Name of Sponsor/Company: Astellas Pharma B.V.		
Name of Finished Product:		
Name of Active Ingredient: ASP8477		

SYNOPSIS

Title of Study: A Phase 2a Enriched Enrollment Randomized Withdrawal Study to Assess Analgesic Efficacy and Safety of ASP8477 in Subjects with Peripheral Neuropathic Pain

Investigators/Coordinating Investigator: TBD

Study Center(s): 12 centers in 3 European countries: Poland (4 sites), Czech Republic (6 sites) and the United Kingdom (2 sites). A total of 10 sites in Poland and the Czech Republic contributed patients to the randomized phase of the study.

Publication Based on the Study: None to date

Study Period: 1 year

Study Initiation Date (Date of First Enrollment): 24 February 2014

Study Completion Date (Date of Last Evaluation): 13 February 2015

Phase of Development: Phase 2a

Objectives: The primary objective was to assess analgesic efficacy of ASP8477 relative to placebo in patients with peripheral neuropathic pain as determined by the change in the average daily pain intensity in responders.

The key secondary objective was to assess analgesic efficacy of ASP8477 relative to placebo in patients with peripheral neuropathic pain, as determined by the time to efficacy failure in responders.

Other secondary objectives included:

- Assessment of additional measures of efficacy of ASP8477.
- Assessment of safety and tolerability of ASP8477 in responders and nonresponders during the Single-blind Period, and relative to placebo during the Double-blind Randomized Withdrawal Period.
- Assessment of pharmacokinetics of ASP8477 in responders and nonresponders.

[redacted]

- [redacted]

Methodology:

This was a phase 2a, enriched enrollment randomized withdrawal study to assess analgesic efficacy and safety of ASP8477 in patients with peripheral neuropathic pain (PNP) resulting from painful diabetic peripheral neuropathy (PDPN) or postherpetic neuralgia (PHN). The study design and dosing is shown graphically in Figure 1. The study consisted of a Screening Period (up to 4 weeks, including a Single-blind Placebo Run-in Period [not shown in Figure]), a Single-blind Treatment Period (approximately 4 weeks, including a 6-day Titration Period and 3-week Maintenance Period), a Double-blind Randomized Withdrawal Period (3 weeks), and a Follow-up Period (2 weeks).

Patients who did not comply with the inclusion or exclusion criteria before the Placebo Run-in Period were classified as screen failures. During the Placebo Run-in Period (1 week duration), patients recorded their daily pain score in an electronic diary. If patients recorded daily pain ratings on at least 5 of 7 days (3 of which are the last 3 days of the week), and the average pain score over the last 3 days was ≥ 4/10 and < 9/10 on the Numeric Pain Rating Scale (NPRS), they entered the Single-blind Treatment Period (dose titration). If patients did not meet these requirements they were classified as Run-in failures and discontinued from the study.

During the Single-blind Treatment Period, patients initiated dosing of ASP8477 at 10 mg twice daily on day 1, and escalated the dose on day 4 to 20 mg twice-daily. A patient who did not tolerate 10 mg twice-daily for these 3 days of dosing was not allowed to titrate up to 20 mg twice-daily nor to continue to participate in the study. A patient completing 3 days at the 20 mg twice-daily dosing regimen with no tolerability issues entered the 3-week Single-blind Maintenance Period at 30 mg twice-daily on day 7. If a patient did not tolerate 20 mg twice-daily dose for 3 days, the patient was not allowed to titrate up to 30 mg twice-daily nor to continue to participate in the study. Patients who discontinued during the Titration Period completed the early discontinuation (ED) and end of study (EOS) visits.

During the Single-blind Maintenance Period a patient who did not tolerate 30 mg twice-daily after 3 to 7 days on the 30 mg twice-daily dose (i.e., after day 10 or day 14) could have their dose reduced to 20 mg twice-daily and continue the study on the 20 mg twice-daily dose for the remainder of the study. Once a patient had reduced the dose to 20 mg, the dose could not be changed again. A patient that required further dose modification was discontinued from the study.

During the Placebo Run-in Period and Single-blind Period, rescue therapy (ketoprofen as needed, up to 200 mg/day) was permitted up to 12 hours before each visit.

Upon completion of the Single-blind Period, only patients who had responded to treatment (i.e., responders) and had been compliant with diary entry (i.e., completed the diary 5 out of 7 days per week on average and on 2 of the last 3 days of the Single-blind Period) were stratified by disease (PDPN or PHN) and randomized in a 1:1 ratio to receive placebo or continue their ASP8477 regimen in the 3-week Double-blind Randomized Withdrawal Period. The response to treatment was defined as a ≥ 30% decrease in the mean average daily pain intensity during the last 3 days of the Single-blind Maintenance Period (baseline of the Double-blind Randomized Withdrawal Period) compared to the pain intensity at the last 3 days of the Placebo Run-in Period (baseline of the Single-blind Period).

Nonresponders (i.e., patients who did not demonstrate a 30% improvement to treatment at the end of the Single-blind Period) and patients who did not comply with diary entries were discontinued from the study and had ED and EOS visit procedures performed.

During the Single-blind Period and Double-blind Randomized Withdrawal Period, patients returned to the clinic regularly for safety, pharmacokinetic, pharmacodynamic, and efficacy procedures. All patients had an EOS follow-up visit approximately 14 days after the last dose of study medication.

Up to 150 patients were planned to be enrolled. Enrollment was to stop when 60 primary responders had been randomized into the Double-blind Randomized Withdrawal Period, or when 150 patients had enrolled into the Single-blind Period (whichever occurred sooner).

The design included a stopping rule for futility. After 75 patients had finished or discontinued the Single-blind Period the study was to be stopped for futility if the following condition held:

- The Bayesian predictive probability of the primary responder rate for 150 patients in the Single-blind Period ≥ 40% was less than 20%.

If the study continued after the futility analysis, the analysis could be repeated on an approximately 4-week schedule until the end of the study.

Number of Patients (Planned, Enrolled and Analyzed): This study was planned for 30 patients per treatment group in the responder population, i.e., for 60 randomized patients. A total of 157 patients participated in this study, and 71 patients were randomized and analyzed.

Diagnosis and Main Criteria for Inclusion:

Patients in this study had PNP resulting from PDPN or PHN. Patients with PDPN had a 1-year history of pain; patients with PHN had a ≥ 6 months history of pain. All patients had an average daily pain score ≥ 4 on an 11-point 0 to 10 NPRS at Screening, and a mean of average daily pain scores of ≥ 4/10 and < 9/10 over the last 3 days of the 7-day Placebo Run-in Period.

Test Product, Dose and Mode of Administration, Batch Numbers: ASP8477 tablets (Lot. No. [redacted], [redacted], [redacted]) were provided as immediate-release tablets in the strength of 10 mg of active substance. Placebo-to-match tablets (Lot. No. [redacted]) were matched to the tablet strength of 10 mg ASP8477.

Duration of Treatment (or Duration of Study, if applicable): Patients enrolled in the Single-blind period received ASP8477 for approximately 4 weeks. At that point, patients were randomly assigned either to continue on ASP8477 for 3 additional weeks or to cease treatment (placebo arm).

Criteria for Evaluation: The primary efficacy endpoint was the change in mean of 24-hour average pain intensity (NPRS) from the Double Blind baseline (last 3 days of the Single-blind Period) to the last 3 days of the Double-blind Randomized Withdrawal Period. The key secondary efficacy variable was time to treatment failure. Other secondary efficacy variables were:

- Responder rate to ASP8477 in the Single-blind Period
- Patient Global Impression of Change (PGIC) for overall patient status at the end of treatment (EOT) or early discontinuation (ED) visit for all patients

[redacted]

[redacted]

Plasma concentrations by dose level of ASP8477 at the final dose given to each patient were measured in responders and nonresponders after one week of administration of ASP8477 (Single-blind Period).

[redacted]

Statistical Methods: The following 7 analysis sets were used for the analyses:

- The full analysis set 1 (FAS1) was the primary analysis set for efficacy and safety data in the Single-blind Period, and consisted of all patients who started the Single-blind Period and received at least one dose of study drug.
- The full analysis set 2 (FAS2) was the primary analysis set for efficacy analyses for the Double-blind Period, and consisted of all patients who were responders (i.e., had a ≥ 30% decrease in mean average daily pain intensity at baseline of the Double-blind Randomized Withdrawal Period versus baseline of the Single-blind Period), who received at least one dose of Double-blind study drug after randomization, and who had a pain intensity score at Double-blind baseline and at least one pain intensity score postbaseline during the Double-blind treatment period.
- The safety analysis set 1 (SAF1) was used for the statistical summary of the safety data during the Placebo Run in, and consisted of all patients who took at least one dose of study medication during the Placebo Run-in Period.
- The safety analysis set 2 (SAF2) was used for safety analyses of safety data for those patients who entered the Double-blind Randomized Withdrawal Period, and consisted of all patients who took at least one dose of double-blind study medication after randomization.
- The pharmacokinetic analysis set (PKAS) consisted of all patients in the FAS1 population for whom at least one quantifiable plasma concentration of ASP8477 was obtained and for whom the time of dosing on the day of sampling was known.
- [redacted]
- [redacted]

The primary variable, change in mean of 24-hour average pain intensity (NPRS) from the Double Blind baseline (last 3 days of the Single-blind Period) to the last 3 days of the Double-blind Randomized Withdrawal Period, was summarized by treatment group for the FAS2.

The key secondary efficacy variable, time to treatment failure, was defined as time from randomization to the first of 3 consecutive days in which mean 24-hour pain intensity was ≥ 4, and with at least a 30% increase in pain intensity (on each day) relative to baseline of the Double-blind Randomized Withdrawal Period and estimated by the Kaplan-Meier method for the FAS2. The responder rate to ASP8477 in the Single-blind Period was summarized for the FAS1, and responders were defined as patients having a ≥ 30% reduction in pain intensity from average of last 3 days NPRS score in Placebo Run-In to the average of the NPRS score of the

final 3 days in the Single-blind Period. The score for PGIC was summarized by treatment group and was analyzed at visit 8 (day 28), visit 10 (EOT/ED) and visit 11 (EOT) by a Cochran-Mantel-Haenszel (CMH) test stratified by pooled sites for the FAS2.

Plasma concentrations of ASP8477 are summarized (including mean concentration-time profiles [both linear and log-linear] and individual patient concentration-time profiles [both linear and log-linear]) and presented in tabular and graphic formats.

[redacted]

All safety and tolerability data were summarized using descriptive statistics and were listed and summarized in tabular and/or graphical form by treatment and assessment day. MedDRA version v14.0_A (APUS) was used to summarize treatment-emergent adverse events (TEAEs) by system organ class and preferred term. Summaries were also provided for treatment related TEAEs, severe TEAEs, serious TEAEs and non-TEAEs.

Summary of Results/Conclusions: The ASP8477 study in peripheral neuropathic pain did not meet the primary endpoint.

In the Single-blind period, administration ASP8477 60mg daily demonstrated pain relief with an overall mean percent change from baseline in NPRS score of -35.9% (Single-blind baseline mean = 6.23; End of Single-blind Period mean= 4.02; Δ = -2.22). A $\geq$ 30% decrease in mean average daily pain intensity (NPRS score) during the Single-blind Period was observed in 57.8 % of patients.

In the 3-week Double-blind Randomized Withdrawal Period, both treatment groups maintained the levels of improvement observed at the end of Single-blind Period. No evidence of a clinical effect of ASP8477 over placebo was observed for the endpoint of 24-hour average pain intensity (primary endpoint) in the primary analysis set (FAS2). The difference in least squares means of NPRS scores (ASP8477 – placebo) was +0.11 (one-sided 95% CI: [–, 0.59]; P = 0.644), indicating no evidence of a clinical effect of ASP8477 treatment over placebo at the end of the Double-blind Period. No significant difference was seen between groups in the time to treatment failure, nor in the PGIC.

[redacted]

During the Single-blind period 22% of patients reported TEAEs. During the Double-blind Randomized Withdrawal Period, 8.1% of patients in the ASP8477 arm experienced TEAEs, while in the placebo arm, 18% of patients experienced TEAEs. Overall, ASP8477 was well tolerated during both periods, with no apparent effect on orthostatic blood pressure.

Efficacy/Pharmacokinetic/Pharmacodynamic Results:
Efficacy: An overview of the disposition of patients is shown in Figure 2 and Table 1. A total of 157 patients were screened in the study, of which 132 patients were enrolled and entered the Placebo Run-in Period (comprising the SAF1 analysis set). No patient died in the study, and 2 patients had 3 AEs of moderate severity that resulted in discontinuation of study drug.

During the Placebo Run-in period, 16 patients discontinued treatment, leaving 116 patients who entered the Single-blind Period and who comprised the FAS1 analysis set.

During the Single-blind Period, there were 49 nonresponders, including 2 patients who discontinued treatment due to TEAEs, 2 due to protocol deviations, and 2 who withdrew consent. Of the latter 6 patients, 2 were also discontinued from the study (1 lost to follow-up, 1 withdrew consent). Four of the nonresponders were randomized in error and entered the Double-blind Randomized Withdrawal Period. Thus, 45 of 49 nonresponders were discontinued from treatment by the end of the Single-blind Period and prior to randomization.

A total of 71 patients (including 4 nonresponders randomized in error) were randomized (37 to ASP8477, 34 to placebo). During the Double-blind Randomized Withdrawal Period, 8 patients discontinued treatment, including 4 nonresponders who were randomized by mistake and were excluded from the FAS2, which thus comprised 67 patients (34 in the ASP8477 arm, 33 in the placebo arm). The Double-blind Randomized Withdrawal Period was completed by 63 patients, 31 in the ASP8477 arm and 32 in the placebo arm.

Demographic and baseline characteristics for all patients enrolled (SAF1) and all patients randomized (SAF2) are summarized in Table 2. With respect to all demographic parameters except for sex, the patients who entered into the Double-blind Randomized Withdrawal Period were similar to the population of all enrolled patients, and the patients randomized to the ASP8477 arm were similar to those randomized to placebo. There were relatively fewer men assigned to the ASP8477 arm.

The primary objective of this study was to assess analgesic efficacy of ASP8477 relative to placebo in patients with peripheral neuropathic pain, as determined by the change in the average daily pain intensity in patients responding to ASP8477. To that end, during the Single-blind Treatment Period all participating patients were treated with ASP8477 for a mean period of 27 days. For each of the last 3 days of the Single-blind Treatment Period, the 24-hour average pain intensity (NPRS) was determined for each patient, and the 3-day average became the Double-blind Baseline score. Patients who achieved at least a 30% response during the Single-blind Treatment Period were then randomly assigned either to continue treatment with ASP8477 or to withdraw from treatment and be treated with placebo during the Double-blind Randomized Withdrawal Period, which lasted 20 days.

On the primary endpoint, the average of the 24-hour average pain intensity (NPRS) scores from the last 3 days of the Double-blind Randomized Withdrawal Period was determined for each patient and compared to the Double-blind Baseline score. For the treatment difference (ASP8477 versus placebo), a negative difference shows a benefit for ASP8477 over placebo, and a positive difference shows a benefit of placebo over ASP8477. In the primary analysis set (FAS2), the difference in least squares means (ASP8477 – placebo) was +0.11 (one-sided 95% CI: [–, 0.59]; P = 0.644), indicating no evidence of a clinical effect of ASP8477 treatment over placebo at the end of the Double-blind Period Table 3. Results on the SAF2 were consistent with the results based on the FAS2. A secondary analysis using a repeated measures model found a non-significant small increase in pain in both treatment groups during week 5, followed by small decreases in week 6 and week 7 [Figure 3].

The secondary endpoint of treatment failure was defined as the occurrence of 3 consecutive days in which the mean 24 hour NPRS was ≥ 4, and with at least a 30% increase in pain intensity (on each day) relative to the baseline of the Double-blind Period (the last 3 days of the Single-blind period). Nine patients (5 in the ASP8477 arm and 4 in the placebo arm) experienced treatment failure in the Double-blind Randomized Withdrawal period Figure 4. The hazard ratio and associated 1-sided 95% confidence interval was

0.970 (- ; 3.733) showing no difference in time to treatment failure between the two treatment arms (P [one-sided] = 0.485) [Table 4].

The 24-hour mean (SD) NPRS score at Single-blind Baseline in the FAS1 was 6.23 (1.14), which decreased to 4.02 (1.92) at the end of the Single-blind period, for a mean percent decrease of 35.9%. The percentage of responders at the end of the Single-blind Period was 57.8%.

Pharmacokinetics: The peak plasma concentrations were attained at one hour after taking ASP8477 in patients taking either 40 mg daily or 60 mg daily. Plasma concentrations decreased thereafter.

[redacted]

Safety Results: During the Single-blind period, 22% of patients experienced at least one treatment-emergent adverse event (TEAE) [Table 5]. No patient died, and 1 patient experienced 2 serious TEAEs (constipation and renal failure acute) during the maintenance period. No serious TEAE was considered related to study drug. Study drug related TEAEs were experienced by 13% of patients, mainly during the maintenance period. Two patients discontinued treatment, in each case due to the same 2 AEs (burning sensation and pruritis). The most common TEAE in the Single-blind Period was peripheral edema reported in 3 patients, followed by 10 other conditions affecting 2 patients each [Table 6]. At the MedDRA SOC level, the most common category for TEAEs was Nervous system disorders, followed by Musculoskeletal and connective tissue disorders and Infections and infestations.

During the Double-blind Randomized Withdrawal Period, 8.1% of patients in the ASP8477 arm experienced at least one TEAE, which was considered drug-related in each case. In the placebo arm, 18% of patients experienced at least one TEAE, and 5.9% of patients had drug related TEAEs. There were no deaths in either treatment arm. One patient in the ASP8477 arm discontinued treatment due to a drug-related TEAE (dermatitis allergic on day 42) and 1 patient in the placebo arm experienced 2 serious TEAEs (acute myocardial infarction and osteomyelitis, both on day 35) that were considered not-related to the study drug [Table 7].

The incidence of TEAEs during the Double-blind Randomized Withdrawal Period was slightly lower than during the Single-blind Period, partially due to the fact that only TEAEs that started or worsened during the Double-blind period are presented. No specific TEAE (MedDRA preferred term) occurred in more than one patient [Table 8].

The orthostatic challenge test was administered at each study visit. As per the statistical analysis plan, a positive orthostatic challenge test was defined as a reduction of ≥ 20 mmHg in systolic BP or of ≥ 10 mm Hg in diastolic BP when changing from a supine to a standing position. There were no apparent adverse effects on orthostatic blood pressure measures. No orthostatic-related symptoms were observed in conjunction with the administration of the orthostatic challenge test.

CONCLUSIONS: The ASP8477 study in peripheral neuropathic pain did not meet the primary endpoint.

In the Single-blind period, administration of ASP8477 60mg daily demonstrated pain relief with an overall mean percent change from baseline in NPRS score of -35.9% (Single-blind Baseline mean = 6.23; end of Single-blind Period mean = 4.02; Δ = -2.22). A $\geq$ 30% decrease in mean average daily pain intensity (NPRS score) during the Single-blind Period was observed in 57.8% of patients.

In the 3-week Double-blind Randomized Withdrawal Period, both treatment groups maintained the levels of improvement observed at the end of Single-blind Period. No evidence of a clinical effect of ASP8477 over placebo was observed for the primary endpoint of 24-hour average pain intensity ([ASP8477 – placebo] = +0.11, favoring placebo; one-sided 95% CI: [–, 0.59]; P = 0.644). There also was no evidence of an effect of ASP8477 on time to treatment failure, nor the PGIC.

[redacted]

Overall, there were no adverse events of marked frequency or severity observed in this study. There were no deaths, 2 patients experienced treatment-emergent SAEs (none drug-related), and 3 patients had TEAEs leading to discontinuation of study drug (drug-related in 2 patients). During the Single-blind period 22% of patients reported TEAEs. During the Double-blind Randomized Withdrawal Period, 8.1% of patients in the ASP8477 arm experienced TEAEs, while in the placebo arm, 18% of patients experienced TEAEs. There were no clinically significant effects on laboratory parameters and no apparent adverse effect on vital signs or orthostatic blood pressure measures. Overall, ASP8477 30 mg twice daily was well tolerated during both the Single- and Double-blind periods.

Date of Report: 03 Sep 2015

Figure 1 Dosing Schedule Flow Chart

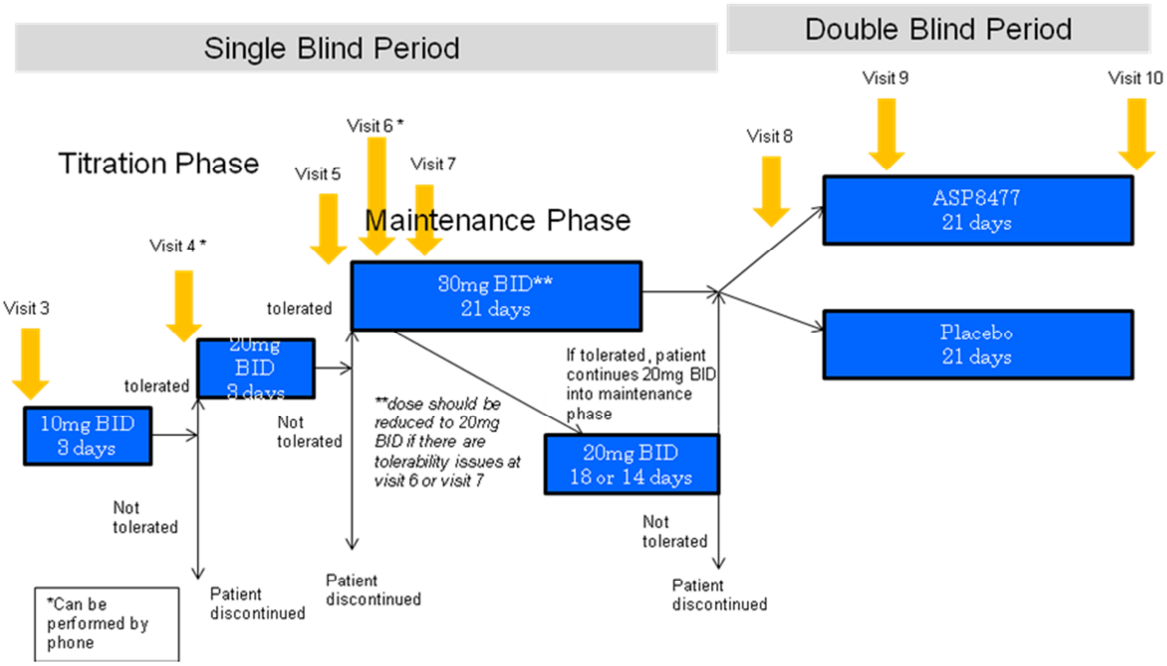
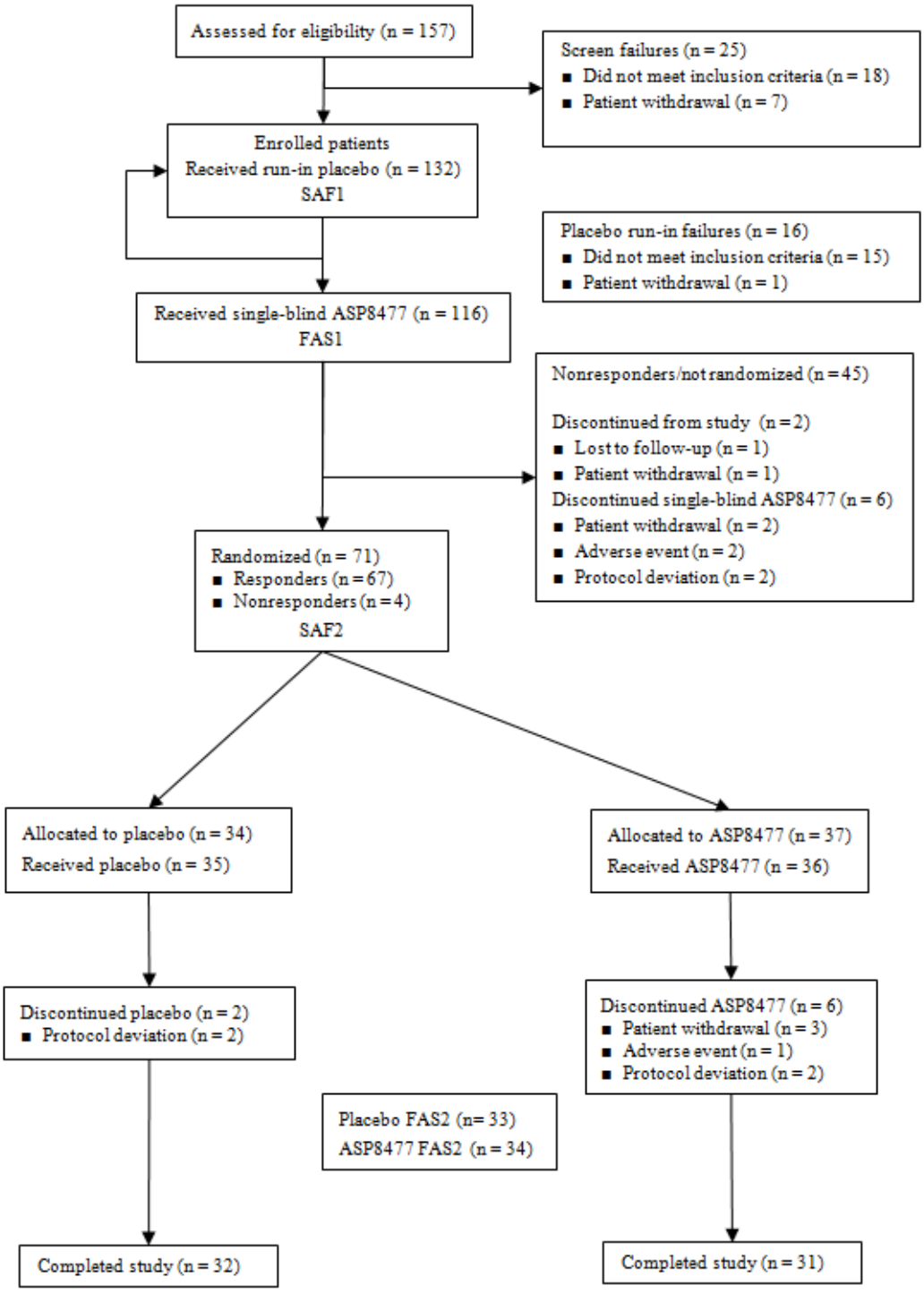


Figure 2 Flow Chart of Patient Disposition



Footnotes appear on next page

FAS1: All patients who started the Single-blind Period and received at least one dose of study drug. FAS2: All patients who were responders, received at least one dose of Double-blind study drug after randomization and had a pain intensity score at Double-blind baseline and at least one pain intensity score postbaseline during the Double-blind treatment period. SAF1: All patients who took at least one dose of study medication during the Placebo Run-in Period. SAF2: All patients who took at least one dose of Double-blind study medication after randomization.

Source: Tables 12.1.1.1, 12.1.1.5, 12.1.1.3.1, 12.1.1.3.2, 12.1.1.3.3,12.1.1.4, 12.3.3, and Appendices 13.2.1.1, 13.2.1.2, 13.2.1.3, 13.2.1.4, 13.2.1.5, 13.2.3.1, 13.2.5.1.1, 13.2.5.1.2, 13.2.5.1.3, 13.2.7.5

Table 1 Patient Disposition

Analysis Set	**Total**
Patients with Informed Consent	157
Screen failures	25
Received Run-In Placebo	132
Discontinued before Single-blind Period †	16
Received ASP8477 during the Single-blind Period	116
Discontinued treatment during Single-blind Period	6
Discontinued treatment/study before Double-blind Period	45
Responder in Single-blind Period ‡	67
Randomized to Double-blind Randomization Withdrawal Period §	71
ASP8477 ¶	37
Placebo	34
Discontinued during Double-blind Randomization Withdrawal Period	8
Completed study	63
ASP8477	31
Placebo	32

† Patients who signed informed consent and received run-in placebo but discontinued before single-blind period were placebo run-in failures.
‡ Responders had a ≥ 30% decrease in mean average daily pain intensity from baseline of the Single-blind Period to end Single-blind Period.
§ 4 patients were nonresponders, but were randomized in error.
¶ One patient actually treated with placebo.

Source: Table 12.1.1.1, 12.1.1.3.1, 12.1.1.3.2, 12.1.1.3.3, 12.1.1.4

Table 2 Demographic Characteristics (SAF1 and SAF2)

Parameter	**SAF1**	**SAF2 (n = 71)**	
Category	**(n = 132)**	**Placebo (n = 34)**	**ASP8477 20/40/60 mg (n = 37)**
Sex (n, %)	132	34	37
Male	82 (62.1%)	25 (73.5%)	17 (45.9%)
Female	50 (37.9%)	9 (26.5%)	20 (54.1%)
Race (n, %)	132	34	37
White	131 (99.2%)	34 (100.0%)	37 (100.0%)
Black or African American	0	0	0
Asian	1 (0.8%)	0	0
Other	0	0	0
Age (years) (n, %)	132	34	37
Mean (SD)	62.7 (9.1)	62.4 (6.6)	62.2 (10.5)
Median	64.0	64.0	63.0
Range	39–88	47–73	40–83
Weight (kg) (n, %)	132	34	37
Mean (SD)	90.37 (15.85)	89.94 (16.23)	89.11 (17.58)
Median	90.40	90.40	92.00
Range	49.0–130.0	55.0–121.8	49.0–122.0
Height (cm) (n, %)	132	34	37
Mean (SD)	172.60 (10.14)	174.71 (9.93)	170.98 (10.75)
Median	173.00	174.50	170.60
Range	145.0–196.0	160.0–196.0	153.0–195.0
BMI (kg/m^2) (n, %)	132	34	37
Mean (SD)	30.19 (3.70)	29.32 (3.87)	30.32 (4.39)
Median	30.65	29.90	32.10
Range	19.6–34.9	21.0–34.9	19.6–34.7

SAF1, all patients who took at least one dose of study medication during the Placebo Run-in Period. SAF2, all patients who took at least one dose of double-blind study medication after randomization.
BMI: body mass index (weight [kg]/height [m^2]).

Source: Tables 12.1.2.1.1 and 12.1.2.1.3

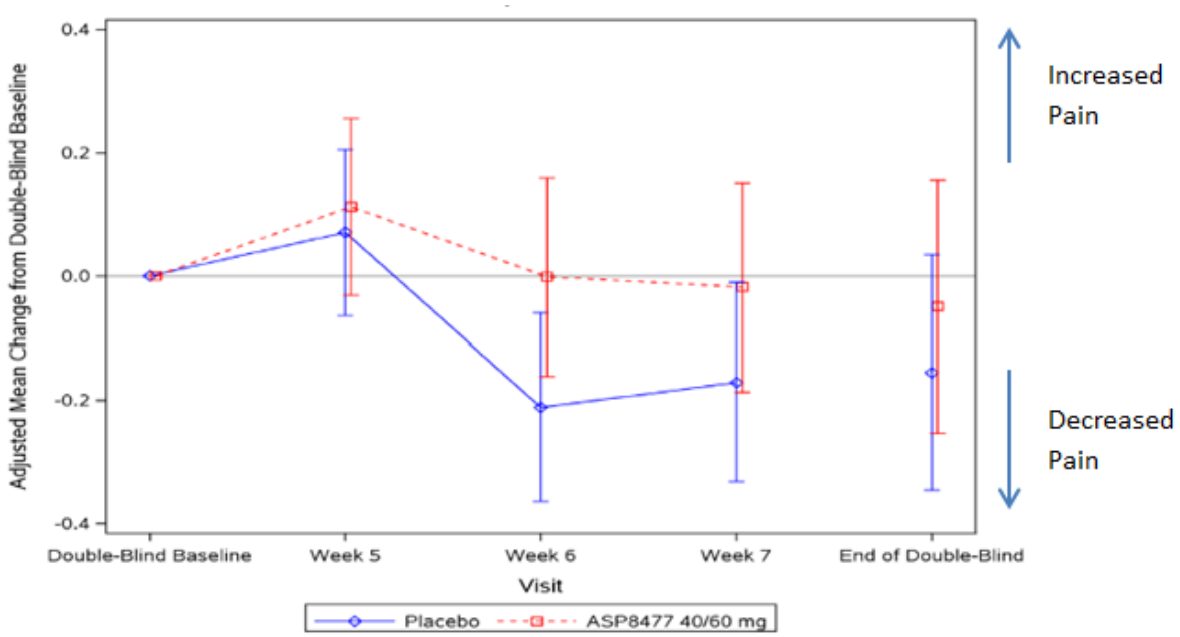
Table 3 Primary Efficacy Endpoint - Change in Mean of 24-Hour Average NPRS Score to End of Double-blind Period (FAS2)

	Placebo (n = 33)	**ASP8477 40/60mg (n = 34)**
Double-blind Baseline NPRS score †		
n	33	34
Mean (SD)	2.57 (1.11)	3.07 (1.36)
Median	2.33	3.00
End of Double-blind Period NPRS score ‡		
n	33	33
Mean (SD)	2.45 (1.32)	2.94 (1.61)
Median	2.00	2.67
Absolute change from Double-blind Baseline		
n	33	33
Mean (SD)	-0.11 (1.01)	-0.13 (1.05)
Median	-0.33	0
Adjusted difference ASP8477 – Placebo §		
n	33	33
LS Mean (SE)	-0.16 (0.19)	-0.05 (0.20)
LS Mean difference (SE)		+0.11 (0.29)
1-sided 95% CI difference ¶		(–; 0.59)
P value ††		0.644

FAS2, all patients who were responders (i.e., had a ≥ 30% decrease in mean average daily pain intensity at baseline of the Double-blind Randomized Withdrawal Period versus baseline of the Single-blind Period), who received at least one dose of Double-blind study drug after randomization, and who had a pain intensity score at Double-blind baseline and at least one pain intensity score postbaseline during the Double-blind treatment period.
LS: least squares; NPRS: numeric pain rating scale.
† Double-blind Baseline NPRS Score is defined as the mean of 24-hour average pain intensity for the last 3 days of the Single-blind Period.
‡ End of Double-blind Period NPRS Score is defined as the mean of 24-hour average pain intensity for the last 3 days of the Double-blind Period.
§ Analysis of covariance model with treatment group and pooled sites as fixed factors and baseline as a covariate.
¶ For the 1-sided 95% CI, only the upper bound is shown.
†† 1-sided.

Source: Table 12.3.1.1

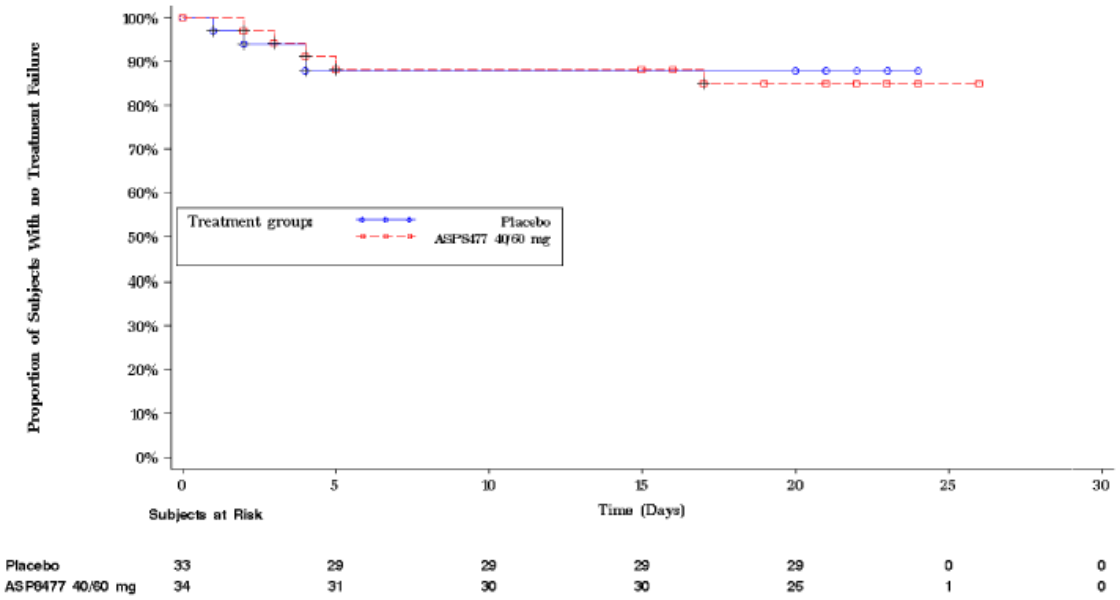
Figure 3 **Adjusted Mean Change from Double-blind Baseline of 24-Hour Average NPRS Score (FAS2)**



FAS2, all patients who were responders (i.e., had a ≥ 30% decrease in mean average daily pain intensity at baseline of the Double-blind Randomized Withdrawal Period versus baseline of the Single-blind Period), who received at least one dose of Double-blind study drug after randomization, and who had a pain intensity score at Double-blind baseline and at least one pain intensity score postbaseline during the Double-blind treatment period.
Error bars show SE.

Source: Figure 12.3.1.1

Figure 4 Time to Treatment Failure (FAS2)



FAS2, all patients who were responders (i.e., had a ≥ 30% decrease in mean average daily pain intensity at baseline of the Double-blind Randomized Withdrawal Period versus baseline of the Single-blind Period), who received at least one dose of Double-blind study drug after randomization, and who had a pain intensity score at Double-blind baseline and at least one pain intensity score postbaseline during the Double-blind treatment period.

Source: Figure 12.3.3

Table 4 Analysis of Time to Treatment Failure (FAS2)

Time to Treatment Failure Parameter	**Placebo (n = 33)**	**ASP8477 40/60 mg (n = 34)**
Treatment failures	4 (12.1)	5 (14.7)
Censored †	29 (87.9)	29 (85.3)
Hazard ratio		0.970
95% CI		(–, 3.733)
P value ‡		0.485

FAS2, all patients who were responders (i.e., had a ≥ 30% decrease in mean average daily pain intensity at baseline of the Double-blind Randomized Withdrawal Period versus baseline of the Single-blind Period), who received at least one dose of Double-blind study drug after randomization, and who had a pain intensity score at Double-blind baseline and at least one pain intensity score postbaseline during the Double-blind treatment period.
One-sided 95% CI (upper limit) shown for treatment comparison (ASP8477 - Placebo).
ED: early discontinuation; EOT: end of treatment.
† Censored patients are those who did not meet the efficacy failure criteria at visit 10 (EOT/ED).
‡ 1-sided P value is for treatment comparisons from the Cox proportional hazards model with covariates for treatment, pooled sites and Double-blind baseline mean of 24-hour average pain intensity as covariates.

Source: Table 12.3.2

Table 5 Overview of Treatment-emergent Adverse Events During Single-blind Period (FAS1)

Event Type **Interval (days)**	**ASP8477** **20/40/60 mg** **(n = 116)**
Adverse events	
Number of events	50
Number of patients (n, %)	26 (22.4%)
Days 1-3 †	4 (3.4%)
Days 4-6 ‡	3 (2.6%)
Days ≥ 7 §	20 (17.2%)
Drug-related AEs ¶	
Number of events	27
Number of patients (n, %)	15 (12.9%)
Days 1-3 †	3 (2.6%)
Days 4-6 ‡	2 (1.7%)
Days ≥ 7 §	11 (9.5%)
Deaths	
Number of events	0
Serious adverse events	
Number of events	2
Number of patients (n, %)	1 (0.9%)
Days ≥ 7 §	1 (0.9%)
Drug-related SAEs ¶	
Number of events	0
Adverse events leading to permanent discontinuation of study drug	
Number of events	4
Number of patients (n, %)	2 (1.7%)
Days 4-6 ‡	1 (0.9%)
Days ≥ 7 §	1 (0.9%)
Drug-related AEs leading to permanent discontinuation of study drug	
Number of events	2
Number of patients (n, %)	1 (0.9%)
Days 4-6 ‡	1 (0.9%)
Orthostatic Challenge Test-related AEs ††	
Number of events	1
Number of patients (n, %)	1 (0.9%)
Days 4-6 ‡	1 (0.9%)
Drug-related Orthostatic Challenge Test-related AEs ¶	
Number of events	1
Number of patients (n, %)	1 (0.9%)
Days 4-6 ‡	1 (0.9%)

FAS1, all patients who started the Single-blind Period and received at least one dose of study drug.
TEAEs which started or worsened during the period from first ASP8477 intake during the Single-blind Period to the start of the Double-blind Randomized Withdrawal Period are shown.
AE: adverse event; TEAE: treatment-emergent adverse event.
† Day 1-3: titration phase, 10 mg twice daily.
‡ Day 4-6: titration phase, 20 mg twice daily.
§ Day 7 to day 28: maintenance phase, 30 mg twice daily (patient may have been down-titrated to 20 mg twice daily after day 10).
¶ Possible or probable, as assessed by the investigator, or records where relationship is missing.
†† Relationship to OCT as assessed by the investigator.

Source: Table 12.6.1.1.2

Table 6 TEAEs Occurring In At Least 2 Patients, Single-blind Period (FAS1)

Adverse Event Preferred Term (MedDRA v14.0)	**ASP8477 20/40/60mg (n = 116)**
Number of patients (n, %)	26 (22.4%)
Oedema peripheral	3 (2.6%)
Burning sensation	2 (1.7%)
Constipation	2 (1.7%)
Disorientation	2 (1.7%)
Dizziness	2 (1.7%)
Myalgia	2 (1.7%)
Nasopharyngitis	2 (1.7%)
Pruritus	2 (1.7%)
Pyrexia	2 (1.7%)
Sensation of heaviness	2 (1.7%)
Somnolence	2 (1.7%)

FAS1, all patients who started the Single-blind Period and received at least one dose of study drug.
TEAEs sorted by incidence frequency during Single-blind Period. Only TEAEs starting or worsening during the Single-blind Period are presented.
TEAE: treatment-emergent adverse event.

Source: Table 12.6.1.2.2

Table 7 Overview of Treatment-emergent Adverse Events During Double-blind Randomized Withdrawal Period (SAF2)

	Placebo (n = 34)	**ASP8477 40/60 mg (n = 37)**
Number of AEs	12	3
Number of patients (n, %)	6 (17.6%)	3 (8.1%)
Drug-related AEs †	2 (5.9%)	3 (8.1%)
Deaths	0	0
Serious AEs	1 (2.9%)	0
Drug-related Serious AEs †	0	0
AEs Leading to Permanent Discontinuation of Study Drug	0	1 (2.7%)
Drug-related AEs Leading to Permanent Discontinuation of Study Drug †	0	1 (2.7%)
Orthostatic Challenge Test Related AEs ‡	0	0

SAF2, all patients who took at least one dose of double-blind study medication after randomization.
TEAEs which started or worsened during the period from first dose of ASP8477 or placebo after randomization until the EOS visit (visit 11) are shown.
AE: adverse event; EOS: end of study; TEAE: treatment-emergent adverse event.
† Possible or probable, as assessed by the investigator, or records where relationship is missing.
‡ Orthostatic challenge test related AEs were assessed by the investigator.

Source: Table 12.6.1.1.3

Table 8 All TEAEs during the Double-blind Randomized Withdrawal Period (SAF2)

Adverse Event Preferred Term (MedDRA v14.0)	**Placebo (n = 34)**	**ASP8477 40/60mg (n = 37)**
Number of patients (n, %)	6 (17.6%)	3 (8.1%)
Dermatitis allergic	0	1 (2.7%)
Increased appetite	0	1 (2.7%)
Musculoskeletal stiffness	0	1 (2.7%)
Acute myocardial infarction	1 (2.9%)	0
Diabetic foot	1 (2.9%)	0
Diarrhoea †	1 (2.9%)	0
Dizziness ‡ §	1 (2.9%)	0
Dyslipidaemia	1 (2.9%)	0
Dyspepsia	1 (2.9%)	0
Hyperuricaemia	1 (2.9%)	0
Hypoglycaemia	1 (2.9%)	0
Nasopharyngitis	1 (2.9%)	0
Osteomyelitis	1 (2.9%)	0

SAF2, all patients who took at least one dose of double-blind study medication after randomization.
Sorted by incidence in ASP8477 during the Double-blind Period. Only TEAEs which started or worsened during the Double-blind Period are presented
TEAE: treatment-emergent adverse event.
† Special interest : Withdrawal/discontinuation event.
‡ Special interest : Vigilance-related event.
§ Special interest : Postural-related change event

Source: Tables 12.6.1.2.3, 12.6.1.11.2, 12.6.1.12.2, 12.6.1.14.2