Clinical trial results:
A Phase 2a Enriched Enrollment Randomized Withdrawal Study to Assess Analgesic Efficacy and Safety of ASP8477 in Subjects with Peripheral Neuropathic Pain (MOBILE)

Summary

EudraCT number	2013-002521-27
Trial protocol	DE CZ GB
Global end of trial date	13 February 2015

Results information

Result version number	v1 (current)
This version publication date	14 July 2016
First version publication date	14 July 2016

Trial information

Trial identification

Sponsor protocol code	8477-CL-0020

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02065349
WHO universal trial number (UTN)	-
Other trial identifiers	Astellas Code: ASP8477

Notes:

Sponsors

Sponsor organisation name	APGD EU, Astellas Pharma B.V.
Sponsor organisation address	Sylviusweg 62, Leiden, Netherlands, 2333 BE
Public contact	Senior Medical Director, APGD US, Astellas.resultsdisclosure@astellas.com
Scientific contact	Senior Medical Director, Global Medical Science, Astellas Pharma B.V., Astellas.resultsdisclosure@astellas.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 February 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to assess analgesic efficacy of ASP8477 relative to placebo in participants with peripheral neuropathic pain (PNP) 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 participants with peripheral neuropathic pain (PNP), as determined by the time to efficacy failure in responders.

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal, national and/or regional legislation related to the privacy and protection of personal information.

Background therapy:

.

Evidence for comparator: -

Actual start date of recruitment	24 February 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Czech Republic: 73
Country: Number of subjects enrolled	Poland: 53
Country: Number of subjects enrolled	United Kingdom: 6
Worldwide total number of subjects	132
EEA total number of subjects	132

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	74
From 65 to 84 years	57
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

In total 12 centers enrolled participants from 3 different countries. Eligible participants were male or female, ≥ 18 years of age with peripheral neuropathic pain (PNP) resulting from painful diabetic peripheral neuropathy (PDPN) or postherpetic neuralgia (PHN).

Pre-assignment

Screening details:

The study consisted of a 4-week Screening Period including a 1-week Single-blind Placebo Run-in Period. Subjects with an average Numeric Pain Rating Scale score of 4-8 on the last 3 days of the Run-in entered a 4-week Single-blind Treatment Period. Responders in the Single-blind Period entered a 3-week Double-blind Randomized Withdrawal Period.

Period 1

Period 1 title	Placebo Run-in Period
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

During the placebo run-in period investigators and study staff instructed participants that they might or might not be receiving active study drug.

Arms

Arm title	Placebo

Arm description:

Participants received 3 placebo tablets twice-daily from Day -7 to Day -1.

Arm type	Placebo
Investigational medicinal product name	Placebo to Match ASP8477
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matched the tablet strength of 10 mg of ASP8477.

Number of subjects in period 1	Placebo
Started	132
Completed	116
Not completed	16
Consent withdrawn by subject	1
Didn't match inclu/exclu criteria	15

Period 2

Period 2 title	Single-blind Treatment Period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

During the single blind period investigators and study staff instructed the participants that they might or might not be receiving active study drug.

Arms

Arm title	ASP8477 20/40/60 mg

Arm description:

Participants received starting dose of ASP8477 10 mg twice-daily for 3 days (Days 1, 2 and 3). If tolerated, the dose was escalated to 20 mg twice-daily administered on Days 4, 5 and 6. Participants entered the maintenance phase at 30 mg dose twice-daily on Day 7 and if the dose was well tolerated continued at that dose for 21 days.

Arm type	Experimental
Investigational medicinal product name	ASP8477
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

ASP8477 immediate-release tablets in the strength of 10 mg of active substance.

Number of subjects in period 2	ASP8477 20/40/60 mg
Started	116
Completed	110
Not completed	6
Consent withdrawn by subject	2
Adverse event, non-fatal	2
Protocol deviation	2

Period 3

Period 3 title	Double-blind Withdrawal Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

During the double-blind withdrawal period participants were randomized to receive ASP8477 or placebo in a double-blind fashion such that neither the investigator, Sponsor’s study management team, clinical staff, nor the patient knew which agent was being administered.

Arms	
Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants were randomly assigned on Day 28 (Visit 8) to receive placebo for 3 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo to Match ASP8477
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matched the tablet strength of 10 mg of ASP8477.

Arm title	ASP8477 40/60 mg

Arm description:

Participants were randomly assigned on Day 28 (Visit 8) to receive ASP8477 at the same dose continued from the Single-blind Maintenance Period (i.e., 20 mg or 30 mg twice daily)

Arm type	Experimental
Investigational medicinal product name	ASP8477
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

ASP8477 immediate-release tablets in the strength of 10 mg of active substance.

Number of subjects in period 3[1]	Placebo	ASP8477 40/60 mg
Started	34	37
Completed	32	31
Not completed	2	6
Adverse event, non-fatal	-	1
Protocol deviation	2	2
Withdrawal by patient	-	3

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Only participants identified as the responders (individuals who had a ≥ 30% decrease in mean average daily pain intensity) were moved to Double-blind Period.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo Run-in Period

Reporting group description:

Baseline characteristics reflect data collected for the SAF1 population, all participants who took at least one dose of study medication during the placebo run-in period.

Reporting group values	Placebo Run-in Period	Total	
Number of subjects	132	132	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 62.7 ± 9.1	 -	
Gender categorical Units:			
Male	82	82	
Female	50	50	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received 3 placebo tablets twice-daily from Day -7 to Day -1.	
Reporting group title	ASP8477 20/40/60 mg
Reporting group description:	
Participants received starting dose of ASP8477 10 mg twice-daily for 3 days (Days 1, 2 and 3). If tolerated, the dose was escalated to 20 mg twice-daily administered on Days 4, 5 and 6. Participants entered the maintenance phase at 30 mg dose twice-daily on Day 7 and if the dose was well tolerated continued at that dose for 21 days.	
Reporting group title	Placebo
Reporting group description:	
Participants were randomly assigned on Day 28 (Visit 8) to receive placebo for 3 weeks.	
Reporting group title	ASP8477 40/60 mg
Reporting group description:	
Participants were randomly assigned on Day 28 (Visit 8) to receive ASP8477 at the same dose continued from the Single-blind Maintenance Period (i.e., 20 mg or 30 mg twice daily)	
Subject analysis set title	ASP8477 40 mg
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants who received ASP8477 20 mg twice daily on day 14 of the single-blind treatment period.	
Subject analysis set title	ASP8477 60 mg
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants who received ASP8477 30 mg twice daily on day 14 of the single-blind treatment period.	

Primary: Change from Double-blind Baseline in Mean of 24-Hour Average NPRS Score to End of Double-blind Period

End point title	Change from Double-blind Baseline in Mean of 24-Hour Average NPRS Score to End of Double-blind Period
End point description:	
The e-diary was used daily to capture the average pain in the past 24 hours using the NPRS scale (an 11-point scale 0 to 10, where "0" anchored "no pain" and "10" meant "pain as bad as you can imagine"). Assessment was based on the question 5 of the Brief Pain Inventory – Diabetic Neuropathy. The scores of the 24-hour average pain intensity (NPRS) assessments from the last 3 days of the double-blind randomized withdrawal period were determined for each participant and compared to the double-blind baseline score. Double-blind baseline NPRS score was defined as the mean of 24-hour average pain intensity for the last 3 days of the single-blind period. The end of double-blind period NPRS score was defined as the mean of 24-hour average pain intensity for the last 3 days of the double-blind period. A negative change from baseline represented a reduction in pain, and a positive change represented an increase in pain.	
End point type	Primary
End point timeframe:	
Last 3 days of single-blind period (study days 25-27) and last 3 days of double-blind withdrawal period (study days 27-49).	

End point values	Placebo	ASP8477 40/60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	33		
Units: Units on a scale				
arithmetic mean (standard deviation)	-0.11 (± 1.01)	-0.13 (± 1.05)		

Statistical analyses

Statistical analysis title	Treatment Difference Between ASP8477 and Placebo

Statistical analysis description:

Analysis of covariance model (ANCOVA) was used with treatment group and pooled sites as fixed factors and baseline as a covariate. 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.

Comparison groups	Placebo v ASP8477 40/60 mg
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.644 [1]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	0.11
Confidence interval	
level	95 %
sides	1-sided
upper limit	0.59
Variability estimate	Standard error of the mean
Dispersion value	0.29

Notes:

[1] - 1-sided

Secondary: Time to Treatment Failure in the Double-blind Randomized Withdrawal Period

End point title	Time to Treatment Failure in the Double-blind Randomized Withdrawal Period

End point description:

Endpoint reports number of participants with treatment failure in the Double-blind Randomized Withdrawal period. Treatment failure is defined as 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 Period.

End point type	Secondary

End point timeframe:

Day 28 (Visit 8) - Day 49 (Visit 10)

End point values	Placebo	ASP8477 40/60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	34		
Units: Participants				
Treatment Failures	4	5		
Censored Participants	29	29		

Statistical analyses

Statistical analysis title	Treatment Failure for Placebo v ASP8477

Statistical analysis description:

Cox proportional hazards model with covariates for treatment, pooled sites and double-blind baseline mean of 24-hour average pain intensity as covariates. One-sided 95% CI (upper limit) shown for treatment comparison.

Comparison groups	Placebo v ASP8477 40/60 mg
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.485 [2]
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	1-sided
upper limit	3.733

Notes:

[2] - 1-sided P value for treatment comparisons

Secondary: Percentage of Participants who Responded in the Single-blind Period to ASP8477 Treatment

End point title	Percentage of Participants who Responded in the Single-blind Period to ASP8477 Treatment

End point description:

Single-blind baseline NPRS score was defined as the mean of 24-hour average pain intensity for the last 3 days of the placebo run-in period. Response to ASP8477 treatment was defined as a ≥ 30% decrease in mean average daily pain intensity (NPRS score) during the last 3 days of the single-blind maintenance period versus the last three days of the placebo run-in period (baseline of single-blind period).

End point type	Secondary

End point timeframe:

Last 3 days of of the placebo run-in period (study days -3 to -1) and last 3 days of the single-blind maintenance period (study days 25-27)

End point values	ASP8477 20/40/60 mg			
Subject group type	Reporting group			
Number of subjects analysed	116			
Units: Percentage of Participants				
number (not applicable)				
Responder Rate	57.8			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with a Patient Global Impression of Change (PGIC) Response for Overall Patient Status

End point title	Number of Participants with a Patient Global Impression of Change (PGIC) Response for Overall Patient Status

End point description:

The PGIC queried participant: "As compared to when you started the treatment on visit 2, how would you rate your overall symptoms now?" The 7 PGIC grades were "very much worse", "much worse", "minimally worse", "no change", "minimally improved", "much improved" or "very much improved". A responder on the PGIC was defined as someone who scored "much improved" or "very much improved" on the scale.

End point type	Secondary

End point timeframe:

Day 28 (Visit 8) and Day 49 (EOT) (Visit 10)

End point values	Placebo	ASP8477 40/60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	34		
Units: Participants				
PGIC Responders at Double-blind Baseline	21	24		
PGIC Responders at Day 49 (EOT) [N=32;33]	22	21		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events During the Single-blind and Double-blind Period

End point title	Number of Participants with Adverse Events During the Single-blind and Double-blind Period

End point description:

A treatment-related AE was defined as any AE whose relationship to study drug was assessed as "possible" or "probable" by the investigator, or where the relationship to study drug was missing.

End point type	Secondary

End point timeframe:

Day 1- Day 49 (EOT)

End point values	ASP8477 20/40/60 mg	Placebo	ASP8477 40/60 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	116	34	37	
Units: Participants				
Adverse Events (AEs)	26	6	3	
Related Adverse Events	15	2	3	
Deaths	0	0	0	
Serious Adverse Events	1	1	0	
Drug-Related Serious AEs	0	0	0	
AEs Lead to Discontinuation of Study drug	2	0	1	
Drug-Related AEs Lead to Discontinuation of Study	1	0	1	
Orthostatic Challenge Test Related AEs	1	0	0	
Drug-Related Orthostatic Challenge Test Related AE	1	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of Pharmacokinetic Plasma Concentration of ASP8477

End point title	Assessment of Pharmacokinetic Plasma Concentration of ASP8477

End point description:

Summary of plasma concentrations for ASP8477 collected for each treatment dose (40 mg and 60 mg daily).Four participants discontinued prior to Day 14 and were therefore not assigned to any ASP8477 dose for this summary. In addition one participant was excluded from analysis due to undetectable levels.

End point type	Secondary

End point timeframe:

Predose and 1, 2, 4, 6 hour postdose on Day 14 (Visit 7)

End point values	ASP8477 40 mg	ASP8477 60 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2	107		
Units: ng/mL				
arithmetic mean (standard deviation)				
Predose [N=2; N= 107]	114.345 (± 70.407)	190.36 (± 166.564)		
Sample time 1 hour [N=2:N=106]	556.755 (± 77.534)	672.035 (± 339.031)		

Sample Time 2 hours [N=2:N=107]	434.305 (± 141.485)	605.364 (± 270.439)		
Sample Time 4 hours [N=2;N=107]	322.92 (± 153.315)	476.742 (± 247.315)		
Sample Time 6 hours [N=2;N=107]	241.155 (± 127.003)	372.442 (± 224.939)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Day 1- Day 49 (EOT)

Adverse event reporting additional description:

Treatment-emergent adverse events (TEAE) include all participants who received at least one dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	ASP8477 20/40/60 mg [FAS1]

Reporting group description:

Participants received starting dose of ASP8477 10 mg twice-daily for 3 days (Days 1, 2 and 3). If tolerated, the dose was escalated to 20 mg twice-daily administered on Days 4, 5 and 6. Participants entered the maintenance phase at 30 mg dose twice-daily on Day 7 and if the dose was well tolerated continued at that dose for 21 days.

Reporting group title	ASP8477 40/60 mg [SAF2]

Reporting group description:

Participants received 20 mg of ASP8477 twice-daily administered on Days 4, 5 and 6. Participants entered the maintenance phase at 30 mg dose twice-daily on Day 7 and if the dose was well tolerated continued at that dose for 21 days.

Reporting group title	Placebo [SAF2]

Reporting group description:

Placebo to match ASP8477

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Overall, there were no adverse events of marked frequency or severity observed in this study. Non-serious adverse events table was based on the frequency threshold of 5%

Serious adverse events	ASP8477 20/40/60 mg [FAS1]	ASP8477 40/60 mg [SAF2]	Placebo [SAF2]
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 116 (1.72%)	0 / 37 (0.00%)	1 / 34 (2.94%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Acute Myocardial Infarction			
subjects affected / exposed	0 / 116 (0.00%)	0 / 37 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			

subjects affected / exposed	1 / 116 (0.86%)	0 / 37 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal Failure Acute			
subjects affected / exposed	1 / 116 (0.86%)	0 / 37 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Ostemyelitis			
subjects affected / exposed	0 / 116 (0.00%)	0 / 37 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	ASP8477 20/40/60 mg [FAS1]	ASP8477 40/60 mg [SAF2]	Placebo [SAF2]
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 116 (0.00%)	0 / 37 (0.00%)	0 / 34 (0.00%)

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 February 2014	Amendment 2 was a substantial amendment issued after the first participant visit. Changes to the protocol included the following; Revised the definition of screen failure to reflect participants who were screened but not enrolled; Clarified that participants who discontinued from the study during the Titration Period should return to the clinic for the ED and EOS visits; Changed the use of concomitant medications; Modified the criterion regarding alcohol use during the study to specify that no more than moderate alcohol consumption by participants was allowed; Modified rescue medication (ketoprofen) dosing from four times daily to PRN; Modified the pharmacokinetic endpoint to base the analysis on individual participant concentrations rather than on Ctrough, Cmax, and AUC0-6, which were not calculated; Added menstrual diary collection to visits 4 and 6 in the Schedule of Assessments; Clarified the timing of pharmacodynamic lab sample collection, so that on day 1, blood samples for hormones that regulate satiety and hunger (leptin, ghrelin, glucagon-like peptide, peptide YY, and cholecystokinin [CCK]) were taken prior to dosing, and that all pharmacodynamic lab samples (for hormones that regulate satiety and hunger and FAAH-substrates) were taken at the same time; Corrected duration of double-blind period to 3 weeks; Clarified that after a participant's dose had been reduced from 30 mg twice-daily to 20 mg twice-daily during the Single-blind Maintenance Phase the dose could not be changed again; a participant requiring further dose modification was to be discontinued from the study; Added instructions to site personnel to counsel the participants on the need to meet compliance with daily diary entries; were not eligible for randomization into the Double-blind Treatment Period; Added criteria for participant discontinuation; the participant experienced an AE and intense pain that required additional medical treatment.
03 March 2014	Amendment 3 was a substantial amendment requested by the Czech authorities and specific for the Czech Republic, it was issued prior to enrollment of the first Czech participants. Changes to the protocol included the following: Pharmacokinetic laboratory samples were not to be taken when the participant's pain score had a value of 7 to 10 on the NPRS scale on that visit. Added a criterion for discontinuation, i.e., if the participant recorded a pain score of 7 to 10 on the NPRS scale for a period of 3 consecutive days during the double-blind Period.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

A futility analysis of the responder rate, based on the FAS1, was performed by Astellas after first 75 participants completed or discontinued from the single-blind period. Test results confirmed study did not meet futility criterion.

Notes: