy-MM-15. 15 will be used for unknown onset data.

3.5 **Protocol Deviations**

Listing for all protocol deviations will be provided.

Listing for major deviations that result in excluding from the PP population will also be provided for blinded phase.

3.6 **Key Data Items**

Study Analysis Population Definition:

- Intend-To-Treat (ITT) population: All subjects who have seizure events and received study drug.
- Modified Intend-to-Treat(mITT) population: All ITT subjects have had at least one efficacy evaluation after study drug dosed
- Per-Protocol (PP) population: All ITT subjects without any major protocol deviations.
- PK Population: All ITT subjects who provided at least one PK data point.
- Safety Population: All ITT subjects who receive at least one dose of study drug.

Important Derived Variables:

- Age (year) = (Screening Date – Date of Birth +1)/365.25.
- Duration of Seizure History (year) = (Screening Date – Epilepsy Onset Date +1)/365.25.
- Prior Medications and Treatments: the medications and treatments started before enrolled to the study without any change after the enrollment.
- Concomitant Medication and Treatments: the medications and treatments started on or after the time of the first dose of the study drug. Any medications and treatments started before but changed after the first dose of the study drug will be considered as concomitant medications and treatments.

- Baseline: All clinical measurements (safety and efficacy data) collected at Day 1 or before the first dose will be analyzed as baseline.
- Post Baseline: All clinical measurements (safety and efficacy data) collected after the first dose will be analyzed as post baseline.
- Treatment emergent Adverse Events (TEAE): Any AEs started on or after the time of the first study drug dosed.

Flags for Efficacy Endpoints:

- Treatment Response Flag
  = 'Yes', if treated seizure stopped within 2 minutes and there are no seizure events within 2 hours (120 minutes);
  = 'No', otherwise;
- Secondary Generalization Flag
  = 'Yes', if at least one post-treatment seizure event was categorized as "a complex partial seizure" or "partial seizures evolving to secondarily generalized seizures" and/or "a generalized tonic-clonic seizure";
  = 'No', otherwise;
- Number of Post-Treatment Seizures
  a. N_4h = # of seizures observed during 0 – 4 hours post-treatment
  b. N_6h = # of seizures observed during 0 – 6 hours post-treatment
  c. N_12h = # of seizures observed during 0 – 12 hours post-treatment
- Time to the next seizure event
  = the next seizure event start time, if the start time > 2 minutes after study drug dosed
  = censored (left censored at 2 minutes), if the start time ≤ 2 minutes after study drug dosed

Formulas of Metric Conversion:

- 1 inch = 2.54 cm
- 1 lb = 0.4536 kg
- °C = (°F – 32)x5/9

LABORATORY ASSESSMENTS

Chemistry (Serum)	**Hematology (Blood)**
Alanine aminotransaminase	Complete blood count
Albumin	Platelet count
Alkaline phosphatase	White blood cell count with differential
Amylase	Hemoglobin
Aspartate aminotransaminase	Hematocrit
Total bilirubin	
Direct bilirubin	**Urinalysis**
Indirect bilirubin	
Blood urea nitrogen	Bilirubin
Calcium	Blood
Carbon dioxide	Clarity
Chloride	Urobilirubin
Creatinine	Glucose, Urine
Creatine kinase	Ketones

Glucose Lipase Total protein Phosphorus Potassium Sodium Uric Acid	Leukocyte Esterase Nitrate pH Protein, Urine Specific Gravity

3.7 **Change to Planned Protocol Analysis**

Not applicable.

4. OUTPUT PLANNED FOR THE STUDY REPORT (BLINDED PHASE)

4.1 **Tables to be Included in Study Report**

In the following sections, the different results are presented in the order in which it is planned to make them appear in the study report.

The table templates are available in the Appendix of the SAP. The content shown in the templates does only mean as an example. It is not based on real study data or details concerning design.

4.1.1 *Summary of Subject Information*

Table 14.1.1 Subject Disposition – All Subjects

Table 14.1.2 Summary of Demographics – ITT Population

Table 14.1.3 Summary of Seizure History – ITT Population

Table 14.1.4.1 Summary of Concomitant Medications – Safety Population

Table 14.1.4.2 Summary of Concomitant Procedures – Safety Population

Table 14.1.4.3 Summary of Rescue Medications – ITT Population

4.1.2 *Summary of Efficacy Endpoints*

Table 14.2.1.1 Result of Treatment Response – mITT Population

Table 14.2.1.2 Result of Treatment Response – PP Population

Table 14.2.2.1 Results of Seizure Episode Severity Scale – mITT Population

Table 14.2.2.2 Results of Seizure Episode Severity Scale – PP Population

Table 14.2.3.1 Result of Use of Rescue Medication – mITT Population

Table 14.2.3.2 Result of Use of Rescue Medication – PP Population

Table 14.2.4.1 Result of Secondary Generalization Evolution – mITT Population

Table 14.2.4.2 Result of Secondary Generalization Evolution – PP Population

Table 14.2.5.1 Summary of Seizure Number after Study Drug Administration – mITT Population

Table 14.2.5.2 Summary of Seizure Number after Study Drug Administration – PP Population

Table 14.2.5.3 Treatment Comparison of Seizure Number after Study Drug Administration – mITT Population

Table 14.2.5.4 Treatment Comparison of Seizure Number after Study Drug Administration – PP Population

4.1.3 *Summary of PK/PD Endpoints*

4.1.4 *Summary of Safety Endpoints*

Table 14.3.5.9 Number and Percentage Subjects with Abnormal Laboratory (Blood Chemistry) Test Results – Safety Set

Table 14.3.5.10 Number and Percentage Subjects with Abnormal Laboratory (Urine) Continuous Test Results – Safety Set

Table 14.3.6.1 Summary of Sedation and Alert Scale VAS – Safety Set

Table 14.3.6.2 Summary of Sleepy and Awake Scale VAS – Safety Set

4.2 Listings to be Included in the Clinical Study Report

4.2.1 *Listings of Subject Information*

Listing 16.1 Discontinued Subjects – Safety Set

Listing 16.2 Demographic Characteristics – Safety Set

Listing 16.3.1 General Medical History – Safety Set

Listing 16.3.2 Seizure History – Safety Set

Listing 16.4.1 Concomitant Medications – Safety Set

Listing 16.4.2 Concomitant Procedures – Safety Set

Listing 16.4.3 Rescue Medications – Safety Set

Listing 16.5 Study Drug Administration – Safety Set

Listing 16.6 Protocol Deviations – Safety Set

Listing 16.7 Visit Date – Safety Set

4.2.2 *Listings of Efficacy Data*

Listing 16.8.1 Clinical Response – Safety Set

Listing 16.8.2 Seizure Episode Severity Scale – Safety Set

Listing 16.8.3 Use of Rescue Medication – Safety Set

Listing 16.8.4 Secondarily Generalized Evolution – Safety Set

Listing 16.8.5 Number of Post Treatment Seizure – Safety Set

Listing 16.8.6 Post-Treatment Seizure – Safety Set

Listing 16.8.7 Time to Next Seizure Event – Safety Set

4.2.3 *Listings of PK Data*

Listing 16.9.1 Plasma PK Concentrations (unit) – Safety Set

Listing 16.9.2 PK Parameter – Safety Set

4.2.4 *Listings of Safety Data*

Listing 16.10.1 Adverse Events – Safety Set

Listing 16.10.2 Serious Adverse Events – Safety Set

Listing 16.10.3 Severe (≥3 CTCAE Grade) Adverse Events – Safety Set

Listing 16.10.4 Study Drug Related Adverse Events – Safety Set

Listing 16.10.5 Adverse Events Leading to Death or Withdrawal – Safety Set

Listing 16.11.1 Results of Laboratory (Hematology) Tests – Safety Set

Listing 16.11.2 Results of Laboratory (Blood Chemistry) Tests – Safety Set
Listing 16.11.3 Results of Laboratory (Urine) Tests – Safety Set
Listing 16.11.4 Results of Urine Drug and Alcohol Tests – Safety Set
Listing 16.11.5 Results of Urine Pregnancy Tests – Safety Set
Listing 16.12 Results of Vital Signs – Safety Set
Listing 16.13 Results of ECG – Safety Set
Listing 16.14 Abnormalities of Physical Examination – Safety Set
Listing 16.15 Abnormalities of Neurological Examination – Safety Set
Listing 16.16 Sedation and Alert VAS – Safety Set
Listing 16.17 Sleepy and Awake VAS – Safety Set
Listing 16.18 Randomization List – Safety Set

4.3 **Figures to be Included in the Clinical Study Report**

Figure 14.4.1 Kaplan-Meier Plot of Time to Next Seizure Event with Start Time >2 Minutes after Study Drug Administration – mITT Population
Figure 14.5.1 Plasma PK Concentrations (in Linear Scale) – PK Evaluable
Figure 14.5.2 Plasma PK Concentrations (in Semi-log Scale) – PK Evaluable

5. REFERENCES

(1) Protocol Engage-E-001: A Double-Blind, Placebo-Controlled, Inpatient, Dose-Ranging Efficacy Study of Staccato Alprazolam (STAP-001) in Subjects with Epilepsy with a Predictable Seizure Pattern, Amendment 6 (v7.0), February 1, 2019, Engage Therapeutics, Inc.

(2) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03: June 14, 2010, U.S. Department of Health and Human Services

6. ATTACHMENT: THE SHELLS OF TABLES, FIGURES AND LISTINGS PLANNED FOR CLINICAL STUDY REPORT

7. APPENDIX: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE, V4.03)

Test	Test Code	Standard Units	Direction of Change	Toxicity Grade				
				0	1	2	3	4
Acidosis	PH	n/a	Decrease/Acidosis	WNL	≥7.3 - <LLN		<7.3	
Activated Partial Thromboplastin Time	APTT	n/a	Increase/Activated partial thromboplastin time prolonged	WNL	>ULN- ≤1.5 xULN	>1.5 xULN - ≤2.5xULN	>2.5 xULN	
Alanine Aminotransferase (ALT/SGPT)	ALT	n/a	Increase/ Alanine aminotransferase increased	WNL	>ULN - ≤3.0 xULN	>3.0 xULN - ≤5.0 xULN	>5.0 xULN - ≤20.0 xULN	>20.0 xULN
Albumin	ALB	g/L	Decrease/Hypoalbumine -mia	WNL	≥30 - <LLN	≥20 - <30	<20	
Alkaline Phosphatase	ALP	n/a	Increase/Alkaline phosphatase increased	WNL	>ULN - ≤2.5 xULN	>2.5 xULN - ≤5.0 xULN	>5.0 xULN - ≤20.0 xULN	>20.0 xULN
Alkalosis	PH	n/a	Increase/Alkalosis	WNL	>ULN- ≤7.5		>7.5	
Amylase	AMYLASE	n/a	Increase/Serum amylase increased	WNL	>ULN - ≤1.5 xULN	>1.5 xULN - ≤2.0 xULN	>2.0 xULN - ≤5.0 xULN	>5.0 xULN
Aspartate Aminotransferase	AST	n/a	Increase/Aspartate aminotransferase increased	WNL	>ULN - ≤3.0 xULN	>3.0 xULN - ≤5.0 xULN	>5.0 xULN - ≤20.0 xULN	>20.0 xULN
Bilirubin	BILI	n/a	Increase/Blood bilirubin increased	WNL	>ULN - ≤1.5 xULN	>1.5 xULN - ≤3.0 xULN	>3.0 xULN - ≤10.0 xULN	>10.0 xULN
Calcium	CA	mmol/L	Increase/Hypercalcemia	WNL	>ULN - ≤2.9	>2.9 - ≤3.1	>3.1 - ≤3.4	>3.4
Calcium	CA	mmol/L	Decrease/Hypocalcemia	WNL	≥2.0 - <LLN	≥1.75 - <2.0	≥1.5 - <1.75	<1.5
Calcium Corrected	CACOR	mmol/L	Increase/Hypercalcemia	WNL	>ULN - ≤2.875	>2.875 - ≤3.125	>3.125 - ≤3.375	>3.375
Calcium Corrected	CACOR	mmol/L	Decrease/Hypocalcemia	WNL	≥2.0 - <LLN	≥1.75 - <2.0	≥1.5 - <1.75	<1.5
Calcium Ionized	CAION	mmol/L	Increase/Hypercalcemia	WNL	>ULN - ≤1.5	>1.5 - ≤1.6	>1.6 - ≤1.8	>1.8
Calcium Ionized	CAION	mmol/L	Decrease/Hypocalcemia	WNL	≥1.0 - <LLN	≥0.9 - < 1.0	≥0.8 - < 0.9	<0.8
CD4	CD4	x10E9/L	Decrease/CD4 lymphocytes decreased	WNL	≥0.5 - <LLN	≥0.2 - < 0.5	≥0.05 - <0.2	<0.05

Test	Test Code	Standard Units	Direction of Change	Toxicity Grade				
				0	1	2	3	4
Cholesterol	CHOL	mmol/L	Increase/Cholesterol high	WNL	>ULN - ≤7.75	>7.75 -≤ 10.34	>10.34 - ≤12.92	>12.92
Creatine Kinase	CK	n/a	Increase/CPK increased	WNL	>ULN - ≤2.5 xULN	>2.5 xULN - ≤5 xULN	>5 xULN - ≤10 xULN	>10 xULN
Creatinine	CREAT	n/a	Increase/Creatinine increased	WNL	>ULN - ≤1.5 xULN	>1.5 xULN - ≤3.0 xULN	>3.0 xULN - ≤6.0 xULN	>6.0 xULN
Fibrinogen	FIBRINO	umol/L	Decrease/Fibrinogen decreased	WNL	<1.0 - 0.75 x LLN	<0.75 - 0.5 x LLN	<0.5 - 0.25 x LLN	0.25xLLN
Gamma Glutamyl Transferase (GGT)	GGT	n/a	Increase/GGT increased	WNL	>ULN - ≤2.5 xULN	>2.5 xULN - ≤5.0 xULN	>5.0 xULN - ≤20.0 xULN	>20.0 xULN
Glucose (fasting)	GLUC	mmol/L	Increase/Hyperglycemia	WNL	>ULN - ≤8.9	>8.9 - ≤13.9	>13.9 - ≤27.8	>27.8
Glucose	GLUC	mmol/L	Decrease/Hypoglycemia	WNL	≥3.0 - <LLN	≥2.2 - <3.0	≥1.7 - <2.2	<1.7
Glucose (fasting)	GLUC	mmol/L	Increase/Hyperglycemia	WNL	>ULN - ≤8.9	>8.9 - ≤13.9	>13.9 - ≤27.8	>27.8
Glucose	GLUC	mmol/L	Decrease/Hypoglycemia	WNL	≥3.0 - <LLN	≥2.2 - <3.0	≥1.7 - <2.2	<1.7
Glucose (fasting)	GLUC	mmol/L	Increase/Hyperglycemia	WNL	>ULN - ≤8.9	>8.9 - ≤13.9	>13.9 - ≤27.8	>27.8
Glucose	GLUC	mmol/L	Decrease/Hypoglycemia	WNL	≥3.0 - <LLN	≥2.2 - <3.0	≥1.7 - <2.2	<1.7
Granulocytes	GRAN	x10E9/L	Decrease/Neutrophil count decreased	WNL	≥1.5 - <LLN	≥1.0 - <1.5	≥0.5 - <1.0	<0.5
Haptoglobin	HAPTOG	µmol/L	Decrease/Haptoglobin decreased	WNL	>0 - < LLN			
Hemoglobin	HGB	g/L	Increase/Hemoglobin increased	WNL	Increase in >0 - 20 g/L above ULN or above baseline if baseline is above ULN	Increase in >20 - 40 g/L above ULN or above baseline if baseline is above ULN	Increase in >40 g/L above ULN or above baseline if baseline is above ULN	
Hemoglobin	HGB	g/L	Decrease/Anemia	WNL	≥100 - <LLN	≥80 - <100.0	<80	
Leukocytes (WBC)	WBC	x10E9/L	Decrease/White blood cell decreased	WNL	≥3.0 - <LLN	≥2.0 - <3.0	≥1.0 - <2.0	<1.0
Lymphocytes	LYM	x10E9/L	Decrease/Lymphocyte count decreased	WNL	≥0.8 - <LLN	≥0.5 - <0.8	≥0.2 - <0.5	<0.2

Test	Test Code	Standard Units	Direction of Change	Toxicity Grade				
				0	1	2	3	4
Magnesium	MG	mmol/L	Increase/Hypermagnese-mia	WNL	>ULN - ≤1.23		>1.23 - ≤3.30	>3.30
Magnesium	MG	mmol/L	Decrease/Hypomagnese-mia	WNL	≥0.5 - <LLN	≥0.4 - <0.5	≥0.3 - <0.4	<0.3
Neutrophils	NEUT	x10E9/L	Decrease/Neutrophil count decreased	WNL	≥1.5 - <LLN	≥1.0 - <1.5	≥0.5 - <1.0	<0.5
Phosphate (Phosphate, Inorganic)	PHOS	mmol/L	Decrease/Hypophosphate-mia	WNL	≥0.8 - <LLN	≥0.6 - <0.8	≥0.3 - <0.6	<0.3
Platelets	PLAT	x10E9/L	Decrease/Platelet count decreased	WNL	≥75.0 - <LLN	≥50.0 - <75.0	≥25.0 - <50.0	<25.0
Potassium	K	mmol/L	Increase/Hyperkalemia	WNL	>ULN - ≤5.5	>5.5 - ≤6.0	>6.0 - ≤7.0	>7.0
Potassium	K	mmol/L	Decrease/ Hypokalemia	WNL		≥3.0 - <LLN	≥2.5 - <3.0	<2.5
Protein (Urine, >16yr)	PROT		Increase/Proteinuria	WNL	1+	2+		
Protein (Urine, <=16yr)	PROT		Increase/Proteinuria	WNL	1+			
Protein/Creatinine (Urine)	PROTCRT		Increase/Proteinuria	WNL		>=0.5 - <=1.9	>1.9	
Prothrombin Intl. Normalized Ratio	INR	n/a	Increase/INR increased	WNL	>ULN - ≤1.5 xULN	>1.5 xULN - ≤2.5 xULN	>2.5 xULN	
Sodium	SODIUM	mmol/L	Increase/Hypernatremia	WNL	>ULN - ≤150	>150 - ≤155	>155 - ≤160	>160
Sodium	SODIUM	mmol/L	Decrease/Hyponatremia	WNL	≥130 - <LLN		≥120 - <130	<120
Triacylglycerol Lipase (Lipase)	LIPASE	n/a	Increase/Lipase increased	WNL	>ULN - ≤1.5 xULN	>1.5 xULN - ≤2.0 xULN	>2.0 xULN - ≤5.0 xULN	>5.0 xULN
Triglycerides	TRIG	mmol/L	Increase/Hypertriglycer-idemia	WNL	>1.71- ≤3.42	>3.42 - ≤5.7	>5.7 - ≤11.4	>11.4

WNL = Within Normal range, LLN = Lower Limit of Normal Range, ULN = Upper Limit of Normal Range

Approval for Statistical Analysis Plan

Title: **A Double-Blind, Placebo-Controlled, Inpatient, Dose-Ranging Efficacy Study of Staccato Alprazolam (STAP-001) in Subjects with Epilepsy with a Predictable Seizure Pattern**

Reference: **ENGAGE-E-001/SAP**
Version: **1.0**
Date effective:

Author: [redacted] **PhD. Biostatistics, Peachtree BRS, Inc.**

Author's signature: Date:

The above Statistical Analysis Plan has been reviewed and approved by the Sponsor:

Name of Reviewer/Approver [redacted], **RN, BSN**

Position: **VP Clinical Operations, Engage Therapeutics, Inc.**

Signature for sponsor: Date:

Name of Reviewer/Approver

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Position: [redacted]

Signature for sponsor: [redacted] Date: [redacted]