CLINICAL STUDY REPORT

SUMMARY published in EudraCT

CLINICAL TRIAL PHASE IIa PROOF OF CONCEPT, DOUBLE BLIND, RANDOMIZED, CONTROLLED WITH PLACEBO IN PATIENTS WITH NEUROPATHIC PAIN DUE TO PERIPHERAL NERVE INJURY

Version: 1; 17 February 2022

1 TITLE PAGE

Study Title:	Clinical trial phase IIa proof of concept, double blind, randomized, controlled with Placebo in patients with neuropathic pain due to peripheral nerve injury.
Investigational product:	PARENTIDE
Indication studied:	Neuropathic pain due to peripheral nerve injury.
Sponsor's Name:	BCN PEPTIDES S.A.
Study Number/Protocol identification:	EudraCT: 2016-002846-21/ PARENTIDE-02
Development phase of study:	Phase IIa
Study Dates:	Initiation date (first patient enrolled): 11 OCT 2017 Study completion date (last patient completed): 19 JUN 2018 Date of early termination: 19 NOV 2018
Investigator(s):	Dr. Joaquim Forés Coordinator of Research of the Institute of Medical and Surgical Specialties Senior Consultant of the Orthopedic Surgery and Traumatology service Hospital Clínic de Barcelona Villarroel, 170 08036 Barcelona Dr. Pere Torner Chief of the Orthopedic Surgery and Traumatology service Corporació Sanitària Parc Taulí Parc del Taulí, 1 08208 Sabadell (Barcelona)
Name of company/sponsor signatory:	Dra. Berta Ponsati. C.E.O. BCN PEPTIDES. Polígon Industrial els Vinyets-Els Fogars 2 08777 Sant Quinti de Mediona (Barcelona), Spain.
Good Clinical Practices:	The study was conducted in accordance with the protocol and the ethical principles of the Declaration of Helsinki, and that are consistent with the GCPs of the International Conference on Harmonization and the current legislation (Royal Decree 1090/2015).
Date of the report:	3 APR 2020

2 SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:</td><td>BCN PEPTIDES S.A.</td><td>Study Number:</td><td>PARENTIDE-02</td><td>EudraCT: 2016-002846-21</td></tr>
<tr><td>Name of Finished Product:</td><td colspan="4">PARENTIDE</td></tr>
<tr><td>Name of Active Ingredient:</td><td colspan="4">PAR</td></tr>
<tr><td>Title of the Study:</td><td colspan="4">Clinical trial phase IIa proof of concept, double blind, randomized, controlled with Placebo in patients with neuropathic pain due to peripheral nerve injury.</td></tr>
<tr><td>Investigator(s):</td><td colspan="4">Dr. Joaquim Forés
Hospital Clínic de Barcelona

Dr. Pere Torner
Corporació Sanitària Parc Taulí</td></tr>
<tr><td>Study Centre(s):</td><td colspan="4">Hospital Clínic de Barcelona Villarroel, 170 08036 Barcelona.

Corporació Sanitària Parc Taulí, 08208 Sabadell (Barcelona).</td></tr>
<tr><td>Publication (reference):</td><td colspan="4">Currently, there are no publications of this study.</td></tr>
<tr><td rowspan="2">Study period:</td><td>Date of first enrolment:</td><td>11 OCT 2017</td><td rowspan="2">Phase of development:</td><td rowspan="2">Phase IIa</td></tr>
<tr><td>Date of last patient completed:</td><td>19 JUN 2018</td></tr>
<tr><td>Objectives:</td><td colspan="4">The Primary objective of this study was to assess the analgesic effect of repeated subcutaneous administration of PARENTIDE on neuropathic pain in subjects with peripheral nerve injury as a result of surgery or trauma.

Secondary study objectives were:
• To investigate the effect of repeated subcutaneous administration of PARENTIDE on dynamic allodynia and mechanical hyperalgesia in patients with neuropathic pain due to peripheral nerve injury as a result of surgery or trauma, as well as its effect on quality of life and sleep cycles.
• To investigate the safety and tolerability of repeated subcutaneous administration of PARENTIDE in patients with neuropathic pain due to peripheral nerve injury as a result of surgery or trauma.
• To assess the pharmacokinetic profile of PARENTIDE and its metabolites (exclusively with the purpose of confirming their levels in patients after first administration).</td></tr>
<tr><td>Methodology:</td><td colspan="4">Patients with a mean daily pain intensity score ≥6 (including the ratings for morning and evening pain) measured for at least four days during the baseline period, were randomized to receive either PARENTIDE or Placebo. Patients went to the hospital a total of nine times: in the screening period (Screening Visit, Day -28 to -8); at the start of the baseline period (Visit 0, Day -7); on the day of randomization (Visit 1, Day 1) for the first administration of PARENTIDE/Placebo(besides blood sampling for pharmacokinetic analysis); on Day 4 (Visit 2, they returned to the hospital for a blood extraction for pharmacokinetic analysis and to repeat the determinations of efficacy); then they returned on Days 8, 15 and 22 for their second, third and fourth administration of PARENTIDE/Placebo (Visits 3, 4 and 5, respectively); and two more times on Day 29 (Visit 6), and 10 days after Visit 6 (follow-up visit, or Visit 7) (Figure 1). During</td></tr>
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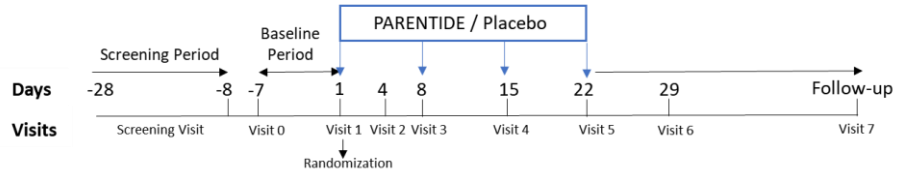
	visits, patients were subjected to the efficacy (SF-12, LANSS and allodynia and hyperalgesia questionnaires) and safety evaluations described in the activity calendar (Table 9.5.1). Efficacy was determined again at the follow-up visit (Visit 7) to investigate the maintenance of pain relief after discontinuing treatment with PARENTIDE.  **Figure 1:** Study design and schedule of assessment. Source: Protocol of PARENTIDE-02 Clinical Trial (P-EC-PAR-151116/01) Version 03. Additionally, patients used the mobile app "PARdolor" daily along the study. The app pushed notifications twice daily that the patient answered to register: – Pain intensity score in the morning (Morning Pain Intensity, MPI score), interference at night, tiredness and mood (in the morning, between 8:00h and 12:00h). – Pain intensity score in the evening (Evening Pain Intensity, EPI score), daily activity interference, tiredness, rescue medication, side effects and mood (in the evening, between 19:00h and 23:00h). Moreover, on demand, patients could register acute episodes of pain.
Number of patients (planned and analyzed):	A total of 80 patients was planned to be included in the study. The 10 first patients were included in group 1 (5 randomized in PARENTIDE and 5 in Placebo arms) to assess safety and tolerability. If no clinically relevant effects advising against the beginning of treatment of group 2, after four administrations of PARENTIDE/Placebo in group 1, based on the Principal Investigator's (PI) expert opinion, the rest of the patients (n=70) would have been recruited and randomized. Finally, due to the early termination of the trial based on the absence of appreciable clinical improvement in the first 10 patients treated (according to the expert opinion of the PI, questioning the benefit of continuing with the Clinical Trial), the statistical analysis was carried out after completing the randomization and treatment of the first 10 patients (5 PARENTIDE and 5 Placebo) recruited in a single-center, *Hospital Clínic de Barcelona*.
Diagnosis and Main criteria for inclusion:	Patients between 18 and 85 years old with a diagnostic of neuropathic pain with a pain intensity score of at least 6 on an 11-point numerical scale (where 0 means “No pain” and 10 means “Extreme pain”) estimated as the mean of daily pain intensity scores (including the ratings for morning and evening pain) during the baseline period and due to peripheral nerve injury as a result of surgery or trauma.
Test product, dose and mode of administration, batch number:	PARENTIDE 10 mg was reconstituted in 1 mL of sodium chloride 0.9% and was administered subcutaneously.
Duration of treatment:	Patients were followed for 10 weeks. The treatment was administered once per week for 4 weeks.

Reference therapy, dose and mode of administration, batch number:	Placebo was reconstituted in 1 mL sodium chloride solution 0.9%.
Criteria for evaluation:	**Efficacy:** Primary variable: • Change in average daily pain intensity score in the evening between the baseline period (V0-V1) and Week 4 of treatment (V5-V6) based on an 11-point numerical scale (0=No pain, 10=Extreme pain). Secondary variables: • Change in average daily pain intensity score in the evening between the baseline period (V0-V1) and Weeks 1, 2 and 3 of treatment and the follow-up period (Week 5, V6-V7). • Change in average daily pain intensity score in the morning between the baseline period (V0-V1) and Weeks 1, 2, 3 and 4 of treatment and the follow-up period (Week 5, V6-V7). • Change in neuropathic pain score in the LANSS neuropathic pain scale between baseline value and V2, V3, V4, V5, V6 and the follow-up Visit (V7). • Assessment of the analgesic effect of PARENTIDE as monotherapy or complementary treatment in the change in average daily pain intensity score (in the morning as well as in the evening). and in the LANSS neuropathic pain scale. • Change in the intensity of dynamic allodynia (rating scale of 0 to 10, with 0=No pain, 10=Maximal imaginable pain)). • Change in the intensity of mechanical hyperalgesia (rating scale of 0 to 10, with 0=No pain, 10=Maximal imaginable pain). • Proportion of subjects who have reduction in average daily pain intensity score (in the morning as well as in the evening • Proportion of subjects with a rating ≥3 for numerical assessment of perception of pain change (answered 3 =Something better or 4 =Much better) based on patient perception • Determination of percentage of patients with acute pain episodes that were administered rescue medication, the amount of medication needed, and the period during which rescue medication was used. • Change in sleep interference scale (pain interference with sleep) • Change in pain interference with daily activities scale • Change in health and wellness scores of the SF-12 questionnaire • Change in mood • Change in tiredness

	If not otherwise stated, all variables were evaluated between the baseline period (V0-V1) and Weeks 1, 2, 3 and 4 of treatment and the follow-up period (Week 5, V6-V7)." Pharmacokinetics: • Determination of plasma concentration of PAR and its metabolites. • Determination of the following pharmacokinetic parameters: C_{max}, t_{max}, k_{el}, $t_{1/2}$, AUC_{last}, AUC_{inf}, %AUCextra, CL/F, V_z/F. **Safety:** • Adverse events. • Vital signs and physical examination. • ECG parameters. • Safety analytical tests (clinical chemistry, hematology and urinalysis). • Local tolerability in the administration site.
Statistical methods:	A descriptive analysis of all study variables was performed. Categorical variables were analyzed using absolute and relative frequencies. Continuous variables were analyzed by estimating the mean, standard deviation (SD), median, minimum and maximum for all variables, the number of missing data was shown as a separate category. The estimation of proportions did not include the missing data category. The *intention-to-treat sample* (ITT) was used for primary and secondary efficacy analysis, the description of demographic data and baseline characteristics. The ITT consisted of all randomized subjects who received at least the first dose of study medication and had at least one post-treatment efficacy assessment. The *Per Protocol* (PP) sample includes all randomized patients who completed the study without protocol violations. All statistical information, including the estimation of derived variables and content of result tables, were detailed in the Statistical Analysis Plan (SAP). SAP was performed prior to database lock. No interim efficacy analysis was planned. The statistical analysis was performed after the early termination of the study.
Summary – Conclusions: Efficacy results	**Primary Efficacy Endpoint** The assessment of the primary efficacy objective was based on the change in average daily pain intensity score in the evening, (Evening Pain Intensity score, EPI score), between the baseline period (V0-V1) and Week 4, and between Active (PARENTIDE) and Placebo groups. Decrease or reduction in average daily EPI score between Week 4 and baseline period (which implies a negative value of change in average daily EPI score) correlates with an analgesic effect. The primary efficacy analysis was performed on the ITT and PP samples: a) In the analysis performed on ITT sample, with non-imputed and imputed data, no significant differences were observed between the study groups regarding the change in average daily EPI scores between Week 4 and baseline period (non-imputed: Active Change vs. Placebo Change = -0.3; *p*= 0.2173; imputed data: Active Change vs. Placebo Change= -0.5 *p*=0.1126; .

Despite the lack of statistical significance differences between groups, the analysis of the ITT sample showed a higher change in average daily EPI score in the Active group (non-imputed data: Active Change W4= -0.4; imputed data: Active Change W4= -0.6) than in the Placebo group (non-imputed and imputed data: Placebo Change W4= -0.1) group.

b) The primary efficacy analysis on the PP sample revealed significant difference in the change in average daily EPI score between groups (Active Change vs. Placebo Change = -0.5; *p*=0.0429).

The results regarding the change in average daily EPI score between the baseline period and Week 4 for each sample are summarized in the following table:

Table 1: Change in average daily EPI score between baseline period and Week 4.

		Active Change	**Placebo Change**	**Active vs. Placebo Difference**	***p*-value**
ITT sample with non-imputed data	n	4	5		
	Mean (SD)	-0.4 (0.3)	-0.1 (0.6)	-0.3	0.2173
ITT sample with imputed data	n	5	5		
	Mean (SD)	-0.6 (0.5)	-0.1 (0.6)	-0.5	0.1126
PP sample	n	4	4		
	Mean (SD)	-0.4 (0.3)	0.1 (0.3)	-0.5	0.0429*

Source: Tables 3.1.1, 3.1.2 and 3.1.3 of the Statistical Analysis Report (SAR) version 1.

Secondary Efficacy Endpoints

The analysis of the change in average daily EPI score between the baseline period (V0-V1) and Weeks 1, 2, and 3 of treatment and the follow-up period (Week 5, V6-V7) was performed.

In the ITT sample, the analysis revealed a significant change in average daily EPI score between follow-up period (Week 5, V6-V7) and baseline period in PARENTIDE-treated patients compared to Placebo patients. The difference between both groups was -0.7 points (Active Change vs. Placebo Change; *p*= 0.0379) (Figure 2). In the PP sample, the difference between groups regarding their change in average daily EPI score between follow-up period (Week 5, V6-V7) and baseline period was also significant (Active Change vs. Placebo Change = -0.8 *p*= 0.0305) (Figure 3).

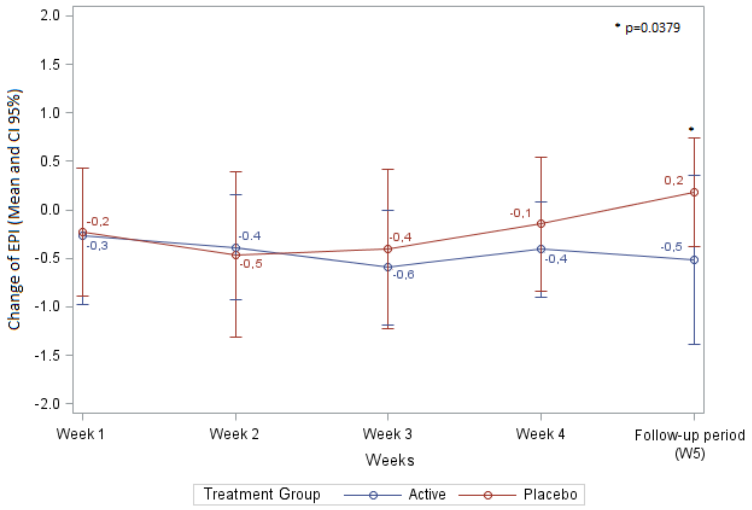


Figure 2: Evolution of the change in average daily EPI score per treatment group for each of the weeks in relation to the baseline period (ITT Sample). Statistical significance of the Active Change vs. Placebo Change: * $p < 0.05$
Source: Figure 4.2.1, corresponding to data included in Tables 3.1.1 and 3.2.1A, of the SAR version 1.

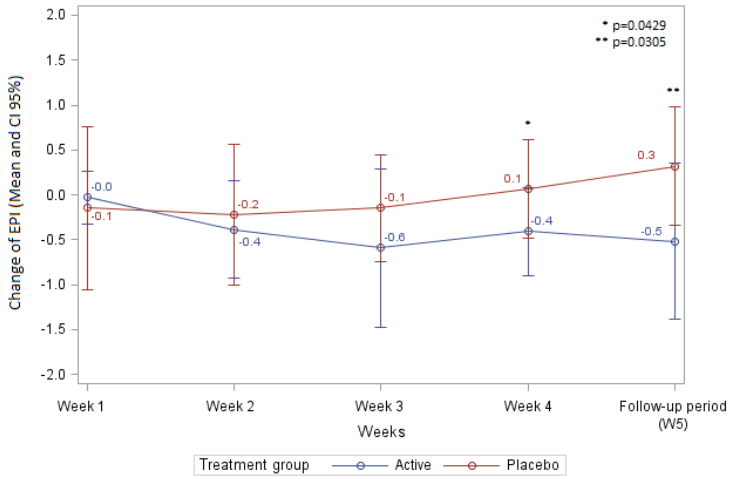


Figure 3: Evolution of the change in average daily EPI score per treatment group for each of the weeks in relation to the baseline period (PP Sample). Statistical significance of the Active Change vs. Placebo Change: * $p < 0.05$; ** $p < 0.05$.
Source: Figure 4.2.2, corresponding to data included in Tables 3.1.3 and 3.2.1B, of the SAR version 1.

No significant differences were observed between treatments in the change in average daily (Morning Pain Intensity score, MPI score) or regarding the progression of neuropathic pain (LANSS scale), dynamic allodynia or mechanical hyperalgesia throughout the study.

Most patients in both groups used rescue medication during the study (Active: n=4 ,80%; Placebo: n= 3; 60%), and reported at least one acute episode of pain during the study (Active: n= 4; 80%, Placebo: n= 4; 80%).

	At the last follow-up visit (V7), 1 (20%) of the 5 patients treated with PARENTIDE rated with ≥3 points (answered 3 = Something better or 4 = Much better) in the satisfaction questionnaire of the "PARdolor" application. No significant differences were observed between treatment groups regarding the change in health and wellness scores of the SF-12 questionnaire (either physical or mental domain) throughout the study. No significant differences were observed between treatments regarding the change in interference of sleep and pain interference with daily activities scale, the mood and morning/evening tiredness.
Summary-Conclusions Safety results:	During the study, seven patients (70%) experienced a total of 11 adverse events (AEs). Of them, 2 AEs from two (20%) patients were probably-related to the treatment and neither of them was considered serious. One patient (10%) experienced pain in the injection site, related to the administration of the test drug, but only with 1st administration. One patient (10%) experienced dry mouth, which was considered a probably-related AE. Overall, PARENTIDE can be considered safe and well-tolerated.
Conclusion:	Taken together, the results of this study, prematurely interrupted due to an apparent absence of appreciable clinical improvement during treatment, showed that patients with neuropathic pain due to peripheral nerve injury as a result of surgery or trauma treated with PARENTIDE 10 mg once a week for 4 weeks showed an analgesic effect, manifested as a reduction in Evening Pain Intensity (EPI) score from baseline period. In the PP sample, a reduction (change) in the average daily EPI score from baseline period was observed in PARENTIDE-treated patients from Week 2. The difference between Active (PARENTIDE) and Placebo groups was statistically significant at Week 4 (main study variable), after the 4th administration of PARENTIDE 10 mg and this significant difference was also maintained in the follow-up period (Week 5, V6-V7), between 7 and 20 days after the last administration. Likewise, in the ITT sample, PARENTIDE-treated patients showed a trend in the reduction in Evening Pain Intensity score at Week 4 (main study variable) that was statistically confirmed in the follow-up period. In summary, the higher reduction in the Evening Pain Intensity score from baseline period observed in the Active group after four administrations (once a week) of PARENTIDE 10 mg in the ITT population, was confirmed with statistical significance in the patients compliant with the protocol (PP sample) and the treatment effect was confirmed with statistically significance in the follow-up period in both populations (ITT and PP). This positive result in such a small population with chronified severe neuropathic pain and non-responding to pregabalin, is indicative of efficacy and should be, therefore, be confirmed in a larger sample. Other assessments regarding the change in average daily MPI score, hyperalgesia and allodynia, and treatment perception were heterogeneous. This study relied on well-validated and widely used instruments such as the SF-12 questionnaire, the LANSS neuropathic pain scale and allodynia and hyperalgesia

	questionnaires, but also on the use of the innovative mobile app "PARdolor" which was developed by Labpsitec, a research team belonging to the *Universitat Jaume I* in *Castellón* with broad experience in the development, validation, and implementation of Information and Communication Technologies applicable to Clinical and Health Psychology. The use of these tools strengthens the internal validity of our results, which were otherwise limited by the high pain scores at baseline period and the early interruption, which severely reduced the size of the sample used in the analyses. Despite these limitations, a significant difference between Active and Placebo was observed in the primary efficacy endpoint, suggesting efficacy of PARENTIDE 10 mg on neuropathic pain after peripheral nerve injury after surgery or trauma. On the other hand, the results of this study suggest that treatment with PARENTIDE is safe, with no potential harms or suspicion of deteriorating the quality of life of patients with neuropathic pain.
Date of the report:	3 APR 2020