Ultramicronized palmitoylethanolamide in spinal cord injury neuropathic pain: A randomized, double-blind, placebo-controlled trial

Sven R. Andresen[a,*], Jette Bing[b], Rikke M. Hansen[a], Fin Biering-Sørensen[b], Inger L. Johannesen[a], Ellen Merete Hagen[a,c,d] , Andrew S.C Rice[e], Jørgen F. Nielsen[f], Flemming W. Bach[g], Nanna B. Finnerup[h]

[a]*Spinal Cord Injury Centre of Western Denmark, Viborg, Denmark*

[b]*Clinic for Spinal Cord Injuries, Rigshospitalet, University of Copenhagen, Denmark*

[c]*Department of Clinical Medicine, University of Bergen, Norway*

[d]*The Autonomic Unit, National Hospital for Neurology and Neurosurgery, Queen Square, University College London, UK*

[e]*Pain Research, Department of Surgery and Cancer, Imperial College, London, UK*

[f]*Hammel Neurorehabilitation and Research Centre, Hammel, Denmark*

[g]*Department of Neurology, Aalborg University Hospital, Denmark*

[h]*Danish Pain Research Center, Department of Clinical Medicine, Aarhus University, Denmark*

*Corresponding author:

Sven Robert Andresen, MD

Spinal Cord Injury Centre of Western Denmark, Neurological Department

Regional Hospital of Viborg, Heibergs Allé 4

DK-8800 Viborg, Denmark

Tel: +45 7844 61 56 or +45 78 44 61 50; fax: +45 78 44 61 59.

E-mail address: sven.robert.andresen@midt.rm.dk

Article type: Clinical Science research report

Number of pages: 28 (17 text including references, 6 tables and 2 figures)

Number of tables: 2

Number of figures: 2

Supplementary material: 1

Summary: This randomized controlled trial found no effect of ultramicronized palmitoylethanolamide as add-on-therapy on neuropathic pain after spinal cord injury.

Abstract

Neuropathic pain and spasticity after spinal cord injury (SCI) represent significant problems. Palmitoylethanolamide (PEA), a fatty acid amide that is produced in many cells in the body, is thought to potentiate the action of endocannabinoids and to reduce pain and inflammation. This randomized, double-blind, placebo-controlled, parallel multicenter study was performed to investigate the effect of ultramicronized PEA (PEA-um) as add-on therapy on neuropathic pain in individuals with SCI. A pain diary was completed and questionnaires were completed before and after the 12-week treatment with either placebo or PEA-um. The primary outcome measure was the change in mean neuropathic pain intensity from the 1-week baseline period to the last week of treatment measured on a numeric rating scale ranging from 0 to 10. The primary efficacy analysis was the intention to treat (baseline observation carried forward). Secondary outcomes included a per protocol analysis and effects on spasticity, evoked pain, sleep problems, anxiety, depression, and global impression of change. We randomized 73 individuals with neuropathic pain due to SCI, of which 5 had a major protocol violation, and thus 68 were included in the primary analysis. There was no difference in mean pain intensity between PEA-um and placebo treatment (*P* = 0.46, mean reductions in pain scores 0.4 (-0.1 to 0.9) vs 0.7 (0.2 to 1.2); difference of means 0.3 (-0.4 to 0.9)). There was also no effect of PEA-um as add-on therapy on spasticity, insomnia, or psychological functioning. PEA was not associated with more adverse effects than placebo.

Keywords

Neuropathic pain, Spasticity, Spinal cord injury, PEA, ultramicronized Palmitoylethanolamide, Randomized Controlled Trial

1. Introduction

Neuropathic pain and spasticity due to spinal cord injury (SCI) remain significant problems [28,34]. About 50-60% develop chronic neuropathic pain and 70% spasticity after SCI [4,10,34]. Neuropathic pain is pain due to a lesion or disease of the somatosensory nervous system, and neuropathic SCI pain is divided into "at-level" and "below-level" pain [5]. Spasticity is here defined as a "disordered sensory-motor control, resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles", including hyperreflexia, increase in muscle tone, spasms, and clonus [28,33].

The usefulness of cannabinoids in the treatment of neuropathic pain is unclear and their use limited by side effects and concerns about long term risks [9,22]. Therefore, efforts concentrate about the development of cannabinoids with a better therapeutic index [22,23,42]. Palmitoylethanolamide (PEA) is an endogenous fatty acid amide that is suggested to potentiate endocannabinoids and to have effect on neuropathic pain and spasticity [1,15,16,19,21,25,31,35,36]. PEA prolongs and potentiates the action of endocannabinoids through an inhibition of fatty acid amide hydrolase [40]. PEA has also been suggested to reduce inflammation and to have neuroprotective mechanisms [13,17,36,39]. In several neuropathic pain models in rats, palmitoylallylamide (L-29), an analogue - of PEA, has effects suggestive of analgesia [30,40]. Micronization and ultramicronization have been used to reduce the large particle PEA to micron- and sub-micron-sized crystals to enhance dissolution and reduce variability of absorption [18]. Case reports and open-label studies suggest an effect of ultramicronized PEA (PEA-um) on neuropathic pain, including central pain [7,12,16,32]. Recent systematic reviews in neuropathic pain and PEA [9,16,36] have only identified 2 randomized placebo-controlled trials, both showing efficacy of micronized PEA (PEA-m) in sciatic pain [6,11]. PEA-um is registered as food for special purposes (FSMP) by the Italian Ministry of Health. PEA-um is not labeled for use in neuropathic pain.

Our randomized clinical trial examined the effect of PEA-um as add-on therapy on neuropathic pain following SCI and furthermore evaluated its effect on spasticity and psychological functions.

1. Methods

2.1. Design

This was an investigator-initiated, randomized, double-blind, placebo-controlled, parallel multicenter study investigating sublingual PEA-um microgranules 600 mg in patients with neuropathic pain after SCI.

2.2. Study population

Inclusion criteria were: 18 years or older and having sustained a traumatic or non-traumatic SCI including cauda equine lesions. The SCI should be at least 6 months old and patients should have at- and/or below-level SCI neuropathic pain [5] that had lasted for at least 3 months with an average pain intensity of at least 4 and not above 9 on a 0-10 point numeric rating scale (NRS) , where 0 is “no pain” and 10 is “the worst pain you could imagine”, during a 7-day baseline period [8]. Patients should have definite neuropathic pain, which requires a pain distribution compatible with the SCI, ie. at- or below-injury level, sensory signs in the same neuroanatomically plausible distribution, and a diagnostic test, typical a MRI, confirming the SCI [38], and the pain should have no primary relation to movement. Musculoskeletal or other nociceptive pain that could explain the pain should be excluded or considered unlikely. Exclusion criteria included known concomitant severe cerebral damage, terminal illness, planned surgery, alcohol or substance abuse, hypersensitivity to PEA-um or excipients, psychiatric disease except reactive depression, pregnancy, and lactation, and if they could not differentiate their neuropathic SCI pain from other types of pain. All women of childbearing age had to use sufficient contraceptives (birth control pills, intrauterine device or sterilization). Patients were allowed to continue concomitant treatment with spasmolytics and drugs for pain in a constant and unchanged dose during the study. If possible, patients were tapered off their pain medication, however none of the patients accepted to be reduced in dose or tapered off. The study was approved by the Ethical Committee of the Central Denmark Region (no. 1-10-72-77-13) and the Danish Data Protection Agency, Copenhagen, Denmark (no. 1-16-02-106-13). The study was conducted in

accordance with the Declaration of Helsinki and was registered at ClinicalTrials.gov (NCT01851499). All patients gave informed written consent.

2.3. Medication

The study drug was a sublingual product based on ultramicronized PEA (Normast®). PEA-um 600 mg or identical placebo was given sublingually twice daily with approximately 12 hours between doses for a period of 12 weeks. Both patients and investigators were blinded, and assignment to treatment was randomized via a computer-generated randomization list with a homogeneous block size of 4 done by Epitech Group SpA, and patients were allocated consecutively.

Assessment of compliance: At the end of the treatment period, the patients returned the remaining sachets, and the amount relative to the daily recordings in the diary of consumption of Normast was recorded in a case report form.

2.4. Procedure

The patients were recruited from May 2013 to December 2014. Patients came for 3 visits. After the first visit, the patients underwent a baseline week, after which they were randomized to Normast or placebo for 12 weeks. Throughout the study (13 weeks), the patients completed a pain diary every evening and recorded their average pain, spasticity, and sleep disturbance experienced in the preceding 24 hours and their use of rescue medication. At visit 1, the patients' history, including pain and spasticity symptoms, was collected, and general and neurological examinations were made. SCI was classified according to the International Standards for Neurological Classification of SCI [20,24], and patients completed the International Spinal Cord Injury Pain Basic Data Set [41].

2.5. Primary outcome

Neuropathic SCI pain was assessed with the NRS (0-10). The predefined primary outcome was the difference in the mean value of the patient's daily ratings of average pain intensity in the baseline week and the last week of the treatment period.

2.6. Secondary outcomes

Average neuropathic pain intensity scores in the treatment weeks (weeks 2-12) and the daily ratings of spasticity and sleep disturbance in the last week of the treatment period were secondary outcome measures. Other secondary outcomes were the intensity of muscle stiffness and spasms rated on a 0-10 NRS, use of rescue medication, neuropathic pain descriptors, impact of the neuropathic pain, health-related quality of life using the Pain Survey (S-TOPS) [14] , evoked pain, spasticity assessed using the Modified Tardieu Scale (MTS) [37] , the Patient Global Impression of Change (PGIC), pain relief, the number needed to treat (NNT), the Insomnia Severity Index (ISI) [26] , the Major Depression Inventory (MDI) [2,3,27], and the Generalized Anxiety Disorder Assessment (GAD-10). For further details on the methods, please see supplementary material.

2.7. Other outcomes

Adverse effects were assessed by open-ended questions, and blindness of both the investigator and the participants was assessed by asking which treatment they believed they had received (active or placebo) and asking them about their reason for this belief.

2.8. Statistical analysis

Our sample size calculation predetermined that 66 patients should complete the study to be able to find a difference in pain score of at least 1.5 point on an NRS (0-10) with an estimated standard deviation (SD) of 2.0 (85% strength, $\alpha = 0.05$). The primary efficacy variable (change in average weekly pain score from baseline to last week) and secondary efficacy variables were analyzed by t-test or Mann-Whitney test,

where applicable. An analysis using ANCOVA with baseline pain intensity, number of rescue tablets, gender, age, and treatment as covariates was also performed.

The main analysis was on the intention-to-treat (ITT) population, including all patients taking the first dose. Five patients were randomized despite an average pain intensity of < 4 or > 9 and were not included in the primary modified ITT analysis. Patients were asked to complete the pain diaries despite their withdrawal from trial medication. In the absence of data from pain diaries and secondary outcomes, "the baseline observation carried forward" (BOCF) method was used. In addition, the "per protocol" (PP) population was analyzed, which was defined as the number of individuals who had been treated with at least 600 mg of ultramicronized PEA twice a day for 8 weeks and who had consumed 70-110% of the expected dose. Statistical analysis was performed with STATA release 12 (StataCorp, College Station, TX, USA).

2. Results

3.1. Patients

Patients were recruited from May 2013 to December 2014 and last follow-up visit was in April 2015. A total of 119 patients were assessed for eligibility and 73 were randomized for treatment, see consort flow diagram (Fig. 1). Of the 73 patients randomized, 5 patients had major protocol violation (did not meet the criteria of baseline pain intensity of $4 \leq NRS \leq 9$) and were thus not included in the primary modified ITT analysis; however, they were included in the safety analysis and in a secondary ITT analysis.

Demographics and patient baseline characteristics included in the safety and secondary ITT analyses are displayed in Table 1. Of the 73 patients, 36 were randomized to PEA-um and 37 to placebo. Average age was 56.3 years (SD: 11.6), average time since injury was 10.3 (SD: 11.7), and average pain intensity during baseline was 6.4 (SD: 1.4) (NRS 0-10).

3.2. Primary outcome

There was no statistically significant difference between PEA-um and placebo on the primary outcome in the ITT (n = 68) population (Δ mean: 0.3, 95% CI: -0.4 to 0.9, *P* = 0.46) (Table 2, Fig. 2). There was also no difference when using ANCOVA with the covariates (gender, age, baseline mean pain intensity, use of rescue medication, and treatments) (modified ITT without protocol violations: n = 68, *P* = 0.82). T-test (Table 2) and ANCOVA analyses also showed no difference between groups when analyses were done for the secondary ITT (including the 5 patients with major protocol violations) (n = 73) and the PP (n = 58) populations.

3.3. Secondary outcomes

The patient group treated with PEA-um had a larger consumption of rescue medication at baseline and had a significantly larger reduction in the use of rescue medication than those treated with placebo; in the latter group baseline use was lower and increased during the observation period (Δ mean: -2.2, 95% CI: -4.0 to -0.3, *P* = 0.02). Patients treated with PEA-um had an increase in self-reported intensity of spasticity from the pain diary recordings compared to a decrease in patients treated with placebo (Δ mean: 1.0, 95% CI: 0.2 to 1.9, *P* = 0.013), but there was no difference in other self-reported or laboratory spasticity outcomes (Supplementary Table 1). For all other secondary outcomes there were no statistically significant differences between treatments (Supplementary material).

3.4. Assessment of blindness

Of those allocated to PEA-um, 16% of patients identified the correct treatment and stated that it was due to pain relief, whereas 84% thought they had received placebo due to lack of effect. Of those who received placebo, 81% identified the correct treatment due to lack of pain relief, whereas 19% thought they had received active treatment due to effect of the treatment. No patient stated that the reason for their

choice was adverse effects. We saw no significant difference between the treatment groups (P = 0.78), suggesting that blinding was preserved.

3.5. Compliance

For patients in the primary modified ITT analysis who were not lost to follow up (n=63), the mean daily dose throughout the treatment period was 1135.4 mg (SD: 122.2) for PEA-um and 1165.1 mg (SD: 76.7) for placebo, and mean treatment length was 11.6 weeks (SD: 1.4) for PEA-um and 11.3 weeks (SD: 2.1) for placebo. 26 of 31 patients treated with PEA-um and 27 of 32 patients treated with placebo completed 12 weeks of treatment. Mean compliance was 94.6 % (SD: 10.2) for PEA-um and 97.1 % (SD: 6.4) for placebo.

3.6. Adverse events

Seven patients reported adverse events, of which 5 were serious adverse events. One patient treated with PEA-um committed suicide, which, after careful investigation, was not considered to be related to the study drug. No other patients dropped out of the study because of adverse events. Other serious adverse events were urinary tract infection, paralytic ileus, cholecystolithiasis, and erysipelas causing hospitalization in 3 patients treated with PEA-um and 1 treated with placebo. In addition, 1 patient treated with PEA-um had fungus infection, and 1 treated with placebo experienced blurred vision.

3. Discussion

In this randomized , double-blind, placebo-controlled study, 1200 mg ultramicronized PEA (600mg BID) as add-on therapy failed to show an effect on SCI neuropathic pain. In addition, PEA-um add-on had no effect on spasticity and other secondary outcomes. However, the patient group treated with PEA-um add-on had a significantly larger reduction in the use of rescue medication (paracetamol) than those treated with placebo. A lower consumption of concomitant medication during treatment with PEA-m has been shown in a study of individuals with lumbar radicular pain [6]. Including the use of rescue medication in the

ANCOVA, we still found no effect of PEA-um as add-on therapy on the primary outcome; consistent with the fact that there is no evidence that paracetamol has any effect on neuropathic pain. We did not correct for multiple comparisons for the secondary outcomes, and this may likely be a chance finding, although we cannot exclude that PEA-um had an effect on other types of pain for which the patients took paracetamol. Placebo was more effective than PEA as add-on therapy on spasticity according to the pain diary, but this was not supported by other spasticity outcomes.

This study is the first randomized, double-blind, placebo-controlled trial examining PEA-um as add-on therapy in central pain. The 12-week treatment period and the dosage of 600 mg twice daily were equal to or higher in our study compared with earlier studies [6,11,12,16], so the lack of effect is not likely to be explained by a suboptimal dose, although we cannot exclude that a higher dose is needed to relieve central SCI pain. It is also not likely to be explained by a floor-effect, because the average pain intensity was 6.4 on a 0-10 NRS. There are limited pharmacokinetic data on PEA-um, and limited penetration to the cerebrospinal fluid could be an explanation for the lack of efficacy. Our study included patients with different causes and levels of SCI, which could impact the outcome, and patients with concomitant medication which could have an impact on the effect of PEA-um, and it is likely that we included some patients that are refractory to pain treatment, which could also contribute to the lack of effect, also considering that more patients randomized to PEA were treated with concomitant medication. Finally it is possible, that the effect seen in experimental studies is driven mainly by reduced inflammation and neuroprotective mechanisms [13,29] and that treating spinal cord-injured individuals with PEA-um in early stages and before neuropathic pain and spasticity develop, may be beneficial.

Our study supports that ultramicronized PEA has good safety and tolerability profiles. Only 1 patient stopped treatment due to an adverse event, which was considered unrelated to the study drug.

In conclusion, this study showed no effect of PEA-um as add-on therapy on neuropathic pain following SCI and any of the secondary outcomes, including spasticity, with exception of rescue drugs use which was decreased in the PEA-um treated group.

Funding

The study was supported by Region Midtjyllands Sundhedsvidenskabelige Forskningsfond, Hospitalenheden Midt forskningspulje and The Danish Society of Polio and Accident Victims (PTU). Epitech Group SLR provided the study drug and placebo and performed the randomization. The funding source (Epitech Group SLR) had the possibility to comment on the design and reporting of the study, but had no role in the collection, analysis, and interpretation of the data. All authors had full access to all data and the corresponding author had the final responsibility for the decision to submit for publication.

Conflict of interest statement

The authors have no conflicts of interest to declare within the submitted work. NBF reports honoraria from Pfizer and Grünenthal and grants from IMI Europain (EU/EFPIA) outside the submitted work. ASCR ASCR is a member of the Scientific Advisory Board, has received research funding from and holds share options in Spinifex. ASCR has undertaken paid consultancy work via Imperial College Consultants which in the last 3 years has included work for Neusentis, Spinifex, Abide, Orion, Merck, Astellas, Medivir, Asahi Kasei, Aquilas, Relmada and Mitsubishi. Within the last 3 years ASCR's laboratory has received grants from Pfizer and Astellas and IMI Europain (EU/EFPIA). ASCR has a patent - Rice A.S.C., Vandevoorde S. and Lambert D.M Methods using N-(2-propenyl)hexadecanamide and related amides to relieve pain. WO 2005/079771. FWB has received investigator fees from Pfizer and Grunenthal. RMH cooperates with Bioarctic,. SRA, JB, EMH and FB-S declare no conflict of interests.

Acknowledgements

We thank Anne Grethe Rasmussen and Henriette Rask, Clinic for Spinal Cord Injury at Rigshospitalet, for their assistance in data collection and Susanne Doessing, Spinal Cord Injury Centre of Western Denmark, for recruitment of SCI individuals.

References

[1] Baker D, Pryce G, Croxford JL, Brown P, Pertwee RG, Makriyannis A, Khanolkar A, Layward L, Fezza F, Bisogno T, Di Marzo V. Endocannabinoids control spasticity in a multiple sclerosis model. FASEB J 2001;15:300–2.

[2] Bech P, Rasmussen NA, Olsen LR, Noerholm V, Abildgaard W. The sensitivity and specificity of the Major Depression Inventory, using the Present State Examination as the index of diagnostic validity. J Affect Disord 2001;66:159–64.

[3] Bech P, Wermuth L. Applicability and validity of the Major Depression Inventory in patients with Parkinson's disease. Nord J Psychiatry 2015;52:305–309.

[4] Biering-Sorensen F, Nielsen JB, Klinge K, Biering-Sørensen F. Spasticity-assessment: a review. Spinal Cord 2006;44:708–722.

[5] Bryce TN, Biering-Sørensen F, Finnerup NB, Cardenas DD, Defrin R, Lundeberg T, Norrbrink C, Richards JS, Siddall P, Stripling T, Treede R-D, Waxman SG, Widerström-Noga E, Yezierski RP, Dijkers M. International spinal cord injury pain classification: part I. Background and description. Spinal Cord 2012;50:413–7.

[6] Canteri L, Petrosino S GG. Reducción del consumo de antiinflamatorios y analgésicos en el tratamiento del dolor neuropático crónico en pacientes afectados por lumbociatalgia de tipo compresivo y en tratamiento con Normast® 300 mg. Dolol 2010;25:227–234.

[7] Cocito D, Peci E, Ciaramitaro P, Merola A, Lopiano L. Short-term efficacy of ultramicronized palmitoylethanolamide in peripheral neuropathic pain. Pain Res Treat 2014;2014:854560.

[8] Dworkin RH, Turk DC, Peirce-Sandner S, Burke LB, Farrar JT, Gilron I, Jensen MP, Katz NP, Raja SN, Rappaport BA, Rowbotham MC, Backonja M-M, Baron R, Bellamy N, Bhagwagar Z, Costello A, Cowan P, Fang WC, Hertz S, Jay GW, Junor R, Kerns RD, Kerwin R, Kopecky EA, Lissin D, Malamut R, Markman JD, McDermott MP, Munera C, Porter L, Rauschkolb C, Rice ASC, Sampaio C, Skljarevski V, Sommerville K, Stacey BR, Steigerwald I, Tobias J, Trentacosti AM, Wasan AD, Wells GA, Williams J, Witter J, Ziegler D. Considerations for improving assay sensitivity in chronic pain clinical trials: IMMPACT recommendations. Pain 2012;153:1148–58.

[9] Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, Gilron I, Haanpää M, Hansson P, Jensen TS, Kamerman PR, Lund K, Moore A, Raja SN, Rice ASC, Rowbotham M, Sena E, Siddall P, Smith BH, Wallace M. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol 2015;14:162–173.

[10] Finnerup NB, Norrbrink C, Trok K, Piehl F, Johannesen IL, Sørensen JC, Jensen TS, Werhagen L. Phenotypes and predictors of pain following traumatic spinal cord injury: a prospective study. J Pain 2014;15:40–8.

[11] G. Guida, A. de Fabiani, F. Lanaia, A. Alexandre, G.M. Vassallo, L. Cantieri, M. de Martino, M. Rogai SP. La palmitoiletanolamida (Normast®) en el dolor neuropático crónico por lumbociatalgia de tipo compresivo: estudio clínico multicéntrico. Dolol 2010;25:35–42.

[12] Gatti A, Lazzari M, Gianfelice V, Di Paolo A, Sabato E, Sabato AF. Palmitoylethanolamide in the treatment of chronic pain caused by different etiopathogenesis. Pain Med 2012;13:1121–30.

[13] Genovese T, Esposito E, Mazzon E, Di Paola R, Meli R, Bramanti P, Piomelli D, Calignano A, Cuzzocrea S. Effects of palmitoylethanolamide on signaling pathways implicated in the development of spinal cord injury. J Pharmacol Exp Ther 2008;326:12–23.

[14] Haroutiunian S, Donaldson G, Yu J, Lipman AG. Development and validation of shortened, restructured Treatment Outcomes in Pain Survey instrument (the S-TOPS) for assessment of individual pain patients' health-related quality of life. Pain 2012;153:1593–601.

[15] Helyes Z, Németh J, Thán M, Bölcskei K, Pintér E, Szolcsányi J. Inhibitory effect of anandamide on resiniferatoxin-induced sensory neuropeptide release in vivo and neuropathic hyperalgesia in the rat. Life Sci 2003;73:2345–53.

[16] Hesselink J. New targets in pain, non-neuronal cells, and the role of palmitoylethanolamide. Open Pain J 2012;5:12–23.

[17] Hesselink JMK. Evolution in pharmacologic thinking around the natural analgesic palmitoylethanolamide: from nonspecific resistance to PPAR-α agonist and effective nutraceutical. J Pain Res 2013;6:625–34.

[18] Impellizzeri D, Bruschetta G, Cordaro M, Crupi R, Siracusa R, Esposito E, Cuzzocrea S. Micronized/ultramicronized palmitoylethanolamide displays superior oral efficacy compared to nonmicronized palmitoylethanolamide in a rat model of inflammatory pain. J Neuroinflammation 2014;11:136.

[19] Jaggar SI, Hasnie FS, Sellaturay S, Rice AS. The anti-hyperalgesic actions of the cannabinoid anandamide and the putative CB2 receptor agonist palmitoylethanolamide in visceral and somatic inflammatory pain. Pain 1998;76:189–99.

[20] Kirshblum SC, Burns SP, Biering-Sorensen F, Donovan W, Graves DE, Jha A, Johansen M, Jones L, Krassioukov A, Mulcahey MJ, Schmidt-Read M, Waring W. International standards for neurological classification of spinal cord injury (revised 2011). J Spinal Cord Med 2011;34:535–46.

[21] Lambert DM, Vandevoorde S, Jonsson K-O, Fowler CJ. The palmitoylethanolamide family: a new class of anti-inflammatory agents? Curr Med Chem 2002;9:663–74.

[22] Lever IJ, Rice ASC. Cannabinoids and pain. Handb Exp Pharmacol 2007:265–306.

[23] Maione S, Costa B, Di Marzo V. Endocannabinoids: a unique opportunity to develop multitarget analgesics. Pain 2013;154 Suppl:S87–93.

[24] Marino RJ, Barros T, Biering-Sorensen F, Burns SP, Donovan WH, Graves DE, Haak M, Hudson LM, Priebe MM. International standards for neurological classification of spinal cord injury. J Spinal Cord Med 2003;26 Suppl 1:S50–6.

[25] Mattace Raso G, Russo R, Calignano A, Meli R. Palmitoylethanolamide in CNS health and disease. Pharmacol Res 2014;86:32–41.

[26] Morin CM, Belleville G, Bélanger L, Ivers H. The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. Sleep 2011;34:601–8.

[27] Olsen LR, Jensen D V, Noerholm V, Martiny K, Bech P. The internal and external validity of the Major Depression Inventory in measuring severity of depressive states. Psychol Med 2003;33:351–6.

[28] Pandyan AD, Gregoric M, Barnes MP, Wood D, Van Wijck F, Burridge J, Hermens H, Johnson GR. Spasticity: clinical perceptions, neurological realities and meaningful measurement. Disabil Rehabil 2005;27:2–6.

[29] Paterniti I, Impellizzeri D, Di Paola R, Navarra M, Cuzzocrea S, Esposito E. A new co-ultramicronized composite including palmitoylethanolamide and luteolin to prevent neuroinflammation in spinal cord injury. J Neuroinflammation 2013;10:91.

[30] Petrosino S, Palazzo E, de Novellis V, Bisogno T, Rossi F, Maione S, Di Marzo V. Changes in spinal and supraspinal endocannabinoid levels in neuropathic rats. Neuropharmacology 2007;52:415–22.

[31] Re G, Barbero R, Miolo A, Di Marzo V. Palmitoylethanolamide, endocannabinoids and related cannabimimetic compounds in protection against tissue inflammation and pain: potential use in companion animals. Vet J 2007;173:21–30.

[32] Schifilliti C, Cucinotta L, Fedele V, Ingegnosi C, Luca S, Leotta C. Micronized palmitoylethanolamide reduces the symptoms of neuropathic pain in diabetic patients. Pain Res Treat 2014;2014:849623.

[33] Sheean G. The pathophysiology of spasticity. Eur J Neurol 2002;9 Suppl 1:3–9; dicussion 53–61.

[34] Siddall PJ, McClelland JM, Rutkowski SB, Cousins MJ. A longitudinal study of the prevalence and characteristics of pain in the first 5 years following spinal cord injury. Pain 2003;103:249–257.

[35] Skaper SD, Facci L, Barbierato M, Zusso M, Bruschetta G, Impellizzeri D, Cuzzocrea S, Giusti P. N-Palmitoylethanolamine and Neuroinflammation: a Novel Therapeutic Strategy of Resolution. Mol Neurobiol 2015;52:1034–1042.

[36] Skaper SD, Facci L, Fusco M, Della Valle MF, Zusso M, Costa B, Giusti P. Palmitoylethanolamide, a naturally occurring disease-modifying agent in neuropathic pain. Inflammopharmacology 2014;22:79–94.

[37] Tardieu G, Shentoub G, Shentoub S, Delarue R. [Research on a technic for measurement of spasticity]. Rev Neurol (Paris) 1954;91:143–4.

[38] Treede R-D, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, Hansson P, Hughes R, Nurmikko T, Serra J. Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology 2008;70:1630–5.

[39] Lo Verme J, Fu J, Astarita G, La Rana G, Russo R, Calignano A, Piomelli D. The nuclear receptor peroxisome proliferator-activated receptor-alpha mediates the anti-inflammatory actions of palmitoylethanolamide. Mol Pharmacol 2005;67:15–9.

[40] Wallace VCJ, Segerdahl AR, Lambert DM, Vandevoorde S, Blackbeard J, Pheby T, Hasnie F, Rice ASC. The effect of the palmitoylethanolamide analogue, palmitoylallylamide (L-29) on pain behaviour in rodent models of neuropathy. Br J Pharmacol 2007;151:1117–28.

[41] Widerström-Noga E, Biering-Sørensen F, Bryce T, Cardenas DD, Finnerup NB, Jensen MP, Richards JS, Siddall PJ. The international spinal cord injury pain basic data set. Spinal Cord 2008;46:818–23.

[42] Woodhams SG, Sagar DR, Burston JJ, Chapman V. The role of the endocannabinoid system in pain. Handb Exp Pharmacol 2015;227:119–43.

Figure legends

Figure 1. Study flow chart

*Personal reasons (e.g. too long study period, to many visits, lack of time, did not want to participate in a trial)

**In addition to participants lost to follow-up

***Did not meet criteria for randomization of average pain intensity in the baseline period of 4 ≤ NRS ≤ 9

****No protocol violation, treatment ≥ 8 weeks and ≥ 70% intake of study medication

Figure 2. Time course of mean pain intensity during study

Mean pain intensity on a numeric rating scale (0-10) from baseline by week of treatment (last week of treatment was week 12) for the Normast (●) and Placebo (○) population (baseline observation carried forward imputation). Error bars are standard error of the mean. NRS=Numeric Rating Scale

Summary:
This randomized controlled trial found no effect of ultramicronized palmitoylethanolamide as add-on-therapy on neuropathic pain after spinal cord injury.

Figure 1

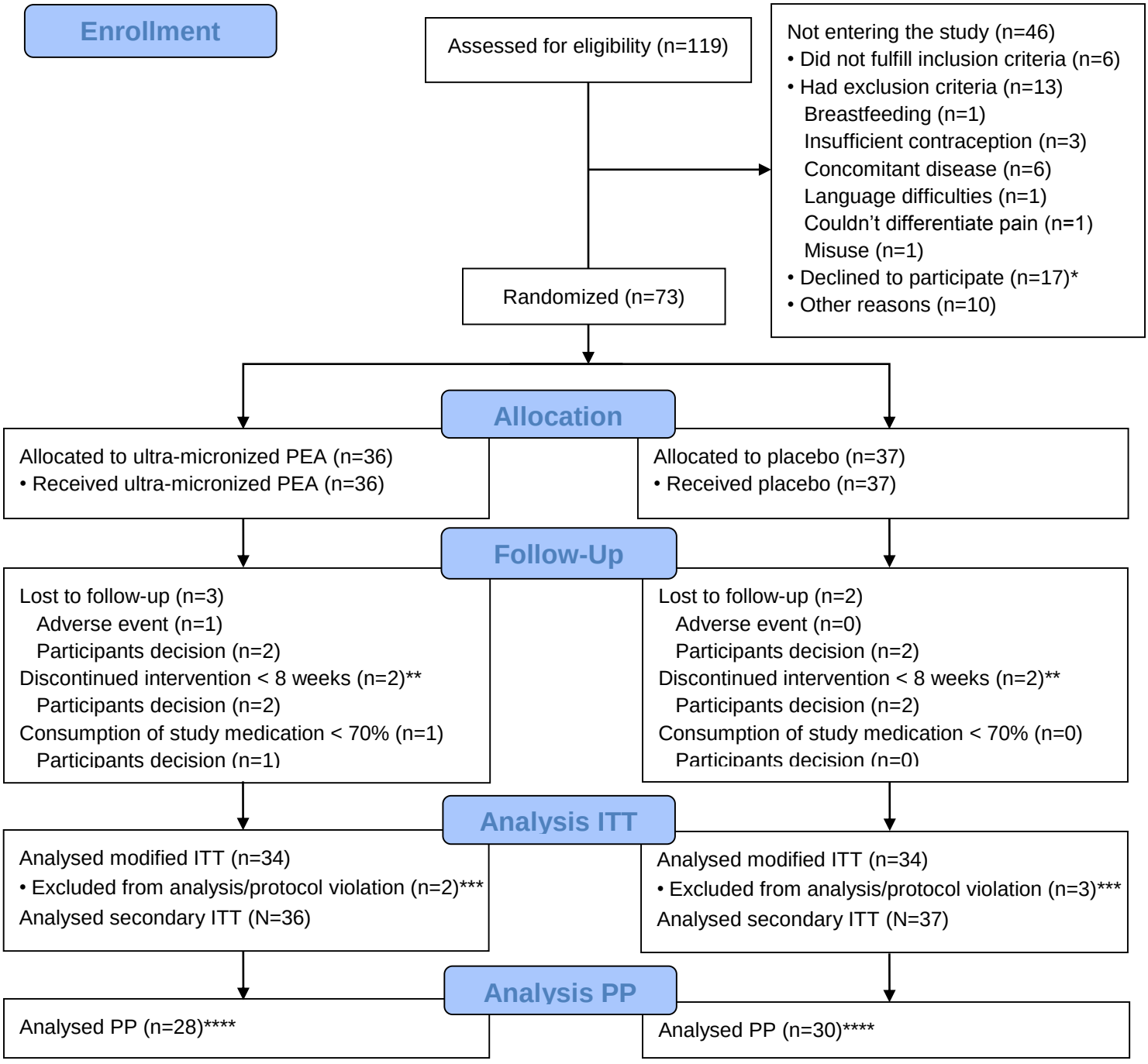
Enrollment
Assessed for eligibility (n=119)
Not entering the study (n=46)
• Did not fulfill inclusion criteria (n=6)
• Had exclusion criteria (n=13)
Breastfeeding (n=1)
Insufficient contraception (n=3)
Concomitant disease (n=6)
Language difficulties (n=1)
Couldn't differentiate pain (n=1)
Misuse (n=1)
• Declined to participate (n=17)*
• Other reasons (n=10)
Randomized (n=73)
Allocation
Allocated to ultra-micronized PEA (n=36)
• Received ultra-micronized PEA (n=36)
Allocated to placebo (n=37)
• Received placebo (n=37)
Follow-Up
Lost to follow-up (n=3)
Adverse event (n=1)
Participants decision (n=2)
Discontinued intervention < 8 weeks (n=2)**
Participants decision (n=2)
Consumption of study medication < 70% (n=1)
Participants decision (n=1)
Lost to follow-up (n=2)
Adverse event (n=0)
Participants decision (n=2)
Discontinued intervention < 8 weeks (n=2)**
Participants decision (n=2)
Consumption of study medication < 70% (n=0)
Participants decision (n=0)
Analysis ITT
Analysed modified ITT (n=34)
• Excluded from analysis/protocol violation (n=2)***
Analysed secondary ITT (N=36)
Analysed modified ITT (n=34)
• Excluded from analysis/protocol violation (n=3)***
Analysed secondary ITT (N=37)
Analysis PP
Analysed PP (n=28)****
Analysed PP (n=30)****

Figure 2. Time course of mean pain intensity during study

Click here to download Figure Figure_2_mean_pain.TIF

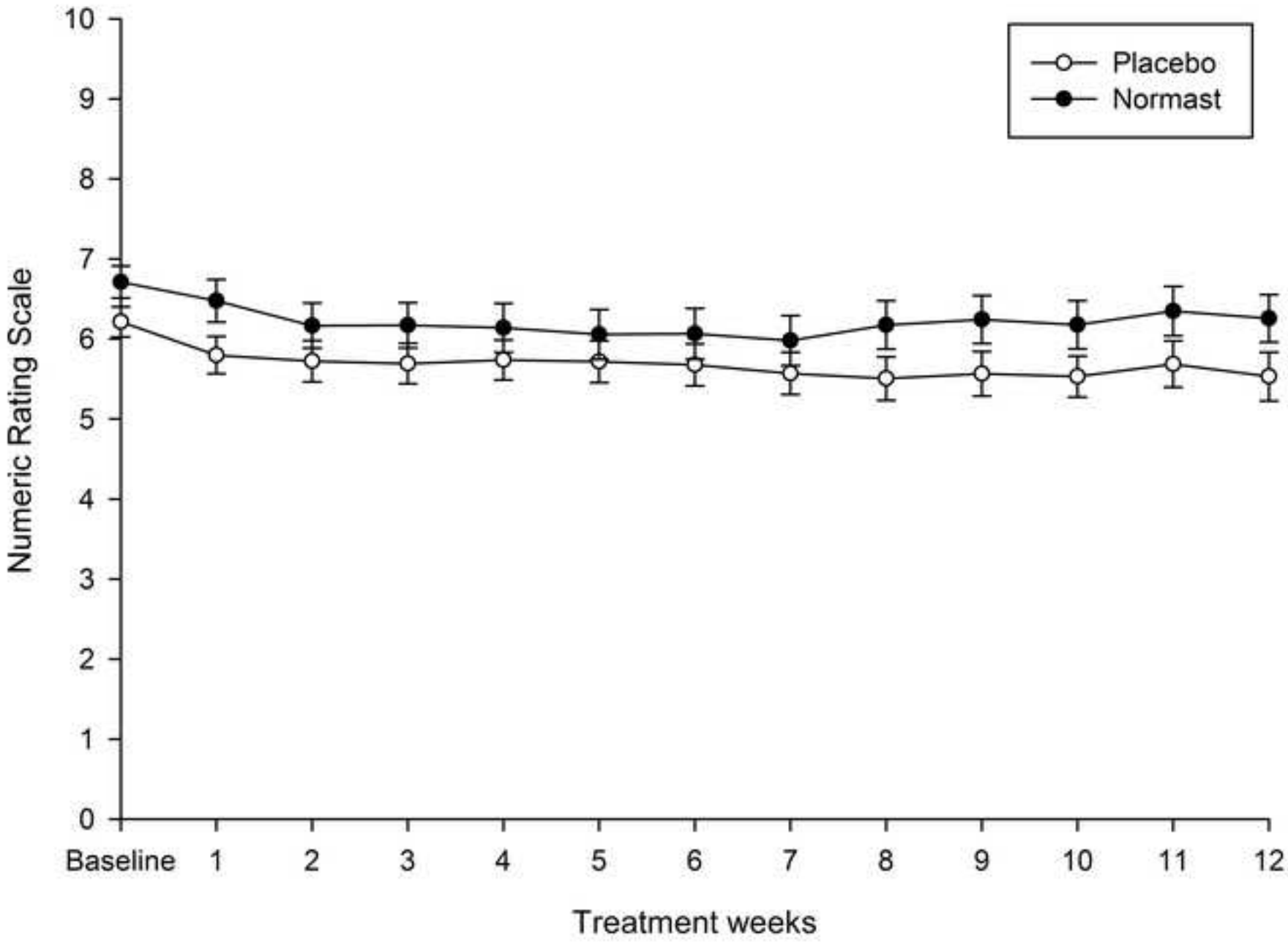

Table 1. Demographics and baseline characteristics

	PEA (n=36)	Placebo (n=37)	Total (n=73)
Age, years, mean (SD)	58.6 (11.3)	54.1 (11.7)	56.3 (11.6)
Gender, n (%)			
Male	22 (61)	32 (86)	54 (74)
Female	14 (39)	5 (14)	19 (26)
Weight, kg, mean (SD)	80.0 (15.8)	74.7 (14.2)	77.3 (15.1)
Time since injury, years, mean (SD)	9.4 (12.8)	11.1 (10.6)	10.3 (11.7)
Baseline score, NRS 0-10			
Pain score, mean (SD)	6.5 (1.4)	6.3 (1.5)	6.4 (1.4)
Spasticity score, mean (SD)	3.1 (2.8)	4.2 (2.7)	3.6 (2.8)
Sleep disturbance, mean (SD)	4.5 (2.7)	3.6 (2.2)	4 (2.5)
Level of neuropathic pain, n (%)			
At-level	9 (25)	7 (18)	16 (22)
At- and below-level	13 (36)	15 (41)	28 (38)
Below-level	14 (39)	15 (41)	29 (40)
Classification of neurological level, n (%)			
Tetraplegia	17 (47)	15 (41)	32 (44)
Paraplegia	19 (53)	22 (59)	41 (56)
ASIA Impairment Scale, n (%)			
A: Complete	13 (36)	11 (30)	24 (33)
B: Incomplete	0 (0)	3 (8)	3 (4)
C: Incomplete	5 (14)	10 (27)	15 (21)
D: Incomplete	18 (50)	13 (35)	31 (42)
Causality of spinal cord injury, n (%)			
Sports	1 (3)	4 (11)	5 (7)
Assault	0 (0)	1 (2)	1 (1)
Transport	14 (39)	7 (19)	21 (29)
Fall	8 (22)	11 (30)	19 (26)
Other traumatic cause	2 (6)	4 (11)	6 (8)
Non-traumatic spinal cord dysfunction	11 (30)	10 (27)	21 (29)
Patients on concomitant pain and spasticity medication, n (%)	35 (97)	29 (78)	64 (88)
TCA	4 (11)	4 (11)	8 (11)
Gabapentin	19 (53)	8 (22)	27 (37)
Pregabalin	9 (25)	12 (32)	21 (29)
Tramadol	5 (14)	5 (14)	10 (14)
Strong opioids	10 (28)	5 (14)	15 (21)
Carbamazepin or Lamotrigin	1 (3)	1 (3)	2 (3)
Paracetamol	20 (56)	9 (24)	29 (40)
NSAID	2 (6)	3 (8)	5 (7)
Baclofen	11 (31)	12 (32)	23 (31)
Tizanidin	0 (0)	1 (3)	1 (1)

PEA=Palmitoylethanolamide, NRS= Numeric rating scale, TCA=Tricyclic antidepressants

Table 2. Primary outcome

Table 2. Primary outcome

	PEA			Placebo				
	Baseline	LWT	Δ[c]	Baseline	LWT	Δ[c]	Δ mean (95% CI)[d]	P-value[d]
Intention-To-Treat:								
Pain intensity, NRS 0-10, n=68	6.7 (1.2)	6.3 (1.7)	0.4 (1.4)	6.2 (1.1)	5.5 (1.8)	0.7 (1.4)	0.3 (-0.4 to 0.9)	0.46
Pain intensity[a], NRS 0-10, n=73	6.5 (1.4)	6.1 (1.8)	0.4 (1.3)	6.3 (1.5)	5.7 (2)	0.7 (1.4)	0.3 (-0.34 to 0.94)	0.36
Per-Protocol:								
Pain intensity[b], NRS 0-10, n=58	6.7 (1.2)	6.2 (1.8)	0.5 (1.5)	6.2 (1.1)	5.6 (1.8)	0.7 (1.4)	0.2 (-0.6 to 0.9)	0.69

Values are presented as mean (SD).

[a]With protocol violations (did not meet criteria for randomization of average pain intensity in the baseline period of $4 \leq NRS \leq 9$).

[b]Treatment ≥ 8 weeks and ≥ 70% intake of study drug without protocol violations.

[c]Change in mean pain intensity (NRS 0-10) (baseline - LWT). Positive values represent a reduction in pain intensity.

[d]Treatment effect PEA versus Placebo. Δmean=ΔPlacebo - ΔPEA. Positive value means larger reduction during placebo than PEA.

*Decrease during PEA compared to decrease during placebo.

PEA=Palmitoylethanolamide, LWT=Last Week of Treatment, NRS=Numeric Rating Scale