Name of Sponsor/Company: Astellas Pharma Global Development, Inc. (APGD)		
Name of Finished Product: Not applicable		
Name of Active Ingredient: ASP0777 drug substance		

SYNOPSIS

Title of Study: A Phase 1b, Multicenter, Double-Blind, Randomized, Placebo-Controlled, Sequential Dose Study of the Safety and Tolerability of ASP0777 in Subjects with Alzheimer's Disease (AD) on Donepezil – ISN 0777-CL-0030

Investigators: [redacted] MD [redacted] PhD

Study Centers: [redacted] Hallandale Beach, FL 33009 [redacted] San Diego, CA 92103

Publication Based on the Study: Results of this study have not been published as the time of report preparation.

Study Period:

Study Initiation Date (Date of First Randomization): June 16, 2011

Study Completion Date (Date of Last Evaluation): November 4, 2011

Phase of Development: Phase 1b

Objectives: The primary objective of this study was to assess the safety and tolerability of ASP0777 in patients with AD taking a stable dose of donepezil.

The secondary objective was to assess the pharmacokinetics of ASP0777 in AD patients who were taking a stable dose of donepezil.

Exploratory objectives were [redacted]

Methodology: This was the first clinical study in patients diagnosed with AD. This study was designed to explore overall safety and tolerability of ASP0777 in a limited number of patients with AD who were being treated with donepezil (Aricept®). The study enrolled 2 sequential dose cohorts:

Cohort 1: 20 patients randomized 3:1 (ASP0777 10 mg: matching placebo) and dosed once daily for 6 weeks.

Cohort 2: 40 patients randomized 3:3:2 to receive 1 of 3 different regimens:

- ASP0777 20 mg once daily for 6 weeks
- ASP0777 10 mg once daily for 1 week followed by ASP0777 20 mg once daily for 5 weeks
- Placebo matching ASP0777 10 mg tablet (2 tablets once daily) for 6 weeks

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Due to the unknown effects of combining ASP0777 with donepezil in the target population, the study included a confinement period of 14 days for each cohort. Eligible patients were admitted to the study clinic on day -1 and remained confined to the clinic for 14 days. After completion of the confinement period, patients were released from the clinic and completed the study dosing period as an outpatient. Study visits were conducted weekly until week 6 and a last follow-up visit was held 2 weeks after the final visit.

After all randomized patients in Cohort 1 completed day 14 study procedures or end of treatment (ET) procedures (if day 14 was not achieved), a decision could then be made whether to proceed with dose escalation and if enrollment of Cohort 2 should occur. Enrollment could begin in Cohort 2 only after all patients in Cohort 1 had completed treatment. Participants in the dose escalation discussion included the Astellas Medical Monitor, a physician from Astellas Pharmacovigilance, the Astellas Global Clinical Pharmacology and Exploratory Development (GCPED) and the principal investigators.

Number of Patients (Planned, Enrolled and Analyzed):

Planned: 60 eligible patients with AD (20 in Cohort 1 and 40 in Cohort 2)

Enrolled: 60 eligible patients with AD (20 in Cohort 1 and 40 in Cohort 2)

Analyzed: Three populations were defined for analysis.

- Safety Analysis Set (SAF): All enrolled patients who received at least 1 dose of study drug: 60 patients (20 in Cohort 1 and 40 in Cohort 2).
- Pharmacokinetics Analysis Set (PKAS): All patients from the SAF whose pharmacokinetic data were adequate for the calculation of primary pharmacokinetic parameters: 59 patients (20 in Cohort 1 and 39 in Cohort 2). One patient in the ASP0777 10/20 mg group decided to discontinues treatment and was subsequently lost to follow-up.
- Pharmacodynamics Analysis Set (PDAS): All patients from the SAF whose pharmacodynamic data were adequate for the calculation of pharmacodynamic parameters: 60 patients (20 in Cohort 1 and 40 in Cohort 2).

Diagnosis and Main Criteria for Inclusion: Eligible study participants were male and female patients at least 50 years of age with a diagnosis of "probable" AD as defined by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) criteria with a MMSE score of 18 to 26 and who had used donepezil for at least 3 months prior to screening with the current dose stable for at least 6 weeks prior to screening. Patients had adequate cognitive, hearing, vision and language skills to complete the requirements of the protocol, were able to ingest oral tablets and were medically stable as determined by the investigator through interview, physical examination and laboratory evaluation. In order to enter the study, the patient had a reliable adult residing with him/her during the outpatient portion of the study who would monitor and assist with dosing while the patient

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was not in the study clinic and assist the patient to thoroughly report all signs and symptoms during the study and who would attend all outpatient visits.

Test Product, Dose and Mode of Administration, Batch Numbers: Donepezil was to be continued according to the dosing regimen in place at study entry. The sponsor did not supply the donepezil.

The test drug was ASP0777 and was supplied by the sponsor in 10 mg strength tablets. ASP0777 was a round, light yellow film coated tablet containing ASP0777 drug substance, D-mannitol, hydroxypropylcellulose, sodium starch glycolate and magnesium stearate, and was coated with OPADRY®.

Cohort 1: One group of 15 patients received ASP0777 10 mg once daily for 6 weeks.

Treatment	*Lot (expiry date)*
ASP0777 10 mg tablets	09209A (30 Nov 2012)

Cohort 2: One group of 15 patients received ASP0777 20 mg once daily for 6 weeks and 1 group of 15 patients received ASP0777 10 mg once daily for 1 week followed by ASP0777 20 mg once daily for 5 weeks

Treatment	*Lot (expiry date)*
ASP0777 10 mg tablets	09209A (30 Nov 2012)

Duration of Treatment (or Duration of Study, if applicable): The planned duration of the study for each patient was approximately 8 weeks.

Reference Product, Dose and Mode of Administration, Batch Numbers: The comparator was a placebo matching the 10 mg ASP0777 tablet and was supplied by the sponsor. The placebo was a round, light yellow film coated tablet identical in size, color and appearance to the ASP0777 tablet and contained D-mannitol, hydroxypropylcellulose, sodium starch glycolate and magnesium stearate and was coated with OPADRY®.

Cohort 1: 5 patients received placebo matching ASP0777 10 mg (2 tablets daily) for 6 weeks.

Treatment	*Lot (expiry date)*
ASP0777 3/10 mg placebo tablets	09205A (30 Nov 2012)

Cohort 2: 10 patients received placebo matching the ASP0777 10 mg tablet daily for 6 weeks.

Treatment	*Lot (expiry date)*
ASP0777 3/10 mg placebo tablets	09205A (30 Nov 2012)

Criteria for Evaluation:

Pharmacokinetics: Blood collection for pharmacokinetic assessment of ASP0777 concentrations was performed as follows: days 1 to 12: 3 hours post dose; day 13: predose (i.e., done within 30 minutes prior to dose) and 1, 3, 6 and 12 hours postdose; predose (i.e., done within 30 minutes prior to dose) on day 14, week 3, week 4, week 5, week 6/end of treatment (ET). Pharmacokinetic parameters were ASP0777 AUC_{tau}, C_{max}, C_{min}, t_{max} on day 13.

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Pharmacodynamics: Exploratory variables were [redacted]

Safety and Tolerability: Variables were adverse events, vital signs, clinical laboratory tests (hematology, chemistry and urinalysis), 12-lead electrocardiograms (ECGs), physical examinations and Cornell Scale for Depression in Dementia (CSDD) and Columbia-Suicide Severity Rating Scale (C-SSRS) assessments. For all variables, the last assessment prior to the first dose of study drug was the baseline to which all post dose assessments were compared.

Adverse events: Any signs or symptoms present prior to the first dose of study drug were recorded as baseline conditions or medical history. Adverse event collection began at the time of the first dose of study drug on day 1 and continued through the duration of the study including the 2-week follow-up visit. Baseline conditions that worsened during the study were to be recorded as adverse events. Adverse events beginning after a patient completed study procedures at the 2-week follow-up were not captured. All observed or spontaneously reported serious adverse events occurring from first dose up to 30 days inclusive after last dosing were to be captured and reported.

Clinical laboratory evaluations: Serum chemistry, hematology and urinalysis were performed at screening and on day -1, day 7, day 14 and week 6/ET. If an increase of serum aminotransferases to > 3 X the upper limit of normal (ULN) or bilirubin > 2 X ULN, at least all 4 of the usual serum hepatic measures (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and total bilirubin) were to be repeated within 48 to 72 hours of notification of the test results. Patients were to be asked if they had any symptoms suggestive of hepatobiliary dysfunction.

Vital signs: Blood pressure and heart rate were obtained prior to dosing daily while confined to clinic and on study visit days after discharge. Height, weight and oral temperature were captured at screening only.

12-lead ECG: A 12-lead ECG was performed at screening and on day -1, day 7, day 14 and week 6/ET. The ECGs were read by a physician at the clinical unit, who initialed and dated and provide his/her clinical interpretation on each rhythm strip. The results (normal, abnormal not clinically significant, abnormal clinically significant) were recorded in the electronic case report form.

CSDD and C-SSRS: The CSDD and C-SSRS were to be completed by an experienced rater at the screening, day -1, day 7, day 14 and week 6/ET visits. The CSDD assessed mood-related signs, behavioral and ideational disturbances and physical signs. The C-SSRS assessed suicidal ideation (presence, intensity) and suicidal behavior (reporting of any suicide attempt, nonsuicidal self-injurious behavior, aborted attempt, preparatory acts or behavior).

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Statistical Methods: All analyses were performed according to study cohort and treatment (placebo or ASP0777 dose) and all data from patients who received placebo in both study cohorts were pooled for analyses. For continuous variables, descriptive statistics included the number of patients (n), mean, SD, median, minimum and maximum. In addition, for continuous pharmacokinetic parameters, the coefficient of variation (CV) and the geometric mean (GM) were calculated. For categorical data, frequencies and percentages were displayed. Percentages by categories were based on the number of patients with no missing data. Events and assessments were identified with the treatment to which the patient was randomized on day 1 in each cohort. All data processing, summarization and analyses were performed using SAS® version 9.1.

Patient Disposition: The number and percentage of patients enrolled, completed, discontinued study and reason(s) for discontinuation were tabulated.

Demographics: Demographics, other baseline characteristics and prior and concomitant medications were provided for the SAF and PKAS by treatment and overall. Descriptive statistics were used to summarize continuous demographic variables age, weight, height and BMI. Number and percentage of patients in each category were used to summarized demographic variables sex, race and ethnicity.

Pharmacokinetics: Individual patient plasma ASP0777 concentrations were used to derive the pharmacokinetic parameters as listed below using a noncompartmental method using WinNonlin software (Pharsight Corp, Mountain View, CA, USA) version 5.3.

Descriptive statistics were used to summarize plasma ASP0777 concentrations at each scheduled time point and plasma ASP0777 pharmacokinetic parameters on day 13 for each ASP0777 dose group. Graphics for plasma ASP0777 concentrations, including mean concentration-time profiles, individual patient concentration-time profiles and overlay ("spaghetti") plots of concentration-time profiles were produced for day 13. The mean and overlay plots were separated by treatment.

An analysis of variance (ANOVA) on natural logarithm transformed ASP0777 AUC_{tau}, C_{max} and C_{min} was performed with treatment as a fixed effect and patient as a random effect. The least squares geometric means (LSGM) ratio and the corresponding 90% confidence intervals (CIs) of the ASP0777 20 mg and 10/20 mg dose groups relative to the ASP0777 10 mg dose group were provided.

Pharmacodynamics: MMSE total baseline and week 6/ET scores and change from baseline at week 6/ET were summarized descriptively for each study group. Descriptive summaries of NPI assessment category total score, corresponding caregiver score and their change from baseline were provided by treatment.

An analysis of covariance (ANCOVA) was performed on MMSE total score with treatment, visit, treatment by visit as fixed effects, patient as a random effect and baseline MMSE total score as a covariate. Based on this analysis, least squares mean treatment difference from placebo and corresponding 95% CIs were provided for each visit by treatment.

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An ANCOVA was performed on NPI total score with treatment, visit, treatment by visit as fixed effects, patient as a random effect and baseline NPI total score as a covariate. Based on this analysis, least squares mean treatment difference from placebo and corresponding 95% CIs were provided for each visit by treatment. Similar analysis was provided for the caregiver distress score within an NPI assessment category.

Safety:

Adverse Events: Verbatim reports of adverse events were reviewed by a physician and the signs and symptoms were coded according to MedDRA version 12.1. Every verbatim term was matched with the appropriate preferred term. Adverse events that started after the first intake of the study drug through the week 6 of the study and including the 2-week follow-up or ET were considered treatment-emergent adverse events. Any treatment-emergent adverse event with a relationship category of possible or probable (as determined by the investigator) was considered as related to study drug.

The number and percentage of patients with treatment-emergent adverse events were summarized for each treatment by system organ class and preferred term. Similar summaries were presented for treatment-emergent adverse events related to study drug, treatment-emergent adverse events by severity, treatment-emergent adverse events related to study drug by severity, treatment-emergent adverse events leading to permanent discontinuation of study drug and treatment-emergent adverse events related to study drug leading to permanent discontinuation of study drug. An overview of treatment-emergent adverse events in the above categories was also provided.

Clinical Laboratory Evaluations: Quantitative laboratory test results and their changes from baseline were summarized descriptively for each treatment at each scheduled time point. Laboratory results were classified as low, normal, or high according to the laboratory supplied reference ranges. Shift tables of reference range changes from baseline to post baseline assessment times were presented for each treatment.

Vital Signs: Descriptive statistics were used to summarize vital signs (i.e., systolic blood pressure, diastolic blood pressure and pulse rate) and their corresponding changes from baseline for each treatment by scheduled time point.

12-lead ECGs: The number and percentage of patients with normal, and abnormalities with clinically significant, and not clinically significant ECG examinations during treatment were tabulated for each treatment at scheduled time point.

CSDD Scores: Descriptive summaries of CSDD total score and its change from baseline were provided by treatment. CSDD total score was the sum of individual patient questionnaire scores at each assessment.

An ANCOVA was performed on CSDD total score with treatment, visit, treatment by visit as fixed effects, patient as a random effect and baseline CSDD total score as a covariate. Based on this analysis, least squares mean treatment difference from placebo and corresponding 95% CIs were provided for each visit by treatment.

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C-SSRS: The frequency and percentages were used to summarize the individual questionnaire responses within suicidal ideation and suicidal behavior subcategories.

- An event of suicidal ideation was defined based on "yes" response to any one of the questions 1 through 5 on the suicidal ideation sub category of the C-SSRS at each assessment. The observed proportion difference and an exact 95% CI of the difference for each treatment relative to placebo were provided.
- An event of suicidal behavior was defined based on "yes" response to the final assessment of suicidal behavior subcategory of the C-SSRS at each assessment. The observed proportion difference and an exact 95% CI of the difference for each treatment relative to placebo were provided.
- An event of suicidality was defined if an event of suicidal ideation or behavior was present at each assessment. The observed proportion difference and an exact 95% CI of the difference for each treatment relative to placebo were provided.

Summary of Results/Conclusions:

Subject Disposition: As planned in the protocol, a total of 60 patients were enrolled in the study (20 in cohort 1 and 40 in cohort 2 after patients in cohort 1 completed the week 6/ET procedures) [Figure 1]. Six patients in cohort 2 (2 in the placebo group and 4 in the 10/20 mg ASP0777 group) discontinued study for the reasons shown in Figure 1.

Demographics and Other Baseline Characteristics: The total study population and each dose group was primarily female (73.3% total), white (95.0% total) and Hispanic or Latino (95.0% total) [Table 1]. The mean age was 66.4 years (range 51 to 83 years). The 4 dose groups were comparable with respect to age, race, ethnicity and mean BMI.

In addition to their primary diagnosis of AD, all patients had medical/surgical history positive for other health and/or surgical conditions and all patients had at least 1 concurrent ongoing health condition with the exception of a [redacted] patient with no other reported health history in the ASP0777 20 mg dose group. The most common ongoing conditions were eye disorders (the most common was presbyopia reported for 46.7% of patients in the placebo group and ASP0777 10 mg and 20 mg dose groups).

At both screening and day -1, the 4 groups of patients were similar in terms of baseline MMSE scores: ranging from 19 to 26 in placebo recipients, from 18 to 26 in the ASP0777 10 mg dose group, from 18 to 26 in the ASP0777 20 mg dose group and from 20 to 26 in the ASP0777 10/20 mg dose group.

Exposure to Study Drug: Each of the 4 dose regimens consisted of daily dosing for 6 weeks (42 days). The same dose was given once daily for 6 weeks except in the 10/20 mg dose group where 10 mg was given for 1 week followed by 20 mg for 5 weeks. Although titration was allowed in the event of intolerance for patients in Cohort 2, it was not necessary to down titrate the 20 mg dose in any patient during the study.

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The mean daily dose received by each of the 3 ASP0777 dose groups was consistent with the protocol defined regimen. Exposure to study drug in terms of mean number of dosing days was 41.5 days for the 10 mg ASP0777 in cohort 1 and was 37.3 days in the 10/20 mg dose group and 42.4 days in the 20 mg dose group in Cohort 2.

Pharmacokinetic/Pharmacodynamic Results:

Pharmacokinetics Results: Mean plasma ASP0777 concentrations determined from serial blood samples on day 13 following the 20 mg dose in both the ASP0777 20 mg and ASP0777 10/20 mg groups were increased approximately 100% at each time point versus the 10 mg dose. These findings indicate plasma concentrations were dose dependent and were not affected by coadministration of donepezil.

Exposure parameters (mean C_{max}, C_{min} and AUC_{tau}) were increased approximately 100% following the ASP0777 20 mg dose in both the ASP0777 20 mg and ASP0777 10/20 mg groups compared to the ASP0777 10 mg dose [Table 2]. Evaluation of the 90% CI of the LS mean ratio for AUC_{tau}, C_{max} and C_{min} in the ASP0777 20 mg and 10/20 mg dose groups versus the ASP0777 10 mg dose group indicated significantly higher ASP0777 exposure following the higher dose [Table 3].

Pharmacodynamic Results: [redacted]

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[redacted] [Table 4].

Safety Results: Administration of ASP0777 in conjunction with donepezil was safe in this patient population and was generally well tolerated.

Adverse Events: The occurrence, type and character of treatment-emergent adverse events were similar during the 6-week treatment period with ASP0777 10 mg, 20 mg and the 10/20 mg. No patient required down-titration from the 20 mg dose of ASP0777.

Most treatment-emergent adverse events in all 4 groups were nervous system disorders consisting primarily of dizziness (13.3% to 40% of patients) and headache (20% to 26.7% of patients) [Table 5]. All cases of dizziness in all 4 groups and all except 3 cases of headache (1 placebo recipient and 1 patient each in the ASP0777 10 mg and 20 mg dose groups) were considered study drug related by the investigator.

All treatment-emergent adverse events reported during the study were categorized as mild or moderate intensity with the exception of severe dizziness in 1 patient in the placebo group (onset day 23 and resolution on day 25) and severe ataxia in 1 patient in the the ASP0777 10/20 mg dose group (onset day 8 and resolution in 1 hour). The severe dizziness was attributed a possible relationship to study drug and the severe ataxia was attributed a probable relationship to study drug by the investigator.

No death or other serious treatment-emergent adverse event occurred during the study. Adverse events were the reason for discontinuation of 2 patients (1 in the placebo group and 1 in the 10/20 mg ASP0777 group):

- Moderate vitreous hemorrhage in the left eye on day 2 that was considered not related to study drug by the investigator and moderate hypertension on day 3 that was attributed a possible relationship to study drug by the investigator were the reasons for withdrawal of a [redacted] in the placebo group. The last dose was on day 3.
- One patient [redacted] in the ASP0777 10/20 mg dose group discontinued dosing on day 33 as result of moderate benign prostatic hypertrophy that was considered not related to study drug by the investigator.

Adverse Events of Special Interest: Mean CSDD scores in the 4 groups varied from 1.5 to 3.7 at baseline and from 0.9 to 3.5 at week 6/ET. All mean changes in the mean score over time were small decreases (varying from -0.1 to -1.9 across the 4 groups) with the exception of week 6/ET in the placebo group (mean increase of 0.1). The maximum individual scores were no more than 9 in any group indicating that none of the patients in the 4 groups had an assessment score indicative of probable depression (score > 12). Statistical analysis of CSDD assessments indicated no statistically significant difference in the total score in any ASP0777 group versus the placebo group at any time point with the exception of day 14 in the ASP0777 20 mg dose group [Table 6].

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With respect to the C-SSRS suicidal ideation assessment, there were 2 positive answers to the statement "Wish to be dead". Both were at baseline and in the ASP0777 20 mg dose group. There were no positive answers to the assessment of suicidal behavior at any time point during the study beginning at baseline.

Other Safety Variables: There was no observed adverse effect on vital signs, clinical laboratory values or ECGs further indicating the safety of coadministration of ASP0777 and donepezil.

CONCLUSIONS:

Safety and tolerability data in this study of ASP0777 in AD patients who were taking a stable dose of donepezil support initiation therapy with 20 mg ASP0777 without titration:

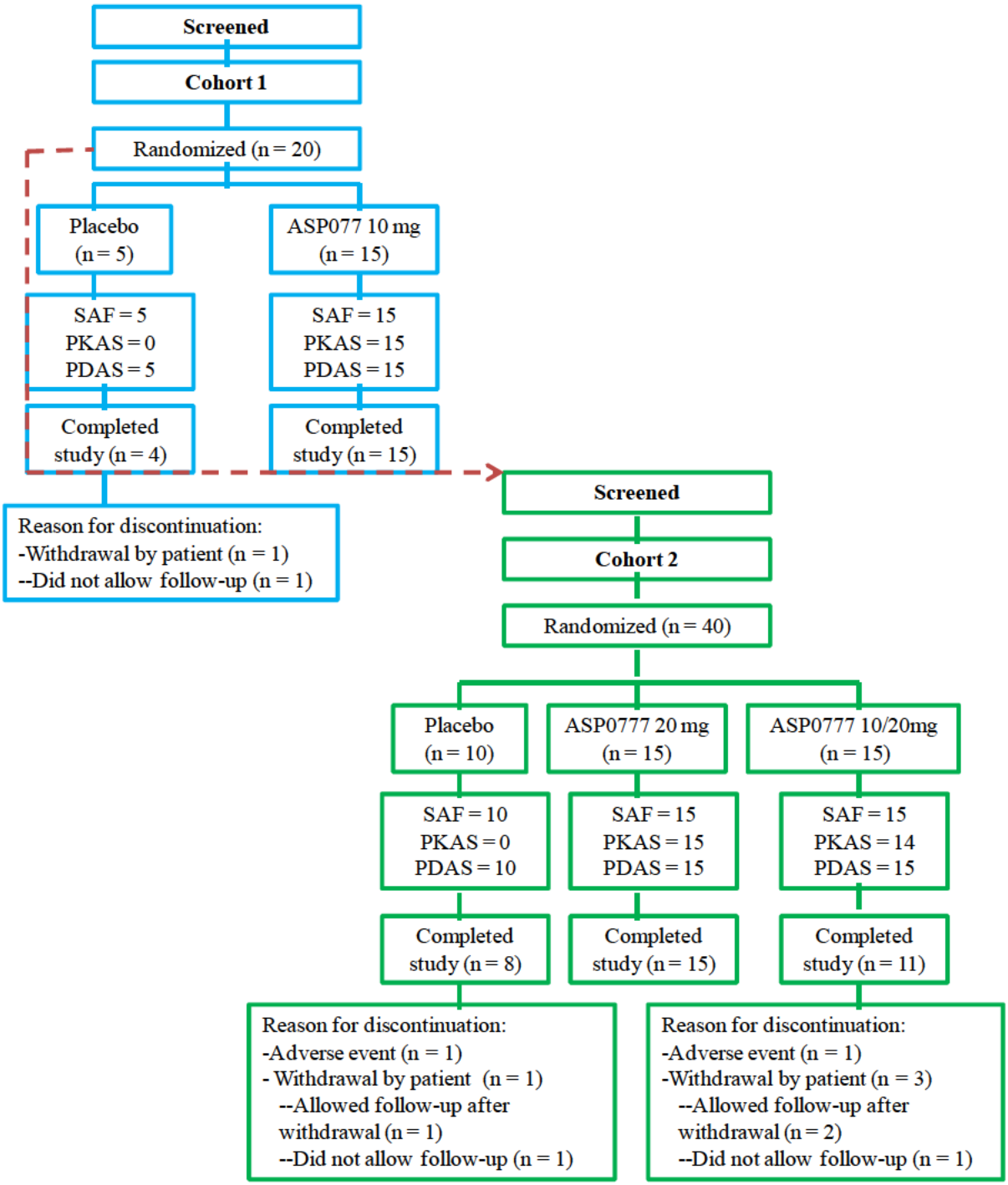
- Addition of ASP0777 to donepezil in this population of 45 AD patients revealed no significant safety or tolerability issues at any dose tested.
- The adverse event profile of ASP0777 in AD patients taking donepezil was similar to that seen in previous phase 1 studies in healthy volunteers with nervous system disorders being the most common and mild, transient dizziness the most frequently reported treatment-emergent adverse event.
- Although allowed at the 20 mg dose if necessitated by adverse events and tolerability assessment, ASP0777 dose reduction was not required in any patient during the study.

Pharmacokinetic data indicated ASP0777 plasma concentrations over 24 hours post dose and exposure parameters were dose-proportional in patients taking a stable dose of donepezil.

[redacted]. While there was no observed improvement, these data showed the clinical status of patients in this study was not adversely affected by the addition of ASP0777 to donepezil treatment for AD.

Date of Report: August 17, 2012

Figure 1 Patient Disposition by Treatment



Safety Analysis Set (SAF): All enrolled patients who received at least 1 dose of study drug. The SAF was used for summaries of demographic and baseline characteristics and all safety and tolerability-related variables.

Pharmacokinetics Analysis Set (PKAS): All patients from the SAF whose pharmacokinetic data were adequate for the calculation of primary pharmacokinetic parameters.

Pharmacodynamics Analysis Set (PDAS): All patients from the SAF whose pharmacodynamic data were adequate for the calculation of pharmacodynamic parameters.

Source: Table 12.1.1.1, Table 12.1.1.2 and Table 12.1.1.3

Table 1 Demographic Characteristics

Parameter Category	Placebo (n = 15)	ASP0777† 10 mg (n = 15)	ASP0777† 20 mg (n = 15)	ASP0777† 10/20 mg (n = 15)	Total (n = 60)
Sex n (%)					
Male	4 (26.7)	6 (40.0)	3 (20.0)	3 (20.0)	16 (26.7)
Female	11 (73.3)	9 (60.0)	12 (80.0)	12 (80.0)	44 (73.3)
Race n (%)					
White	14 (93.3)	14 (93.3)	15 (100.0)	14 (93.3)	57 (95.0)
Black or African American	0	1 (6.7)	0	1 (6.7)	2 (3.3)
American Indian or Alaska native	1 (6.7)	0	0	0	1 (1.7)
Ethnicity n (%)					
Not Hispanic or Latino	1 (6.7)	0	1 (6.7)	1 (6.7)	3 (5.0)
Hispanic or Latino	14 (93.3)	15 (100.0)	14 (93.3)	14 (93.3)	57 (95.0)
Age (Years)					
n	15	15	15	15	60
Mean (SD)	68.2 (8.25)	67.7 (7.90)	65.1 (10.44)	64.4 (7.19)	66.4 (8.47)
Minimum – Maximum	51 – 81	53 – 80	51 – 83	56 – 78	51 – 83
Median	68.0	67.0	63.0	66.0	66.0
Weight (kg)					
n	15	15	15	15	60
Mean (SD)	71.05 (9.828)	79.81 (8.994)	71.23 (12.262)	68.30 (10.424)	72.60 (11.071)
Minimum – Maximum	55.9 – 85.4	68.6 – 100.9	50.4 – 99.5	49.4 – 88.2	49.4 – 100.9
Median	69.10	77.70	69.10	65.40	72.45
Height (cm)					
n	15	15	15	15	60
Mean (SD)	157.3 (10.07)	160.2 (9.38)	157.8 (9.84)	156.4 (9.39)	157.9 (9.53)
Minimum – Maximum	143 – 179	143 – 176	143 – 176	142 – 182	142 – 182
Median	158.0	161.0	155.0	155.0	157.0
BMI (kg/m^2)					
n	15	15	15	15	60
Mean (SD)	28.80 (3.934)	31.38 (5.252)	28.56 (3.732)	27.84 (3.069)	29.15 (4.193)
Minimum – Maximum	21.5 – 37.5	26.3 – 46.1	23.1 – 34.8	23.6 – 34.8	21.5 – 46.1
Median	28.67	29.93	27.67	27.22	27.95

Safety Analysis Set (SAF): All enrolled patients who received at least 1 dose of study drug. The SAF was used for summaries of demographic and baseline characteristics and all safety and tolerability-related variables.

†Dose was given once daily for 6 weeks except in the 10/20 mg group where 10 mg was given for 1 week followed by 20 mg for 5 weeks.

BMI: body mass index.

Source: Table 12.1.2.1

Table 2 Mean Plasma ASP0777 Pharmacokinetic Parameters on Day 13

ASP0777 10 mg†	**C_{max}**	**C_{min}**	**t_{max}**	**AUC_{tau}**
Statistic	**(ng/mL)**	**(ng/mL)**	**(h)**	**(hr•ng/mL)**
n	15	15	15	15
Mean	47.5	24.9	3.00	820
SD	9.99	8.94	0.000	212.4
CV%	21.0	36.0	0.0	25.9
Minimum	32.2	12.3	3.00	541
Median	46.0	21.9	3.00	782
Maximum	67.7	48.4	3.00	1294
GM	46.6	23.5	3.00	796
ASP0777 20 mg†	**C_{max}**	**C_{min}**	**t_{max}**	**AUC_{tau}**
Statistic	**(ng/mL)**	**(ng/mL)**	**(h)**	**(hr•ng/mL)**
n	15	15	15	15
Mean	92.0	47.7	4.00	1599
SD	21.22	14.84	1.472	324
CV%	23.1	31.1	36.8	20.2
Minimum	57.2	18.7	2.98	1037
Median	87.9	46.0	3.00	1563
Maximum	129	73.3	6.07	2190
GM	89.5	45.2	3.78	1567
ASP0777 10/20 mg†	**C_{max}**	**C_{min}**	**t_{max}**	**AUC_{tau}**
Statistic	**(ng/mL)**	**(ng/mL)**	**(h)**	**(hr•ng/mL)**
n	14	14	14	14
Mean	99.1	48.0	5.92	1709
SD	29.6	17.7	6.24	460
CV%	29.9	36.9	105	26.9
Minimum	61.0	2.5	1.00	924
Median	96.7	50.2	3.00	1778
Maximum	159	68.2	23.9	2496
GM	95.2	40.3	4.00	1646

Pharmacokinetics Analysis Set (PKAS): All patients from the SAF whose pharmacokinetic data were adequate for the calculation of primary pharmacokinetic parameters.

† Dose was given once daily for 6 weeks except the 10/20 mg group where 10 mg was given for 1 week followed by 20 mg for 5 weeks.

CV%: coefficient of variation expressed as percentage; GM: geometric mean.

Source: Table 12.4.3.1, Table 12.4.3.2 and Table12.4.3.3

Table 3 Statistical Assessment of Plasma ASP0777 Pharmacokinetic Parameters on Day 13

Parameter (Units)	Treatment†	n	LS Mean‡	LS Mean Ratio§	90% CI of the Ratio§
AUC_{tau} (hr•ng/mL)	ASP0777 10 mg	15	795.9	- -	- -
	ASP0777 20 mg	15	1567.1	196.9	(168.5, 230.0)
	ASP0777 10/20 mg	14	1645.7	206.8	(176.5, 242.2)
C_{max} (ng/mL)	ASP0777 10 mg	15	46.6	- -	- -
	ASP0777 20 mg	15	89.5	192.1	(165.1, 223.4)
	ASP0777 10/20 mg	14	95.2	204.4	(175.3, 238.4)
C_{min} (ng/mL)	ASP0777 10 mg	15	23.5	- -	- -
	ASP0777 20 mg	15	45.2	192.3	(136.9, 270.3)
	ASP0777 10/20 mg	14	40.3	171.4	(121.2, 242.3)

Pharmacokinetics Analysis Set (PKAS): All patients from the SAF whose pharmacokinetic data were adequate for the calculation of primary pharmacokinetic parameters.

† Dose was given once daily for 6 weeks except the 10/20 mg group where 10 mg was given for 1 week followed by 20 mg for 5 weeks.

‡ ANOVA on log transformed parameter with treatment as a fixed effect was performed and the least squares means were reported in the original scale.

§ LS mean ratios and corresponding 90% CI are relative to the ASP0777 10 mg dose group and are reported as percentages.

LS Mean: least squares mean; CI: confidence interval; - -: comparator group.

Source: Table 12.4.4

Table 5 Treatment-emergent Adverse Events

MedDRA (v12.1) System Organ Class Preferred Term	Placebo (n = 15) n (%)	ASP0777† 10 mg (n = 15) n (%)	 20 mg (n = 15) n (%)	 10/20 mg (n = 15) n (%)
Overall	**9 (60.0%)**	**8 (53.3%)**	**10 (66.7%)**	**10 (66.7%)**
Nervous System Disorders	**8 (53.3%)**	**8 (53.3%)**	**7 (46.7%)**	**8 (53.3%)**
Dizziness	4 (26.7%)	2 (13.3%)	6 (40.0%)	5 (33.3%)
Headache	4 (26.7%)	4 (26.7%)	3 (20.0%)	3 (20.0%)
Somnolence	1 (6.7%)	3 (20.0%)	2 (13.3%)	1 (6.7%)
Ataxia	0	0	0	1 (6.7%)
Gastrointestinal Disorders	**3 (20.0%)**	**3 (20.0%)**	**3 (20.0%)**	**2 (13.3%)**
Nausea	2 (13.3%)	1 (6.7%)	3 (20.0%)	1 (6.7%)
Vomiting	1 (6.7%)	1 (6.7%)	1 (6.7%)	0
Diarrhoea	0	1 (6.7%)	1 (6.7%)	0
Constipation	1 (6.7%)	1 (6.7%)	0	0
Gastrooesophageal reflux disease	0	0	0	1 (6.7%)
Abdominal pain upper	1 (6.7%)	0	0	0
Psychiatric Disorders	**2 (13.3%)**	**2 (13.3%)**	**1 (6.7%)**	**1 (6.7%)**
Depression	1 (6.7%)	0	1 (6.7%)	0
Confusional state	0	0	0	1 (6.7%)
Insomnia	0	1 (6.7%)	0	0
Mood swings	0	1 (6.7%)	0	0
Nightmare	0	1 (6.7%)	0	0
Abnormal dreams	1 (6.7%)	0	0	0
Musculoskeletal and Connective Tissue Disorders	**2 (13.3%)**	**1 (6.7%)**	**1 (6.7%)**	**1 (6.7%)**
Muscle spasms	1 (6.7%)	1 (6.7%)	0	1 (6.7%)
Back pain	1 (6.7%)	0	1 (6.7%)	0
General Disorders and Administration Site Conditions	**0**	**0**	**2 (13.3%)**	**1 (6.7%)**
Fatigue	0	0	1 (6.7%)	1 (6.7%)
Asthenia	0	0	1 (6.7%)	0
Skin and Subcutaneous Tissue Disorders	**0**	**0**	**2 (13.3%)**	**0**
Hyperhidrosis	0	0	1 (6.7%)	0
Pruritus	0	0	1 (6.7%)	0
Ear and Labyrinth Disorders	**1 (6.7%)**	**0**	**1 (6.7%)**	**0**
Vertigo	1 (6.7%)	0	1 (6.7%)	0
Injury, Poisoning and Procedural Complications	**1 (6.7%)**	**0**	**0**	**1 (6.7%)**
Arthropod bite	0	0	0	1 (6.7%)
Thermal burn	1 (6.7%)	0	0	0
Cardiac Disorders	**0**	**0**	**1 (6.7%)**	**0**
Palpitations	0	0	1 (6.7%)	0
Investigations	**0**	**0**	**1 (6.7%)**	**0**
Alanine aminotransferase increased	0	0	1 (6.7%)	0
Reproductive System and Breast Disorders	**0**	**0**	**0**	**1 (6.7%)**
Benign prostatic hypertrophy	0	0	0	1 (6.7%)
Respiratory, Thoracic and Mediastinal Disorders	**0**	**0**	**1 (6.7%)**	**0**
Rhinorrhea	0	0	1 (6.7%)	0
Eye Disorders	**1 (6.7%)**	**0**	**0**	**0**
Vitreous haemorrhage	1 (6.7%)	0	0	0
Immune System Disorders	**1 (6.7%)**	**0**	**0**	**0**
Food allergy	1 (6.7%)	0	0	0

Table continued on next page

MedDRA (v12.1) System Organ Class Preferred Term	Placebo (n = 15) n (%)	ASP0777† 10 mg (n = 15) n (%)	 20 mg (n = 15) n (%)	 10/20 mg (n = 15) n (%)
Infections and Infestations	**1 (6.7%)**	**0**	**0**	**0**
Cellulitis	1 (6.7%)	0	0	0
Vascular Disorders	**1 (6.7%)**	**0**	**0**	**0**
Hypertension	1 (6.7%)	0	0	0

Safety Analysis Set (SAF): All enrolled patients who received at least 1 dose of study drug. The SAF was used for summaries of demographic and baseline characteristics and all safety and tolerability-related variables.

†Dose was given once daily for 6 weeks except in 10/20 mg group where 10 mg was given for 1 week followed by 20 mg for 5 weeks.

Source: Table 12.6.1.2

Table 6 Statistical Analysis of CSDD Assessments Total Score

Visit	Statistics‡	Placebo (n = 15)	ASP0777† 10 mg (n = 15)	 20 mg (n = 15)	 10/20 mg (n = 15)
Baseline	LS Mean	2.65	2.91	2.18	2.08
	LS Mean difference from placebo		0.25	-0.48	-0.58
	95% CI for the difference		-1.01, 1.51	-1.74, 0.79	-1.85, 0.69
Day 7	LS Mean	0.73	1.44	1.64	1.41
	LS Mean difference from placebo		0.71	0.91	0.68
	95% CI for the difference		-0.59, 2.01	-0.40, 2.22	-0.63, 1.99
Day 14	LS Mean	0.73	1.37	**2.11**	2.07
	LS Mean difference from placebo		0.64	**1.38**	1.34
	95% CI for the difference		-0.66, 1.94	**0.07, 2.69***	0.01, 2.67
Week 6/ET	LS Mean	2.67	2.71	1.78	1.54
	LS Mean difference from placebo		0.04	-0.89	-1.13
	95% CI for the difference		-1.24, 1.32	-2.18, 0.39	-2.42, 0.16

Safety Analysis Set (SAF): All enrolled patients who received at least 1 dose of study drug. The SAF was used for summaries of demographic and baseline characteristics and all safety and tolerability-related variables.

† Dose was given once daily for 6 weeks, except in the 10/20 mg group where 10 mg was given for 1 week followed by 20 mg for 5 weeks.

‡ An ANCOVA on CSDD total score with treatment, visit, treatment by visit as fixed effects, patient as a random effect and baseline CSDD total score as covariate.

* Bold font indicates statistical significance.

Each CSDD question was assigned a numerical score as: 0 = Absent; 1 = Mild or intermittent; 2 = Severe. CSDD total score is the sum of individual patient questionnaire scores at each assessment.

Source: Table 12.6.6.2