Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: Not applicable		
Name of Active Ingredient: ASP6981		

SYNOPSIS

Title of Study: A Phase 1 Randomized, 2-way, Crossover Study to Assess the Safety, Tolerability, Pharmacodynamics and Pharmacokinetics of ASP6981 in Patients with Schizophrenia (6981-CL-0004)

Investigators/Coordinating Investigator: [redacted], MD (Site Number [redacted]); [redacted], MD (Site Number [redacted])

Study Center(s): Site Number [redacted] US; Site Number [redacted] US

Publication Based on the Study: Not applicable

Study Period: 1Q2018 to 2Q2018

Study Initiation Date (Date of First Enrollment): 22 Jan 2018

Study Completion Date (Date of Last Evaluation): 30 May 2018

Phase of Development: Phase 1

Objectives: The primary objectives of this study were to evaluate the safety and tolerability of ASP6981 in patients with schizophrenia and to evaluate the pharmacodynamics of ASP6981 in patients with schizophrenia as measured by cognitive function and neurophysiological biomarkers. The secondary objective of this study was to evaluate the pharmacokinetics of ASP6981 in patients with schizophrenia.

Methodology:

This was a randomized, patient- and investigator-blinded, placebo-controlled, 2-way crossover study to evaluate the safety, tolerability, pharmacodynamics and pharmacokinetics of ASP6981 in stable patients with schizophrenia on stable doses of up to 2 second generation antipsychotic drugs for at least 2 months prior to screening.

Patients were screened for up to 29 days prior to study drug administration on day 1 of period 1. Eligible patients were admitted to the clinical unit on day -3 of each period and randomized to 1 of 4 treatment sequences according to Table 1, receiving oral doses of 50 or 135 mg ASP6981 or matching placebo twice daily (every 12 hours) for 14 days (days 1 through 14) in each period (only in the morning of day 14). Each patient participated in 2 periods separated by a washout of 14 to 21 days (depending on the patient's availability to return to the clinical unit) between the last study drug administration in period 1 and the first study drug administration in period 2. Assessments of cognitive function and electroencephalogram (EEG) parameters were completed at baseline and on days 1, 7 and 14 of the period as well as the end-of-study visit (ESV). Patients were discharged from the clinical unit on day 15 of each period after all study procedures had been

performed. Patients returned to the clinical unit for the ESV 14 days (± 1 day) after washout from period 2 (or early termination).

Number of Patients (Planned, Enrolled and Analyzed):

With a planned total of 32 patients (8 patients per treatment sequence, 16 patients per dose level) an effect size of approximately 0.45 (a minimally observed difference of 0.45 with SD of the difference of 1.0) would have achieved statistical significance, using a 1-sided 5% significance level. The effect size was a standardized measure of the treatment effect relative to the pooled SD of the treatment groups.

In total, 24 of the 56 patients who provided written informed consent were screen failures. Subsequently, 32 (100%) patients (8 [100%] patients in each treatment sequence) were randomized.

A total of 31 (96.9%) randomized patients who took at least 1 dose of study drug were included in the safety analysis set, pharmacokinetic analysis set and pharmacodynamic analysis set Table 2. One (12.5%) patient in the 135 mg ASP6981 twice daily/135 mg placebo twice daily treatment sequence withdrew from the investigational period on day 36 (i.e., patient discontinued the treatment, investigational and follow-up periods).

Two (6.5%) patients discontinued treatment. One (12.5%) patient in the 50 mg placebo twice daily/50 mg ASP6981 twice daily treatment sequence withdrew from the study on day 27 (i.e., patient discontinued the treatment, investigational and follow-up periods). One (12.5%) patient in the 135 mg placebo twice daily/135 mg ASP6981 twice daily treatment sequence withdrew from the investigational period on day -1 in period 1 and did not receive any treatment (i.e., patient discontinued the investigational and follow-up periods). A major protocol deviation was reported for a patient who had received the incorrect number of capsules for the afternoon dose of placebo to match 135 mg ASP6981on day 3 of period 1. Although the patient did not receive the planned number of placebo capsules at the evening dose administration, the missed dose during the study was concluded not to have any impact on the study results.

Diagnosis and Main Criteria for Inclusion:

Male or female patients with a diagnosis of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition criteria, who were otherwise healthy patients between 18 to 55 years of age (inclusive at screening) were eligible for inclusion in this study. Patients were considered operationally stable if the patients had a low to moderate positive symptom score and moderate negative symptom score on the Positive and Negative Syndrome Scale (PANSS): no more than moderate rating on more than 2 PANSS items P1, P2, P3, P5, P6 (positive symptom section); no more than moderate severity rating for the negative items, N1, N2, N3, N4, N5, N6, N7 (negative symptom section); total PANSS score no more than 80. Patients must have been in ongoing maintenance antipsychotic therapy (i.e., second generation antipsychotics other than clozapine oral or depot), on a stable (≤ 25% change in dose) medication treatment regimen (approved oral or depot formulations of risperidone, quetiapine, olanzapine, ziprasidone, brexpiprazole, aripiprazole, paliperidone or lurasidone; up to 2 permitted on condition that the second medication was not required to control treatment resistance or intractable psychotic symptoms, as judged by the investigator) for ≥ 2 months for oral formulations or ≥ 3 months for depot formulations prior to screening, including concomitant psychotropic medications, such as, trazodone and zolpidem for sleep. Patients with a body mass index within the range of 18.5 to 40.0 kg/m^2 (inclusive) and weighed at least 50 kg (at screening), who provided written informed consent and to whom all of the inclusion and none of the exclusion criteria applied were eligible for inclusion in this study.

Patients were required to continue taking their prescribed antipsychotic drugs throughout the study at their usual dosing time and interval. Permitted antipsychotics included risperidone, quetiapine, olanzapine, ziprasidone, brexpiprazole, aripiprazole, paliperidone and lurasidone. Other than the antipsychotics listed, patients were not allowed to take any prescribed or nonprescribed drugs in the 2 weeks prior to study drug administration until the ESV, except for intermittent use of short-acting hypnotic agents (trazodone or zolpidem [no less than 12 hours prior to dosing]), use of medication for the treatment of hypertension, hyperlipidemia or diabetes mellitus, intermittent use of anticholinergic compounds, occasional use of acetaminophen (up to 2 g/day), hormonal contraceptives and hormone replacement therapy.

Test Product, Dose and Mode of Administration, Batch Numbers:

ASP6981 capsules were supplied as 1, 10 and 30 mg capsules.

- ASP6981 1-mg capsules
  - Lot numbers: 16100D and 16100E; re-evaluation date: 28 Feb 2018
- ASP6981 10-mg capsules
  - Lot number: 16101C; re-evaluation date: 28 Feb 2018
- ASP6981 30-mg capsules
  - Lot number: 17008B; re-evaluation date: 28 Feb 2018

Patients received oral doses of 50 or 135 mg ASP6981 or matching placebo twice daily (every 12 hours) for 14 days (days 1 through 14) in each period (only in the morning of day 14) with 240 mL of water or for doses requiring intake of ≥ 10 capsules with 360 mL of water.

In the morning on days 1 and 14 doses were administered under fasting conditions (overnight fast with last meal at least 10 hours predose and first meal at least 4 hours postdose, water was not allowed within 1 hour before and after dosing). A standard meal was served approximately 1 hour prior to dosing on the rest of the days. The meal did not interfere with planned study procedures and was served at a consistent time on each day.

Duration of Treatment:

Patients received their assigned treatment for 14 days in each period separated by a washout of 14 to 21 days.

Reference Product, Dose and Mode of Administration, Batch Numbers:

Placebo capsules were administered orally for doses matching doses of ASP6981. Placebo capsules had the same appearance and storage conditions as the ASP6981 capsules.

Placebo to match (PTM) ASP6981 was provided as 1, 10 and 30 mg capsules.

- PTM ASP6981 1-mg capsules
  - Lot number: 16099C; re-evaluation date: 28 Feb 2018
- PTM ASP6981 10-mg capsules
  - Lot number: 16099C; re-evaluation date: 28 Feb 2018
- PTM ASP6981 30-mg capsules
  - Lot number: 17007C; re-evaluation date: 28 Feb 2018

Criteria for Evaluation:

Safety Assessments

The primary safety parameters included the following:

- Nature, frequency and severity of adverse events (AEs)
- Vital signs (blood pressure, pulse and oral body temperature)
- Clinical laboratory tests (hematology, biochemistry [including serum prolactin] and urinalysis)
- Routine 12 lead electrocardiogram (ECG)
- Columbia - Suicide Severity Rating Scale (C-SSRS)
- Metabolic parameters (waist circumference, lipid panel and glucose level) and weight
- Movement disorder (Abnormal Involuntary Movement Scale [AIMS], Barnes Akathisia Rating Scale [BARS] and Simpson Angus Scale [SAS])

Pharmacodynamic Assessments

The primary pharmacodynamic parameters included the following:

- Cogstate: general composite score of executive function and memory cognitive testing (composed by Groton Maze Learning, One Back, One Card and International Shopping List tests) on day 14 of both periods 1 and 2
- EEG: electrophysiological measures of P300 (i.e., P3a) and Mismatch Negativity (MMN) on day 14 of periods 1 and 2

The secondary pharmacodynamic parameters included the following:

- Cogstate: composite score of attention cognitive testing (composed by Detection Test and Identification) on day 14 of periods 1 and 2
- EEG: electrophysiological measures of Auditory Steady State Response (ASSR), N100, P200, P300 (i.e., P3b) and resting state on day 14 of periods 1 and 2

Pharmacokinetic Assessments

The secondary pharmacokinetic parameters included the following:

- ASP6981 and its metabolites, if necessary (plasma):
  - Day 1 of periods 1 and 2: t_{max}, C_{max}, AUC_{12}
  - Day 7 of periods 1 and 2, day 13 of period 2: C_{trough}
  - Day 14 of periods 1 and 2: t_{max}, C_{max}, AUC_{tau}, C_{trough}

Statistical Methods:

Safety

AEs were coded using MedDRA (version 19.1). The number and percentage of patients with treatment-emergent adverse events (TEAEs), study drug-related TEAEs, TEAEs leading to withdrawal of treatment, study drug-related TEAEs leading to withdrawal of treatment and common TEAEs excluding serious adverse events (SAEs) were summarized by SOC, preferred term and treatment group.

Descriptive statistics (n, mean, SD, median, minimum and maximum) were used to summarize vital signs, laboratory tests, metabolic parameters (waist circumference, lipid panel and glucose level), weight, movement

disorders and changes from baseline. All AE data, vital signs data, laboratory data, the overall interpretation of routine 12-lead ECGs results, metabolic parameters, weight and results from the AIMS, BARS and SAS assessments were listed.

C-SSRS scores were calculated and summarized by ASP6981 treatment group and pooled placebo, and time point. C-SSRS results for patients who responded 'yes' to any question were listed.

Pharmacodynamics

The pharmacodynamic parameters from cognitive testing (specific Cogstate's panel for schizophrenia) and electrophysiological measures (ASSR, P3a, MMN, P3b, N100 and P200) were summarized using descriptive statistics (n, mean, SD, median, minimum and maximum) for each visit and time point and for change from the baseline of each period (day -1) to each postdose visit, if applicable. Pharmacodynamic endpoints were analyzed using an analysis of covariance (ANCOVA) model and period-specific baseline was used as covariate. Pairwise comparison between ASP6981 and matching placebo was made within the framework of the analysis of variance model for each dose level. Least squares means of treatments, treatment differences, standard errors and 90% confidence intervals of the differences were provided.

A sensitivity analysis was performed to assess the presence of carryover effect on each pharmacodynamic endpoint. Carryover effect term was added in the aforementioned ANCOVA model. In addition, overall carryover effect for Cogstate and EEG was evaluated separately.

Pharmacokinetics

Descriptive statistics (n, mean, SD, coefficient of variation [CV], geometric mean, geometric CV, median, minimum and maximum) were used to summarize plasma ASP6981 concentrations at each scheduled time point as well as pharmacokinetic parameters for days 1 and 14 of each period. Standard graphics including both linear and logarithmic-linear mean concentration-time profiles, mean concentration-time spaghetti (overlay) plots and individual patient concentration-time profiles were produced.

Attainment of steady state in repeated dosing was examined using visual inspection of individual patient profiles (spaghetti plot) of trough concentrations versus day overlaid with the mean profile.

There were no changes from the planned analyses.

Summary of Results/Conclusions:

Population:

Patient disposition and analysis sets can be found in Table 2 and demographic and baseline characteristics can be found in Table 3.

Pharmacokinetic/Pharmacodynamic Results:

Pharmacokinetic Results

After single dose administration, ASP6981 was rapidly absorbed with peak concentrations occurring 1 to 2 h after dosing (Day 1 C_{max}: 104 ng/mL and 253 ng/mL for ASP6981 50 mg and 135 mg, respectively) and declined by an order of magnitude by 12 h postdose. On day 14, quantifiable drug concentrations were observed at predose and also peaked 1 to 2 h after dosing (Day 14 C_{max}: 172 ng/mL and 494 ng/mL for ASP6981 50 mg and 135 mg, respectively). Based on C_{trough}, steady-state drug concentrations were observed by

day 13 (Day 13 $C_{trough:}$ 44.6 ng/mL and 136 ng/mL for ASP6981 50 mg and 135 mg, respectively). Exposure appeared to be dose proportional between 50 mg and 135 mg (Day 1 AUC_{12}: 321 h•ng/mL and 759 h•ng/mL for ASP6981 50 mg and 135 mg, respectively).

Pharmacodynamic Results:

Primary Endpoints

The primary pharmacodynamic endpoints of the Cogstate General Composite Score and electrophysiological measures on EEG of P300-P3a and MMN on day 14 of periods 1 and 2 did not indicate a difference between ASP6981 and placebo Table 4. The sensitivity analyses of the primary pharmacodynamic endpoints did not indicate any carryover effect from one period to the other.

Secondary Endpoints

The secondary pharmacodynamic endpoints of the Cogstate Composite Score of Attention Cognitive Testing and electrophysiological measures on EEG of ASSR, N100, P200, P300-P3b and resting state on day 14 of periods 1 and 2 did not indicate a difference between ASP6981 and placebo. The carryover effect for the parameter of EEG ASSR (Fz, evoked power, 1-500 msec [mean abs. power,] [uVolts2]) was statistically significant) for 135 mg ASP6981; the sensitivity analyses of the other secondary pharmacodynamic endpoints did not indicate any carryover effect from one period to the other.

Safety Results:

There were no deaths, other SAEs or TEAEs that led to withdrawal of treatment.

Overall, 14 TEAEs were reported for 9 (29.0%) patients who received ASP6981 during the conduct of the study (5 TEAEs reported for 3 [18.8%] patients after receiving 50 mg ASP6981 twice daily and 9 TEAEs reported for 6 [40.0%] patients after receiving 135 mg ASP6981 twice daily). Of these, a total of 7 TEAEs reported for 4 (12.9%) patients were considered by the investigator to be drug-related (3 TEAEs reported for 2 [12.5%] patients after receiving 50 mg ASP6981 twice daily and 4 TEAEs reported for 2 [13.3%] patients after receiving 135 mg ASP6981 twice daily).

There was no clinically relevant increase in the frequency of TEAEs in ASP6981- versus placebo-treated patients or with an increase in ASP6981 dose.

All TEAEs reported for patients who received study drug were considered by the investigator not to be serious in severity. The most commonly reported TEAE was somnolence within the SOC nervous system disorders (reported for 1 [3.2%] patient after receiving placebo twice daily, 1 [6.3%] patient after receiving 50 mg ASP6981 twice daily and 1 [6.7%] patient after receiving 135 mg ASP6981 twice daily) [Table 5].

AEs of special interest related to musculoskeletal disorders included musculoskeletal stiffness, akathisia and extrapyramidal disorder.

AEs of special interest related to abuse included nausea, musculoskeletal stiffness and headache.

Apart from the high Mg^{2+} and the low creatine kinase (CK) levels of 1 patient with a TEAE of musculoskeletal stiffness, there were no other potentially clinically relevant changes observed in any of the clinical laboratory analyses (hematology, biochemistry and urinalysis). No patients had laboratory values that met the potentially clinically significant criteria for hepatotoxicity or had concomitant elevations in alanine aminotransferase (ALT)

or aspartate aminotransferase (AST) with total bilirubin (TBL) or that required further liver function investigation.

No potentially clinically significant vital sign measurements were observed across treatment groups.

ECG abnormalities were observed across treatment groups and postdose time points; however, none these abnormalities was considered to be clinically significant.

No patient responded "yes" to any question on the C-SSRS.

There were no potentially clinically relevant changes observed in any of the metabolic parameters (waist circumference, lipid panel and glucose level) and weight measurements.

Slight mean changes in the AIMS, BARS and SAS results were recorded for all of the treatment groups from baseline to day 14 (predose).

CONCLUSIONS:

ASP6981 was absorbed rapidly, and exposure appeared to be dose-proportional from 50 to 135 mg, reaching steady-state by day 13.

The results of this study indicate that there was no difference between 50 or 135 mg ASP6981 and placebo in the primary, secondary or exploratory pharmacodynamic endpoints.

There were no deaths, other SAEs or TEAEs that led to withdrawal of treatment during the conduct of the study. The incidence of TEAEs was low and there was no consistent pattern that would indicate a treatment-related effect. All TEAEs reported for patients who received study drug were considered by the investigator not to be serious in severity. The most commonly reported TEAE was somnolence within the SOC nervous system disorders (reported for 1 [3.2%] patient after receiving placebo twice daily, 1 [6.3%] patient after receiving 50 mg ASP6981 twice daily and 1 [6.7%] patient after receiving 135 mg ASP6981 twice daily).

AEs of special interest related to musculoskeletal disorders included musculoskeletal stiffness, akathisia and extrapyramidal disorder. AEs of special interest related to abuse included nausea, musculoskeletal stiffness and headache.

Apart from the high Mg^{2+} and the low CK levels of 1 patient with a TEAE of musculoskeletal stiffness, there were no other potentially clinically relevant changes observed in any of the clinical laboratory analyses (hematology, biochemistry and urinalysis). No patients had laboratory values that met the potentially clinically significant criteria for hepatotoxicity or had concomitant elevations in ALT or AST with TBL or that required further liver function investigation.

No potentially clinically significant vital sign measurements were observed across treatment groups. ECG abnormalities were observed across treatment groups and postdose time points; however, none these abnormalities was considered to be clinically significant.

Overall, twice daily dosing of 50 and 135 mg ASP6981 was considered safe and well-tolerated in stable patients with schizophrenia.

Date of Report: 30 Oct 2018

Table 1 Study Treatment Assignments for Periods 1 and 2

Sequence	n	Period 1	Period 2
1	8	50 mg ASP6981	PTM 50 mg ASP6981
2	8	PTM 50 mg ASP6981	50 mg ASP6981
3	8	135 mg ASP6981	PTM 135 mg ASP6981
4	8	PTM 135 mg ASP6981	135 mg ASP6981

PTM: placebo to match

Table 2 Patient Disposition and Analysis Sets by Treatment Sequence

Analysis Set	50 mg ASP6981 bid/ 50 mg Placebo bid (n = 8) n (%) E	50 mg Placebo bid/ 50 mg ASP6981 bid (n = 8) n (%) E	135 mg ASP6981 bid/ 135 mg Placebo bid (n = 8) n (%) E	135 mg Placebo bid/ 135 mg ASP6981 bid (n = 8) n (%) E	Total (n = 32) n (%)
Randomized	8 (100)	8 (100)	8 (100)	8 (100)	32 (100)
Safety Analysis Set†	8 (100)	8 (100)	8 (100)	7 (87.5)	31 (96.9)
Pharmacokinetic Analysis Set‡	8 (100)	8 (100)	8 (100)	7 (87.5)	31 (96.9)
Pharmacodynamic Analysis Set§	8 (100)	8 (100)	8 (100)	7 (87.5)	31 (96.9)
Investigational Period Discontinuation	0	1 (12.5)	1 (12.5)	1 (12.5)	3 (9.4)
Treatment Discontinuation	0	1 (12.5)	1 (12.5)	0	2 (6.5)

E: number of events

† All randomized patients who took at least 1 dose of study drug.

‡ All randomized patients who took at least 1 dose of study drug and had sufficient plasma concentration data to facilitate derivation of at least 1 pharmacokinetic parameter.

§ All randomized patients who took at least 1 dose of study drug and had sufficient pharmacodynamic data to facilitate derivation of at least 1 pharmacodynamic parameter.

Source: End-of-Text Tables 12.1.1.1, 12.1.1.3 and 12.1.1.4

Table 3 Summary of Demographic and Baseline Characteristics by Treatment Sequence (All Randomized Patients)

Parameter Category/Statistics	50 mg ASP6981 bid/ 50 mg Placebo bid (n = 8)	50 mg Placebo bid/ 50 mg ASP6981 bid (n = 8)	135 mg ASP6981 bid/ 135 mg Placebo bid (n = 8)	135 mg Placebo bid/ 135 mg ASP6981 bid (n = 8)	Total (n = 32) n (%)
Sex, n (%)					
Male	6 (75.0)	5 (62.5)	8 (100.0)	6 (75.0)	25 (78.1)
Female	2 (25.0)	3 (37.5)	0	2 (25.0)	7 (21.9)
Ethnicity, n (%)					
Hispanic or Latino	2 (25.0)	0	1 (12.5)	1 (12.5)	4 (12.5)
Not Hispanic or Latino	6 (75.0)	8 (100.0)	7 (87.5)	7 (87.5)	28 (87.5)
Race, n (%)					
White	3 (37.5)	2 (25.0)	1 (12.5)	1 (12.5)	7 (21.9)
Black or African American	5 (62.5)	6 (75.0)	7 (87.5)	7 (87.5)	25 (78.1)
Asian	0	0	0	0	0
American Indian or Alaska Native	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Other	0	0	0	0	0
Age (years)					
Mean (SD)	39.1 (7.3)	36.5 (5.5)	41.4 (5.0)	44.9 (6.9)	40.5 (6.7)
Median	38.5	35.0	41.0	47.0	40.0
Min - Max	30 - 52	31 - 47	35 - 50	33 - 52	30 - 52
EudraCT Age Category					
≥ 18 years to ≤ 64 years	8 (100)	8 (100)	8 (100)	8 (100)	32 (100)
Weight (kg)					
Mean (SD)	84.66 (21.74)	88.16 (17.03)	89.43 (22.91)	88.74 (10.35)	87.75 (17.84)
Median	82.70	93.30	81.40	90.70	84.35
Min - Max	57.8 – 114.0	60.3 – 112.4	63.3 – 132.0	72.2 – 100.8	57.8 – 132.0
Height (cm)					
Mean (SD)	173.1 (11.4)	175.6 (10.6)	174.7 (11.3)	173.3 (8.3)	174.2 (10.0)
Median	176.5	176.6	176.2	171.9	176.0
Min - Max	150 - 187	157 - 193	152 - 190	163 - 184	150 - 193
BMI (kg/m^2)					
Mean (SD)	28.17 (6.29)	28.71 (5.88)	29.55 (7.86)	29.61 (3.33)	29.01 (5.79)
Median	27.78	30.40	27.34	29.61	29.74
Min - Max	19.7 – 36.4	21.1 – 38.9	20.4 – 40.0	24.4 – 35.1	19.7 – 40.00

BMI: body mass index (weight [kg]/height^2 [m^2]); Max: maximum; Min: minimum

Source: End-of-Text Table 12.1.2.1

Table 4 Primary Pharmacodynamic Endpoints at Baseline, Change from Baseline on Day 14 and Statistical Assessment After Multiple Dosing of ASP6981 or Placebo by Treatment Group (Pharmacodynamic Analysis Set)

Parameter Statistic		Placebo (n = 32)	ASP6981 50 mg (n = 15)	ASP6981 135 mg (n = 15)
Cogstate General Composite Score (Z-score)				
Baseline	Mean (SD)	-0.031 (0.687)†	-0.133 (0.681)	0.237 (0.661)
	Min - Max	-1.67 to 1.08	-1.63 to 1.12	-1.01 to 1.13
	Median	0.002	0.047	0.363
Day 14	Mean Change (SD)	0.116 (0.453)‡	0.106 (0.438)	0.070 (0.387)
	Min - Max	-0.86 to 1.01	-0.81 to 0.93	-0.75 to 0.56
	Median	0.140	0.115	0.185
Statistical Assessment	Placebo - LS Mean	--	0.0296§	0.205¶
	ASP6981 - LS Mean	--	-0.0359	0.270
	Estimated Difference (90% CI)	--	-0.0655 (-0.240; 0.109)	0.0647 (-0.222; 0.352)
	Effect Size	--	-0.255	0.144
EEG Passive Auditory Oddball Paradigm, Fz, P300-P3a (uVolts)				
Baseline	Mean (SD)	2.191 (0.923)††	2.062 (1.042)	2.465 (1.437)¶
	Min – Max	0.17 to 4.17	0.35 to 4.00	0.23 to 4.72
	Median	2.088	1.847	2.302
Day 14	Mean Change (SD)	-0.040 (0.820)‡‡	-0.137 (1.327)	-0.590 (1.546)¶
	Min – Max	-2.29 to 1.64	-2.21 to 1.97	-3.80 to 0.92
	Median	0.080	0.175	-0.025
Statistical Assessment	Placebo - LS Mean	--	2.16	2.11¶
	ASP6981 - LS Mean	--	1.95	1.84
	Estimated Difference (90% CI)	--	-0.208 (-0.714, 0.297)	-0.271 (-0.926, 0.384)
	Effect Size	--	-0.276	-0.339
EEG Passive Auditory Oddball Paradigm, Fz, Mismatch Negativity (Mean Amp.) (uVolts)				
Baseline	Mean (SD)	-2.658 (1.584)††	-2.551 (1.627)	-2.714 (1.703)¶
	Min - Max	-6.21 to -0.53	-5.74 to -0.46	-5.21 to -0.67
	Median	-2.938	-2.140	-2.133
Day 14	Mean Change (SD)	0.066 (0.766)‡‡	-0.099 (0.666)	-0.355 (1.493)¶
	Min – Max	-1.22 to 1.51	-1.27 to 1.16	-2.47 to 2.20
	Median	-0.007	0.052	-0.216
Statistical Assessment	Placebo - LS Mean	--	-2.45	-2.71¶
	ASP6981 - LS Mean	--	-2.64	-3.13
	Estimated Difference (90% CI)	--	-0.187 (-0.567, 0.192)	-0.420 (-0.936, 0.0963)
	Effect Size	--	-0.340	-0.579

All randomized patients who took at least 1 dose of study drug and who had sufficient pharmacodynamic data to facilitate derivation of at least 1 pharmacodynamic parameter.

The baseline refers to the last observation prior to first dose in the respective treatment period.

Z-score = (x – mean [x at baseline]) / SD (x at baseline) × multiplicand.

Assessment based on an analysis of covariance with sequence, treatment, period and period specific baseline as fixed effects and patient as a random effect.

Effect size = mean within patient difference / standard deviation of residual error

Footnotes continued on next page

CI: confidence interval; EEG: electroencephalogram; LS: least squares; n: number of patients with nonmissing observation in the period of the treatment; Max: maximum; Min: minimum

† n = 31

‡ n = 30

§ n = 16

¶ n = 14

†† n = 29

‡‡ n = 28

Source: End-of-Text Tables 12.5.1, 12.5.2, 12.5.3.1 and 12.5.3.2

Table 5 Incidence of Treatment-emergent Adverse Events by Treatment (Safety Analysis Set)

MedDRA v19.1 System Organ Class Preferred Term	Placebo (n = 31) n (%)	ASP6981 50 mg bid (n = 16) n (%)	ASP6981 135 mg bid (n = 15) n (%)	ASP6981 Total (n = 31) n (%)
Overall	**6 (19.4)**	**3 (18.8)**	**6 (40.0)**	**9 (29.0)**
Gastrointestinal Disorders	**0**	**0**	**2 (13.3)**	**2 (6.5)**
Dry mouth	0	0	1 (6.7)	1 (3.2)
Nausea	0	0	1 (6.7)	1 (3.2)
Injury, Poisoning and Procedural Complications	**0**	**0**	**1 (6.7)**	**1 (3.2)**
Conjunctival laceration	0	0	1 (6.7)	1 (3.2)
Musculoskeletal and Connective Tissue Disorders	**0**	**1 (6.3)**	**0**	**1 (3.2)**
Musculoskeletal stiffness	0	1 (6.3)	0	1 (3.2)
Pain in extremity	0	1 (6.3)	0	1 (3.2)
Nervous System Disorders	**5 (16.1)**	**1 (6.3)**	**2 (13.3)**	**3 (9.7)**
Somnolence	1 (3.2)	1 (6.3)	1 (6.7)	2 (6.5)
Headache	1 (3.2)	0	1 (6.7)	1 (3.2)
Akathisia	2 (6.5)	0	0	0
Dizziness	0	1 (6.3)	0	1 (3.2)
Extrapyramidal disorder	1 (3.2)	0	0	0
Psychiatric Disorders	**1 (3.2)**	**1 (6.3)**	**2 (13.3)**	**3 (9.7)**
Anxiety	0	0	1 (6.7)	1 (3.2)
Insomnia	0	0	1 (6.7)	1 (3.2)
Nightmare	0	1 (6.3)	0	1 (3.2)
Restlessness	1 (3.2)	0	0	0
Respiratory, Thoracic and Mediastinal Disorders	**0**	**0**	**1 (6.7)**	**1 (3.2)**
Cough	0	0	1 (6.7)	1 (3.2)

All randomized patients who took at least 1 dose of study drug.

A treatment-emergent adverse event was defined as an adverse event with onset at any time from first dosing until last scheduled procedure.

Sorting order: ascending order by SOC code and descending by the number of patients of ASP6981 group by preferred term. In case of ties, ascending order by preferred term was applied.

Source: End-of-Text Table 12.6.1.2