Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: Not applicable		
Name of Active Ingredient: ASP3662		

SYNOPSIS

Title of Study: A Phase 2a, Randomized, Double-Blind, Multicenter, Placebo and Active Controlled Study to Assess Analgesic Efficacy and Safety of ASP3662 in Subjects with Painful Diabetic Peripheral Neuropathy

Investigators/Coordinating Investigator: [redacted] MD, CCRP; [redacted] DO; [redacted] MD; [redacted] DO; [redacted] MD; [redacted] MD, FACP; [redacted] DO; [redacted] DO, MS; [redacted] DO,CPI, MRO, FACOFP; [redacted] MD, FAAFP; [redacted] MD; [redacted] MD; [redacted] MD; [redacted] MD; [redacted] MD; [redacted] MD; [redacted] MD; [redacted] MD; [redacted] MD; [redacted] MD; [redacted] PhD, MD; [redacted] MD; [redacted] DO; [redacted] MD; [redacted] MD, CPI

Study Center(s): Twenty-four investigative sites in the US conducted this study

Publication Based on the Study: None.

Study Period: One year: May 2015 to May 2016

Study Initiation Date (Date of First Enrollment): 27 May 2015

Study Completion Date (Date of Last Evaluation): 20 May 2016

Phase of Development: Phase 2a

Objectives: The primary objective of this study was to assess analgesic efficacy of ASP3662 relative to placebo in patients with painful diabetic peripheral neuropathy (PDPN) as determined by the change in mean 24-hour average pain intensity score in the Numerical Pain Rating Scale (NPRS). In addition, this study assessed the safety and tolerability of ASP3662 relative to placebo.

Methodology:

This phase 2a, multicenter, randomized, double-blind, placebo- and active-controlled study was to assess the analgesic efficacy and safety of ASP3662 in patients with PDPN.

The study consisted of 4 study periods that included:

1. An up to 35-day screening period to complete screening procedures, washout of prohibited medications
2. A 7-day diary run-in; a baseline period including completion of the last procedure prior to first dose of study drug
3. A double-blind period including 1 week of titration, 5 weeks of treatment and a 1 week taper
4. A follow-up period for 1 week post last dose

During screening, patients who preliminarily met the eligibility criteria (medical history, physical examination, vital signs and laboratory assessments) were instructed, as necessary, to washout of any nonpermitted medications.

At visit 2, patients were provided with an electronic diary (e-diary). Patients were to begin recording their daily pain scores (NPRS and Brief Pain Index – Diabetic Neuropathy [BPI-DN]). Patients requiring washout of any nonpermitted medications were given an e diary following the completion of washout to begin recording daily pain scores (NPRS and BPI-DN).

At visit 3, patients were required [redacted]. Any patient who did not meet the minimum threshold for pain was considered a screen failure and was not allowed to continue.

Patients who met the pain score eligibility requirements at this visit completed all baseline assessments and were randomized into the study.

Patients were instructed to begin study drug dosing in the morning on day 1 following randomization on day 0.

Patients randomized to the ASP3662 group received ASP3662 10 mg once daily (morning) and pregabalin placebo 3 times daily (morning, midday and evening) for titration and treatment/weeks 1 to 6, and ASP3662 placebo once daily (morning) and pregabalin placebo 3 times daily (morning, midday and evening) for taper/week 7.

Patients randomized to the pregabalin group received a 150 mg daily dose of pregabalin (50 mg 3 times daily [morning, midday and evening]) for titration/week 1; a 300 mg daily dose (100 mg 3 times daily [morning, midday and evening]) for treatment/weeks 2 to 6; and a 150 mg daily dose in taper/week 7. In the double-blind period (titration, treatment and taper, weeks 1 to 7), patients received ASP3662 placebo once daily (morning).

Patients randomized to the placebo group received matching ASP3662 placebo once daily (morning) with pregabalin placebo 3 times daily (morning, midday and evening) in the double-blind period (titration, treatment and taper/weeks 1 to 7).

Beginning on day 1 through week 6/early discontinuation (ED)/end of treatment (EOT), patients recorded all daily pain scores (NPRS and BPI-DN), date and time of study drug dosing and any acetaminophen use in the e-diary. All clinical reported outcomes (including pain scores and patient questionnaires) were completed in an e-diary. Patients were instructed to use the same device for the duration of the study and that the assessments were to be completed without the aid of the study staff or family members so as to not influence the responses provided by the patient.

Only acetaminophen was allowed as rescue therapy during the double-blind period, and was permitted up to 12 hours prior to each study visit. Patients were not allowed to use any other type of rescue therapy for pain relief during the study. If rescue therapy was taken, patients were to continue taking study drug and complete all protocol assessments.

Patients were not to take rescue therapy more than 3 times per week, and doses were to be limited to up to 1000 mg per dose and were not to exceed 2 grams per day. Patients were instructed to check the labels of other nonprescription medications to ensure that they did not contain acetaminophen so that the recommended dose was not exceeded.

Use of rescue therapy was to be recorded in the patient e-diary. Acetaminophen taken for conditions other than PDPN (e.g., headache, common cold) was also to be recorded in the e diary. Rescue therapy was not provided by the sponsor.

Patients returned to the study site approximately 1 and 2 weeks following the randomization visit, and returned to the study site approximately every 2 weeks thereafter until week 6/ED/EOT. Patients returned to the study site at week 7 and at week 8/end of study (EOS [Visits 4 to 9]). During these visits, patients underwent safety, efficacy, pharmacodynamic/pharmacokinetic procedures, and completed electronic patient reported outcome (ePRO) measurements and cognitive testing. Patients were instructed to bring the e diary to each study visit for the site staff to review study drug compliance, to assess rescue therapy use and to complete the patient questionnaires.

Sample collection for pharmacokinetics was obtained at [redacted] Patients were asked to take the morning dose at the site after all study assessments had been performed to allow for pharmacokinetic sample collection. For the other intervals, the patient was to take the morning dose at home prior to the study visit.

Cognitive testing was facilitated by the investigator and/or site staff, as appropriately trained, and patient reported outcome (PRO) measurements were to be completed without the aid of the site staff or family members so as not to influence the responses given by the patient.

This study design included a stopping rule for futility. [redacted]

An Independent Data Monitoring Committee (IDMC) was responsible for the interim futility evaluation of efficacy data defined in an IDMC Charter. [redacted]

If the study reached the futility criteria, the study was to be recommended for discontinuation and no new patients were to be enrolled. Additionally, patients who were already randomized were to be discontinued and were to return to the site for the week 6/ED/EOT visit assessments.

Patients who did not complete the titration and treatment were to be asked to complete an ED visit (week 6/ED/EOT/visit 7 procedures) and were offered a 7-day drug taper card.

All patients had an EOS visit up to 1 week following the end of taper (visit 9).

Total study duration for a patient was up to 13 weeks.

Number of Patients (Planned, Enrolled and Analyzed):

It was planned that 210 eligible patients would be randomized in a 1:1:1 ratio to receive ASP3662, pregabalin or placebo. A total of 115 patients were randomized and 114 received study treatment and were analyzed.

Diagnosis and Main Criteria for Inclusion:

The patient was required to meet all protocol-defined inclusion criteria to be enrolled; the key inclusion criteria specific to this study included:

- Patient had all of the following:
  a. Established diagnosis of diabetes (Type I or II) with painful diabetic peripheral neuropathy and glycosylated hemoglobin (HgbA1c) [redacted] at Screening.
  b. Stable diabetic regimen [redacted]
  c. At least a [redacted] history of PDPN.
  d. Diagnosis of PDPN was confirmed by [redacted] at Screening.
- Patient had a pain intensity score(s) [redacted] at Screening Visit and prior to randomization.
- Patient agreed to complete pain diaries and was compliant with the daily pain recording prior to randomization as defined by [redacted]
- Patient was willing to maintain current nonpain medications at their same prescribed dose throughout the study.
- Patient's antidiabetic regimen was anticipated to be stable throughout the study.
- Patient was willing to washout of all medications currently being taken to treat his/her PDPN (chronic and occasional/as needed) and remained off of those pain medications while participating in the study.

The patient was required not to meet any protocol defined exclusion criteria to be enrolled; the key exclusion criteria specific to this study included:

- Patient had received prior treatment with pregabalin for PDPN and was considered unresponsive or intolerant.
- Patient had tried and failed [redacted] to treat PDPN within the [redacted]. Drugs had to have been administered at therapeutic doses and had to have been administered for an adequate period of time.
- Patient had a known hypersensitivity to ASP3662, pregabalin, gabapentin or acetaminophen, or their formulation components.
- Patient had significant pain (moderate or above) due to causes other than PDPN (e.g., compression-related neuropathies [e.g., spinal stenosis, fibromyalgia or arthritis]) that may have interfered with assessment of PDPN-related pain. In addition, patient had significant chronic pain that could not be differentiated from, or conditions that may have interfered with the assessment of, the PDPN such as plantar fasciitis, heel spurs, tibial neuropathy, Morton's neuroma, bunions, metatarsalgia, arthritis in the feet, peripheral vascular disease (ischemic pain), neurologic disorders unrelated to diabetic neuropathy (e.g., phantom limb pain); skin condition in the area of neuropathy that could alter sensation.
- Patient had a history of painful peripheral neuropathy due to a cause other than diabetes. Examples include, but are not limited to: vitamin B deficiency, drug-induced neuropathies (e.g., chemotherapy-

induced neuropathy), hypothyroidism, autoimmune disease (e.g., lupus), infectious and inherited diseases (e.g., Charcot-Marie-Tooth disease).

- Patient had any lower extremity amputation. Patient had a documented history of a post-traumatic amputation (e.g., loss of a leg, foot or toe due to an accident) would be allowed into the study.
- Patient had a current or previous foot ulcer within the past 3 months as described by medical history and/or medical examination.
- Patient had a Hospital Anxiety and Depression Scale (HADS) score > 12 on either subscale at Screening.
- Patient had an established history of major depressive disorder within the last 3 years.
- Patient had a history of suicidal behavior and/or ongoing suicidal ideation (a level of 4 [intent to act] or 5 [specific plan and intent to act]) as judged by the investigator using the Columbia-Suicide Severity Rating Scale (C-SSRS) at Screening and/or at Randomization.

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

- ASP3662 10 mg from [redacted] administered orally.
- Placebo to match ASP3662 10 mg from [redacted] administered orally.

Duration of Treatment (or Duration of Study, if applicable):

The study included 7 weeks of treatment (titration week 1, double-blind week 2 to week 6, taper week 7)

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

- Lyrica 50 mg commercial/Pfizer purchased in US from [redacted].
- Over-encapsulated pregabalin 50 mg from [redacted] administered orally.
- Lyrica 100 mg commercial/Pfizer purchased in US from [redacted].
- Over-encapsulated pregabalin 100 mg from [redacted] administered orally.
- Placebo to match pregabalin 50 mg or 100mg from [redacted] administered orally.

Criteria for Evaluation:

The primary objective of this study is to assess analgesic efficacy of ASP3662 relative to placebo in subjects with painful diabetic peripheral neuropathy (PDPN) as determined by the change in average daily pain score in the Numeric Pain Rating Scale (NPRS). In addition, this study will assess the safety and tolerability of ASP3662 relative to placebo.

The primary efficacy endpoint was:

- Change from Baseline to Week 6/End of Treatment (EOT) in mean 24-hour average pain intensity as reported on the NPRS (Appendix 3)

The primary analysis population was all randomized subjects who received at least one dose of study medication and at least one postbaseline efficacy measurement.

Secondary endpoints included:

- Percentage of Responders (at least 30% or 50% reduction) in mean 24-hour average pain intensity score (NPRS) from Baseline to Week 6/EOT
- Change from Baseline to Weeks 1, 2, 4 and 6 in mean 24-hour average pain intensity score (NPRS)
- Change from Baseline to Weeks 1, 2, 4 and 6 in mean daily worst pain score (BPI-DN)
- Change from Baseline to Weeks 1, 2, 4 and 6 in mean daily average pain score (BPI-DN)

- Patient Global Impression of Change (PGIC) at Week 6/EOT
- Clinical Global Impression of Change (CGIC) at Week 6/EOT

The safety endpoints were:

- Treatment-emergent adverse events/serious adverse events
- Clinical safety laboratory tests
- Vital signs
- 12-lead ECGs
- Columbia-Suicide Severity Rating Scale (C-SSRS)

Statistical Methods:

In general, all data were summarized with descriptive statistics (number of subjects, mean, standard deviation, minimum, median and maximum) for continuous endpoints, and frequency and percentage for categorical endpoints.

Unless otherwise specified, statistical tests were one-sided for efficacy analyses and two-sided for selected safety analyses and the null hypothesis was rejected at the significance level of $\alpha = 0.05$. For all efficacy and safety analyses, the primary comparison was between the ASP3662 group and placebo group. In addition, the treatment differences between the pregabalin group and the placebo group were also summarized, analyzed and presented, if applicable, and treatment differences in the primary efficacy variable between ASP3662 and pregabalin groups were explored.

When a study center was included in efficacy analyses, centers that did not enroll a sufficient number of subjects were pooled according to a prespecified algorithm.

A total sample size of 210 subjects was planned to be randomized in a 1:1:1 ratio into 3 treatment groups. This sample size, [redacted] would provide approximately [redacted] between ASP3662 and placebo in the primary efficacy variable.

Detailed criteria for analysis sets were laid out in classification specifications, and the allocation of subjects to analysis sets was determined prior to database hard-lock and included a full analysis set (FAS), per protocol set (PPS), safety analysis set (SAF), pharmacokinetic analysis set (PKAS) and pharmacodynamic set (PDAS).

Demographics and other baseline characteristics were summarized by treatment group for the FAS, PPS and SAF. Descriptive statistics included the number of subjects, mean, standard deviation, minimum, median and maximum for continuous endpoints, and frequency and percentage for categorical endpoints.

Efficacy analysis was conducted on the FAS and PPS. The interpretation of results from statistical tests was based on the FAS. The PPS was used to assess the robustness of the results from the statistical analyses based on the FAS.

Safety analyses were conducted using the SAF, unless otherwise stated in the statistical analysis plan (SAP) for the study.

Summary of Results/Conclusions:

Population

A total of 115 patients, from 24 investigative sites in the US, provided written informed consent and were randomized into 3 groups: 38 patients to ASP3662 10 mg once daily, 40 patients to pregabalin 100 mg 3 times daily and 37 patients to placebo. One patient in the pregabalin group was randomized in error and did not receive any study drug. Detailed data on all randomized patients who completed treatment and those who discontinued treatment (by primary reason), including discontinued treatment due to AEs, are shown in Table 1. Detailed data on all randomized patients who discontinued from the study, including the primary reasons for discontinuation, are also shown in Table 1.

Table 1 Patient Disposition and Analysis Sets

	Placebo (n = 37)	ASP3662 10 mg QD (n = 38)	Pregabalin 100 mg TID (n = 40)	Total (n = 115)
Analysis Sets, n (%)				
Randomized	37 (100)	38 (100)	40 (100)	115 (100)
Subjects Who Took Study Drug	37 (100)	38 (100)	39 (97.5)	114 (99.1)
Subjects Who Did Not Take Study Drug	0	0	1 (2.5%)	1 (0.9%)
Safety Analysis Set†	37 (100)	38 (100)	39 (97.5)	114 (99.1)
Full Analysis Set‡	37 (100)	38 (100)	39 (97.5)	114 (99.1)
Per Protocol Set§	33 (89.2)	32 (84.2)	38 (95)	103 (89.6)
Pharmacokinetics Analysis Set¶	0	29 (76.3)	0	29 (25.2)
Pharmacodynamic Analysis Set ††	36 (97.3)	36 (94.7)	38 (95)	110 (95.7)
Treatment Discontinuation, n (%)				
No	33 (89.2)	27 (71.1)	32 (80.0)	92 (80.0)
Yes	4 (10.8)	11 (28.9)	8 (20.0)	23 (20.0)
Primary End of Treatment Reason, n (%)				
Adverse Event	2 (5.4)	2 (5.3)	1 (2.5)	5 (4.3)
Lost to Follow-up	0	0	1 (2.5)	1 (0.9)
Protocol Deviation	0	2 (5.3)	0	2 (1.7)
Withdrawal by Subject	1 (2.7)	4 (10.5)	2 (5.0)	7 (6.1)
Study Terminated by Sponsor	1 (2.7)	2 (5.3)	3 (7.5)	6 (5.2)
Site Terminated by Sponsor	0	0	0	0
Other	0	1 (2.6)	1 (2.5)	2 (1.7)

† All subjects who were randomized and received at least one dose of study drug.

‡ All subjects who were randomized and received at least one dose of study drug and had at least one postbaseline efficacy measurement.

§ All subjects in the Full Analysis Set who do not meet criteria for exclusion from the Per Protocol Set.

¶ All subjects in the Safety Analysis Set for which sufficient plasma concentration data are available to facilitate derivation of at least one pharmacokinetic parameter and for whom the time of dosing on the day of sampling is known.

†† All subjects in the Safety Analysis Set for whom sufficient pharmacodynamics measurements were collected.

Source: Table 12.1.1.2, Table 12.1.1.3

Demographics for patients in the FAS are presented in Table 2. In general, treatment groups were similar with respect to demographics.

Table 2 Demographic Characteristics

Characteristic	Placebo (n = 37)	ASP3662 10 mg QD (n = 38)	Pregabalin 100 mg TID (n = 40)	Total (n = 115)
Sex				
Male	21 (56.8)	21 (55.3)	21 (53.8%)	63 (55.3)
Female	16 (43.2)	17 (44.7)	18 (46.2)	51 (44.7)
Race				
White	27 (73.0)	29 (76.3)	30 (76.9)	86 (75.4)
Black or African American	8 (21.6)	9 (23.7)	9 (23.1)	26 (22.8)
Asian	2 (5.4)	0	0	2 (1.8)
Ethnicity				
Non-Hispanic or –Latino	31 (83.8)	30 (78.9)	29 (74.4)	90 (78.9)
Hispanic or Latino	6 (16.2)	8 (21.1)	10 (25.6)	24 (21.1)
Age Group (years)				
< 65 Years	23 (62.2)	26 (68.4)	30 (76.9)	79 (69.3)
65 – 75 Years	14 (37.8)	12 (31.6)	9 (23.1)	35 (30.7)
> 75 Years	0	0	0	0
Age (years)				
Mean (SD)	60.8 (9.4)	60.1 (9.8)	57.7 (7.7)	59.5 (9.0)
Median	61.0	60.5	57.0	60.0
Minimum-Maximum	39-75	32-74	41-72	32-75
Height (cm)				
Mean (SD)	170.4 (9.1)	170.4 (10.4)	169.7 (10.2)	170.1 (9.9)
Median	170.1	171.0	170.2	170.6
Minimum-Maximum	152-188	149-188	147-191	147-191
Weight (kg)				
Mean (SD)	98.4 (13.7)	93.6 (18.2)	94.3 (20.7)	95.4 (17.8)
Median	100.7	98.7	97.5	98.9
Minimum-Maximum	67-121	52-120	55-133	52-133

All patients who were randomized and received at least one dose of study drug and had at least one postbaseline efficacy measurement (Full Analysis Set).

Source: Table 12.1.2.1.3

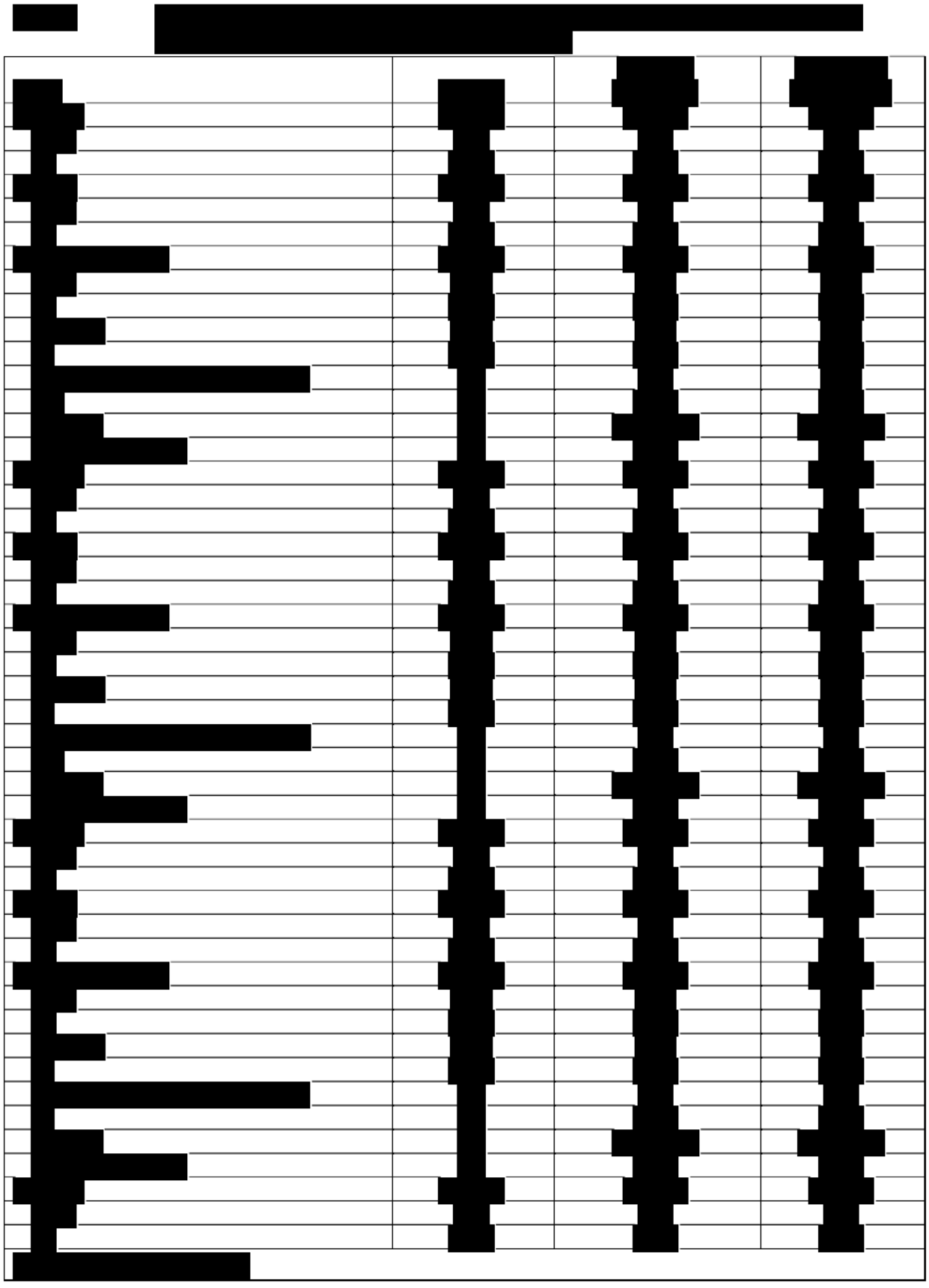
Efficacy/Pharmacokinetic/Pharmacodynamic Results:

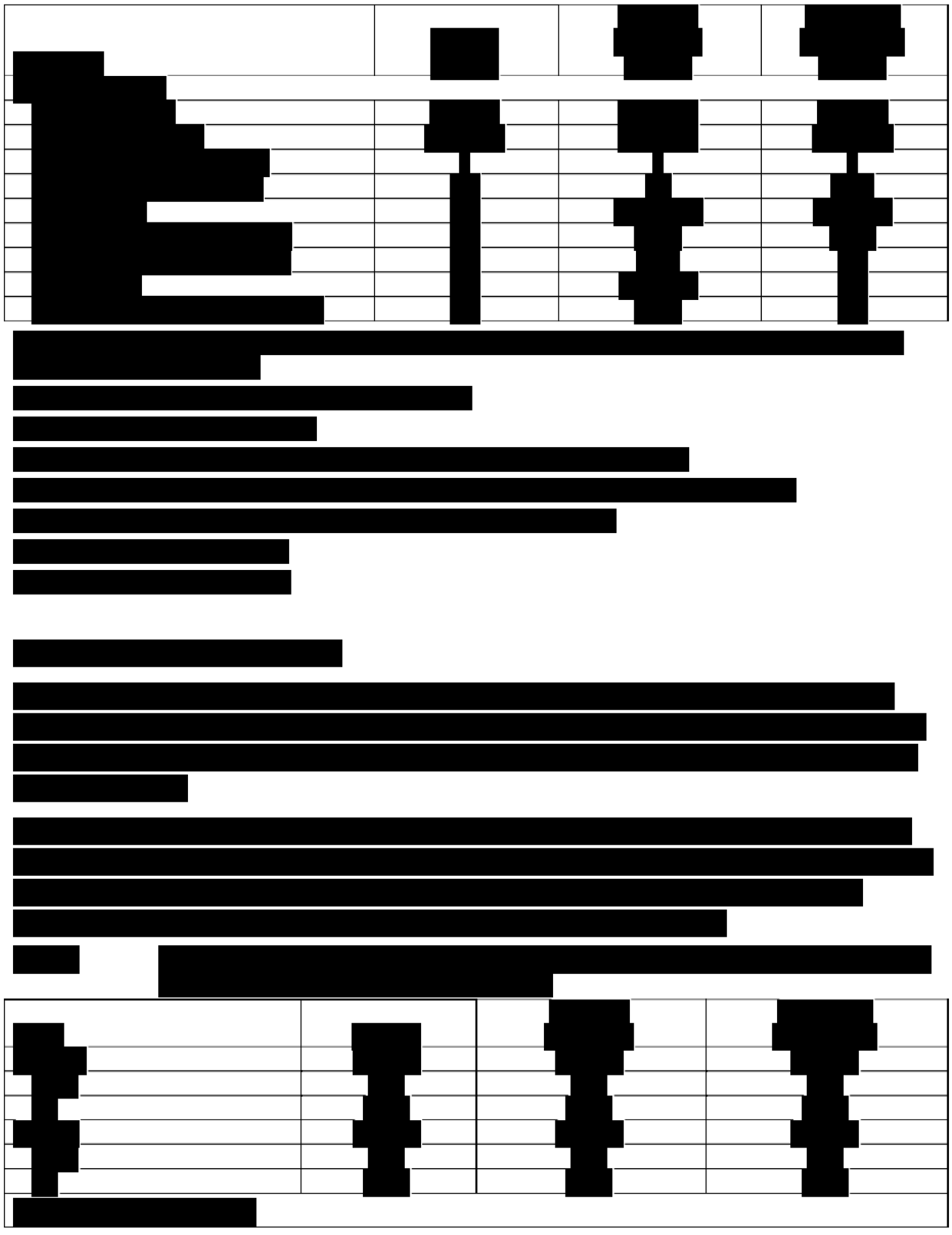
Primary Efficacy

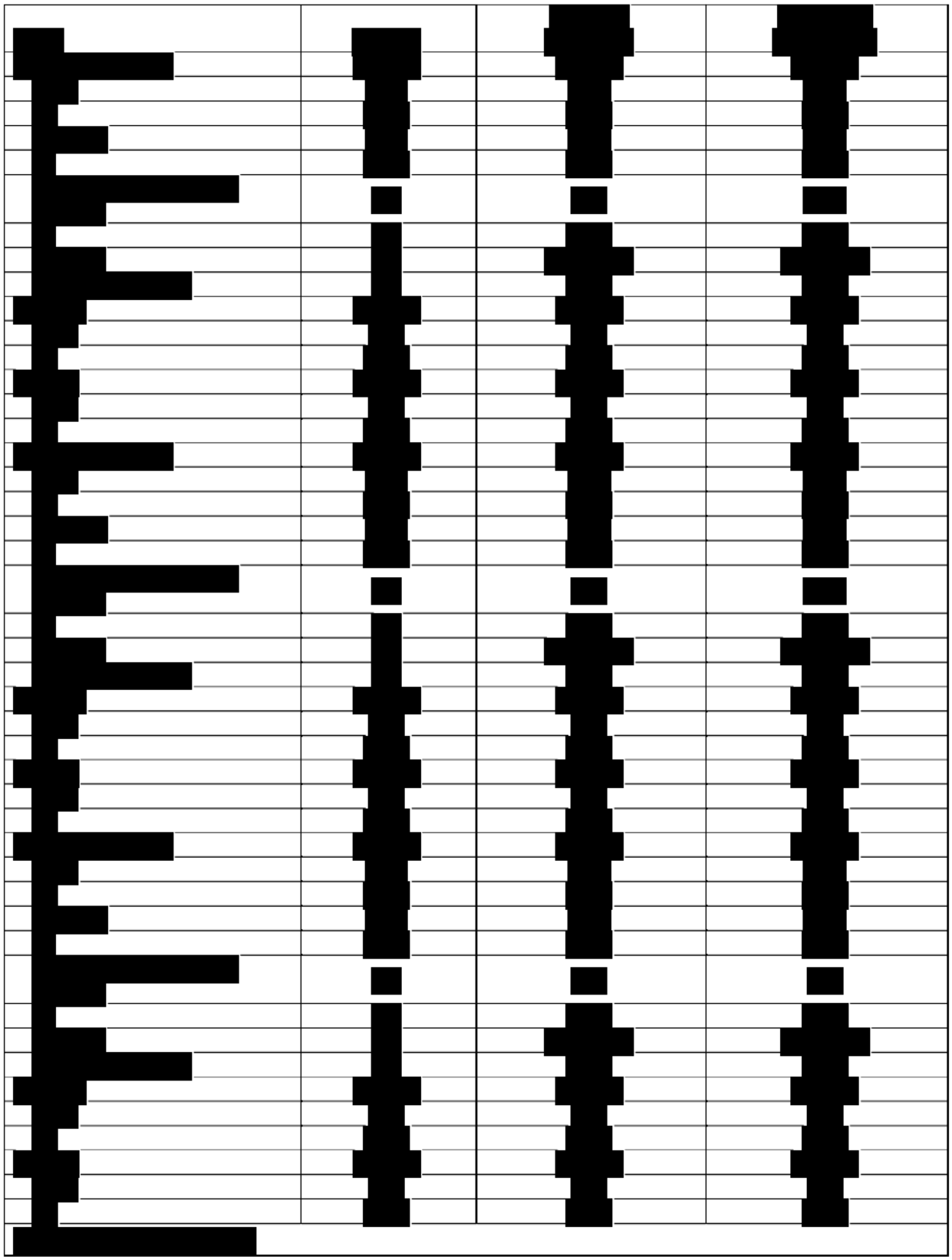
The 24-hour average pain intensity measurement was the primary efficacy assessment in this study. The primary measure used to capture the average pain score in the last 24 hours on a daily basis in the e-diary was the NPRS (11 point scale 0 – 10, where 0 anchors “no pain” and 10 “worst pain imaginable”).

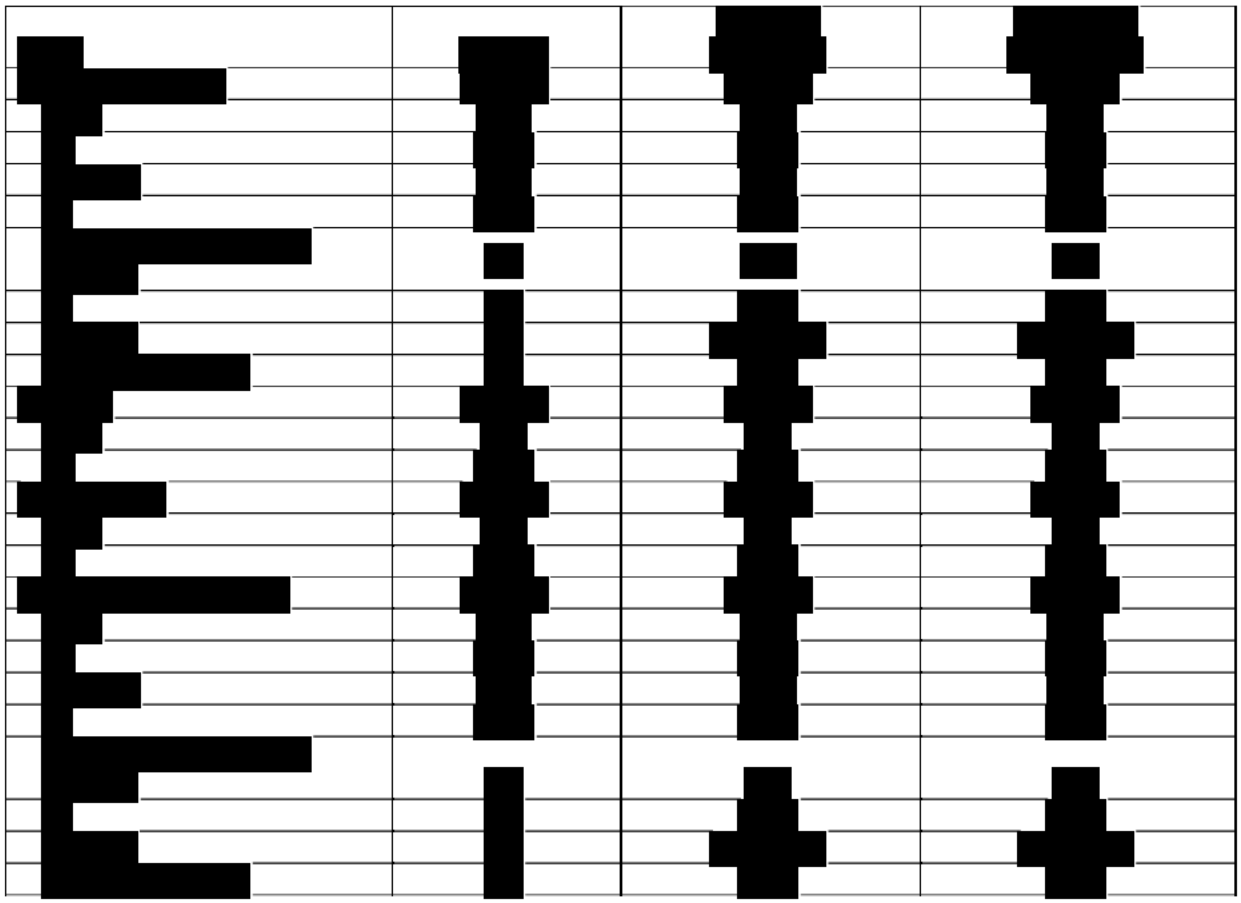
The primary treatment comparison was between ASP3662 and placebo. The treatment group differences between ASP3662 and pregabalin and pregabalin and placebo were also evaluated. The study endpoint was after 6 weeks of treatment or earlier for patients who discontinued treatment. There were no statistically significant treatment differences observed and results numerically favor placebo [Table 3].

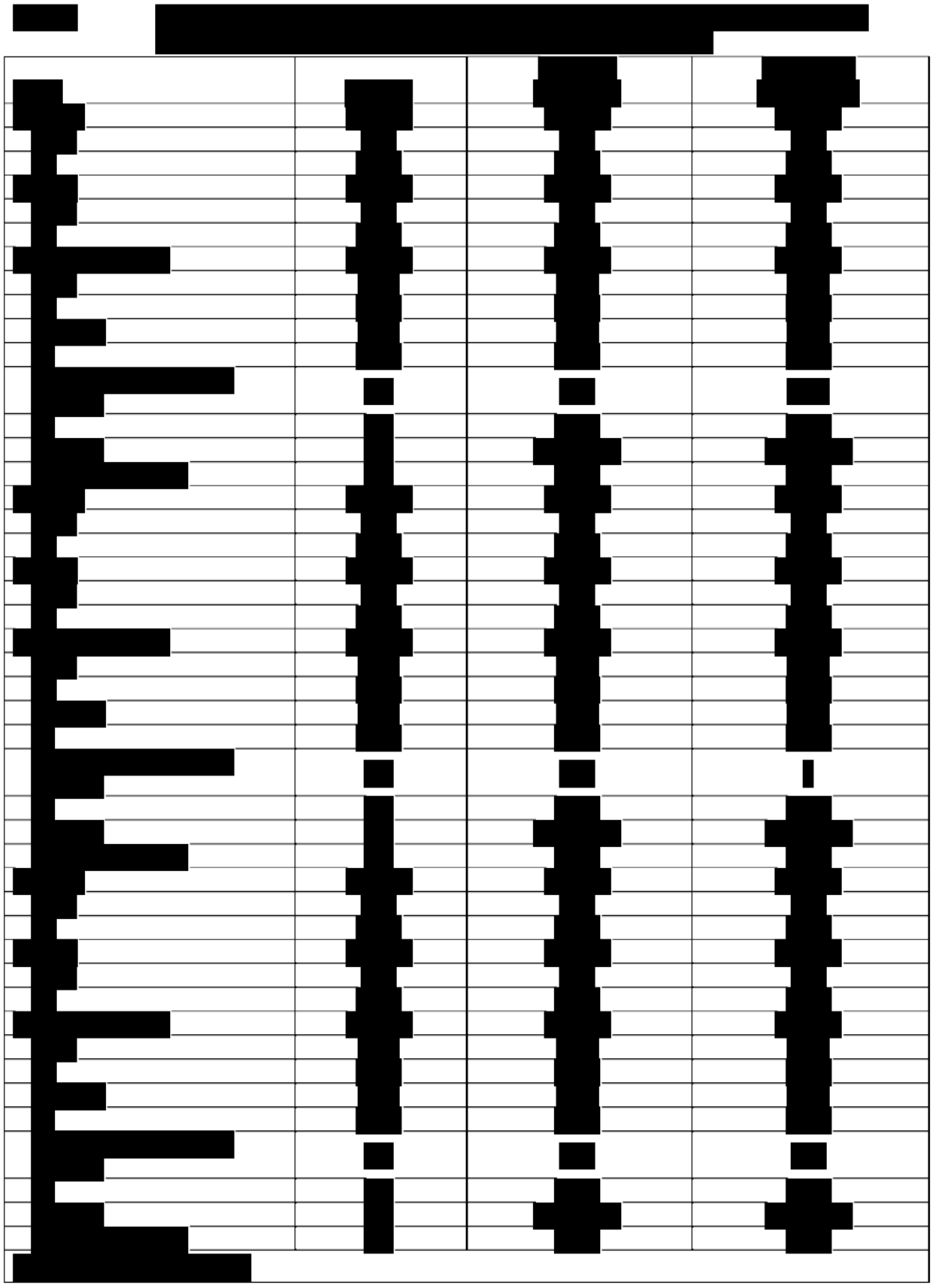
[redacted]

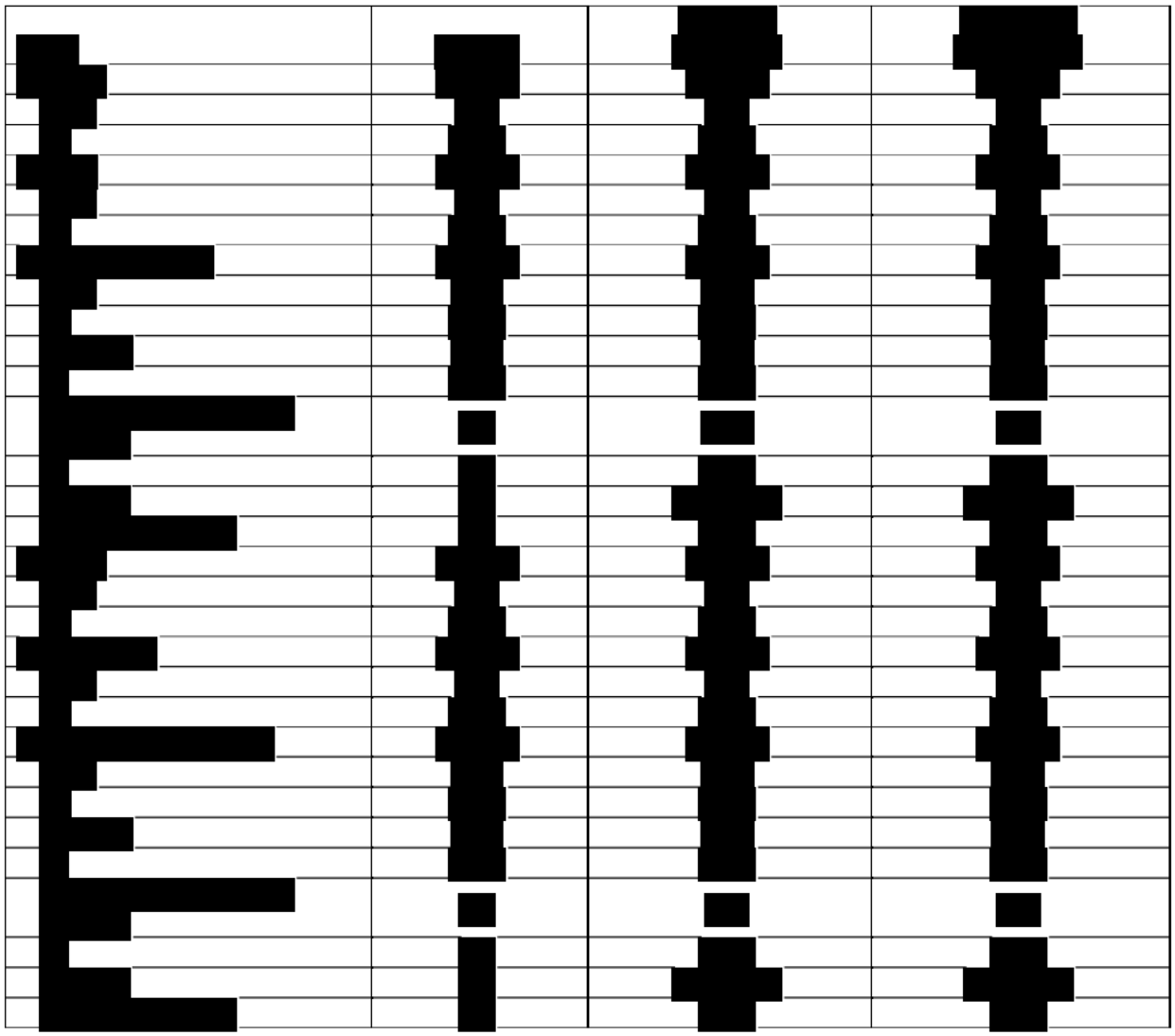




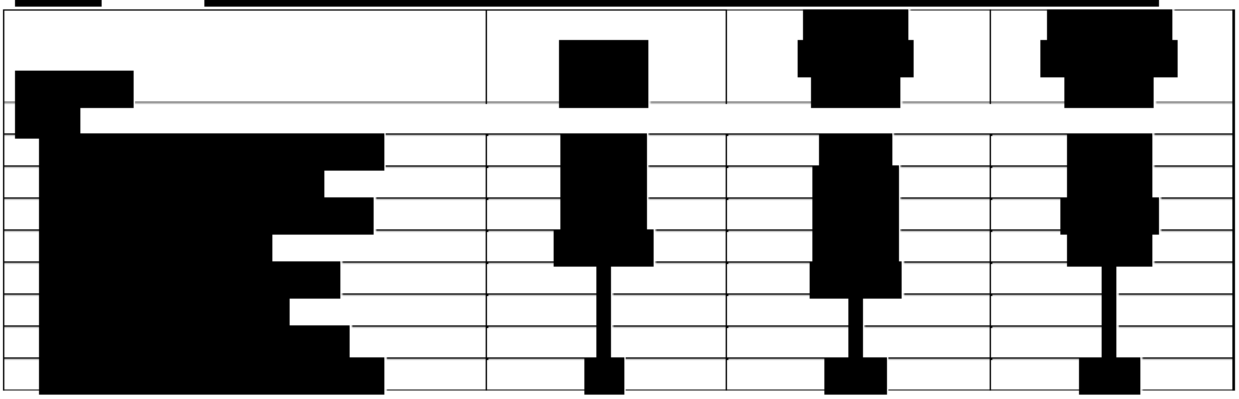








[redacted]



[redacted]

[redacted]

The study was stopped for futility [redacted]

[redacted]

There was no statistically significant treatment difference in efficacy observed among treatment groups, and results numerically favored placebo.

Pregabalin failed to demonstrate its assay sensitivity for the PDPN patients in the study.

Pharmacokinetics

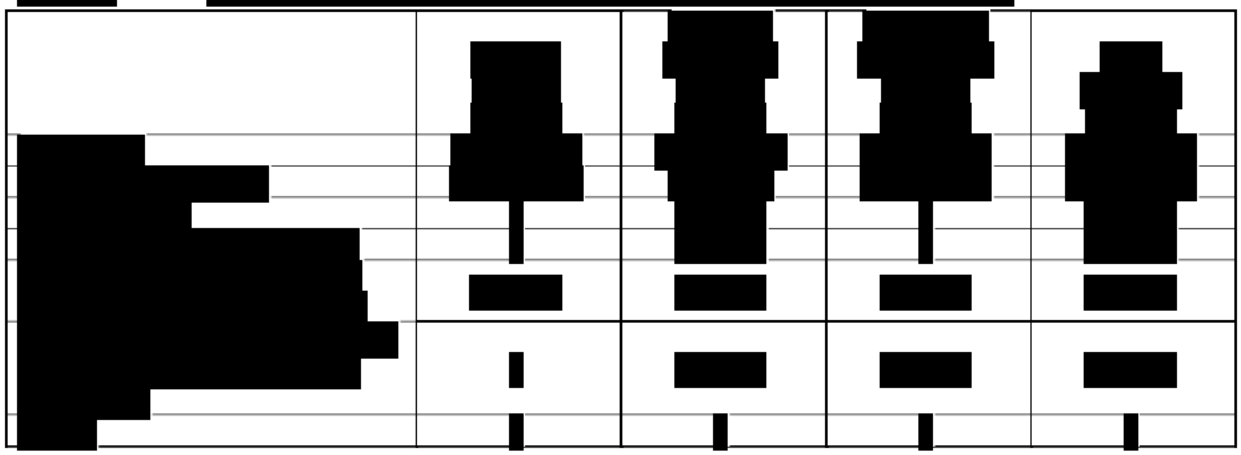
[redacted]

Pharmacodynamics

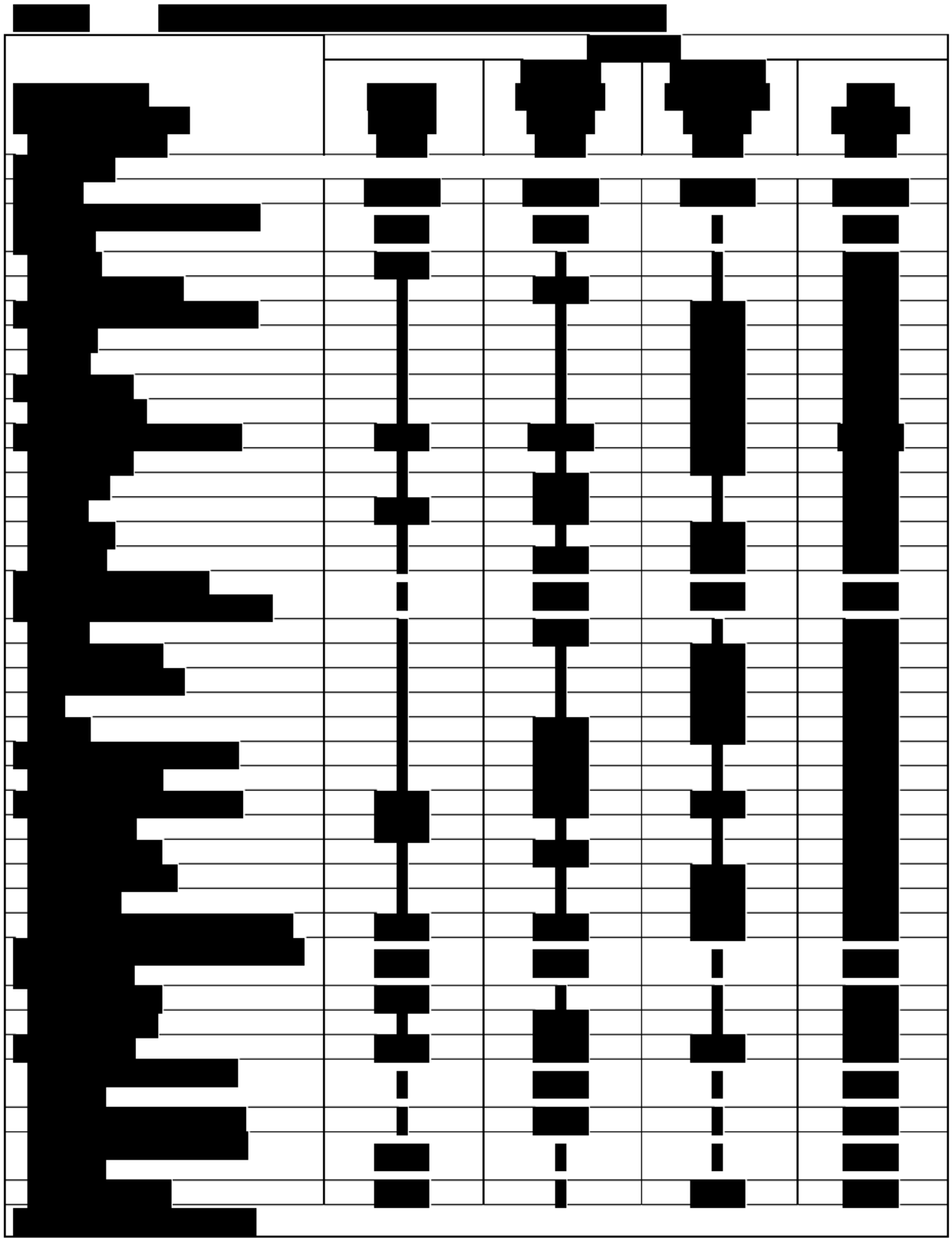
[redacted]

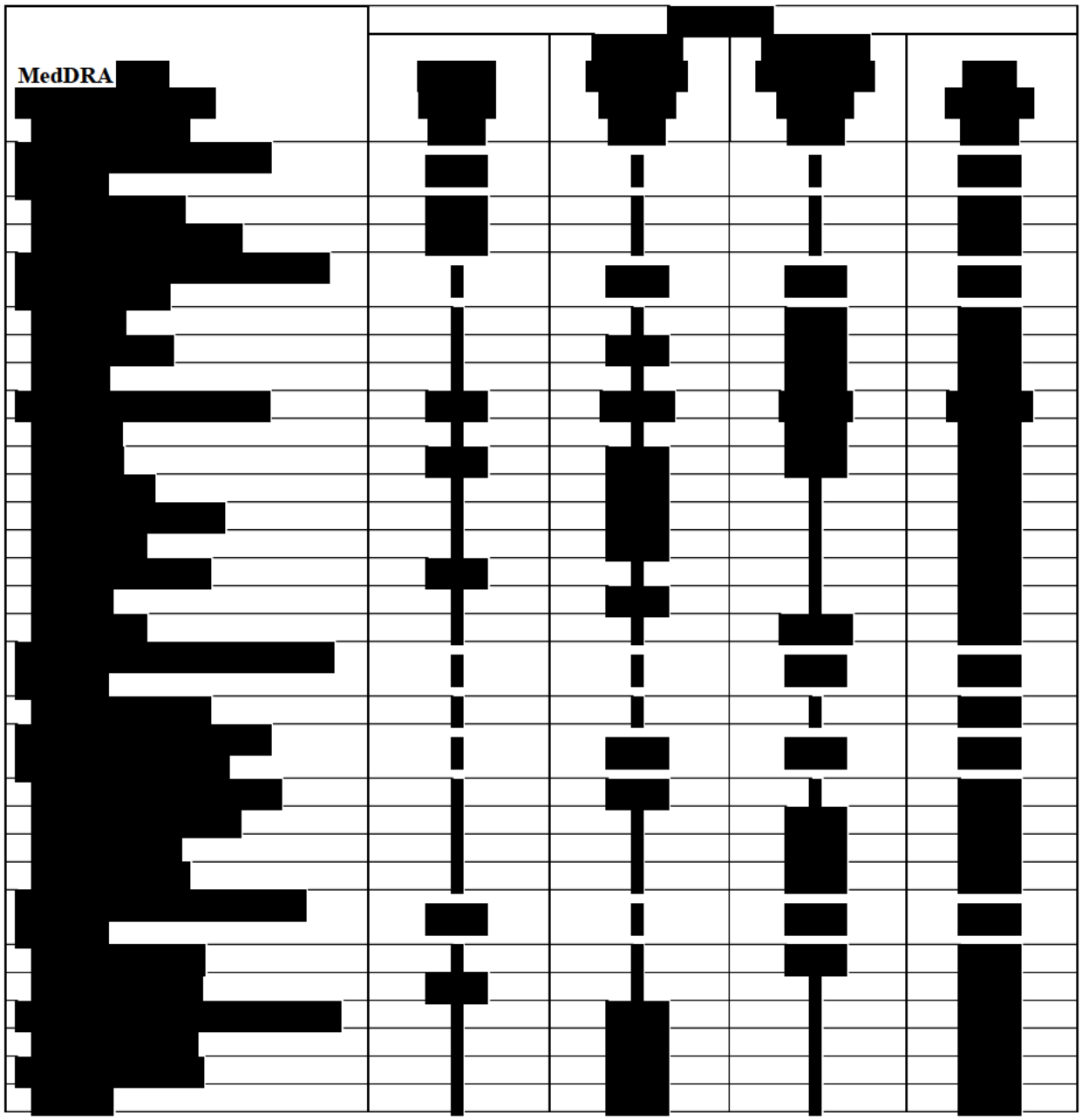
Safety Results:

[redacted]

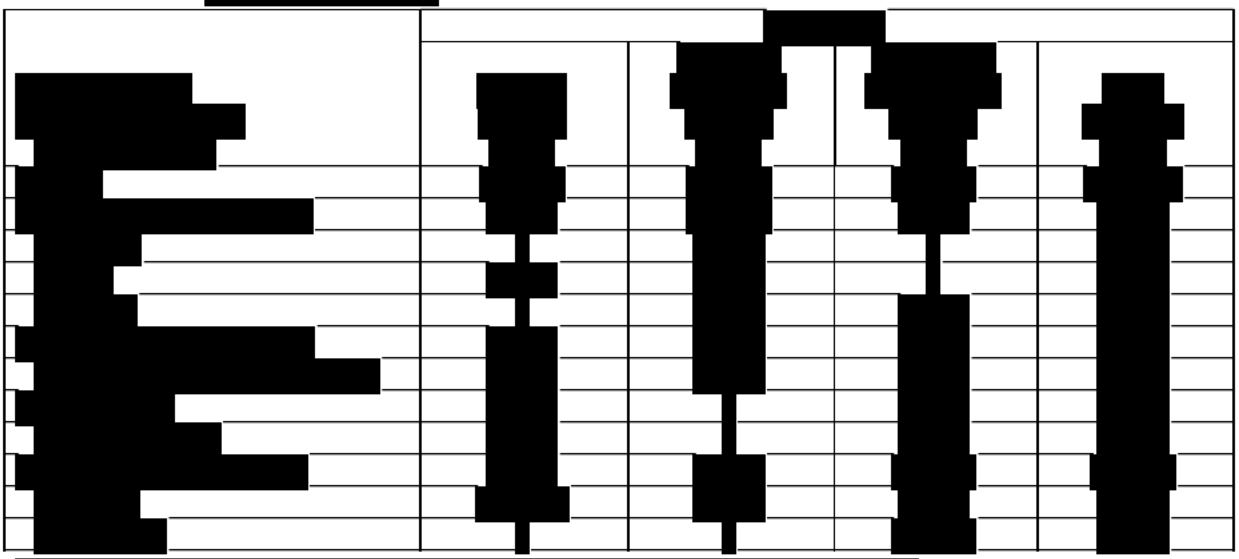


[redacted]

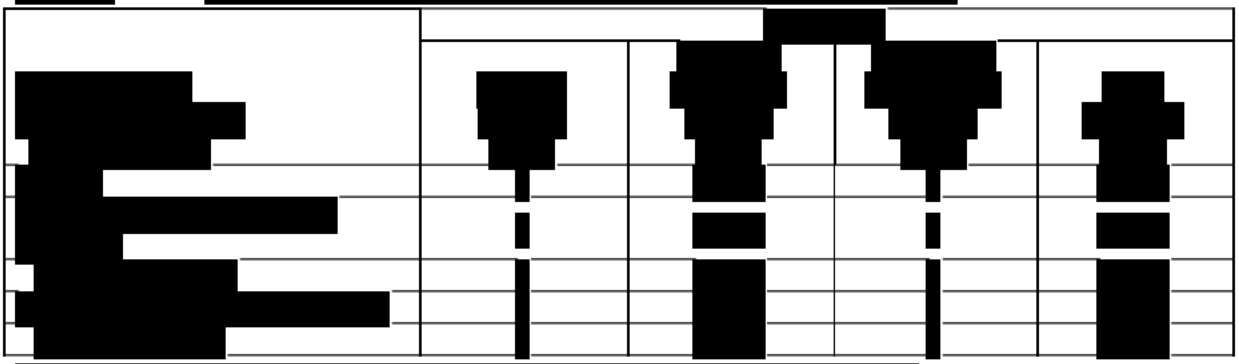



MedDRA

[redacted]

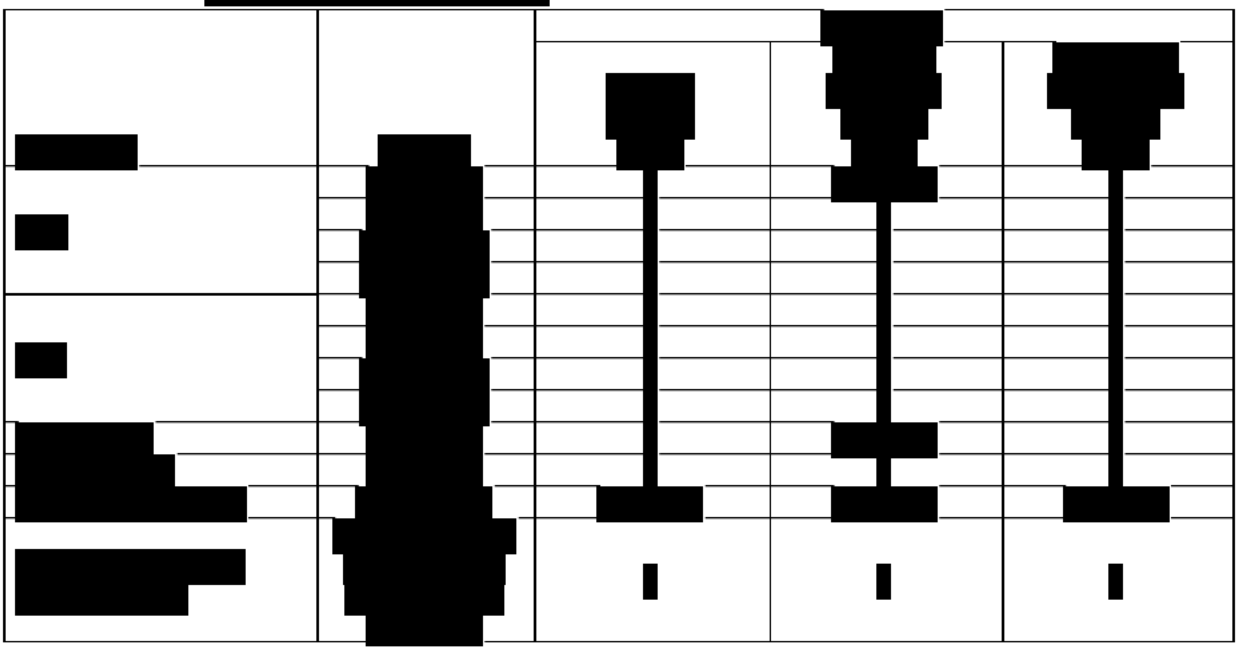


[redacted]



[redacted]

[redacted]



[redacted]

[redacted]

CONCLUSIONS:

ASP3662 did not appear to exert analgesic effects in patients with PDPN compared to placebo as assessed by the primary endpoint, the NPRS, or any of the secondary endpoints. However, the positive comparator pregabalin also failed to exert analgesic effects in patients with PDPN compared to placebo as assessed by the NPRS or any of the secondary endpoints.

The trough plasma concentrations of ASP3662 at weeks 2, 4 and 6 were comparable to those reported for 10 mg QD in healthy volunteers.

ASP3662 reduced peripheral 11β-HSD1 activity [redacted] There was no evidence for 11β-HSD2 inhibition [redacted] All of these pharmacodynamic changes are consistent with previous phase 1 results with ASP3662. Both the pharmacodynamic and pharmacokinetic changes support general compliance with ASP3662 prescribed dosing.

ASP3662 appeared to be safe and well tolerated compared to placebo with respect to TEAEs, vital signs, ECGs and laboratory analytes. [redacted]

The adverse event profile associated with pregabalin, given the modest sample size, suggests adequate treatment compliance.

[redacted] ASP3662 10 mg once daily for 6 weeks in patients with PDPN was safe and well tolerated. [redacted]

Date of Report: 21 Nov 2016