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Results from a randomized, controlled trial on efficacy and tolerability of a 5% Lidocaine-Medicated Plaster vs. Pregabalin in patients with Post-Herpetic Neuralgia (PHN) and Painful Diabetic Polyneuropathy (DPN)

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Introduction

- Post-herpetic neuralgia (PHN) and diabetic polyneuropathy (DPN) represent common peripheral neuropathic pain syndromes of focal (PHN) and polyneuropathic, or generalised distribution (DPN) type.
- Oral pregabalin is an effective treatment for PHN and DPN.[2,3] However, as with other systemic treatments,[4,5] pregabalin is associated with dose-limiting side effects. These include dizziness, somnolence, peripheral oedema, and cognitive and gait impairments.[6,3]
- Topical treatment with 5% lidocaine medicated plaster has been recommended as a first line therapy for the management of peripheral neuropathic pain syndromes.[10,11] The lidocaine in the hydrogel plaster has a substantial local effect but undergoes minimal systemic absorption so that side effects are usually limited to mild-to-moderate skin reactions at the site of plaster application.[6,7]
- The analgesic efficacy and good tolerability of lidocaine plaster have been observed in patients with a range of peripheral neuropathic pain syndromes.[8,9]
- Here we report the results of a randomised, controlled clinical trial that compared the pain relieving efficacy, tolerability, and safety of the locally-acting 5% medicated plaster to that of systemic pregabalin in the treatment of PHN and painful DPN. This study represents the first head-to-head comparison of these treatments for patients with peripheral neuropathic pain.

Patients and methods

Patients and study design

- Male or female patients ≥ 18 years of age with PHN or DPN entered a planned Phase III, open-label, randomized, multicentre trial performed at 53 sites in 14 countries.
  - PHN was defined as neuropathic pain present for ≥ 3 months after healing of a herpes zoster skin rash.
  - DPN was defined as painful, distal, symmetrical, sensorymotor polyneuropathy of the lower extremities for ≥ 3 months with at least two of the following symptoms present: burning sensation, tingling or prickling, paraesthesias, painful heat or cold sensation in patients with type 1 or type 2 diabetes mellitus.
- Screening phase: 14-days drug wash-out period (reduced to ≥ 3 days in patients suffering unbearable pain). Eligible patients with a recalled average pain intensity during the previous 3 days of > 4 on an 11-point Numerical Rating Scale (NRS-3) entered the 4-week initial comparative phase ***(Figure 1)*** in which they were randomized (1:1 ratio) to receive one of two treatments:
  - 5% lidocaine medicated plaster (700 mg lidocaine/plaster; ≤ 3 [PHN] or ≤ 4 [DPN] plasters/day over the area of maximal pain for ≤ 12 hours/day).
  - Oral pregabalin (starting dose 75 mg twice daily; titrated to 300 mg/day during the first week in all patients. The dose was increased to 600 mg/day in patients whose response to 300 mg/day was inadequate after one week (NRS-3 score > 4).

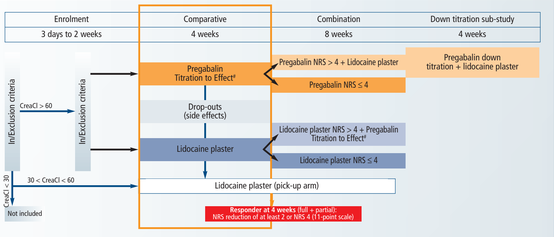


Figure 1: Phases of the study.

- The trial was planned and conducted using an adaptive design with one planned interim analysis of the data collected from the first 150 patients. The aim of this trial was to show non-inferiority of 5% lidocaine medicated plaster in comparison to pregabalin.
- The per protocol set (PPS, comprising patients who adhered to the study protocol) was defined as the primary analysis set in the study protocol. The full analysis set (FAS) refers to patients analysed on an intent to treat basis.
- This poster presents the final results of the comparative phase ***(see figure 1)*** of the trial.

Efficacy endpoints

- The primary efficacy endpoint was a ≥ 2 point reduction from baseline in NRS-3 or an overall score of ≤ 4 after 4 weeks (day 28) of treatment, expressed as a response rate. All drop-outs were classified as non-responders.
- Secondary endpoints included the following comparisons between baseline and week 4 data:
  - Percentage of patients with ≥ 30% and ≥ 50% reductions in baseline NRS-3 scores.
  - Change in Neuropathic Pain Symptom Inventory (NPSI) score (11-point scale).
  - Change in allodynia severity rating ('extremely painful', 'painful', 'uncomfortable', 'no pain').

Safety assessment

- Adverse event (AE) data including relationship to active treatment (drug-related adverse events [DRAEs]) were collected throughout the trial.

	PHN		DPN		Overall		Overall
Characteristic	Lidocaine plaster (n = 45)	Pregabalin (n = 43)	Lidocaine plaster (n = 99)	Pregabalin (n = 94)	Lidocaine plaster (n = 144)	Pregabalin (n = 137)	(n = 281)
Male, n (%)	26 (57.8)	22 (51.2)	41 (41.4)	43 (45.7)	67 (46.5)	65 (47.4)	132 (47.0)
Age, mean ± SD (years)	65.3 (11.8)	63.5 (12.6)	60.9 (10.2)	60.6 (8.9)	62.3 (10.9)	61.5 (10.3)	61.9 (10.6)
BMI, mean ± SD (kg/m²)	28.2 (4.5)	27.7 (5.4)	30.1 (5.2)	30.9 (4.8)	29.5 (5.0)	29.9 (5.2)	29.7 (5.1)

BMI: body mass index **PHN:** postherpetic neuralgia
DPN: diabetic polyneuropathy **SD:** standard deviation

Table 1: Baseline patient characteristics (Per protocol set).

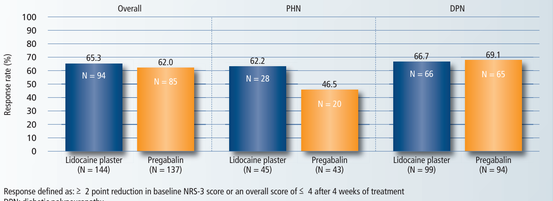
Results

Patient disposition and baseline characteristics

- The PPS comprised 281 patients. Of the 88 patients with PHN, 45 received 5% lidocaine medicated plaster and 43 received pregabalin. One hundred and ninety three suffered from DPN and 99 were treated with 5% lidocaine medicated plaster while 94 received pregabalin. All patients were Caucasian, 47% were male, mean age was 61.9 ± 10.6 years, and mean duration of pain was 50.9 ± 55.0 months. Median and range time since healing of the skin rash (PHN patients) was 18.5 (2-433) months ***(Table 1)***.
  - The lidocaine plaster and pregabalin treatment groups as well as PHN and DPN subgroups were comparable according to the baseline characteristics. Baseline characteristics were also similar between the PPS and FAS.
- Safety data are available for 308 patients. Ninety eight of these were PHN patients and 210 had DPN.

Efficacy

- The overall response rate was numerically comparable in patients receiving 5% lidocaine medicated plaster and patients receiving pregabalin (65.3% vs. 62.0%; p = 0.0066, combined p-value from a two-stage adaptive design according to Bauer & Köhne[12], testing for non-inferiority, significance level: 0.0038; analysis of the FAS indicated non-inferiority: p-value 0.0023, further p-values are exploratory).
- The same applied to patients with DPN (66.7%for 5% lidocaine medicated plasters and 69.1% for pregabalin). For patients with PHN, there was a trend for greater improvement with 5% lidocaine medicated plaster (62.2%) compared with pregabalin (46.5%) ***(Figure 2)***.



Response defined as: ≥ 2 point reduction in baseline NRS-3 score or an overall score of ≤ 4 after 4 weeks of treatment
DPN: diabetic polyneuropathy
PHN: post-herpetic neuralgia

Figure 2: Response rates in patients with PHN and DPN in the per protocol set.

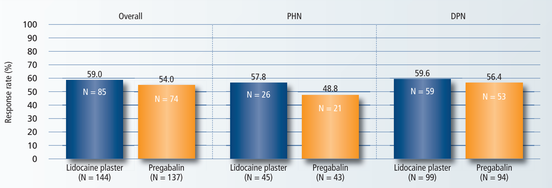


Figure 3A: Proportion of patients (per protocol set) experiencing ≥ 30% reductions in baseline pain intensity (NRS-3 scores) after treatment with 5% lidocaine medicated plasters or pregabalin in patients with post-herpetic neuralgia (PHN), diabetic polyneuropathy (DPN) and in both groups 'overall'.

- The proportion of PHN patients who showed ≥ 30% reduction in NRS-3 was 57.8% in the 5% lidocaine medicated plaster group and 48.8% in the pregabalin group. A ≥ 50% reduction in NRS-3 was achieved by 35.6% (5% lidocaine medicated plaster) and 20.9% (pregabalin) of PHN patients ***(Figure 3)***.
- Among DPN patients, ≥ 30%reductions were achieved by 59.6%of lidocaine plaster-treated and 56.4% of pregabalin-treated patients, and ≥ 50% reductions were achieved by 40.4% of lidocaine plaster-treated and 37.2% of pregabalin-treated patients ***(Figure 3)***.
- After 4 weeks of treatment, there was a significant change from baseline in 'burning pain' (11-point scale NPSI) in the lidocaine plaster group (-2.4; p < 0.0001) and in the pregabalin group (-1.8, p = 0.0002) in the combined patient population. Significant reductions from baseline scores were also observed in both treatment groups for 'stabbing pain': (-1.9; p = 0.0003 for lidocaine plaster and -1.9; p < 0.0001 for pregabalin).
- For allodynia severity rating, a trend towards greater improvement was observed in patients treated with the 5% lidocaine medicated plaster ***(Figure 4)***. The proportion of patients reporting 'no pain or discomfort to touch/uncomfortable but tolerable to touch' increased from 46.7% to 75.0%in the 5% lidocaine medicated group and from 34.9%to 58.8% in the pregabalin group.

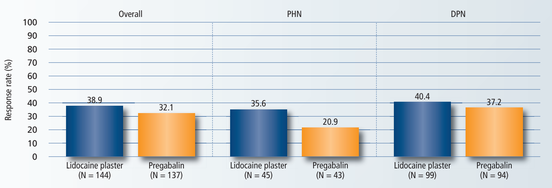
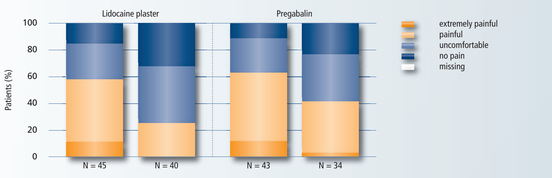


Figure 3B: Proportion of patients (per protocol set) experiencing ≥ 50% reductions in baseline pain intensity (NRS-3 scores) after treatment with 5% lidocaine medicated plasters or pregabalin in patients with post-herpetic neuralgia (PHN), diabetic polyneuropathy (DPN) and in both disease groups 'overall'.

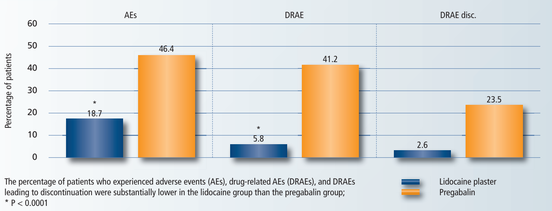


The graph shows the percentage of patients (per protocol set) with PHN in each treatment group who reported the severity of allodynia in response to a touch stimulus as 'no pain', 'uncomfortable', 'painful', or 'extremely painful' at baseline (randomisation) and after 4 weeks of treatment (Day 28). The percentage of lidocaine-treated patients reporting 'no pain' or 'uncomfortable' to touch was comparable in the two groups at baseline.

Figure 4: Severity of allodynia symptoms reported in patients with PHN treated with 5% lidocaine medicated plasters or pregabalin.

Safety

- In the safety analysis set (comprising 308 patients who received at least one treatment) fewer lidocaine plaster-treated patients than pregabalin-treated patients experienced AEs and DRAEs (p < 0.0001) ***(Figure 5)***.
- Fewer patients in the 5% lidocaine medicated plaster group experienced DRAEs (9 patients, 5.8%) compared with those receiving pregabalin (63 patients, 41.2%) (p < 0.0001) ***(Figure 5)***.
- Drug-related AEs leading to discontinuation occurred in 36 (23.5%) pregabalin-treated patients (mainly nervous system disorders) and in 4 (2.6%) lidocaine plaster-treated patients (mainly application site irritation) ***(Figure 5)***.
- The majority of treatment emergent AEs experienced by patients receiving either treatment were mild to moderate in severity. However, patients receiving pregabalin experienced more "severe" events than lidocaine recipients: 20/153 events (13.1%) vs. 7/155 events (4.5%).



The percentage of patients who experienced adverse events (AEs), drug-related AEs (DRAEs), and DRAEs leading to discontinuation were substantially lower in the lidocaine group than the pregabalin group;
* P < 0.0001

Figure 5: Proportion of patients experiencing adverse events, drug-related adverse events (DRAEs) and DRAEs leading to discontinuation after treatment with 5% lidocaine medicated plasters or pregabalin.

Summary and conclusions

- This analysis of a randomized, controlled trial of patients with PHN and DPN indicates that topical treatment with 5% lidocaine medicated plaster provides comparable pain relieving efficacy to systemic treatment with pregabalin in patients with peripheral neuropathic pain.
- Data from the PHN cohort suggest that the 5% lidocaine medicated plaster may be particularly effective at producing analgesic responses in these patients, as well as relieving their allodynia, burning and stabbing pain symptoms.
- The 5% lidocaine medicated plaster was better tolerated in DPN and PHN patients because treatment was associated with fewer DRAEs compared with pregabalin. Fewer patients receiving the 5% lidocaine medicated plaster discontinued therapy due to DRAEs than pregabalin recipients.
- These data suggest that, when used in patients with typical peripheral neuropathic pain syndromes like PHN and DPN, 5% lidocaine medicated plaster may possess a pain relieving efficacy comparable to that of pregabalin combined with an improved safety and tolerability profile (fewer DRAEs and fewer discontinuations due to DRAEs).

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