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STATISTICAL REVIEW(S)



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Statistical Review and Evaluation

CLINICAL STUDIES

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1. Executive Summary

Study P261-101 was a Phase 1, double-blind, double-dummy, active- and placebo-controlled, within-subject, randomized crossover acute dose-effect comparison study of IN USL261 spray vs oral midazolam syrup and placebo.

The primary objective of this trial was to evaluate the abuse liability of IN USL261 compared with that of oral midazolam and placebo in adult subjects with a history of recreational benzodiazepine use. The Emax on the bipolar Drug Liking VAS was the primary pharmacodynamic endpoint.

The main study included a Screening visit, a Qualification Phase, a Double-Blind Dose Evaluation Phase, and Follow-up visit. In the Double-Blind Dose Evaluation Phase, each subject received up to 7 study treatments in a randomized, double-blind, double-dummy manner (one at each treatment period) according to a 7x7 Williams design as follows:

- Treatment A: IN USL261 spray (low dose)
- Treatment B: IN USL261 spray (moderate dose)
- Treatment C: IN USL261 spray (high dose)
- Treatment D: oral midazolam syrup (low dose)
- Treatment E: oral midazolam syrup (moderate dose)
- Treatment F: oral midazolam syrup (high dose)
- Treatment G: placebo (matching oral and IN [USL261] treatments)

The reviewer analyzed the primary PD endpoint Drug Liking, and the secondary PD endpoints: High, Take Drug Again and Overall Drug Liking. The results from the statistical reviewer's analyses established that:

- For the validation test: The validity of the study was determined from the comparison of Drug Liking Emax between each positive control and placebo. The Drug Liking VAS Emax for all doses of oral midazolam syrup was statistically significantly higher than placebo ($p < 0.05$), confirming study validity.
- No statistically significant differences were observed between equivalent doses of oral midazolam syrup and IN USL261 spray (5 mg vs 5 mg, 10 mg vs 10 mg, or 15 mg vs 15 mg) on the Drug Liking VAS Emax (primary endpoint) and Emax of secondary endpoints: High VAS, Overall Drug Liking VAS and Take Drug Again VAS, indicating that IN USL261 is associated with a strong signal for abuse potential similar to oral midazolam
- In addition, there is no significant difference between Nasal spray USL261 10 mg and 15 mg oral midazolam (p values are all > 0.05), and no significant difference between Nasal spray USL261 5 mg and 10 mg oral midazolam (p values are all > 0.05) on the Emax of Drug Liking, High, Overall Drug Liking and Take Drug Again.

Overall, the PD results from this study demonstrated that IN USL261 is associated with a strong signal for abuse potential similar to oral midazolamin subjects with a history of recreational benzodiazepine use and history of IN administration.

2. Review Report on Study P261-101

2.1 Introduction

Seizure clusters, also known as acute repetitive seizures (ARS), occur in a subset of epilepsy patients. Seizure clusters have distinguishable characteristics that are easily recognized by patients, caregivers, and physicians and include a consistent onset (auras, prodrome) that may be indicative of convulsive or nonconvulsive symptoms.

The primary goals of seizure cluster treatment are seizure cessation and prevention of seizure recurrence. Acute benzodiazepine treatment is effective for seizure control and often results in rapid seizure cluster termination; however, most treatment options rely on intervention by emergency medical personnel and therefore delay treatment until emergency medical personnel are present. The development of an easily administered outpatient treatment of seizure clusters may reduce emergency medical intervention and decrease seizure cluster duration.

Midazolam is a benzodiazepine with potent inhibitory activity at the gamma-aminobutyric acid (GABA) A receptor and demonstrates anticonvulsant properties. Like other benzodiazepines, midazolam administration may cause sedation, anxiolysis, and amnesia. Sedative effects usually occur within 5 minutes of IV administration and within 15 minutes of intramuscular administration.

Intranasal (IN) midazolam may be safe and effective for the rapid interruption of seizure activity in outpatient settings.

Ikano Therapeutics, Inc. (ITI, [previously Intranasal Therapeutics, Inc.]) initiated development of a midazolam rescue treatment designed specifically for IN delivery (ITI 111) for patients who require control of intermittent bouts of seizure activity, including seizure clusters. In June 2010, USL obtained exclusive global rights to ITI 111 (renamed as USL261), assuming all continued development, testing, and clinical studies for the treatment of seizure clusters. The proprietary formulation of USL261 delivers adequate drug concentrations in a small volume (100 µL) and preliminary human studies show positive pharmacokinetic (PK) and bioavailability properties with good safety and tolerability.

Study Rationale

Midazolam is a benzodiazepine and is a controlled drug in the United States (schedule IV) and internationally. Although there is little abuse data in the United States for midazolam, abuse has been noted in other countries, particularly by the IV route. Although animal abuse potential studies suggest that midazolam is similar to other benzodiazepines, only one clinical abuse potential study of IN midazolam has been published in the literature; however, this study had serious design flaws (single-blind, no positive control, performed in healthy volunteers and cocaine users) and cannot be considered confirmatory. Considering the efficacy of IN midazolam for the rescue treatment of seizures, USL261 is being developed as a proprietary formulation, purposely built for IN delivery of midazolam that delivers improved bioavailability in a dosing form that is convenient, fast, and appropriate for administration by both nonmedical as well as medical professionals in an emergency situation.

The impact of relatively small differences in rate of onset for benzodiazepines on abuse potential, such as between IN and oral midazolam (ie, 10 to 20 minutes vs 15 minutes to 1 hour), has not been established. Results from a small pilot study with an IN formulation of alprazolam have

suggested that abuse liability is not substantially higher with IN benzodiazepines compared to oral forms, despite differences in PK. Therefore, the purpose of this study was to determine whether the differences in rate of onset between IN USL261 and oral midazolam resulted in differences in abuse liability or other PD effects (such as psychomotor impairment) between the 2 routes of administration.

2.1.1 Objectives of the study

Primary Objective

The primary objective of the study was to evaluate the abuse liability of IN USL261 compared with that of oral midazolam and placebo in adult subjects with a history of recreational benzodiazepine use.

Secondary Objectives

The secondary objectives of the study were:

- To evaluate other PD effects of IN USL261 compared with that of oral midazolam and placebo in adult subjects with a history of recreational benzodiazepine use.
- To evaluate the PK of IN USL261 compared with that of oral midazolam in adult subjects with a history of recreational benzodiazepine use.
- To evaluate the safety of IN USL261 in adult subjects with a history of recreational benzodiazepine use.

2.1.2 Overall Study Design and Plan-Description

This was a Phase 1, double-blind, double-dummy, active- and placebo-controlled, within-subject, randomized crossover acute dose-effect comparison study of IN USL261 spray vs oral midazolam syrup and placebo. The study included a Part A (Pilot Study) and a Part B (Main Study). Subjects were recruited in cohorts and resided as inpatients at the study center for the duration of participation in each study phase.

Because the onset of IN USL261 effects relative to those of oral midazolam has not been directly assessed, the time course of PD effects (including onset time) of midazolam via each route of administration was confirmed during the Pilot Study (Part A).

Pilot Phase (Part A)

- **Pilot Phase (Cohort 1)**

The objective of this phase was to assess the time course of the PD effects of IN USL261 spray vs oral midazolam syrup. Subjects in the Pilot Phase participated in a Screening visit, a Treatment Phase (2 treatment periods, each separated by at least 48 hours), and a Follow-up visit (approximately 2 to 7 days after the last treatment administration). A 20-mg oral dose of midazolam syrup and a 20-mg IN dose of USL261 spray were administered in a randomized, double-blind, crossover manner (one dose of 1 treatment at each period).

- **Dose Selection Phase (Cohorts 2 and 3)**

The objective of this phase was to evaluate the effects of IN USL261 spray and oral midazolam syrup to determine the most appropriate dose to use in the Main Study (Part B). Subjects in the Dose Selection Phase participated in a Screening visit, a Treatment Phase (2 treatment periods, each separated by at least 48 hours), and a Follow-up visit (approximately 2 to 7 days after the last treatment administration). A single 10-mg oral dose of midazolam syrup and a single 10-mg IN dose of USL261 spray were administered in a randomized, double-blind, double-dummy, crossover manner (one treatment at each period) in Cohort 2. Safety, PD, and PK (if available) data were reviewed by the Data Review Committee (DRC) to determine the dose for subsequent cohorts. Results from Cohort 2 were used to determine dose escalation or reduction in Cohort 3 to determine the sedation limiting dose (SLD) and doses for use in Part B of the study.

Main Study (Part B)

Subjects in Part B participated in a Screening visit, a Qualification Phase, a Double-Blind Dose Evaluation Phase, and Follow-up visit (approximately 2 to 7 days after the last treatment administration). During the Qualification Phase, subjects underwent a pharmacologic qualification to ensure that they could distinguish and like the subjective effects of the positive control drug (oral midazolam syrup). The Qualification Phase was to occur no more than 28 days after Screening, each subject received single oral doses of placebo or midazolam syrup in a double-blind crossover manner with each administration separated by at least 24 hours. The dose of oral midazolam syrup selected for the Qualification Phase was determined based on the data collected in Part A. Subjects were discharged following the completion of the 23-hour assessments after the second treatment at the discretion of the investigator or designee.

The first drug administration in the Double-Blind Dose Evaluation Phase occurred at least 48 hours after the last drug administration in the Qualification Phase. Each subject received up to 7 study treatments in a randomized, double-blind, double-dummy manner (one at each treatment period) according to a Williams design (ie, two 7 X 7 Williams' squares) as follows:

- Treatment A: IN USL261 spray (low dose)
- Treatment B: IN USL261 spray (moderate dose)
- Treatment C: IN USL261 spray (high dose)
- Treatment D: oral midazolam syrup (low dose)
- Treatment E: oral midazolam syrup (moderate dose)
- Treatment F: oral midazolam syrup (high dose)
- Treatment G: placebo (matching oral and IN [USL261] treatments)

Up to 3 doses of each active treatment (oral midazolam syrup and IN USL261 spray) were selected by the DRC based on all available study data. The doses of oral midazolam syrup were based on doses equivalent to those selected for IN USL261 spray (eg, weight [mg] matched or PK equivalence) that could be safely tolerated without significant adverse events (AEs) that would have compromised subject safety or data integrity. Each treatment was administered following a washout interval of at least 48 hours. The administration of oral comparator and IN study drug was temporally offset to mask the differences in onset time.

Pharmacodynamic Endpoints (Main Study):

Primary PD Endpoint: Bipolar Drug Liking VAS Emax

Key Secondary PD Endpoints:

- Overall Drug Liking VAS Emax
- High VAS Emax

Additional secondary endpoints (maximum values and/or minimum values [Emax and/or Emin] and TA_AUE and/or TB_AUE) to be determined in this study were based on the following measures:

- Balance of effects: Drug Liking VAS (Emin and TA_AUE), Overall Drug Liking VAS Emin, Take Drug Again VAS (Emax)
- Positive effects: Good Effects VAS (Emax and TA_AUE), High VAS (TA_AUE), Addiction Research Center Inventory (ARCI) Morphine Benzedrine Group (MBG) scale (Emax and TA_AUE)
- Negative effects: Bad Effects VAS (Emax and TA_AUE), ARCI Lysergic Acid Diethylamide (LSD) scale (Emax and TA_AUE)
- Sedative effects: ARCI Pentobarbital-Chlorpromazine-Alcohol (PCAG) scale (Emax and TA_AUE), Alertness/Drowsiness VAS (Emin and TA_AUE)
- Other subject drug effects (Any Effects VAS [Emax and TA_AUE])
- Objective and observer-rated measures of sedation and cognitive impairment: OAA/S (Emin and TB_AUE of composite and sum scores), Choice Reaction Time (CRT) (CFBmax and TB_AUE of motor reaction time [MRT], recognition reaction time [RRT], and total reaction time [TRT]; CFBmin and TB_AUE of percentage correct), DSST (CFBmin and TB_AUE of number of symbols completed; CFBmin and TB_AUE of rate of completion; CFBmax and TB_AUE of number of errors; CFBmin and TB_AUE of percent correct; CFBmin and TB_AUE of correct completion rate; CFBmax and TB_AUE of incorrect completion rate)

Time to Emax/Emin (TEmax/TEmin) or time to CFBmax/CFBmin was also calculated as supportive endpoints. Derived PD endpoints (only Emax/Emin or CFBmax/CFBmin, as appropriate) were also calculated for measures administered during the Qualification Phase.

2.1.3 Number of subjects (planned and analyzed):

Number of Planned Subjects

Main Study: Approximately 50 subjects were to be randomized to the Double-Blind Dose Evaluation Phase to ensure completion of at least 35 subjects.

Number of Analyzed Subjects

Pilot Phase (Cohort 1; Protocol Amendment 1): Twelve subjects received at least 1 dose of the study drug (20-mg); however, all 12 subjects were discontinued from study participation after the first treatment period as some subjects experienced excessive sedation and were not able to complete the PD measures.

Dose Selection Phase (Cohorts 2 and 3; Protocol Amendment 2): Sixteen subjects (8 subjects per cohort) received at least 1 dose of the study drug and all subjects were included in the PD, PK and safety analyses. Doses used for Cohorts 2 and 3 were 10-mg and 12.5-mg, respectively.

Main Study:

All 47 subjects who received at least 1 dose of the study drug were included in the PK and safety analyses. Of the 47 subjects who received at least 1 dose, 2 subjects ((b) (6) and (b) (6)) did not complete the study and 7 subjects ((b) (6), and (b) (6)) received the incorrect dose of oral midazolam syrup in Treatment Period 2. Therefore, a total of 38 subjects were included in the PD analysis.

A supplemental PD analysis was also performed on 45 subjects who received all study treatments, which includes the 7 subjects who were dispensed and administered an unintended treatment.

2.1.4 Pharmacodynamic Statistical Methodology used in Sponsor's analyses

Part A: Pilot Study

Pharmacodynamic data from the Pilot Study was summarized by treatment and dose using descriptive statistics and graphical displays for the mean values at each time point and CFB (for DSST), as well as descriptive statistics of derived endpoints (Emax, Emin, CFBmax, CFBmin, TA_AUE, and TB_AUE). Ratios of Emax/min, CFBmax/min, and 90% confidence intervals for IN midazolam spray (USL261) to oral midazolam syrup were provided for each dose level examined in Part A for cohorts where both oral and IN treatments were administered, as applicable.

Onset time of PD effect for each subject was defined as a score ≥ 30 points on the Any Effects VAS. In order to avoid unblinding any subjects, the earliest observed onset time based on this criterion in Part A was used to define the temporal offset in Part B, with a margin of 5 minutes (eg, if the earliest onset time observed in Part A was 15 minutes postdose, a 10-minute offset was used in Part B). If the earliest onset time was ≤ 5 minutes, no temporal offset was used. All PD data for each subject were evaluated; however, certain data collected when the subject was unable to complete assessments due to somnolence may not have been included in the assessment.

Pharmacodynamic data for subjects in Cohort 1 (Pilot Phase) were analyzed and reported separately from subjects in Cohorts 2 and 3 (Dose Selection Phase).

Part B: Main Study

Qualification Phase

Pharmacodynamic derived endpoints (Emax and/or Emin, as appropriate) from the Qualification Phase were summarized using standard descriptive statistics by treatment (ie, oral midazolam

syrup and placebo). The data was evaluated to confirm that an appropriate population was selected for the Double-Blind Dose Evaluation Phase. Individual by-time point values were listed.

Double-Blind Dose Evaluation Phase

Pharmacodynamic raw values at each time point were summarized by treatment using descriptive statistics and presented graphically. Derived endpoints were summarized using standard descriptive statistics. Calculations of PD parameters for each treatment were based on actual dosing times for the respective treatments. Calculations for placebo used time zero (ie, start time of dosing with the IN treatments). Pharmacodynamic data were presented in tables and graphical displays with time zero assigned to the dosing time of each active and placebo treatment.

Treatment comparisons for the primary endpoint, Drug Liking VAS Emax, were performed using a mixed-effect model for a crossover study. The model included treatment, period, sequence and first-order carryover effect as fixed effects, baseline (predose) measurement as covariate where applicable, and subject nested within treatment sequence as random effect. If the carryover effect was found to be nonsignificant at the 25% level, then the term was dropped from the analysis model. The residuals from the mixed-effect model were investigated for normality using the Shapiro-Wilk W-test. Parameters were analyzed as having a normal distribution if the probability value was ≥ 0.05 . Parameters that did not meet this criterion were analyzed nonparametrically. Overall treatment effect was assessed using Friedman's test; pairwise treatment comparisons were assessed using the Wilcoxon signed-rank test on the within-subject differences or the sign test, as appropriate based on the skewness value.

The treatment comparisons to assess the abuse potential of USL261 included the following, as applicable:

Study validation: Each dose of oral midazolam syrup vs placebo

For study validity purposes, the primary endpoint, Drug Liking VAS Emax, was compared between the positive control (oral midazolam syrup) and placebo. If a statistically significant difference in Drug Liking VAS Emax was observed at oral midazolam dose level(s) for the primary comparison(s), it would confirm the sensitivity of the study.

Primary (Direct-by-Dose Comparisons):

- IN USL261 spray (moderate dose) vs oral midazolam syrup (equivalent dose)
- IN USL261 spray (high dose) vs oral midazolam syrup (equivalent dose)

Contrasts or pairwise comparisons were adjusted, as appropriate, based on the final doses selected. For each of the contrasts or pairwise comparisons, the null hypothesis was: there was no treatment effect difference between the tested pair, and the alternative hypothesis was: there was a treatment effect difference between the tested pair. A 5% Type-I error rate with a p-value less than 0.05 was considered as statistically significance for all individual hypothesis tests. All statistical tests were performed using two-tailed significance criteria. Due to the exploratory nature of the study, there was no adjustment for multiple comparisons.

The same analyses were performed for the secondary endpoints (Emax, Emin, CFBmax, CFBmin, and TA_AUE/TB_AUE as appropriate). Baseline adjusted AUE (OAA/S and DSST

parameters only), TEmax and/or TEmin were summarized descriptively; however, additional inferential analyses may have been undertaken, if appropriate.

2.1.5 Sponsor's Pharmacodynamic Conclusions

Part B: Double-Blind Dose Evaluation Phase

- Statistically significant differences in Drug Liking VAS Emax were observed between each dose of oral midazolam syrup and placebo administered in the study. Therefore, the study can be considered valid.
- No statistically significant differences were observed between equivalent doses of oral midazolam syrup and IN USL261 spray (5 mg vs 5 mg, 10 mg vs 10 mg, or 15 mg vs 15 mg) on the Drug Liking VAS Emax (primary endpoint).
- No statistically significant differences were also observed between equivalent doses of oral midazolam syrup and IN USL261 spray on Overall Drug Liking VAS Emax and High VAS Emax (key secondary endpoints).
- No consistent differences were observed between equivalent doses of oral midazolam syrup and IN USL261 spray on the majority of secondary endpoints assessing balance (Take Drug Again), positive effects (Good Effects, ARCI-MBG), sedative effects (Alertness/Drowsiness, ARCI-PCAG), and other PD effects (Any Effects, OAA/S, CRT, DSST) across dose levels.
- Treatment comparisons showed no statistically significant differences between equivalent doses of oral midazolam syrup and IN USL261 spray on measures evaluating negative effects (Bad Effects, ARCI-LSG). Mean Emax values for negative effects were relatively lower in comparison to positive effects, indicating weak negative effects.
- Overall, although statistical differences were observed in some measured endpoints, the differences were small and not deemed clinically significant.
- Consistent with effects that were comparable to oral midazolam, statistically significant differences were observed between IN USL261 spray and placebo on most endpoints.
- No major differences in the analysis were observed between 38 subjects (Pharmacodynamic Population) vs 45 subjects (population that included subjects with dispensing error).

Overall, the PD results from this valid study demonstrated that IN USL261 spray showed no statistically significant or clinically-relevant differences in subjective abuse potential compared to oral midazolam syrup in subjects with a history of recreational benzodiazepine use and history of IN administration.

2.2 Data Location

The analysis datasets are located at

<\\CDSESUB1\evsprod\NDA211321\0006\m5\datasets\p261-101\analysis\adam\datasets>

2.3 Reviewer's Assessment

All analyses were conducted from the stand point of the pharmacodynamics analysis.

2.3.1 Descriptive Statistics

The descriptive statistics of $E_{\max}$ and $TE_{\max}$ for the primary PD endpoint Drug Liking, and secondary PD endpoints, High, Overall Drug Liking and Take Drug Again are provided in Table 1 and Table 2. $E_{\max}$ is calculated as the maximum effect in the first 24 hours in the review's analysis. Table 1 summarizes the mean, standard deviation, minimum, the first quartile (Q1), median, the third quartile (Q3), and maximum of $E_{\max}$ for the six treatments in the study. Table 2 summaries the information of $TE_{\max}$.

Table 1. Emax Descriptive Statistics for Drug Liking, High, Overall Drug Liking and Take Drug Again, PD Population (N=38)

Parameter	Treatment	Mean	Std Dev	Min	Q1	Median	Q3	Max
Drug Liking VAS	A-USL261 5 mg	74.97	17.32	50.00	62.00	74.00	91.00	100.00
	B-USL261 10 mg	83.24	17.27	50.00	67.00	88.50	100.00	100.00
	C-USL261 15 mg	82.71	14.05	51.00	73.00	83.50	100.00	100.00
	D-midazolam 5 mg	75.03	18.28	50.00	60.00	74.00	95.00	100.00
	E-midazolam 10 mg	77.63	16.01	50.00	65.00	77.50	96.00	100.00
	F-midazolam 15 mg	81.32	15.57	51.00	67.00	82.00	100.00	100.00
	G-Placebo	53.18	8.78	50.00	50.00	51.00	51.00	100.00
High VAS	A-USL261 5 mg	65.45	33.42	0.00	35.00	76.00	94.00	100.00
	B-USL261 10 mg	79.45	26.51	0.00	62.00	94.50	100.00	100.00
	C-USL261 15 mg	79.03	22.20	1.00	68.00	86.00	100.00	100.00
	D-midazolam 5 mg	61.21	34.37	0.00	32.00	71.00	86.00	100.00
	E-midazolam 10 mg	72.92	25.22	0.00	59.00	80.50	94.00	100.00
	F-midazolam 15 mg	76.76	23.88	0.00	60.00	84.00	100.00	100.00
	G-Placebo	9.97	18.83	0.00	0.00	0.00	5.00	57.00
Overall Drug Liking VAS	A-USL261 5 mg	73.21	21.04	25.00	55.00	71.50	92.00	100.00
	B-USL261 10 mg	75.05	22.55	24.00	51.00	76.00	100.00	100.00
	C-USL261 15 mg	78.45	20.86	24.00	61.00	81.50	100.00	100.00
	D-midazolam 5 mg	75.26	20.13	27.00	60.00	73.00	98.00	100.00
	E-midazolam 10 mg	73.82	21.82	0.00	61.00	74.00	92.00	100.00
	F-midazolam 15 mg	78.63	20.30	35.00	61.00	79.50	100.00	100.00
	G-Placebo	53.87	16.15	0.00	50.00	50.00	51.00	100.00

Take Drug Again VAS	A-USL261 5 mg	65.03	37.43	0.00	38.00	80.50	100.00	100.00
	B-USL261 10 mg	74.37	30.13	0.00	50.00	85.50	100.00	100.00
	C-USL261 15 mg	75.66	30.08	0.00	53.00	89.00	100.00	100.00
	D-midazolam 5 mg	71.74	32.14	0.00	54.00	80.50	100.00	100.00
	E-midazolam 10 mg	69.63	32.69	0.00	50.00	78.50	100.00	100.00
	F-midazolam 15 mg	73.45	31.43	0.00	60.00	84.00	100.00	100.00
	G-Placebo	16.26	32.17	0.00	0.00	0.00	3.00	100.00

In Table 1, for Drug Liking VAS Mean Emax scores were numerically similar for the 5-mg dose IN USL261 spray (74.97) and 15-mg dose IN USL261 spray (82.71) compared to 5-mg oral midazolam syrup (75.03) and 15-mg oral midazolam syrup (81.32), respectively. Mean Emax value was slightly higher for 10-mg IN USL261 spray (83.24) compared to 10-mg oral midazolam syrup (77.63).

For High VAS, Mean High VAS Emax for placebo was low (<10.0), and median values for Emax was approximately zero. Mean Emax values were high for 10-mg and 15-mg doses of oral midazolam syrup and IN USL261 spray, although IN USL261 spray had the highest Emax values (79.45 [10 mg] and 79.03 [15 mg]).

For Overall Drug Liking VAS, mean Overall Drug Liking VAS Emax values (key secondary endpoint) were near the neutral range for placebo (53.87), whereas responses for the active treatments were comparable, with slightly higher mean Emax values for the 15-mg dose of oral midazolam syrup (78.63) or IN USL261 spray (78.45) relative to the other doses.

For the Take Drug Again VAS, mean Emax values ranged from 65.03 to 75.66 for all active treatments, which were significantly higher than placebo (16.26), indicating that subjects were willing to take the study drug again.

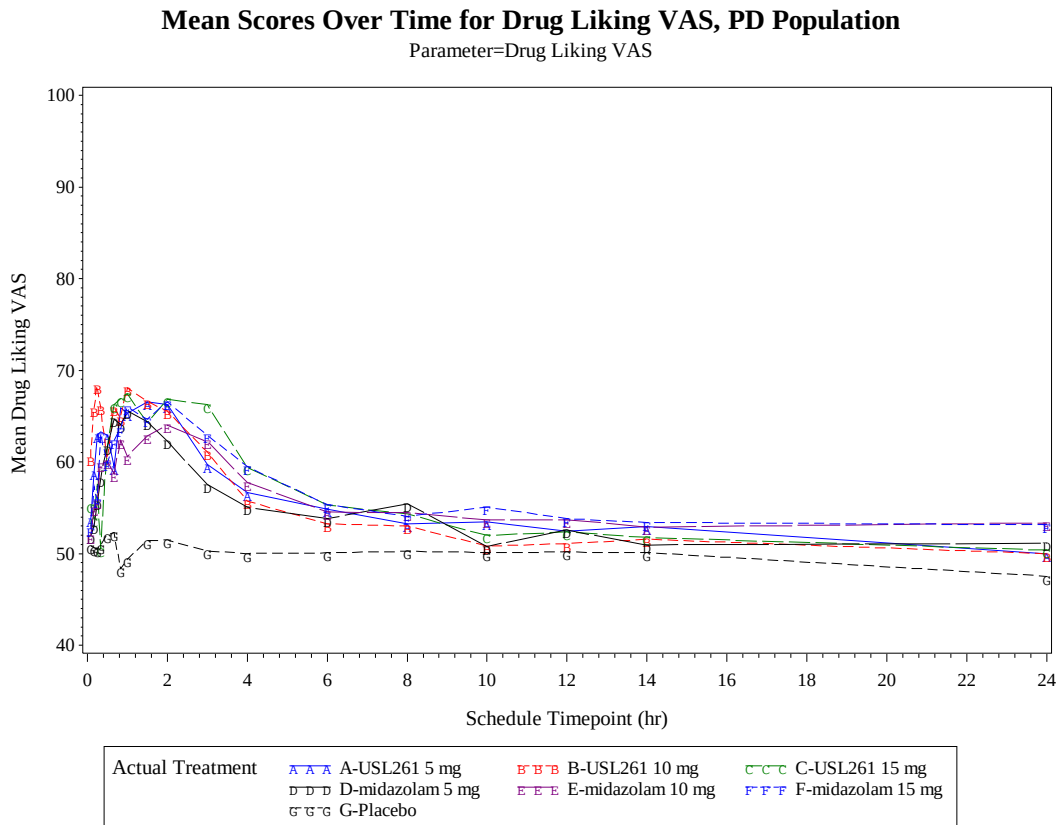
Table 2. TEmax (hours) Descriptive Statistics for Drug Liking, High, PD Population (N=38)

Parameter	Treatment	Mean	Std Dev	Min	Q1	Median	Q3	Max
Drug Liking	A-USL261 5 mg	1.01	1.60	0.08	0.25	0.75	1.00	10.00
	B-USL261 10 mg	0.71	0.76	0.08	0.17	0.50	1.00	4.00
	C-USL261 15 mg	1.50	2.02	0.08	0.67	1.00	2.00	12.00
	D-midazolam 5 mg	0.90	1.27	0.08	0.50	0.67	1.00	8.00
	E-midazolam 10 mg	1.09	0.79	0.08	0.50	0.92	1.50	3.00
	F-midazolam 15 mg	1.29	1.21	0.08	0.50	0.83	1.50	6.00
	G-Placebo	0.99	3.87	0.08	0.08	0.08	0.33	24.00
High	A-USL261 5 mg	0.75	0.69	0.00	0.25	0.58	1.00	3.00
	B-USL261 10 mg	0.80	0.75	0.00	0.33	0.67	0.83	3.00
	C-USL261 15 mg	1.67	3.80	0.08	0.50	0.83	1.50	24.00
	D-midazolam 5 mg	0.69	0.37	0.00	0.50	0.67	1.00	1.50
	E-midazolam 10 mg	1.01	0.71	0.00	0.33	0.83	1.50	3.00
	F-midazolam 15 mg	1.13	0.87	0.00	0.50	1.00	1.50	4.00
	G-Placebo	0.31	1.00	0.00	0.00	0.00	0.25	6.00

In Table 2, for Drug Liking VAS, median time of Peak effects occurred between 0.500 and 1.000 hour for the IN USL261 spray and between 0.67 and 0.92 hours for oral midazolam syrup.

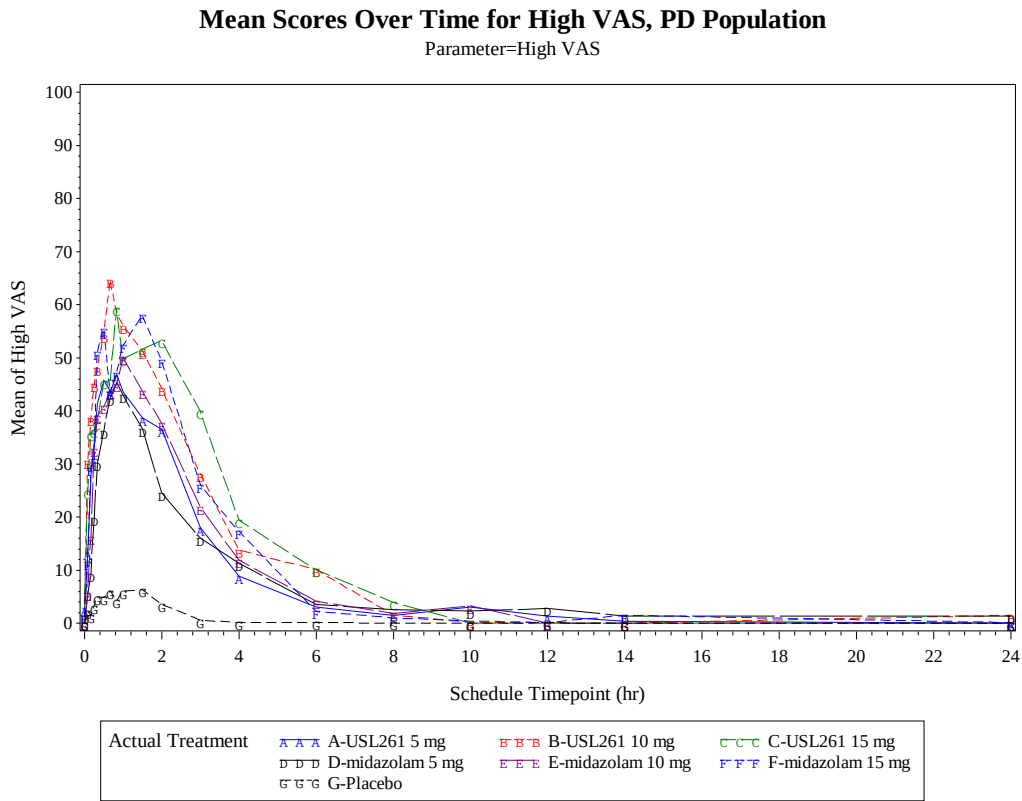
For High VAS, the median time of High peak effects (TE_{max}) occurred between 0.58 and 0.83 hours for IN USL261 spray, and 0.67 and 1.000 hour for oral midazolam syrup.

Figure 1. Mean Drug Liking VAS Scores over time (PD Population, N=38)



Mean curves over time for Drug Liking are presented graphically by treatment in Figure 1. As judged graphically, administration of either oral midazolam syrup or IN USL261 spray resulted in the expected increase in mean Drug Liking VAS values, while mean placebo values remained near neutral (50) for the duration of the session, with median values at 50.0 at all timepoints. A higher peak effect and an earlier onset at approximately 0.5 hours were observed for 10-mg IN USL261 spray compared to other active treatments. Intranasal USL261 spray at 15-mg dose was associated with a slower decline in effects at 3 hours postdose, whereas all other active treatments were steadily declining to neutral. Mean values for all active treatments gradually returned to neutral by approximately 6 hours postdose based on visual inspection.

Figure 2. Mean High VAS Scores over time (PD Population, N=38)



Mean curves over time for Drug Liking are presented graphically by treatment in Figure 2. As judged graphically, administration of either oral midazolam syrup or IN USL261 spray resulted in the expected increase in mean Drug Liking VAS values, while mean placebo values remained near neutral (50) for the duration of the session, with median values at 50.0 at all timepoints. A higher peak effect and an earlier onset at approximately 0.5 hours were observed for 10-mg IN USL261 spray compared to other active treatments. Intranasal USL261 spray at 15-mg dose was associated with a slower decline in effects at 3 hours postdose, whereas all other active treatments were steadily declining to neutral. Mean values for all active treatments gradually returned to neutral by approximately 6 hours postdose based on visual inspection.

Individual E_{max} scores are displayed by subject for all treatments from Figure 3 to Figure 6. Each row represents one patient with 7 treatments. The darker color means more liking. The heatmaps show general placebo remains neutral for all four PD endpoints, no significant differences were observed between equivalent doses of oral midazolam syrup and IN USL261 spray (5 mg vs 5 mg, 10 mg vs 10 mg, or 15 mg vs 15 mg).

Figure 3. Heatmap for Emax of Drug Liking VAS by treatment

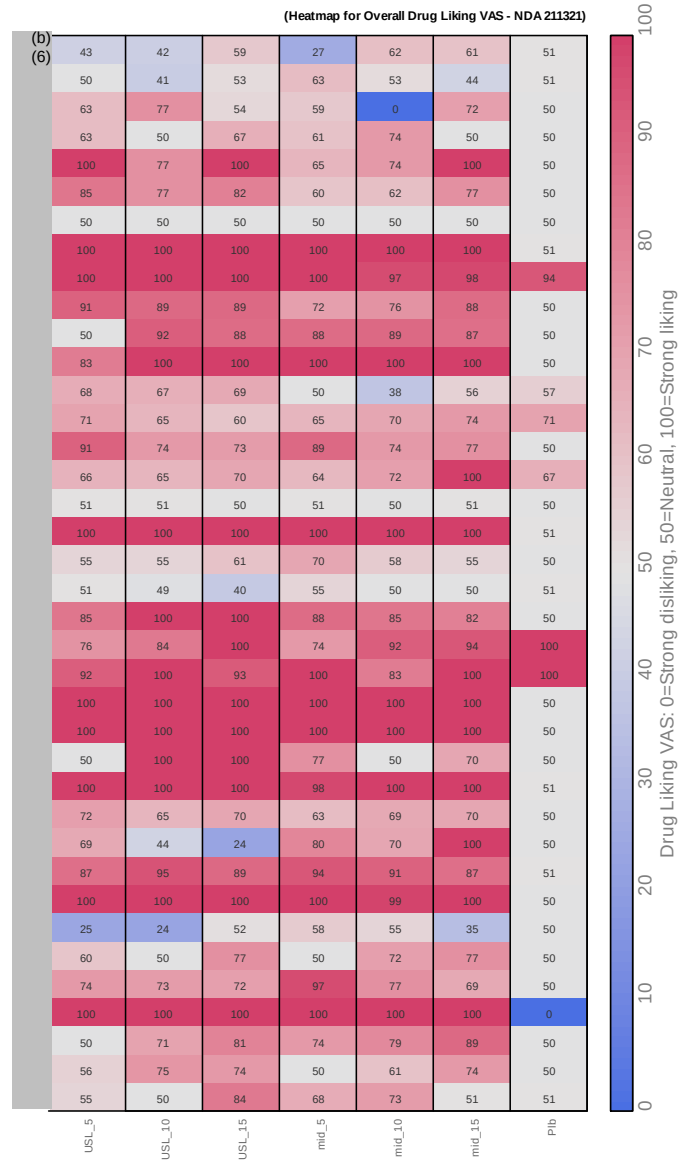


Figure 4. Heatmap for Emax of High VAS by treatment

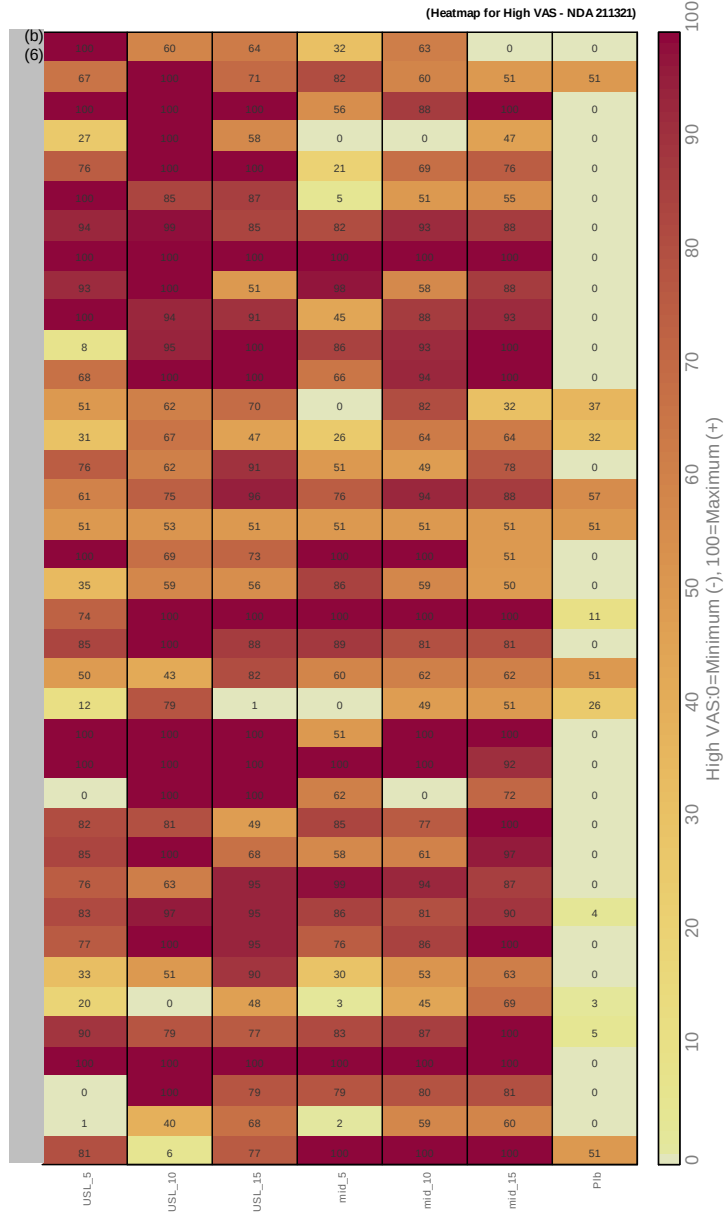


Figure 5. Heatmap for Emax of Overall Drug Liking VAS by treatment

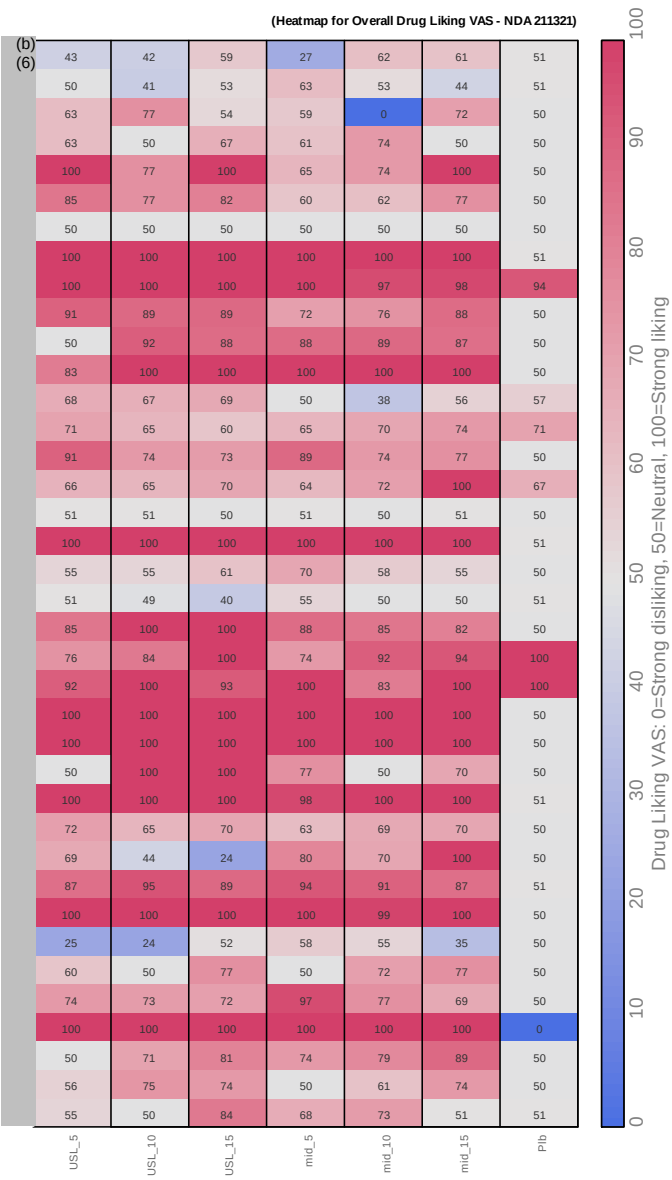
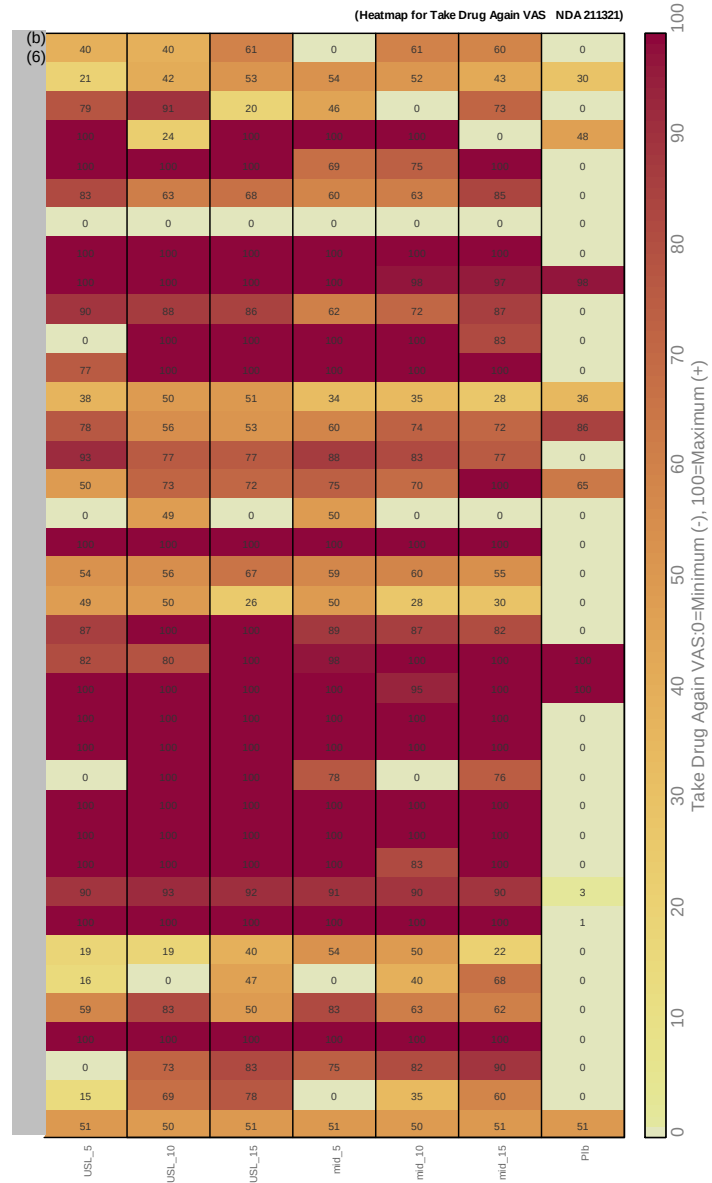


Figure 6. Heatmap for Emax of Take Drug Again VAS by treatment



2.3.2 Statistical Analysis

The statistical analysis of a HAP study should address whether:

- The known drug of abuse (positive control) produces reliable abuse-related responses compared to placebo.
- The test drug produces abuse-related responses that are smaller than the positive control.
- The test drug produces abuse-related responses that are similar to placebo.

To address these issues, the following hypotheses should be tested:

1. Validation of the Appropriateness of the Positive Control

(1) Primary endpoint: Drug Liking Emax

For study validity purpose, the primary endpoint, Emax for Drug Liking VAS, will be compared between each of the positive controls and placebo. Each comparison will assess the null hypothesis that the mean difference in Drug Liking Emax between the positive control and placebo is less than or equal to 15 against the alternative hypothesis that the mean difference in Drug Liking Emax between the positive control and placebo is greater than 15. The hypothesis can be expressed as:

$$H_0: \mu_C - \mu_P \leq 15 \text{ versus } H_a: \mu_C - \mu_P > 15$$

where μ_C is the mean for the positive controls, and μ_P is the mean for placebo. If the treatment difference is statistically significant and the lower confidence limit for the difference exceeds 15, then validity is established for the study.

2. Comparison between the positive controls and the test drug

Comparison between the positive controls and the test drug can be expressed as (where μ_T is the mean for the test drug):

$$H_0: \mu_C - \mu_T \leq 0 \text{ versus } H_a: \mu_C - \mu_T > 0$$

3. Comparisons between each dose of the test drug and placebo

The hypothesis for comparison between each dose of the test drug, and placebo will be:

$$H_0: \mu_T - \mu_P \geq 11 \text{ versus } H_a: \mu_T - \mu_P < 11$$

The primary endpoint and key secondary endpoints will be analyzed using a mixed-effect model if the distribution of the residuals is normal. The model will include treatment, period, sequence, as fixed effects, and subject as a random effect. If this criterion is not met, each paired difference will be investigated for normality using the Shapiro-Wilk W-test. If the p-value for the distribution of the paired difference is ≥ 0.05 or the distribution is quite symmetric (skewness between -0.5 and 0.5), a paired t-test will be used. Means, SE, and one-sided 95% CIs for treatment differences will be presented. P-values will be provided for the contrasts from the paired t-tests. If the paired differences are not normally distributed and not symmetric, pairwise treatment comparisons will be assessed using the sign test. The median, first and third quartiles,

1-sided 95% CI, and the p-value for the paired difference will be presented. In this study, the normality assumption tests were met.

Table 3 summaries the results of Comparison of Drug Liking VAS Emax for the three tests.

Table 3. Comparison of Drug Liking VAS Emax – Primary endpoint, PD Population

Treatments	LS Mean	StdE	Lower	Upper	
A-USL261 5 mg	75.42	2.44	70.62	80.22	
B-USL261 10 mg	83.49	2.78	78.03	88.96	
C-USL261 15 mg	83.44	2.19	79.12	87.76	
D-midazolam 5 mg	75.14	2.90	69.44	80.85	
E-midazolam 10 mg	78.48	2.36	73.83	83.12	
F-midazolam 15 mg	81.44	2.37	76.78	86.10	
G-Placebo	53.89	1.59	50.75	57.03	
Contrasts	LS Mean	StdE	P-value	Lower	Upper
Positive Controls vs. Placebo (Trial Validity, $H_0: \mu_C - \mu_P \leq 15$)					
D-midazolam 5 mg vs. G-Placebo	21.25	3.27	0.0286	15.85	Infy
E-midazolam 10 mg vs. G-Placebo	24.58	2.79	0.0003	19.98	Infy
F-midazolam 15 mg vs. G-Placebo	27.54	2.82	<.0001	22.89	Infy
Test Drugs vs. Positive Controls (Relative Abuse Potential, $H_0: \mu_C - \mu_T \leq 0$)					
A-USL261 5 mg vs D-midazolam 5 mg	-0.28	3.74	0.5297	-6.45	Infy
B-USL261 10 mg vs E-midazolam 10 mg	-5.02	3.61	0.9173	-10.97	Infy
C-USL261 15 mg vs F-midazolam 15 mg	-2.01	3.19	0.735	-7.27	Infy
Test Drugs vs. Placebo (Absolute Abuse Potential, $H_0: \mu_T - \mu_P \geq 11$)					
A-USL261 5 mg vs G-Placebo	21.53	2.87	0.9999	-Infy	26.26
B-USL261 10 mg vs G-Placebo	29.60	3.16	1	-Infy	34.82
C-USL261 15 mg vs G-Placebo	29.55	2.66	1	-Infy	33.93

Table 3 presents, for Drug Liking:

- For the validation test: The validity of the study was determined from the comparison of Drug Liking Emax between each positive control and placebo. The Drug Liking VAS Emax for all doses of oral midazolam syrup was statistically significantly higher than placebo ($p < 0.05$), confirming study validity.
- For the relative abuse potential test: USL261 was evaluated by the comparison of Drug Liking Emax scores of each positive control versus each dose of USL261. Pairwise comparisons showed no statistically significant differences between the equivalent doses of the IN and oral formulation.
- Since all 3 doses of test drug USL261 failed to reject the null hypothesis in the comparison with positive controls, there is no need to run the test of comparing test drug with placebo

according to the closed testing procedure. However, for informational purpose, the reviewer ran the third tests. The results indicated that Drug Liking VAS Emax for all doses of IN USL261 spray was significantly higher than placebo (all three p-values are close to 1).

Table 4. Comparison of High VAS Emax – PD Population

Treatments	LS Mean	StdE	Lower	Upper	
A-USL261 5 mg	65.40	5.01	55.53	75.27	
B-USL261 10 mg	78.92	4.20	70.65	87.19	
C-USL261 15 mg	79.39	3.57	72.35	86.43	
D-midazolam 5 mg	60.40	5.22	50.12	70.68	
E-midazolam 10 mg	73.43	3.48	66.57	80.29	
F-midazolam 15 mg	76.05	3.83	68.50	83.61	
G-Placebo	10.29	3.46	3.47	17.10	
Contrasts	LS Mean	StdE	P-value	Lower	Upper
Test Drugs vs. Positive Controls (Relative Abuse Potential, $H_0: \mu_C - \mu_T \leq 0$)					
A-USL261 5 mg vs D-midazolam 5 mg	-5.00	7.16	0.7573	-16.82	Infty
B-USL261 10 mg vs E-midazolam 10 mg	-5.49	5.38	0.8459	-14.37	Infty
C-USL261 15 mg vs F-midazolam 15 mg	-3.34	5.17	0.7407	-11.89	Infty
Test Drugs vs. Placebo (Absolute Abuse Potential, $H_0: \mu_T - \mu_P \geq 11$)					
A-USL261 5 mg vs G-Placebo	55.11	6.02	1	-Infty	65.06
B-USL261 10 mg vs G-Placebo	68.64	5.37	1	-Infty	77.50
C-USL261 15 mg vs G-Placebo	69.11	4.88	1	-Infty	77.16

Table 4 shows that for High VAS:

- For the relative abuse potential test: USL261 was evaluated by the comparison of High Emax scores of each positive control versus each dose of USL261. No statistically significant differences were observed between equivalent doses of oral midazolam syrup and IN USL261 spray based on Emax.
- For the absolute abuse potential test, statistically significant differences were observed in High VAS Emax (all three p-values are equal 1) between IN USL261 and placebo.

Table 5. Comparison of Overall Drug Liking VAS Emax, PD Population

Treatments	LS Mean	StdE	Lower	Upper	
A-USL261 5 mg	74.21	2.94	68.42	80.00	
B-USL261 10 mg	75.88	3.20	69.57	82.18	
C-USL261 15 mg	79.51	3.16	73.28	85.74	
D-midazolam 5 mg	76.05	3.06	70.03	82.08	
E-midazolam 10 mg	75.11	3.24	68.72	81.50	
F-midazolam 15 mg	79.53	2.67	74.27	84.80	
G-Placebo	55.20	2.93	49.44	60.97	

Contrasts	LS Mean	StdE	P-value	Lower	Upper
Test Drugs vs. Positive Controls (Relative Abuse Potential, $H_0: \mu_C - \mu_T \leq 0$)					
A-USL261 5 mg vs D-midazolam 5 mg	1.84	4.17	0.3298	-5.05	Infty
B-USL261 10 mg vs E-midazolam 10 mg	-0.77	4.50	0.5675	-8.19	Infty
C-USL261 15 mg vs F-midazolam 15 mg	0.03	4.09	0.4974	-6.73	Infty
Test Drugs vs. Placebo (Absolute Abuse Potential, $H_0: \mu_T - \mu_P \geq 1$)					
A-USL261 5 mg vs G-Placebo	19.01	4.09	0.9744	-Infty	25.76
B-USL261 10 mg vs G-Placebo	20.67	4.28	0.9876	-Infty	27.74
C-USL261 15 mg vs G-Placebo	24.30	4.24	0.999	-Infty	31.30

Table 5 presents that for Overall Drug Liking VAS:

- No statistically significant differences were observed between equivalent doses of oral midazolam syrup and IN USL261 spray based on Emax.
- For the absolute abuse potential test, statistically significant differences were observed in Overall Drug Liking VAS Emax (P values are all closed to 1) between IN USL261 and placebo.

Table 6. Comparison of Take Drug Again VAS Emax, PD Population

Treatments	LS Mean	StdE	Lower	Upper	
A-USL261 5 mg	66.44	5.30	56.00	76.88	
B-USL261 10 mg	75.86	4.17	67.65	84.07	
C-USL261 15 mg	77.03	3.78	69.58	84.48	
D-midazolam 5 mg	73.05	4.71	63.78	82.32	
E-midazolam 10 mg	71.06	4.63	61.94	80.17	
F-midazolam 15 mg	75.11	4.15	66.94	83.28	
G-Placebo	17.63	6.14	5.54	29.72	
Contrasts	LS Mean	StdE	P-value	Lower	Upper
Test Drugs vs. Positive Controls (Relative Abuse Potential, $H_0: \mu_C - \mu_T \leq 0$)					
A-USL261 5 mg vs D-midazolam 5 mg	6.61	6.99	0.1727	-4.94	Infty
B-USL261 10 mg vs E-midazolam 10 mg	-4.80	6.13	0.7829	-14.93	Infty
C-USL261 15 mg vs F-midazolam 15 mg	-1.93	5.53	0.636	-11.06	Infty
Test Drugs vs. Placebo (Absolute Abuse Potential, $H_0: \mu_T - \mu_P \geq 1$)					
A-USL261 5 mg vs G-Placebo	48.81	8.04	1	-Infty	62.09
B-USL261 10 mg vs G-Placebo	58.23	7.34	1	-Infty	70.36
C-USL261 15 mg vs G-Placebo	59.41	7.12	1	-Infty	71.16

Table 6 shows for Take Drug Again VAS:

- No statistically significant differences were observed between equivalent doses of oral midazolam syrup and IN USL261 spray based on Emax.
- For the absolute abuse potential test, statistically significant differences were observed in Take Drug Again VAS Emax (P values are all equal to 1) between IN USL261 and placebo.

In reviewing the drug concentration data, it appears that PK values of 15mg of oral midazolam are similar to 10mg of nasal spray and PK values of 10mg of oral drug are similar to 5mg of nasal spray. CSS requests to do the following analyses for primary and secondary endpoints:

- Nasal spray 10mg vs oral 15 mg (B-USL261 10 mg vs F-midazolam 15 mg)
- Nasal spray 5mg vs oral 10 mg (A-USL261 5 mg vs E-midazolam 10 mg)

Table 7 Summary results for extra comparisons requested by CSS

Test Drugs vs. Positive Controls (Relative Abuse Potential, $H_0: \mu_C - \mu_T \leq 0$)						
PD Endpoint	Treatments	LS Mean	StdE	P-value	Lower	Upper
Drug Liking VAS (Primary)	A-USL261 5 mg vs E-midazolam 10 mg	3.05	3.36	0.1818	-2.49	Infy
	B-USL261 10 mg vs F-midazolam 15 mg	-2.06	3.60	0.716	-8.00	Infy
High VAS	A-USL261 5 mg vs E-midazolam 10 mg	8.03	6.04	0.0925	-1.94	Infy
	B-USL261 10 mg vs F-midazolam 15 mg	-2.87	5.60	0.6958	-12.11	Infy
Overall Drug Liking VAS	A-USL261 5 mg vs E-midazolam 10 mg	0.90	4.32	0.418	-6.24	Infy
	B-USL261 10 mg vs F-midazolam 15 mg	3.66	4.10	0.1867	-3.12	Infy
Take Drug Again VAS	A-USL261 5 mg vs E-midazolam 10 mg	4.62	6.96	0.2539	-6.88	Infy
	B-USL261 10 mg vs F-midazolam 15 mg	-0.75	5.77	0.5518	-10.29	Infy

Table 7 presents the summary results for these comparisons for all four PD endpoints. The results show that there is no significant difference between Nasal spray 10mg and oral 15 mg (p values are all >0.05), and no significant difference between Nasal spray 5mg vs oral 10 mg (p values are all >0.05) in all endpoints.

3. Conclusions

The primary objective of this trial was to evaluate the abuse liability of IN USL261 compared with that of oral midazolam and placebo in adult subjects with a history of recreational benzodiazepine use.

The reviewer analyzed the primary PD endpoint Drug Liking, and the secondary PD endpoints: High, Take Drug Again and Overall Drug Liking. The results from the statistical reviewer's analyses indicates that:

- For the validation test: The validity of the study was determined from the comparison of Drug Liking Emax between each positive control and placebo. The Drug Liking VAS Emax for all

doses of oral midazolam syrup was statistically significantly higher than placebo ($p < 0.05$), confirming study validity.

- No statistically significant differences were observed between equivalent doses of oral midazolam syrup and IN USL261 spray (5 mg vs 5 mg, 10 mg vs 10 mg, or 15 mg vs 15 mg) on the Emax of Drug Liking VAS (primary endpoint) and Emax of secondary endpoints: High VAS, Overall Drug Liking VAS and Take Drug Again VAS, indicating IN USL261 is associated with a strong signal for abuse potential similar to oral midazolam
- In addition, there is no significant difference between Nasal spray USL261 10 mg and 15 mg oral midazolam (P values are all > 0.05), and no significant difference between Nasal spray USL261 5mg and 10 mg oral midazolam (P values are all > 0.05) on the Emax of Drug Liking, High, Overall Drug Liking and Take Drug Again.

Overall, the PD results from this study demonstrated that IN USL261 is associated with a strong signal for abuse potential similar to oral midazolam in subjects with a history of recreational benzodiazepine use and history of IN administration.

4. References

- 1) Guidance for Industry: Assessment of Abuse Potential for Drugs (January 2017)
<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm198650.pdf>

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #: 211,321

Drug Name: Nayzilam™ (midazolam nasal spray)

Indication(s): Intermittent bouts of increased seizure activity

Applicant: Proximagen

Date(s): Submission date: 5/29/2018
PDUFA Date: 3/29/2019

Review Priority: Standard Review

Biometrics Division: Division of Biometrics I

Statistical Reviewer: Xiang Ling, Ph.D.

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1 EXECUTIVE SUMMARY

The submitted data overall provided statistical evidence to support the efficacy of Nayzilam in treating patients with intermittent bouts of increased seizure activity.

The primary efficacy analysis demonstrated a statistically significant larger proportion of subjects with treatment success in the Nayzilam group compared to the placebo group (difference =19%; 1-sided $p=0.0069$ compared to a significance level of 0.0085). The treatment effect was robust and consistent across subgroups by age, gender, race, and region.

Nayzilam demonstrated a statistically significant treatment effect on both secondary endpoints: time to next seizure with a start time >10 minutes after the study drug administration; and the proportion of subjects with recurrence between 10 minutes to 4 hours after study drug administration.

2 INTRODUCTION

2.1 Overview

Nayzilam™ (midazolam nasal spray; MDZ NS) is being developed under IND #77421 as an acute treatment for the rapid interruption of increased seizure activity (eg, seizure clusters) in outpatient settings. Seizure clusters can be seizures of any type that occur in groups or clusters over a number of hours or days. Seizure clusters may end on their own, but some may evolve into more serious sequelae such as prolonged seizure and status epilepticus. The primary goals of seizure cluster treatment are seizure cessation and prevention of seizure recurrence. The original sponsor was USL, and Proximagen assumed the role of Sponsor for the development in 2017. Midazolam was previously approved by the FDA for a variety of sedation and pre-anesthesia indications.

The efficacy of Nayzilam was demonstrated via the Phase 3 Study P261-401 in adult and adolescent subjects 12 years of age and older with seizure clusters. Overall, 201 patients were randomized in this study (134 patisiran group, 67 placebo) worldwide. The primary efficacy endpoint was the proportion of subjects with treatment success. Additional efficacy data were collected (b) (4).

Table 1: Phase 3 Studies Comprising the Clinical Development Program

Study	Population (N)	Intent / Design
P261-401	Patients with Seizure Clusters (201)	Randomized, Double-blind, Placebo-controlled; Single dose 5 mg MDZ NS vs PBO administered in outpatient setting (blinded); option to take Second 5 mg dose, if needed (open-label); Multi-center US, Europe, Australia
P261-301	Patients in EMU (62); refractory epilepsy; diagnosis of seizure clusters not necessary	Randomized, double-blind, placebo controlled; Single 5 mg dose; Multi-center US, Europe, Australia

2.2 Data Sources

Materials reviewed for this application include the clinical study reports, raw and derived datasets, SAS codes used to generate the derived datasets and tables, protocols, statistical analysis plans, which are in the following directory: <\\CDSESUB1\evsprod\NDA211321\0001>.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

This reviewer could trace how the primary endpoint was derived from the raw data. Documentation of statistical analysis methods was included with sufficient details for this reviewer to reproduce the applicant's key efficacy results.

3.2 Evaluation of Efficacy

3.2.1 Study P261-401

3.2.1.1 Study Design and Endpoints

Study P261-401 was initiated on 24 June 2011 and completed on 20 March 2017. The original protocol (dated 30 March 2011) was amended 5 times but the last amendment was not implemented. Amendment 2 (dated 20 October 2014) modified the trial to utilize a group sequential design with 3 interim analyses, and increased the sample size from 132 to a maximum of approximately 240 subjects. The last versions prior to conducting the first interim analysis were protocol amendment 3 (dated 26 February 2015) and statistical analysis plan (SAP) version 2.4 (dated 25 February 2015). The final protocol amendment 4 was dated 20 May 2015 with updates applicable only to the US. The final SAP was dated 14 April 2017, in which an early study termination analysis was added in the event that the trial had not crossed a boundary for early success or early futility and yet was stopped early before reaching the pre-specified maximum sample size of 240 subjects.

Study Design

Study P261-401 was a multinational, randomized, double-blind, placebo-controlled, study of Nayzilam in patients with epilepsy on a stable regimen of antiepileptic drugs who were identified by their physicians as having seizure clusters. The study consisted of 2 phases, an open-label Test Dose Phase followed by a double-blind, placebo-controlled, Comparative Phase (Figure 1). In the Test Dose Phase, subjects received 2 doses of open-label Nayzilam 5 mg administered 10 minutes apart at the study center. Patients were excluded from further participation in the study if experienced adverse reaction. Before any subject continued to the Comparative Phase, safety data from 26 subjects in the Test Dose Phase were reviewed by an independent Data and Safety Monitoring Board (DSMB).

In the Comparative Phase, subjects were randomized in a 2:1 ratio to receive Nayzilam 5 mg or placebo in an outpatient setting. The subject's caregiver administered the double-blind study drug when the subject experienced a seizure cluster that met the study criteria, as described in the subject's individualized Patient Management Plan (PMP). The double-blind dose of study drug (Nayzilam or placebo) may have been followed by a single dose of 5 mg Nayzilam (open-label) if the following occurred:

- The treated seizure cluster did not terminate within 10 minutes or another seizure occurred between 10 minutes and 6 hours after the initial drug administration;
- AND the subject did not have < 8 breaths per minute, did not require emergency rescue treatment and assisted breathing or intubation, and did not have excessive uncharacteristic sedation.

The subject's caregiver collected seizure data for efficacy evaluation in the Subject Workbook. Any seizures occurring within 24 hours after administration of study drug were recorded. All subject data were reviewed by the Epilepsy Study Consortium. Any time between 24 to 120 hours after study drug administration, subjects and caregivers returned to the study center for a post-dose study visit.

Figure 1. Study Design



The study was originally planned to have 132 completed subjects. However, the applicant increased the sample size to a maximum of 240 completed subjects, based on external information (higher placebo response rate reported in publication). Additionally, the applicant added 3 interim analyses (IAs) to occur after 132, 165, and 204 subjects completed the Comparative Phase, with possible study stopping at interim analyses for futility or efficacy.

The trial was to be stopped for futility if the predictive probability of success at the maximum sample size was less than 10%. At each interim analysis, a one-sided Fisher's Exact test on the two proportions was to be performed and compared to the Lan-DeMets Pocock approximation boundary critical values. Prior to the conduct of 3rd IA, the sponsor terminated the study based on business reasons not related to safety or efficacy information from the ongoing clinical studies, with an actual sample size of 201.

Efficacy Endpoints

The primary efficacy endpoint was treatment success, defined as:

- (1) termination of seizure(s) within 10 minutes of first dose of study drug, and
- (2) no recurrence of seizure(s) during the window from 10 minutes to 6 hours of first dose of study drug, and
- (3) no second dose of study drug within 6 hours of the first dose.

The secondary endpoints included:

- Time to next seizure with a start time >10 minutes after the study drug administration;
- The proportion of subjects with recurrence of seizure(s) between 10 minutes to 4 hours after study drug administration.

3.2.1.2 Statistical Methodologies

Efficacy endpoints were analyzed using mITT population, defined as all randomized subjects who had at least 1 dose of study drug during the Comparative Phase and had any post-treatment efficacy assessments.

Analysis of the Primary Endpoint

The primary efficacy endpoint (proportion of subjects with treatment success) and its components (seizure termination and recurrence) were analyzed using Fisher's exact test. A chi-squared test was performed as a sensitivity analysis.

Subjects with missing data impacting determination of treatment success or its components were to be treated as "not a treatment success." However, there were no subjects who had missing data in this study.

Adjusting for Baseline Covariates

A sensitivity analysis was conducted using Cochran-Mantel-Haenszel (CMH) test stratified by age (< 18 years, ≥ 18 to < 65 years, ≥ 65 years).

An exploratory logistic regression on treatment success was also conducted with a backward selection of covariates in which covariates with a $p > 0.10$ were dropped from the model. The following covariates were used:

- Age (< 18 years, ≥ 18 to < 65 years, ≥ 65 years);
- Sex (male/female);

- Weight (kg);
- BMI standardized categories (underweight/normal [< 25], overweight [≥ 25 - < 30], and obese [≥ 30]);
- Geographic region of clinical site (North America and similar [US, Canada, Australia, and New Zealand], Eastern Europe [Hungary, Poland, Ukraine], and Western Europe [Spain, Germany, Italy, and Israel]);
- Enzyme-inducing antiepileptic drugs (AEDs) used within 14 days prior to administration of blinded study drug vs. others.

Analyses of the Key Secondary Endpoints

Time to next seizure with a start time >10 minutes after double-blind study drug administration was analyzed by a log-rank test. Subjects who did not have another seizure before the end of the 24-hour observation period and was not administered the second dose of study drug would be censored at the end of the observation period. Subjects administered the second dose of study drug who did not have a seizure before the administration of the second dose would be censored at the time of the second dose administration. Additional analysis was conducted in which all subjects administered the second dose of study drug were considered as events (failure).

A Cox proportional hazards regression model was used to evaluate the difference between treatment groups adjusting for the covariates. Interactions between treatment and each covariate were evaluated at the 0.10 significance level; if not significant, they were removed from the final model.

The proportion of subjects with recurrence of seizure(s) within 4 hours, with a start time > 10 minutes after administration of double-blind study drug, was analyzed using Fisher's Exact test. A Chi-squared test was performed as a sensitivity analysis. Subjects who had been administered the second dose of study drug within 4 hours of double-blind study drug administration were counted as if they had a recurrence of seizure.

Multiplicity Adjustment

Based on the Lan-DeMets spending function approximation of the Pocock boundary, the 1-sided p-value required for success for the final analysis at the maximum sample size of 240 was 0.0085 (Table 2).

Table 2: Lan-DeMets Pocock Approximation Spending Function

Analysis	Number of patients	Alpha level (1-sided)
IA1	132	0.0166
IA2	165	0.0094
IA3	204	0.0089
Final analysis	240	0.0085

Two IAs were conducted by an Interim Analysis Monitoring Committee (IAMC) independent of both the sponsor and DSMB. IA1 was conducted when 132 subjects completed the Comparative

Phase (ie, received at least 1 dose of study drug during the Comparative Phase and completed post-dose visit) with a data cut-off of 10 March 2015. IA2 was conducted when 165 subjects completed the Comparative Phase with a data cutoff of 02 November 2015. Neither results ($p=0.1644$ and 0.0293 respectively) met the criteria for stopping. On 22 February 2017, prior to the conduct of IA3, the sponsor informed the Division of the decision to end subject enrollment, based on business reasons not related to safety or efficacy information from the ongoing clinical studies. Additionally, the applicant proposed to conduct final analyses with all available subjects ($n = 201$) at the alpha level of 0.0085 (1-sided) which was planned for the final analysis with the maximum sample size.

The type I error control for secondary endpoints was achieved by a hierarchical testing procedure, with the order listed in the previous section. The SAP did not clearly specify the significance level for the secondary endpoints. However, the secondary endpoints would not have the full alpha of 0.05 (2-sided) because of the IAs conducted.

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 292 entered into the Test Dose Phase and 262 subjects were randomized in the Comparative Phase. During the Comparative Phase, 201 subjects (134 in the Nayzilam group and 67 in the placebo group) were treated and included in the mITT Population. In the Nayzilam group, 91 subjects received only the double-blind dose and 43 received both the double-blind and open-label doses of Nayzilam 5 mg. In the placebo group, 26 subjects received double-blind placebo only and 41 received double-blind placebo and open-label Nayzilam 5 mg. All but 1 subject completed the study: Subject (b) (6) withdrew consent prior to completing study procedures at post-dose visit (Table 3).

Table 3: P261-401: Subject Disposition (mITT Population)

	MDZ NS (N=134) n (%)	Placebo (N=67) n (%)	Total (N=201) n (%)
Received 1 dose (double-blind) in Comparative Phase	91 (67.9)	26 (38.8)	117 (58.2)
Received 2 doses in Comparative Phases	43 (32.1)	41 (61.2)	84 (41.8)
Completed study	133 (99.3)	67 (100.0)	200 (99.5)
Discontinued prematurely	1 (0.7)	0	1 (0.5)

Source: CSR Table 14.1.1.4.

Overall, the 2 treatment groups were comparable regarding demographic characteristics. The mean age was 33 years, 51% were female, and 95% were white. The majority of patients were from North America and similar, or Eastern Europe (Table 4).

Table 4: Demographic Characteristics

	MDZ NS			Placebo			Total (N = 201)
	MDZ NS 5 mg (N = 91)	MDZ NS 5 + 5 mg (N = 43)	Total (N = 134)	Placebo (N = 26)	Placebo +5 mg (N = 41)	Total (N = 67)	
Age (years)							
Mean (SD)	33.9 (11.0)	34.4(11.8)	34.0 (11.2)	28.3 (12.5)	33.5 (12.8)	31.5 (12.8)	33.2 (11.8)
Median	32.0	33.0	32.0	25.5	35.0	27.0	32.0
Min, Max	15, 60	14, 61	14, 61	12, 62	13, 56	12, 62	12, 62
Age Group, n (%)							
< 18	3 (3.3)	2 (4.7)	5 (3.7)	2 (7.7)	3 (7.3)	5 (7.5)	10 (5.0)
≥ 18	88 (96.7)	41 (95.3)	129 (96.3)	24 (92.3)	38 (92.7)	62 (92.5)	191 (95.0)
Sex, n (%)							
Male	41 (45.1)	27 (62.8)	68 (50.7)	13 (50.0)	17 (41.5)	30 (44.8)	98 (48.8)
Female	50 (54.9)	16 (37.2)	66 (49.3)	13 (50.0)	24 (58.5)	37 (55.2)	103 (51.2)
Race, n (%)							
White	84 (92.3)	41 (95.3)	125 (93.3)	26 (100.0)	39 (95.1)	65 (97.0)	190 (94.5)
Non-white	7 (7.7)	2 (4.7)	9 (6.7)	0	2 (4.9)	2 (3.0)	11 (5.5)
Asian	2 (2.2)	0	2 (1.5)	0	0	0	2 (1.0)
American Indian or Alaska Native	1 (1.1)	1 (2.3)	2 (1.5)	0	0	0	2 (1.0)
Black or African American	3 (3.3)	0	3 (2.2)	0	1 (2.4)	1 (1.5)	4 (2.0)
Other	1 (1.1)	1 (2.3)	2 (1.5)	0	1 (2.4)	1 (1.5)	3 (1.5)
Region, n (%)							
North America and Similar	52 (57.1)	13 (30.2)	65 (48.5)	11 (42.3)	13 (31.7)	24 (35.8)	89 (44.3)
Eastern Europe	29 (31.9)	20 (46.5)	49 (36.6)	11 (42.3)	25 (61.0)	36 (53.7)	85 (42.3)
Western Europe	10 (11.0)	10 (23.3)	20 (14.9)	4 (15.4)	3 (7.3)	7 (10.4)	27 (13.4)

Source: Table 14.1.3.2 of CSR.

Baseline disease characteristics in general were balanced between the two treatment groups (Table 5). Subjects had experienced seizure clusters for a median of 5 years. Subjects had a median of 18 seizure cluster episodes in the 1 year prior to study and a median of 6 seizures per episode. The median duration of seizure cluster was 65 minutes. The most common seizure types in the clusters was complex partial seizures (52%), followed by secondarily generalized tonic-clonic convulsion (33%) and simple partial seizures (20%). About 58% of the patients were classified as AED-induced (ie, used enzyme-inducing AEDs within a 14-day window before administration of the blinded study drug).

Table 5: Baseline Disease Characteristics Seizure

Parameter	MDZ NS (N = 134)	Placebo (N = 67)	All Randomized (N = 201)
Typical duration of seizure cluster (minutes)			
n	129	63	192
Mean (SD)	271 (573)	239 (528)	260 (557)
Median	65	60	65
Min, Max	3, 4320	8, 2880	3, 4320
Number of years that subject has had seizure clusters			
n	133	64	197
Mean (SD)	9.9 (10.1)	6.7 (6.3)	8.8 (9.2)
Median	5.0	5.0	5.0
Min, Max	0.3, 48.0	0.5, 32.0	0.3, 48.0
Number of seizure cluster episodes in 1 year before study			
n	134	67	201
Mean (SD)	56.3 (128.5)	49.1 (98.4)	53.9 (119.1)
Median	18.0	15.0	18.0
Min, Max	3, 999	4, 600	3, 999
Number of seizures in cluster episode			
n	134	67	201
Mean (SD)	12.8 (23.6)	14.2 (25.6)	13.3 (24.2)
Median	5.3	6.0	6.0
Min, Max	2, 200	2, 170	2, 200
Seizure type(s) in cluster to be treated in study, n (%)			
Simple partial seizure	23 (17.2)	17 (25.4)	40 (19.9)
Complex partial seizure	71 (53.0)	33 (49.3)	104 (51.7)
Secondarily generalized tonic clonic convulsion	46 (34.3)	20 (29.9)	66 (32.8)
Primary generalized tonic clonic convulsion	8 (6.0)	7 (10.4)	15 (7.5)
Absence	7 (5.2)	0	7 (3.5)
Myoclonus	3 (2.2)	3 (4.5)	6 (3.0)
Tonic	8 (6.0)	3 (4.5)	11 (5.5)
Atonic	2 (1.5)	0	2 (1.0)
Other	7 (5.2)	0	7 (3.5)
Subjects classified as AED-induced			
n (%)	83 (61.9)	33 (49.3)	116 (57.7)

Source: CSR Table 8 and Table 10.

3.2.1.4 Results and Conclusions

3.2.1.4.1 Analyses of the Primary Endpoint

As shown in Table 6, the proportion of subjects with treatment success was greater in the Nayzilam group (54%) as compared with the placebo group (34%). The 1-sided p-value for the primary analysis based on Fisher's Exact test was 0.0069, smaller than the proposed statistical significance level of 0.0085 (1-sided) for the final analysis, suggesting that the difference of 19% between the Nayzilam and placebo groups was statistically significant.

Had the study been planned with a sample size of 201 and with only two IAs as actually performed, the alpha left for the final analysis would be 0.013 (1-sided; based on the reviewer's calculation). However, to protect study integrity, unplanned changes should generally be avoided after unblinded analyses have been conducted. Based on the SAP prior to conducting the first interim analysis, a 1-sided p-value <0.0085 for the analysis with $n=201$ (close to the planned sample size of 204 for IA3) would cross the Pocock boundary either as the IA3 or as the final analysis. Therefore, the applicant's proposal of using a significance level of 0.0085 was reasonable in this situation.

Note that as Fisher's exact test does not correspond to a test statistic that has a symmetric distribution, its 2-sided p-value is in general not twice the 1-sided value, which may lead to different conclusions. For the inference of the result for this study, the 1-sided alpha level was prespecified hence the 1-sided Fisher's exact test should be considered the primary analysis. For the Chi-square test ($p=0.0094$; Table 6), the 2-sided alpha level ($2*0.0085=0.017$) should be used as it is a 2-sided test.

Fisher's exact test was proposed as the original planned sample size was relatively small. Along with the increase of the sample size and addition of 3 interim analyses, the applicant proposed using Chi-square test as the primary analysis. The Agency conveyed concerns with the major changes to the study design at a late stage (based on original plan) of the study. However, had the Agency agreed with the increased sample size of 240, Fisher's exact test would not be necessary, and the Chi-square test would be considered appropriate for the primary analysis. While Fisher's exact test is still valid for a larger sample size, it tends to be conservative due to the discreteness of the outcome space. Nonetheless, the results from both analyses crossed the efficacy boundary, indicating a statistically significant treatment effect of Nayzilam.

Analyses with baseline covariate adjustment also supported the robustness of the primary analysis. The CMH test stratified by age group indicated that the proportion of subjects with treatment success was greater in the Nayzilam group (odds ratio = 2.2, 2-sided nominal $p=0.0092$; Table 6). The logistic regression model with a backward selection of covariates yielded similar results, with the covariates of age, sex, BMI, geographic region, and AED-inducer status included in the final model.

Table 6: Analyses of Treatment Success

	MDZ NS (N = 134)	Placebo (N = 67)
Treatment success		
n (%)	72 (53.7)	23 (34.3)
95% CI	(45.3, 62.2)	(23.0, 45.7)
MDZ NS difference from placebo	19.4%	
p-value from Fisher's Exact test (1-sided, primary analysis*)	0.0069	
p-value from Fisher's Exact test (2-sided)	0.0109	
p-value from Chi-squared test	0.0094	
Odds ratio (MDZ NS: placebo) (95% CI)		
CMH test, stratified by age group	2.2 (1.2, 4.1) p=0.0092	
logistic regression	2.3 (1.2, 4.3) p=0.0116	

* A significance level of 0.0085 is used for primary analysis of 1-sided Fisher's exact test. All other tests are 2-sided at a nominal significance level of 0.017.

Source: CSR Table 14.2.1.1.1 and Table 14.2.1.3, and this reviewer.

Nayzilam group had higher proportion of patients achieving each of the components of treatment success. Seizure termination occurred within 10 minutes in 81% of subjects treated with Nayzilam compared with 70% of subjects in the placebo group. In the Nayzilam and placebo groups, 67% and 57% of subjects respectively did not experience seizures from 10 minutes to 6 hours after study drug administration; and 69% and 39% of subjects respectively did not have second dose within 6 hours of first dose of study drug.

Table 7: Analyses of the Components of Treatment Success

	MDZ NS (N = 134) n(%)	Placebo (N = 67) n(%)
Termination of seizure(s) within 10 minutes	108 (80.6)	47 (70.1)
No recurrence of seizure(s) with start time > 10 minutes and ≤ 6 hours	90 (67.2)	38 (56.7)
No second dose within 6 hours of first dose of study drug	92 (68.7)	26 (38.8)
No recurrence of seizure(s) with start time > 10 minutes and ≤ 6 hours and No second dose within 6 hours of first dose of study drug	78 (58.2)	25 (37.3)

Source: CSR Table 14.2.1.2 and this reviewer.

3.2.1.4.2 Analyses of the Secondary Endpoints

The secondary endpoints would not have the full alpha of 0.05 (2-sided) because of the IAs conducted. As the SAP did not clearly specify the alpha level for the secondary endpoint, a conservative approach was to use the same alpha level of 0.017 (2-sided) specified for the primary endpoint.

The results for secondary endpoint could be confounded by whether the seizure being treated by the double-blind study drug was terminated and when the seizure was terminated. If the seizure

stopped later (a worse outcome), the next seizure may start later (a better outcome for the secondary endpoint of time to next seizure). If the seizure did not stop within 4 hours after the double-blind drug administration (a bad outcome), then the next seizure would not occur within 4 hours (a good outcome for the secondary endpoint of recurrence of seizure between 10 minutes to 4 hours). Therefore, the results for the secondary endpoints regarding the recurrence of seizure cannot be interpreted independent of the result for the treatment effect on the initial seizure.

Time to next Seizure with a start time > 10 minutes after study drug administration

A total of 50 subjects (37%) in the Nayzilam group and 31 subjects (46%) in the placebo group experienced a seizure between 10 minutes and 24 hours after double-blind study drug administration. The probability of having next seizure within 24 hours was 42% for Nayzilam versus 63% for placebo. The median time to next seizure was 12.1 hours for the placebo group, and not estimated for the Nayzilam group as less than half of the patients experienced a seizure between 10 minutes and 24 hours after double-blind study drug administration. The log rank test suggested a statistically significant difference between the two groups on the time to next seizure within 24 hours after study drug administration ($p=0.0124$). The estimated hazard ratio was 0.57 by a Cox model without covariates, indicating a risk reduction of 43% for Nayzilam.

Table 8: Time to Next Seizure with a Start Time at Least 10 Minutes After Double-Blind Study Drug Administration

	MDZ NS (N=134)	Placebo (N=67)
Occurrence of next seizure within 24 hours; n (%)	50 (37.3)	31 (46.3)
Median Time (hours) to next seizure	--	12.1
Probability of having next seizure in 24 hours (%) ^a	41.7	62.9
p-value ^a	0.0124	
Hazard ratio (MDZ NS:Placebo) (95% CI) ^b	0.57 (0.36, 0.89) p =0.0138	

Source: CSR Table 14.2.2.2.1.1 and this reviewer.

Subjects administered the second dose of study drug and not having a seizure before the administration of the second dose were censored at the time of the second dose.

^a Based on log-rank test; statistically significant at level 0.017.

^b Based on Cox model including treatment as the independent variable; statistically significant at level 0.017.

In the applicant's analysis, subjects administered the second dose of study drug who did not have a seizure before the administration of the second dose would be censored at the time of the second dose. This reviewer conducted an analysis in which all subjects administered the second dose of study drug were considered as events (failure) at the time of second dose. The results supported the treatment effect on the time to next seizure within 24 hours after study drug administration.

Table 9: Time to Next Seizure with a Start Time at Least 10 Minutes After Double-Blind Study Drug Administration (Reviewer's Analysis)

	MDZ NS (N=134)	Placebo (N=67)
Occurrence of next seizure within 24 hours n (%)	66 (49.3)	50 (74.6)
Median Time (hours) to next seizure	--	1.3
p-value ^a	0.0001	
Hazard ratio (MDZ NS:Placebo) (95% CI) ^b	0.50 (0.34, 0.72) p =0.0002	

Source: FDA reviewer.

Subjects who had been administered the second dose of study drug within 24 hours of double-blind study drug administration were assumed to have had a seizure.

^a Based on log-rank test; statistically significant at level 0.017.

^b Based on Cox model including treatment as the independent variable; statistically significant at level 0.017.

Recurrence of Seizure(s) between 10 minutes to 4 hours after study drug administration

A total of 51 subjects (38%) in the Nayzilam group and 40 subjects (60%) in the placebo group experienced recurrence of seizure(s) from 10 minutes to 4 hours after administration of double-blind study drug. The Fisher's Exact test suggested a statistically significant difference between the two group (p =0.0043; 2-sided). For this analysis, subjects who received the second dose of study drug within 4 hours of double-blind study drug administration were assumed to have had a recurrence of seizure (Table 10).

Table 10: Recurrence of Seizure(s) from 10 Minutes to 4 Hours After Double-Blind Study Drug Administration:

	MDZ NS (N=134)	Placebo (N=67)
Recurrence of seizure		
n (%)	51 (38.1)	40 (59.7)
95% CI	(29.8, 46.3)	(48.0, 71.4)
p-value from Fisher's Exact test	0.0043	
p-value from Chi-square test	0.0037	

Source: CSR Table 14.2.2.1, confirmed by this reviewer.

3.3 Evaluation of Safety

Please see the clinical review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age and Region

Subgroup analyses demonstrated consistent treatment effect on treatment success across subgroups by age, gender, race, and region, except for the Western Europe subgroup and Non-

white subgroup, for which there were insufficient subjects to provide a reliable estimate (Table 11).

Table 11: Treatment Success by Subgroup

Subgroup Category		Treatment Success n/N (%)		Difference (%)
		MDZ NS	Placebo	
Age group	< 18 years	3/5 (60.0)	2/5 (40.0)	20.0
	18 to < 65 years	69/129 (53.5)	21/62 (33.9)	19.6
Age group Median = 31.5 years	< Median	34/63 (54.0)	16/37 (43.2)	10.8
	≥ Median	38/71 (53.5)	7/30 (23.3)	30.2
Sex	Male	35/68 (51.5)	12/30 (40.0)	11.5
	Female	37/66 (56.1)	11/37 (29.7)	26.4
Race	White	66/125 (52.8)	23/65 (35.4)	17.4
	Non-white	6/9 (66.7)	0/2 (0)	66.7
Region	North America and similar	40/65 (61.5)	11/24 (45.8)	15.7
	Eastern Europe	27/49 (55.1)	10/36 (27.8)	27.3
	Western Europe	5/20 (25.0)	2/7 (28.6)	-3.6

Source: CSR Table 21.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

For the analysis after the pivotal study was terminated early, the sponsor proposed to use the significance level of 0.0085 (1-sided) planned for the final analysis at the maximum sample size. Had the study been planned with a sample size of 201 and with only two IAs as actually performed, the alpha left for the final analysis would be 0.013 (1-sided). However, to protect study integrity, unplanned changes should generally be avoided after unblinded analyses have been conducted. Based on the SAP prior to conducting the first interim analysis, a 1-sided p-value <0.0085 for the analysis with n =201 (close to the planned sample size of 204 for IA3) would cross the Pocock boundary either as the IA3 or as the final analysis. Therefore, the applicant's proposal was reasonable in this situation.

Fisher's exact test was proposed as the original planned sample size was relatively small. Along with the increase of the sample size and addition of 3 interim analyses, the applicant proposed using Chi-square test as the primary analysis. The Agency conveyed concerns with the major changes to the study design at a late stage (based on original plan) of the study. However, had the Agency agreed with the increased sample size of 240, Fisher's exact test would not be necessary, and the Chi-square test would be considered appropriate for the primary analysis. While Fisher's exact test is still valid for a larger sample size, it tends to be conservative due to the discreteness

of the outcome space. However, this is not much of an issue as the results from both analyses crossed the efficacy boundary.

The secondary endpoints would not have the full alpha of 0.05 (2-sided) because of the IAs conducted. As the SAP did not clearly specify the alpha level for the secondary endpoint, a conservative approach was to use the same alpha level of 0.017 (2-sided) specified for the primary endpoint.

The results for secondary endpoint could be confounded by whether the seizure being treated by the double-blind study drug was terminated and when the seizure was terminated. If the seizure stopped later (a worse outcome), the next seizure may start later (a better outcome for the secondary endpoint of time to next seizure). If the seizure did not stop within 4 hours after the double-blind drug administration (a bad outcome), then the next seizure would not occur within 4 hours (a good outcome for the secondary endpoint of recurrence of seizure between 10 minutes to 4 hours). Therefore, the results for the secondary endpoints regarding the recurrence of seizure cannot be interpreted independent of the result for the treatment effect on the initial seizure.

5.2 Collective Evidence

The primary efficacy analysis demonstrated a statistically significant larger proportion of subjects with treatment success in the Nayzilam group compared to the placebo group (difference =19%; 1-sided $p=0.0069$ compared to a significance level of 0.0085). The Nayzilam group had a higher proportion of subjects achieving each component of treatment success compared with the placebo group: termination of seizure(s) within 10 minutes; and no recurrence of seizures with start time > 10 minutes and < 6 hours. The effect on treatment success was robust and consistent across subgroups with sufficient subjects.

Nayzilam demonstrated a statistically significant treatment effect on both secondary endpoints. The time to next seizure with a start time >10 minutes of double-blind study drug administration was significantly longer in the Nayzilam group compared to the placebo group ($p=0.0124$ compared to a significance level of 0.017). The proportion of subjects with recurrence of seizure(s) from 10 minutes to 4 hours after double-blind study drug administration was significantly lower in the Nayzilam group (38%) compared with the placebo group (60%; $p=0.0043$ compared to a significance level of 0.017). The positive results for the secondary endpoint support the finding for the primary endpoint, although the point estimates and p-values for the secondary endpoint have limited interpretation, as discussed in the previous section.

5.3 Conclusions and Recommendations

The data overall provided statistical evidence to support the efficacy of Nayzilam 5 mg in treating subjects with seizure clusters.

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/s/

XIANG LING
02/01/2019 09:48:03 AM

KUN JIN
02/01/2019 10:34:59 AM
I concur with the review.

HSIEN MING J HUNG
02/01/2019 10:39:04 AM