2 SYNOPSIS

TITLE OF TRIAL: Safety and efficacy of lidocaine 5% medicated plaster in comparison with pregabalin in postherpetic neuralgia and diabetic polyneuropathic pain

SPONSOR/COMPANY: Grünenthal

INTERNATIONAL COORDINATING INVESTIGATOR: [redacted] Kiel, Germany.

TRIAL CENTERS: A total of 51 centers in 14 European countries (Austria, Belgium, Croatia, Czech Republic, Germany, Ireland, Italy, Poland, Portugal, Russia, Slovenia, Spain, Sweden, and the United Kingdom).

PUBLICATION REFERENCES:

Baron R, Binder A, Koroschetz J, Serpell MG, Steigerwald I. Efficacy and tolerability of a 5% lidocaine-medicated plaster versus pregabalin in patients with post-herpetic neuralgia (PHN) and painful diabetic polyneuropathy (DPN): results from an interim analysis of a randomized, controlled trial (PW 228). Abstracts of the 12th World Congress on Pain, Glasgow, 17-22 August 2008. International Association for the Study of Pain.

Schattschneider J, Baron R, Binder A, Wasner G, Steigerwald I. A comparison of quality of life and safety outcomes from a randomized, controlled trial of a topical lidocaine-medicated plaster versus pregabalin for patients with post-herpetic neuralgia (PHN) and painful diabetic polyneuropathy (DPN) (PH 185). Abstracts of the 12th World Congress on Pain, Glasgow, 17-22 August 2008. International Association for the Study of Pain.

TRIAL PERIOD (YEARS):	First subject enrolled	04 January 2007
	Last subject completed	14 January 2008
	Database lock	04 April 2008
PHASE OF DEVELOPMENT:	IIIb	

OBJECTIVES:

The primary objective of this trial was to evaluate the safety and efficacy of lidocaine 5% medicated plaster versus pregabalin after 4 weeks of treatment in subjects with either postherpetic neuralgia or diabetic polyneuropathic pain.

The secondary objectives of this trial were to:

- Estimate the suitability of lidocaine 5% medicated plaster as a stand-alone medication, as an alternative to and in combination with pregabalin.
- Evaluate the safety and efficacy of lidocaine 5% medicated plaster in combination with pregabalin.

- Evaluate the pregabalin-sparing effect of lidocaine 5% medicated plaster by tapering down pregabalin.

DESIGN AND METHODOLOGY:

This trial was a Phase III, adaptive 2-stage, open-label, randomized and stratified by indication, multiple-administration, multi-center trial.

After a wash-out phase of 2 weeks, including the taper-off of previous medication, subjects with pain from PHN and painful DPN received either lidocaine 5% medicated plaster or capsules of pregabalin 75 mg in the Comparative Phase (4 weeks). A limited number of subjects (N = 52) with a creatinine clearance between 30 mL/min and 60 mL/min were offered treatment with lidocaine 5% medicated plaster for 12 weeks in the Lidocaine Pick-up Arm.

In the Comparative Phase, subjects receiving lidocaine 5% medicated plaster were allowed to apply up to 3 (PHN) or 4 (DPN) plasters once daily for up to 12 h within a period of 24 h. Pregabalin was titrated to effect according to the current SmPC (oral dosing twice daily): 1 week at 150 mg/day, 1 week at 300 mg/day. At the end of the second week, subjects with an NRS-3 ≤4 (recalled average pain intensity during the last 3 days as entered in the Case Report Form) continued to be administered 300 mg pregabalin/day, while subjects with an NRS-3 >4 were increased to 600 mg pregabalin/day.

Depending on their current NRS-3 at the end of the Comparative Phase, subjects continued with their current treatment/dose (as monotherapy if NRS-3 ≤4) in the Combination Phase (8 weeks) or they received pregabalin/lidocaine 5% medicated plaster as an additional medication to their current treatment (combination treatment if NRS-3 >4). Pregabalin was up-titrated according to SmPC.

In the following Down-titration Phase subjects treated with pregabalin in the Comparative Phase who had an NRS-3 ≤4 as well as those treated with pregabalin in combination with lidocaine 5% medicated plaster who had an NRS-3 ≤4 were offered another 4 weeks of treatment in a sub-trial, in which pregabalin was tapered down as far as possible (stop criterium for tapering down: increase in NRS). Subjects who did not continue the trial were tapered off according to the pregabalin SmPC.

Subjects who, at any time during the Comparative Phase, dropped out of the pregabalin arm due to AEs were given the offer to enter the Lidocaine Pick-up Arm at a Switch Visit and received continuous treatment with lidocaine 5% medicated plaster for the remainder of their 12-week trial period. Pregabalin was tapered down according to SmPC.

NUMBER OF SUBJECTS:

It was planned that the data from the first 150 subjects were to be used for an interim analysis to determine the number of subjects required for the second stage of the trial. Recruitment for the second stage continued while this interim analysis was performed. Although the total number was estimated at 300 subjects on the basis of a fixed-size sample calculation, the actual number of subjects could have been adjusted to the number needed to demonstrate non-inferiority based on differences in the response rates as calculated in the interim analysis.

In total, 431 subjects were screened. An interim analysis was performed for both the first 152 subjects randomized and the first 29 subjects allocated to the Lidocaine Pick-up Arm (the latter

is not part of the interim report). Based on the results of the interim analysis it was decided that the 311 subjects enrolled up to that point continue the trial but enrollment of further subjects was ceased.

SUBJECT DISPOSITION:

A total of 431 subjects were screened; 68 were not included in the treatment period of the trial for the reasons shown below (more than 1 reason was possible).

Reason for withdrawal	Number (%) of subjects N = 431
Any reason	68 (15.8)
Withdrawal of informed consent	25 (5.8)
Violation of exclusion criteria	17 (3.9)
Violation of inclusion criteria	18 (4.2)
Other reason	10 (2.3)

In total, 363 subjects were included in the trial; 52 were allocated to the Lidocaine Pick-up Arm at Visit 2 because of partial renal impairment. Of the 311 subjects who were randomized to the Comparative Phase; 61 subjects withdrew from the Comparative Phase for the reasons shown below (more than 1 reason was possible).

	Number (%) of subjects	
Reason for withdrawal	**Lidocaine 5% medicated plaster N = 157**	**Pregabalin N = 154**
Any reason	17 (10.8)	44 (28.6)
Adverse event	9 (5.7)	8 (5.2)
- Drug-related AE [a]	4 (2.5)	6 (3.9)
Switched to Lidocaine Pick-up Arm due to drug-related AE[a]	–	30 (19.5)
Informed consent withdrawal	2 (1.3)	6 (3.9)
Lack of efficacy	4 (2.5)	–
Protocol deviation	1 (0.6)	2 (1.3)
Other reasons	5 (3.2)	2 (1.3)

a) 36 out of 38 subjects discontinued or switched due to drug-related AEs.

In total, 250 subjects participated in the Combination Phase; 20 subjects withdrew for the reasons shown below (more than 1 reason was possible).

Reason for withdrawal	Number (%) of subjects VS N = 79	PS N = 63	VP N = 60	PV N = 48
Any reason	4 (5.1)	3 (4.8)	7 (11.7)	6 (12.5)
Adverse event	1 (1.3)	1 (1.6)	7 (11.7)	5 (10.4)
- Drug-related AE (pregabalin)	-	1 (1.6)	4 (6.7)	1 (2.1)
- Drug-related AE (lidocaine)	1 (1.3)		1 (1.7)	–
Informed consent withdrawal	2 (2.5)	1 (1.6)	2 (3.3)	–
Lack of efficacy	–	–	–	1 (2.1)
Other reasons	1 (1.3)	–	–	–
Protocol deviation	1 (1.3)	1 (1.6)	1 (1.7)	–

PS = pregabalin during the Comparative Phase and continued monotherapy with pregabalin during the Combination Phase, PV = pregabalin during the Comparative Phase plus lidocaine 5% medicated plaster as additional treatment during the Combination Phase, VP = lidocaine 5% medicated plaster during the Comparative Phase plus pregabalin as additional treatment during the Combination Phase, VS = lidocaine 5% medicated plaster during the Comparative Phase and continued monotherapy with lidocaine 5% medicated plaster during the Combination Phase

There were 31 subjects who entered the Down-titration sub-trial from the PV treatment group of the Combination Phase; no subject withdrew.

There were 82 subjects who entered the Lidocaine Pick-up Arm; 27 withdrew for the reasons shown below (more than 1 reason was possible).

Reason for withdrawal	Number (%) of subjects Visit 2 subjects N = 52	Switched subjects N = 30
Any reason	20 (38.5)	7 (23.3)
Adverse event	8 (15.4)	3 (10.0)
- Drug-related AE (lidocaine)	4 (7.7)	1 (3.3)
Informed consent withdrawal	3 (5.8)	–
Lack of efficacy	8 (15.4)	4 (13.3)
Other reasons	2 (3.8)	1 (3.3)
Protocol deviation	1 (1.9)	–

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Subjects 18 years and older, suffering from either postherpetic neuralgia (PHN) or painful diabetic polyneuropathy (DPN), and having an average pain intensity (during last 3 days prior to screening and enrollment visit) of above 4 on the 11-point Numeric Rating Scale (NRS) were included in the trial. PHN was defined as neuropathic pain persisting for at least 3 months after healing of a herpes zoster skin rash. Subjects with PHN had to have intact skin in the area of topical treatment. Subjects with painful DPN had to have controlled, treated type 1 or 2 diabetes mellitus with glycosylated hemoglobin (HbA1c) ≤11% and painful, distal, symmetrical, sensomotor polyneuropathy of the lower extremities for ≥3 months (below the knees on both extremities) with at least 2 of the following symptoms present: burning sensation, tingling or prickling, paresthesias, painful heat or

cold sensation (e.g., warm or cold water). In addition, in subjects with painful DPN the most painful area could be covered by no more than 4 plasters.

INVESTIGATIONAL MEDICINAL PRODUCTS:

Test product	**Lidocaine 5% medicated plaster, 700 mg lidocaine HCl per plaster**
Dose	Up to 3 (PHN subjects) or 4 (painful DPN subjects) plasters daily for a maximum of 12 hours (plaster-free interval: at least 12 hours)
Mode of administration	Topical
Batch number	76282
Duration of treatment	Up to 12 weeks

Comparator product	**Pregabalin capsules containing 75 mg of pregabalin**
Dose	Up to 600 mg/day (300 mg twice daily)
Mode of administration	Oral
Batch number	0380056D
Duration of treatment	Up to 16 weeks

CRITERIA FOR EVALUATION:

Efficacy:

The primary endpoint was the decrease of NRS-3 after 4 weeks of treatment with lidocaine 5% medicated plaster or pregabalin as stand-alone medication, i.e., between Visit 2 (Baseline or the Comparative Phase) and Visit 4, expressed as response rate. Response was defined as a reduction of at least 2 points or a value of 4 or less on the NRS-3 scale after 4 weeks of treatment.

Secondary efficacy endpoints were: Subject Global Impression of Change (SGIC), Clinical Global Impression of Change (CGIC), subject satisfaction with the treatment, NRS-3, percentage of subjects with 30% and 50% reduction in NRS-3, average pain intensity during the last 24 hours (A-NRS) and worst pain intensity during the last 24 hours (W-NRS), time to onset of response, time to onset of pain relief, Neuropathic Pain Symptom Inventory (NPSI), Short Form McGill Pain Questionnaire (SF-MPQ), Short Form-36 health survey (SF-36), EuroQol-5 dimension quality of life index (EQ-5D), Chronic Pain Sleep Inventory (CPSI), allodynia severity rating, and use of rescue medication. A special endpoint criterion (the pregabalin-sparing effect of lidocaine 5% medicated plaster) was assessed in the Down-titration sub-trial.

Safety:

Safety was assessed by monitoring adverse events (AEs), laboratory evaluations (hematology, clinical chemistry, and urinalysis), vital signs, physical examinations, concomitant medications, and time to withdrawal due to AEs and drug-related AEs.

STATISTICAL METHODS:

Sample size calculation:

The sample size calculation for this trial was based on a non-inferiority margin of 8% (non-inferiority of lidocaine 5% medicated plaster compared to pregabalin), a 1-sided significance level of 2.5%, and a power of 80% (please note that this non-inferiority margin seemed to be sufficient, as the difference between pregabalin and placebo for 50% pain reduction was assessed in several trials to exceed 15% [EMEA 2004b]). For the interim analysis, the primary endpoint was analyzed using a 1-sided equivalence test for 2 proportions. The resulting p-value was the basis for the decision about continuation as described by Bauer and Köhne (1994) or discontinuation based on feasibility or clinical reasons.

Datasets for analysis:

Overall, 3 trial populations were defined for the statistical analyses: the safety population (SAF), the full-analysis set (FAS), and the per-protocol (PP) set.

Subjects were assigned to SAF and/or FAS and their data were analyzed in a given trial phase (Comparative Phase, Combination Phase, Down-titration sub-trial, and Lidocaine Pick-up Arm) if the date of trial end was after the beginning of the trial phase.

Subjects were evaluated on the basis of the actual treatment received instead of treatment randomized, allocated, or otherwise specified by the protocol.

Within the PP population, there were 2 distinct subsets: the Comparative Phase PP set and the Combination Phase PP set (PP_{comb}). For each analysis, the population relevant for the phase of the analysis presented was used.

No PP analyses were performed for the Down-titration sub-trial or the Lidocaine Pick-up Arm.

Statistical analyses:

The primary analysis of the primary endpoint, the response rate after 4 weeks of treatment, was a 1-sided equivalence test for 2 proportions according to the Bauer-Köhne procedure. This analysis was performed for the Comparative Phase in the PP set. Only this test of the primary endpoint was confirmatory; all other analyses were considered exploratory. Comparisons between treatment groups were performed only for the primary efficacy analysis and AEs; in all other cases, changes from Baseline were compared within treatment groups, with the null hypothesis being that there was no change from Baseline. The analysis of the primary endpoint was presented for both trial stages, i.e., before the interim analysis (Stage 1) and after interim analysis (Stage 2), and overall, whereas analyses of all other endpoints were only presented for the trial overall.

The primary endpoint was also analyzed with a logistic regression model including treatment, center, underlying disease (PHN and painful DPN), and Baseline NRS-3 as factors. Crude and adjusted odds ratios for each of these factors were presented together with the corresponding 95% confidence intervals. For the adjusted odds ratios, the full logistic model was calculated as well as a model containing only significant factors (resulting from backward stepwise regression).

Continuous secondary efficacy variables were tested within each treatment group using an analysis of variance (ANOVA). For the categorical variables of SF-MPQ (single items and present pain intensity), NPSI (Questions 4 and 7), CPSI, and the allodynia severity rating, within-treatment shifts

from Baseline were tested by a Bowker test. Kaplan-Meier analyses were performed for time to onset of pain relief.

For the primary endpoint and for EQ-5D, SF-36, SGIC, CGIC, and subject satisfaction (for the Comparative Phase), missing values at Visit 4 were imputed via last observation carried forward (LVCF).

The incidence of drug-related AEs (Preferred Term) occurring in at least 2% of the subjects in at least 1 treatment group were compared between treatment groups via Fisher's exact test for the Comparative Phase.

For the Down-titration sub-trial, the pregabalin-sparing effect was calculated and an exact 95% confidence interval was calculated using the Clopper-Pearson formula.

Summary descriptive statistics were performed for all variables. For continuous and semi-continuous variables by time of collection, these analyses included number of subjects, mean, standard deviation (SD), minimum value, 25th percentile, median, 75th percentile, and maximum value. For categorical variables by time of collection, these analyses included number of subjects, number of occurrences, and percent of occurrences for each category.

SUMMARY AND CONCLUSIONS FOR THE COMPARATIVE PHASE:

Disposition of subjects and baseline characteristics:

In total, 311 subjects were randomized to the Comparative Phase. The SAF comprised 308 subjects. The FAS comprised 300 subjects, 96 with PHN and 204 with painful DPN. The PP set comprised 281 subjects, 88 with PHN and 193 with painful DPN. A higher percentage of subjects in the pregabalin group than in the lidocaine 5% medicated plaster group withdrew from the Comparative Phase (28.6% versus 10.8%), primarily due to subjects in the pregabalin group switching to the Lidocaine Pick-up Arm due to intolerability of treatment with pregabalin.

Sex, age, height, weight, BMI, and ethnic group were equally distributed between the lidocaine 5% medicated plaster group and the total pregabalin group in the FAS or PP set. In the PP set, about 47% of the subjects were men and 53% women. The mean age for both treatment groups was approximately 62 years.

All subjects with painful DPN in the PP set had pain in the lower extremities. The location of pain for the majority of PHN subjects was the torso (62.2% in the lidocaine 5% medicated plaster group and 72.1% in the pregabalin group in the PP set).

The average NRS-3 values and SF-MPQ and EQ-5D scores at Baseline were comparable between treatment groups. Subjects with painful DPN had worse SF-36 values at Baseline than subjects with PHN, but these values were comparable between treatment groups. At Baseline, painful allodynia was more frequent in subjects with PHN than subjects with painful DPN, as expected, but was comparable between treatment groups.

Efficacy results:

Primary endpoint: NRS-3 response rate at Visit 4

Response rates for lidocaine 5% medicated plaster showed consistent effects throughout the trial (i.e., both in Stage 1 and Stage 2) and in both subjects with PHN and painful DPN, with values

between 61.1% and 67.3%. Higher response rates were observed in subjects with PHN in the lidocaine 5% medicated plaster group than in the pregabalin group whereas the response rates for subjects with painful DPN were comparable for both treatment groups.

The response rate at Visit 4 was slightly higher in the lidocaine 5% medicated plaster group (65.3%) than in the pregabalin group (62.0%) (PP set). However, the combined non-inferiority p-value was 0.00656 (above the critical value of 0.0038) with a lower limit of CI –9.15. This was slightly below the predefined non-inferiority margin of –8 percentage points, the lower limit to prove the non-inferiority of the lidocaine 5% medicated plaster compared to pregabalin.

The analysis of the response rates for the FAS suggested the non-inferiority of lidocaine 5% medicated plaster to pregabalin (response rates of 66.4% versus 61.5% in the pregabalin group, combined p = 0.00229, lower CI –7.03).

Secondary endpoints

In PHN, the lidocaine 5% medicated plaster group showed a higher response rate than both pregabalin dosage groups. In DPN, the lidocaine 5% medicated plaster group showed a response rate comparable to both pregabalin dosage groups.

As with the response rates, larger decreases in NRS-3 at Visit 4 relative to Baseline were seen for subjects with PHN in the lidocaine 5% medicated plaster group compared to subjects treated with pregabalin; whereas for subjects with painful DPN the decreases were comparable for the 2 treatment groups (see summary table).

The percentage of subjects with 30% and 50% reduction of the NRS-3 value at Visit 4 was higher in the lidocaine 5% medicated plaster group than in the overall pregabalin group, mainly due to a more pronounced improvement for the lidocaine 5% medicated plaster in the PHN group (see summary table). These results were also supported by those of the A-NRS and W-NRS (see summary table).

W-NRS value decreases in the lidocaine 5% medicated plaster group showed that satisfactory efficacy can be maintained with a 12-hours on/off regimen for the lidocaine 5% medicated plaster without occurrence of relevant breakthrough episodes due to insufficient pain relief.

A higher percentage of subjects in the pregabalin group than in the lidocaine 5% medicated plaster group withdrew from the Comparative Phase (28.6% versus 10.8%). This difference in withdrawal rates could primarily be attributed to subjects discontinuing pregabalin due to adverse drug reactions and switching to the Lidocaine Pick-up Arm.

Between Baseline and Visit 4, the mean daily number of paracetamol tablets (allowed concomitant medication) decreased steadily and comparably for subjects with painful DPN in both treatment groups. Subjects with PHN in the lidocaine 5% medicated plaster group required clinically relevant less additional, non-prohibited pain medication.

The NPSI total score suggested comparable, clinically relevant improvement in pain intensity for the lidocaine 5% medicated plaster group and the pregabalin group (see summary table). Within PHN, subjects in the lidocaine 5% medicated plaster group showed larger improvement for the NPSI single items ‘pain that feels like burning’, ‘pain that feels like stabbing’, and ‘pain that feels like pins and needles’ than in the pregabalin group.

For the SF-MPQ total score, the reduction of pain from Baseline to Visit 4 was greater in subjects treated with lidocaine 5% medicated plaster than in subjects treated with pregabalin (see summary table). The effect was more pronounced in subjects with PHN than in subjects with painful DPN. These results were supported by those of the SF-MPQ pain intensity rating during the last 7 days, the sensory and affective sub-scores. For note, subjects with PHN treated with lidocaine 5% medicated plaster improved significantly in the single items shooting, stabbing, sharp, and hot/burning pain, but not subjects with PHN treated with pregabalin.

There was an expected higher occurrence of painful allodynia within the PHN group compared to the DPN population. Changes from Baseline in subjects with PHN were significant for the lidocaine 5% medicated plaster group, but not for the pregabalin (see summary table). Subjects with painful DPN showed comparable improvement for both treatment groups. The low frequency of painful allodynia in subjects with DPN associated with high response rates related to NRS-3 based parameters supports the effectiveness of topical lidocaine in peripheral neuropathic pain syndromes irrespective of the presence of allodynia.

Under treatment with lidocaine 5% medicated plaster, subjects with PHN and those with painful DPN experienced overall a more pronounced improvement of health-related quality of life (EQ-5D, estimated health state) after 4 weeks (versus Baseline) compared with pregabalin (see summary table).

For both treatment groups, improvements were seen for mean scores in all 8 dimensions measured by the SF-36. Improvement of bodily pain correlates to pain relief measured by the NRS-3 score. Subjects on lidocaine 5% medicated plaster showed a clear tendency towards greater improvement in the components general health, social functioning, and vitality than those on pregabalin (see summary table).

According to the SGIC, subjects had a comparably positive impression of change for both treatments. In subjects with PHN, the improvement was greater for subjects in the lidocaine 5% medicated plaster group than in the pregabalin group. For subjects with painful DPN, data were comparable between treatment groups. For SGIC it is of particular interest to consider that this score is largely insensitive to typical CNS effects related to pregabalin trials.

Results of the CGIC were similar to those of the SGIC.

At Visit 4, 75.6% of the subjects in the lidocaine 5% medicated plaster group versus 67.9% of the subjects in the pregabalin group reported ‘good’, ‘very good’, or ‘excellent’ satisfaction with the treatment, reflecting favorable results for both treatment groups with advantages for lidocaine 5% medicated plaster group.

Limitations due to small sample size, reflected by standard deviation and p-values, particularly in the smaller PHN group, have to be taken into account when discussing clinical relevance of quality of life parameters.

Secondary efficacy results in the FAS reflect those in the PP set.

Summary table on changes at Visit 4 relative to Baseline of secondary efficacy parameters (per-protocol population)

Questionnaire	Lidocaine 5% medicated plaster	Pregabalin	ANOVA descriptive p-value	
	Changes from Baseline at Visit 4 (mean [SD]) or percentage of subjects		Lidocaine	Pregabalin
NRS-3	–2.5 (2.01)	–2.3 (1.95) (all)	<0.0001	<0.0001
		-2.2 (2.17) (300 mg)		<0.0001
		2.4 (1.81) (600 mg)		<0.0001
A-NRS at Day 28	-2.6 (2.00)	-2.7 (2.41) (all)		
		-3.8 (2.95) (300 mg)		
		-1.6 (1.14) (600 mg)		
W-NRS at Day 27	-2.7 (1.87)	-2.7 (2.21) (all)		
		-3.2 (2.51) (300 mg)		
		-2.3 (2.01) (600 mg)		
Reduction in pain				
- at least 30%	59.0%	54.0% (all)		
		52.9% (300 mg)		
		54.7% (600 mg)		
- at least 50%	38.9%	32.1% (all)		
		41.2% (300 mg)		
		26.7% (600 mg)		
NPSI				
- total score	-1.6 (1.67)	-1.6 (1.59) (all)	<0.0001	<0.0001
		-1.9 (1.59) (300 mg)		<0.0001
		-1.5 (1.60) (600 mg)		<0.0001
- burning	–2.4 (2.80)	–1.8 (2.78) (all)	<0.0001	0.0002
- stabbing	–1.9 (2.83)	–1.9 (2.94) (all)	0.0003	<0.0001
- pins and needles	–2.0 (2.77)	–1.7 (2.65) (all)	<0.0001	<0.0001
- tingling	–2.0 (2.98)	–2.2 (2.68) (all)	<0.0001	<0.0001
SF-MPQ				
- total	-7.9 (8.18)	-6.5 (7.22) (all)	<0.0001	<0.0001
		-6.1 (7.05) (300 mg)		0.0166
		-6.7 (7.33) (600 mg)		<0.0001
- sensory	-5.5 (5.82)	-5.0 (5.68) (all)	<0.0001	<0.0001
- affective	-2.2 (2.78)	-1.5 (2.44) (all)	<0.0001	<0.0001
- pain intensity rating during the last 7 days	-23.6 (23.24)	-21.4 (21.93) (all)	<0.0001	<0.0001
EQ-5D thermometer	3.5 (20.24)	2.3 (16.49) (all)	0.2339	0.2346
		2.4 (15.19) (300 mg)		0.6112
		2.2 (17.22) (600 mg)		0.2783
	7.3 (24.14) (PHN)	-0.4 (16.24) (PHN)	0.1185	0.3304
	1.8 (18.16) (DPN)	3.6 (16.55) (DPN)	0.7464	0.2717
EQ-5D estimated health state	0.12 (0.240)	0.04 (0.235) (all)	0.0002	0.0297
		0.07 (0.234) (300 mg)		0.0600
		0.03 (0.236) (600 mg)		0.2042
	0.12 (0.231) (PHN)	-0.00 (0.276) (PHN)	0.0621	0.8916
	0.13 (0.245) (DPN)	0.06 (0.211) (DPN)	0.0005	0.0006
SF-36				
- physical functioning	5.3 (12.18)	3.2 (14.25)	0.0216	0.01665
- role physical	7.3 (18.17)	6.5 (20.84)	0.0889	<0.0001
- bodily pain	12.9 (17.64)	10.3 (17.45)	<0.0001	<0.0001

Questionnaire	Lidocaine 5% medicated plaster		Pregabalin		ANOVA descriptive p-value	
	Changes from Baseline at Visit 4 (mean [SD]) or percentage of subjects				Lidocaine	Pregabalin
- general health	4.8 (10.58)		1.0 (12.13)		0.0003	0.1905
- vitality	5.4 (10.79)		3.0 (11.59)		0.0032	0.0148
- social functioning	9.0 (19.10)		4.1 (18.57)		0.0004	0.0215
- role emotional	2.1 (16.93)		3.0 (19.63)		0.6396	0.5213
- mental health	2.6 (9.81)		2.2 (11.04)		0.1078	0.4502
Allodynia severity rating (all subjects)	**Visit 2**	**Visit 4**	**Visit 2**	**Visit 4**	<0.0001 [a]	<0.0001 [a]
- no pain/discomfort to touch	31.9%	48.5%	26.3%	44.6%		
- uncomfortable, tolerable to touch	29.2%	38.6%	37.2%	37.5%		
- painful	34.7%	12.9%	31.4%	16.1%		
- extremely painful	4.2%	-	5.1%	0.9%		
- missing	-	-	-	0.9%		
(subjects with PHN)					0.0138 [a]	0.1051 [a]
(subjects with DPN)					0.0003 [a]	0.0008 [a]

a) from a Bowker test for symmetry for the shift from Baseline
PHN = postherpetic neuralgia, DPN = diabetic polyneuropathy

Safety results:

Superior safety and tolerability of lidocaine 5% medicated plaster in comparison to pregabalin was observed as a result of the analyses of AEs during the Comparative Phase. Fewer subjects in the lidocaine 5% medicated plaster group than in the pregabalin group reported TEAEs (18.7% [29/155] versus 46.4% [71/153]) and drug-related AEs (5.8% [9/155] versus 41.2% [63/153]). These differences were clinically relevant and statistically significant (descriptive p-value <0.0001). Furthermore, the numbers of subjects with AEs leading to discontinuation and with drug-related AEs leading to discontinuation were considerably lower in the lidocaine 5% medicated plaster group than in the pregabalin group (5.8% [9/155] versus 25.5% [39/153] and 2.6% [4/155] versus 23.5% [36/153], respectively).

In the lidocaine 5% medicated plaster group, the incidence of drug-related AEs was low compared with the incidence of TEAEs (5.8% [9/155] versus 18.7% [29/155]). Most individual TEAEs were reported by only 1 subject, with only back pain and headache being reported in 3 subjects each in the lidocaine 5% medicated plaster group. There were very few drug-related AEs reported in the lidocaine 5% medicated plaster group; 2 subjects reported application site irritation and 2 subjects reported headache. Three subjects discontinued from this group due to problems with the application site of the plaster (application site irritation in 2 subjects and application site rash in 1 subject).

In the pregabalin group, the incidence of drug-related AEs was nearly as high as the incidence of TEAEs (41.2% [63/153] versus 46.4% [71/153]), i.e., most subjects who experienced TEAEs had drug-related AEs. Moreover, the incidence of drug-related AEs leading to discontinuation in the pregabalin group was nearly as high as the incidence of AEs leading to discontinuation (23.5% versus 25.5%), i.e., over 90% of AEs leading to discontinuation were considered drug-related. The most common TEAEs for the pregabalin group were dizziness, fatigue, vertigo, headache, and somnolence, which, except for headache, were also the most common drug-related AEs, the most

common AEs leading to discontinuation, and the most common drug-related AEs leading to discontinuation.

Of the drug-related AEs reported, a relatively higher percentage was considered mild for the lidocaine 5% medicated plaster group than for the pregabalin group. The percentages of drug-related AEs considered moderate and severe were higher in the pregabalin group than in the lidocaine 5% medicated plaster group. As with all TEAEs, the higher percentage of drug-related AEs considered mild for the lidocaine 5% medicated plaster group compared with the pregabalin group was more pronounced in subjects with painful DPN (63.6% versus 31.6%) than in subjects with PHN (40.0% versus 42.7%). Only 1 application site reaction was rated 'severe' in the lidocaine 5% medicated plaster group.

No deaths occurred in the Comparative Phase. Three subjects treated with lidocaine 5% medicated plaster and 1 subject treated with pregabalin experienced an SAE. None of the SAEs was rated by both the Investigator and Sponsor as related to trial medication. Only 1 SAE of mental disorder due to a general medical condition was considered by the Investigator to be possibly related to lidocaine 5% medicated plaster. In the opinion of the Sponsor, the event was unlikely related to lidocaine 5% medicated plaster. The information provided in this single case does not appear to adversely affect the risk assessment of lidocaine 5% medicated plaster.

An analysis of AEs separately for PHN and painful DPN indications revealed higher overall reports of TEAEs and drug-related AEs for PHN subjects than for painful DPN subjects which might be expected in an older, multi-morbid population. However, the incidence of TEAEs was consistently lower for the lidocaine 5% medicated plaster group than the pregabalin group for both indications. Thus, the highest relative frequency of TEAEs and drug-related AEs were reported by PHN subjects in the pregabalin treatment group.

Clinically relevant effects on laboratory parameters or vital signs were not observed under treatment with lidocaine 5% medicated plaster or pregabalin.

Results strongly support the better benefit-risk ratio for lidocaine 5% medicated plaster in relation with its systemic comparator.

SUMMARY AND CONCLUSIONS FOR THE COMBINATION PHASE:

Disposition of subjects and baseline characteristics:

In total, 139/155 (89.7%) subjects allocated to lidocaine treatment at baseline (Visit 2) but only 111/153 (72.5%) subjects allocated to pregabalin completed the Comparative Phase. These 250 subjects were allocated to the 4 treatment groups of the Combination Phase according to NRS-3 ≤4 and NRS-3 >4. Of the 139 subjects who completed the Comparative Phase in the lidocaine 5% medicated plaster group, 79 (56.8%) entered the VS group (subjects who received lidocaine 5% medicated plaster as monotherapy) and 60 (43.2%) entered the VP group (subjects who received both lidocaine 5% medicated plaster and pregabalin). Of the 111 subjects who completed the Comparative Phase in the pregabalin group, 63 (56.8%) entered the PS group (pregabalin as monotherapy) and 48 (43.2%) entered the PV group (subjects who received both pregabalin and lidocaine 5% medicated plaster).

The FAS comprised 250 subjects, 74 with PHN and 176 with painful DPN. The PP_{comb} set comprised 229 subjects, 68 with PHN and 161 with painful DPN.

The demographic characteristics for the subjects who participated in the Combination Phase were in line with those of the Comparative Phase. The only slight demographic difference was in the sex distribution among the treatment groups; the VP and PV groups had a larger proportion of women. However, it is noteworthy that there were few differences among the treatment groups in demographic characteristics as the 4 treatment groups were not randomized.

At the Combination Baseline (Visit 4), the mean NRS-3 values for the VP and PV groups were higher than those of the VS and PS groups, which were expected since the subjects were allocated to these 2 groups at Visit 4 according to their NRS-3 values.

Efficacy results:

For subjects in the monotherapy groups, the analgesic efficacy observed in the Comparative Phase was maintained throughout the Combination Phase. Across treatment groups there was a steady decrease in NRS-3 from Visit 4 to Visit 7, of comparable magnitude for the VS and PS groups.

Subjects experiencing insufficient efficacy during the Comparative Phase and therefore allocated to combination therapy achieved clinically relevant improvement in NRS-3 values during the 8 weeks of the Combination Phase on top of the improvement they had achieved during the 4 weeks of the Comparative Phase. The improvement was comparable for the VP and PV groups.

These trends were supported by the results of the NPSI, SF-MPQ, and allodynia severity rating.

Quality of life results provide a deeper insight into subject's experiencing treatment outcomes.

The EQ-5D thermometer showed significant improvements in the VS group versus Baseline (Visit 2) for the overall population and for subjects with PHN. Significant improvements could be demonstrated for none of the pregabalin groups. Regarding the estimated health state and the SF-36 improvements could be observed for all treatment groups.

For subjects staying on monotherapy, 21 of 22 (95.4%) in the lidocaine 5% medicated plaster group experienced a 'much' to 'very much' improvement compared with 8 of 11 (72.8%) in the pregabalin group. Both groups reported high treatment satisfaction.

Subjects on combination therapy reported considerable improvements and treatment satisfaction in both treatment groups VP and PV.

The trends were supported by the CGIC as rated by the Investigator.

Regarding daily clinical practice, the results demonstrate that subjects experiencing insufficient efficacy during monotherapy can benefit from combination therapy in a clinically meaningful way.

Safety results:

Analyses of AEs during the Combination Phase demonstrated the safety of lidocaine 5% medicated plaster in combination with pregabalin. The relative frequency of subjects reporting TEAEs was lowest in the VS group and highest in the VP group.

Subjects who continued lidocaine 5% medicated plaster as monotherapy (VS) reported a similar frequency of TEAEs (19.0% [15/79]) in the Combination Phase (over 8 weeks) compared with the lidocaine 5% medicated plaster group in the Comparative Phase (18.7% [29/155], over 4 weeks),

suggesting that the frequency of AEs does not increase with longer use of lidocaine 5% medicated plaster.

The relative frequency of subjects reporting TEAEs in the PS group (28.6% [18/63]) was lower than that of subjects in the pregabalin group reporting TEAEs in the Comparative Phase (46.4% [71/153]). This is likely due to the fact that some subjects taking pregabalin in the Comparative Phase withdrew from the trial due to intolerability to pregabalin and thus did not participate in the Combination Phase. It may be speculated that those subjects who continued monotherapy with pregabalin in the Combination Phase might have developed tolerance to certain systemic AEs.

Subjects in the VP group reported the highest relative frequency of TEAEs and drug-related AEs. These were mostly pregabalin-related AEs, which suggests that subjects experienced these AEs once they started taking pregabalin in addition to lidocaine 5% medicated plaster. This is supported by the fact that most pregabalin-related AEs occurred with the 150 mg dose of pregabalin (i.e., during the first week of pregabalin intake).

The frequency of TEAEs reported in the PV group was relatively low (25.0% [12/48]). As with the PS subjects, these subjects had not withdrawn from the trial during the Comparative Phase due to intolerance to pregabalin. The few AEs that were reported in this group fell into 2 categories; they were either consistent with use of lidocaine 5% medicated plaster (e.g., application site pruritus and application site eczema) or typical AEs that eventually occur in a trial of this length (e.g., nasopharyngitis).

Application site pruritus was the only TEAE that occurred in more than 2 subjects in the VS group. The TEAEs that occurred in more than 2 subjects in the PS group were headache and dizziness, which was consistent with the commonly-reported TEAEs for subjects taking pregabalin in the Comparative Phase. Likewise, the TEAEs occurring in more than 2 subjects in the VP group, with the exception of rash, were similar to those reported in subjects taking pregabalin in the Comparative Phase (e.g., dizziness and fatigue). With the exception of nasopharyngitis, which occurred in 3 subjects, all individual TEAEs reported by subjects in the PV group occurred in only 1 subject each.

The most common AEs considered related to lidocaine 5% medicated plaster in the VS group were application site erythema, application site pruritus, and application site rash, each occurring in 2 (2.5%) subjects, which is consistent with findings for subjects in the lidocaine 5% medicated plaster group in the Comparative Phase.

The most common AEs considered related to pregabalin were headache and dizziness in the PS group, and dizziness, fatigue, somnolence, and depressed level of consciousness in the VP group. These types of AEs were not considered related to lidocaine 5% medicated plaster in all but 2 cases (i.e., single reports of dizziness and fatigue, which were considered related to lidocaine 5% medicated plaster in the VP group).

A higher percentage of subjects discontinued from the Combination Phase due to an AE in the VP (11.7% [7/60]) and PV (10.4% [5/48]) groups (i.e., subjects who received both lidocaine 5% medicated plaster and pregabalin) than in the VS (1.3% [1/79]) and PS (1.6% [1/63]) groups (i.e., subjects who received single treatment with either lidocaine 5% medicated plaster or pregabalin).

The overall incidence of discontinuations due to drug-related AEs was low (i.e., 8 subjects). The only group in which more than 1 subject discontinued due to a drug-related AE was the VP group,

in which 4 of 60 (6.7%) subjects discontinued from the trial mainly because they did not tolerate newly occurring pregabalin-related AEs: Two subjects withdrew due to central nervous system disorders rated as related to pregabalin by the Investigator (depressed level of consciousness, headache, dizziness, and somnolence); 2 further subjects withdrew due to fatigue, oedema peripheral, or dyspnoea. One of 60 (1.7%) subjects in the VP group discontinued due to a lidocaine 5% medicated plaster-related application site erythema and bruising. One of 48 (2.1%) subjects in the PV group discontinued due to pregabalin-related diarrhea. During monotherapy, 1 of 79 (1.3%) subjects in the VS group discontinued from the trial due to erythema related to lidocaine 5% medicated plaster and 1 of 63 (1.6%) subjects in the PS group discontinued due to pregabalin-related headache.

No deaths occurred in the Combination Phase. One subject in the VS group, 1 subject in the VP group, and 2 subjects in the PV group experienced 1 or more SAEs. None of these SAEs was considered by the Investigator to be related to lidocaine 5% medicated plaster or to pregabalin.

An analysis of AEs separately for PHN and painful DPN indications revealed that, similar to what was observed in the Comparative Phase, a higher percentage of subjects with PHN reported TEAEs and drug-related AEs than subjects with painful DPN in the VS and the PS groups; however, this pattern was not shown in the VP and the PV groups. All SAEs occurred in subjects with painful DPN. Otherwise, no pattern of differences between the 2 indications could be observed for the relative frequencies of individual types of AEs or for AEs examined by frequency, relationship, intensity, expectedness, outcome, countermeasures, duration, time to onset, or time to withdrawal.

Treatment with lidocaine 5% medicated plaster in combination with pregabalin did not have clinically relevant effects on laboratory parameters or vital signs.

Results support the use of lidocaine 5% medicated plaster as first-line option for monotherapy and as a suitable combination partner devoid of typical side effects associated with systemic drug-drug combinations.

SUMMARY AND CONCLUSIONS FOR THE DOWN-TITRATION SUB-TRIAL:

Disposition of subjects and baseline characteristics:

There were 31 subjects who entered the Down-titration sub-trial from the PV treatment group of the Combination Phase.

Efficacy results:

In the Down-titration sub-trial, subjects with PHN (N = 10) were able to completely abandon pregabalin without increase in the average NRS-3 or decrease in quality of life. All subjects with painful DPN except for 1 were also able to taper down their pregabalin dosage by at least 150 mg. Five of 17 (29.4%) subjects on pregabalin 600 mg could discontinue pregabalin, and 7 of these 17 (41.2% of subjects) could decrease their pregabalin dose by 75%. Four further subjects taking pregabalin 300 mg could reduce their dose by 50%.

Regarding daily clinical practice the results suggest a relevant pregabalin-sparing effect when combined with topical lidocaine.

Safety results:

Treatment with lidocaine 5% medicated plaster and pregabalin during the Down-titration sub-trial was safe. Only 2 TEAEs were reported; only 1 TEAE of application site sensitivity was considered

possibly related to lidocaine 5% medicated plaster. No deaths, other SAEs, discontinuations due to AEs, or clinically relevant effects on laboratory parameters or vital signs occurred during the Down-titration sub-trial.

Results of the efficacy section on this substudy demonstrated the sparing effect for pregabalin when lidocaine 5% medicated plaster is coadministered in peripheral neuropathic pain. This is further supported in this section by its favorable side effect profile.

SUMMARY AND CONCLUSIONS FOR THE LIDOCAINE PICK-UP ARM:

Disposition of subjects and baseline characteristics:

The SAF_{pu} (safety-analysis set for the Lidocaine Pick-up Arm) and FAS_{pu} (full-analysis set for the Lidocaine Pick-up Arm) each comprised 82 subjects, 42 with PHN and 40 with painful DPN. Of these 82 subjects, 52 subjects were allocated at Visit 2 on the basis of creatinine clearance (CL_{CR}) values and 30 subjects randomized to and treated in the pregabalin arm during the Comparative Phase switched to the Lidocaine Pick-up Arm due to pregabalin-related AEs.

For Visit 2 subjects, the mean age was 75.7 years; 28.8% of the subjects were men and 71.2% women. For Switched subjects, the mean age was 62.4 years and 43.3% of the subjects were men and 56.7% women.

All subjects with painful DPN in the FAS_{pu} had pain in the lower extremities. The location of pain for the majority of PHN subjects was the torso (60.0% Visit 2 subjects and 66.7% Switched subjects). Mean and median NRS-3 values at Visit 2 were similar for both groups and indications. For Switched subjects, values at the Switch Visit were lower than those at Visit 2, which indicates that the treatment with pregabalin, which these subjects received before switching to the Lidocaine Pick-up Arm had an effect on the NRS-3 value before a tolerability problem led to the switch.

In both groups, allodynia was more severe for PHN subjects than for painful DPN subjects at Baseline. At Baseline, the Visit 2 subjects with painful DPN were relatively equally distributed among painful, uncomfortable, and no pain. Switched subjects with painful DPN at both baselines were mostly concentrated in uncomfortable.

The average NPSI, SF-MPQ, and SF-36 scores at Baseline were comparable for Visit 2 subjects and Switched subjects.

For Visit 2 subjects, EQ-5D scores at Baseline were lower for subjects with PHN (mean 0.42) than subjects with painful DPN (mean 0.54). For Switched subjects, EQ-5D scores at Baseline were higher for subjects with PHN (mean 0.67) than subjects with painful DPN (mean 0.57). No difference between indications was observed for Switched subjects at the Switch Visit (mean 0.55).

Efficacy results:

NRS-3 response rate at Visit 4

Improvement in pain intensity was observed for Visit 2 subjects and for Switched subjects. The shifts from Baseline at Visit 7 were significant ($p = 0.0005$ for Visit 2 subjects, $p = 0.0004$ for Switched subjects relative to the Pick-up Baseline, and $p < 0.0001$ for Switched subjects relative to the Comparative Baseline).

The response rate at Visit 4, analyzed only for the Visit 2 subjects in FAS_{pu}, was 61.5% and similar for the 2 indications: 60.0% for subjects with PHN and 63.6% for subjects with painful DPN. These data were similar to the results for the lidocaine 5% medicated plaster group in the Comparative Phase.

Secondary endpoints

Between Visit 2 and Visit 7, Visit 2 subjects and Switched subjects showed clinically relevant decreases in mean (SD) NRS-3 pain values: –2.3 (2.62) and –2.4 (2.24) (relative to Pick-up Baseline), respectively.

Both groups were able to decrease intake of rescue medication across the visits.

Reduction in pain, NPSI scores, and SF-MPQ scores demonstrated improvement in pain intensity for both groups and both indications.

Clinically relevant improvement in the allodynia severity rating was observed between Baseline and Visit 7 for both groups.

For both groups, stronger improvement was seen for subjects with painful DPN than for subjects with PHN for the change in NRS-3 between Visit 3 and Visit 7, the SF-36 dimension bodily pain, and the SF-MPQ total score and sub-scores. For NPSI, Visit 2 subjects with painful DPN showed better values than Visit 2 subjects with PHN.

Regarding quality of life parameters (EQ-5D, SGIC, CGIC, and satisfaction scores), overall,Visit 2 subjects and Switched subjects showed improvement, particularly Switched subjects, with more pronounced improvements in the PHN subset.

Both groups showed increases at Visit 7 for mean scores in all 8 dimensions measured by the SF-36, except general health for Visit 2 subjects.

Safety results:

Lidocaine 5% medicated plaster was well-tolerated in subjects who were allocated to the Lidocaine Pick-up Arm based on low CL_{CR} values and those who showed difficulty tolerating pregabalin. The incidence of TEAEs was 48.1% (25/52) for Visit 2 subjects and 36.7% (11/30) for Switched subjects.

The most commonly-reported TEAEs were application site erythema, fatigue, and back pain. Most other types of events occurred in only 1 subject in either group.

The incidence of drug-related AEs was 21.2% (11/52) for Visit 2 subjects and 13.3% (4/30) for Switched subjects. Taking into consideration that these numbers represent cumulated incidences over 12 weeks, that Visit 2 subjects were more impaired considering comorbidities including renal function, and that the Switched subjects could have experienced AEs attributable to wash-out from pregabalin after the switch, these incidences can be considered low. The most common AEs related to lidocaine 5% medicated plaster in the Lidocaine Pick-up Arm were skin problems at the application site of the plaster, which occurred predominantly for Visit 2 subjects.

One death occurred in an 87-year-old man due to the AE of metastatic rectal cancer, which was considered not related to lidocaine 5% medicated plaster. Three subjects experienced 4 other SAEs. None of these SAEs was considered by the Investigator to be related to lidocaine 5% medicated plaster.

The incidences of TEAEs, drug-related AEs, SAEs, and AEs leading to discontinuation were notably higher in subjects with PHN than in subjects with painful DPN. More Visit 2 subjects with PHN than painful DPN had TEAEs that were expected. Otherwise, no meaningful pattern of differences between the 2 indications could be observed.

Treatment with lidocaine 5% medicated plaster did not have clinically relevant effects on laboratory parameters or vital signs.

Results support the favorable safety and tolerability profile of 5% lidocaine medicated plaster in patients not suited for systemic pregabalin treatment due to renal impairment and in those discontinuing pregabalin due to systemic AEs.

OVERALL CONCLUSIONS:

Comparative Phase:

The response rate after 4 weeks was slightly higher for the lidocaine 5% medicated plaster group (65.3%) than in the pregabalin group (62.0%) (PP set). Although the non-inferiority of lidocaine 5% medicated plaster to pregabalin was not formally demonstrated by the primary analysis (PP set) with a lower limit of CI –9.15 (slightly below the predefined non-inferiority margin of –8 percentage points), this was suggested from the FAS analysis with a lower limit of CI –7.03. These results are driven by higher numbers for subjects with painful DPN.

The efficacy results demonstrate clear benefits for lidocaine 5% medicated plaster in the indication of PHN as a representative of focal neuropathic pain. In the indication of painful DPN, a polyneuropathy, lidocaine 5% medicated plaster demonstrated clinical efficacy comparable to pregabalin.

These results were consistent with those of 30% and 50% reduction of pain intensity with similar advantages in PHN for lidocaine 5% medicated plaster. Furthermore, a trend towards better results regarding allodynia severity rating was observed for topical lidocaine in PHN, where painful allodynia is more prominent.

Superior safety and tolerability of lidocaine 5% medicated plaster was demonstrated in comparison to pregabalin for subjects with PHN and subjects with painful DPN in the first 4 weeks. Significantly fewer subjects in the lidocaine 5% medicated plaster group than in the pregabalin group reported drug-related AEs (5.8% [9/155] versus 41.2% [63/153], descriptive p-value <0.0001). Furthermore, the number of subjects with drug-related AEs leading to discontinuation were considerably lower in the lidocaine 5% medicated plaster group than in the pregabalin group (5.8% [9/155] versus 25.5% [39/153] and 2.6% [4/155] versus 23.5% [36/153], respectively).

Accordingly, under treatment with lidocaine 5% medicated plaster, all subjects, those with PHN, and those with painful DPN experienced a more pronounced improvement of quality of life parameters in general after 4 weeks (versus baseline) compared with pregabalin, supporting the improved benefit risk-ratio of topical lidocaine.

Lidocaine 5% medicated plaster provided at least comparable clinical benefit to that of pregabalin with a favorable safety/tolerability profile and a lower risk of discontinuation due to adverse drug reactions.

Combination Phase:

During the Combination Phase, the subjects who were sufficiently treated by monotherapy in the Comparative Phase and continued to receive monotherapy in the Combination Phase not only maintained the pain reduction they had achieved in the Comparative Phase; additional improvement was demonstrated by further decreases in pain intensity. The improvement shown over the 8 weeks of the Combination Phase was comparable for the VS and PS groups.

Those subjects who were not sufficiently treated by monotherapy at the end of the Comparative Phase received combined treatment with lidocaine 5% medicated plaster and pregabalin in the Combination Phase. These subjects also demonstrated clinically meaningful further pain reduction.

Drug-related adverse event rates were low in the monotherapy (VS, PS) and the PV arm, while most newly occurring side effects and those leading to discontinuation occurred in the VP arm, after pregabalin was added.

Results support the use of lidocaine 5% medicated plaster as the first-line option for monotherapy and as a suitable combination partner in peripheral neuropathic pain states devoid of typical side effects associated with systemic drug-drug combinations.

Down-titration sub-trial:

As a result of the favorable efficacy-tolerability ratio of lidocaine 5% medicated plaster, subjects with PHN were able to taper down their pregabalin dosage completely without compromising pain relief.

Subjects with painful DPN were able to reduce their pregabalin dosage significantly, with a lower proportion being able to stop systemic treatment completely compared to subjects with PHN.

Efficacy results of this sub-study demonstrated a clinically relevant sparing effect for pregabalin as a typical representative of systemic drugs when lidocaine 5% medicated plaster is coadministered in peripheral neuropathic pain, further supported by its favorable side effect profile.

Lidocaine Pick-up Arm:

Lidocaine 5% medicated plaster was efficacious and well tolerated in subjects with impaired renal function (i.e., subjects with CL_{CR} ≥30 mL/min and ≤60 mL/min) and in subjects with a demonstrated intolerability for pregabalin. These subjects achieved reduction in pain intensity and symptoms comparable to the subjects in the other trial phases, as demonstrated by changes in the NRS-3 values, NPSI scores, allodynia severity ratings, and SF-MPQ scores over the 12 weeks.

For NRS-3, shifts from Baseline at Visit 7 were significant ($p = 0.0005$ for Visit 2 subjects, $p = 0.0004$ for Switched subjects relative to the Pick-up Baseline, and $p < 0.0001$ for Switched subjects relative to the Comparative Baseline).

The profile of drug-related AEs was consistent with the findings of the other trial phases. More TEAEs were observed with Visit 2 subjects possibly due to longer exposure in the Lidocaine Pick-up Arm and with TEAEs of Switched subjects related to pregabalin counted for the previous comparative arm.

Results support the favorable safety and tolerability profile of 5% lidocaine medicated plaster in subjects not suitable for systemic pregabalin treatment due to moderate renal impairment and in those subjects who did not tolerate pregabalin.

All trial phases:

Lidocaine 5% medicated plaster has been shown to be effective and safe as a monotherapy and as an add-on medication to augment existing insufficient systemic treatment. Clinically comparable (in certain instances even better) efficacy and fewer adverse drug reactions compared with pregabalin were demonstrated in this trial.

Lidocaine 5% medicated plaster works well for both typical types of neuropathic pain, DPN representing a polyneuropathy and PHN representing a focal neuropathy.

Efficacy results for the lidocaine 5% medicated plaster were particularly favorable in subjects with PHN.

In addition, analyses of AEs and other safety data demonstrated a favorable safety profile for lidocaine 5% medicated plaster for both types of neuropathic pain in the different phases of the trial.

Quality of life parameters support these assumptions of an overall favorable benefit-risk ratio.

Furthermore, clear sparing effects for systemic pregabalin could be demonstrated for PHN and DPN when adding lidocaine 5% medicated plaster.

Topical lidocaine also proved to be an effective and safe alternative for patients for whom systemic pregabalin is not suitable due to renal impairment or intolerability (Lidocaine Pick-up Arm).

With these results, a clearly positive benefit-risk ratio for lidocaine 5% medicated plaster in peripheral neuropathic pain syndromes is supported, making it a first choice for starting with monotherapy or as a combination partner when patients are already pretreated. Furthermore, it is a viable alternative for patients not suited or failing on systemic therapy.

ICTR SYNOPSIS SUPPLEMENT

KF10004/03

Original ICTR issue date:	16 Jun 2010	**DMS version:**	4.0
ICTR synopsis supplement date:	11 Feb 2015	**DMS version:**	1.0

1 SUPPLEMENT CONTENT

This document contains information about the trial that is not already covered in the synopsis of the corresponding clinical trial report.

2 INFORMATION ABOUT PROTOCOL AMENDMENTS

There were 02 amendments to the protocol.

Protocol amendment S01 dated 10 November 2006, before any subjects had been screened

The main changes introduced by this amendment were as follows:

- Correction of the storage requirements (maximum storage temperatures) of the IMPs and the rescue medication. Neither the IMPs nor paracetamol required any special storage conditions according to the most recent information on the IMP or the SmPC except that the lidocaine 5% medicated plaster was not to be frozen or refrigerated.
- The duration of participation in the trial was reduced to approximately 14 to 16 weeks for each subject.
- SGIC, CGIC, and subject satisfaction questionnaires were added and defined as source data.
- The text for Visit 3 in the time schedule was amended to reflect the protocol synopsis. The inserted text specified that subjects treated with pregabalin were to start titration to 600 mg if their NRS was >4. Otherwise, the dose was not to be changed.
- Skin check was to be performed in all subjects at Visit 2 and the Switch Visit.
- EQ-5D: The third page of this questionnaire was deleted.

Protocol amendment NS02 dated 29 March 2007, after 60 subjects had been screened

The primary reason for the creation of the amended version NS02, dated 29 March 2007, was the availability of a new version of the SmPC for pregabalin (Lyrica®), which was included in the trial protocol.

The other main changes introduced by this amendment were as follows:

- Inclusion criterion 3 for all subjects was specified to read: ‘Negative urine test for drugs of abuse with the exception of short and medium acting benzodiazepine users for insomnia and currently used medications for the treatment of neuropathic pain’ because tapering of currently used medications for treatment of neuropathic pain was allowed during the wash-out period until Visit 2 and may have resulted in a positive drug abuse test at Visit 1.

The time from withdrawal from or completion of the trial to the Follow-up Visit was allowed to be shortened from 14 days in the case of unbearable pain. Subjects were to have been off the IMPs for at least 1 day (the day after withdrawal of the last lidocaine 5% medicated plaster and/or the day after the last intake of pregabalin after completion of the down titration) prior to the Follow-up Visit.

3 INFORMATION REGARDING CLINICAL HOLD OR EARLY TERMINATION

This clinical trial was not subjected to a clinical hold or early termination.

4 NAMES AND ADDRESSES OF PRINCIPAL INVESTIGATORS

The names of principal investigators for all sites are not included in the list below because consent for public disclosure was not obtained.

Site number	Investigator	Site address
AT003	(Name not given, since no consent given)	1090 Wien, Austria
BE002	(Name not given, since no consent given)	6534 Gozée, Belgium
CZ001	(Name not given, since no consent given)	656 91 Brno, Czech Republic
CZ002	(Name not given, since no consent given)	128 00 Praha 2, Czech Republic
CZ003	(Name not given, since no consent given)	625 00 Brno-Bohunice, Czech Republic
CZ004	(Name not given, since no consent given)	180 00 Praha 8, Czech Republic
CZ005	(Name not given, since no consent given)	120 00 Praha 2, Czech Republic
CZ006	(Name not given, since no consent given)	516 01 Rychnov nad Kněžnou, Czech Republic
DE002	(Name not given, since no consent given)	22149 Hamburg, Germany
DE003	(Name not given, since no consent given)	94550 Künzing, Germany
DE006	(Name not given, since no consent given)	45355 Essen, Germany
DE007	(Name not given, since no consent given)	40225 Düsseldorf, Germany
DE009	(Name not given, since no consent given)	10629 Berlin, Germany
DE010	(Name not given, since no consent given)	10117 Berlin, Germany
DE011	(Name not given, since no consent given)	13125 Berlin, Germany
DE012	(Name not given, since no consent given)	04103 Leipzig, Germany
DE013	(Name not given, since no consent given)	20249 Hamburg, Germany
DE014	(Name not given, since no consent given)	23538 Lübeck, Germany, Germany
ES001	(Name not given, since no consent given)	08907 Barcelona, Spain
ES002	(Name not given, since no consent given)	31008 Pamplona, Spain
ES004	(Name not given, since no consent given)	18014 Granada, Spain
ES005	(Name not given, since no consent given)	11009 Cádiz, Spain
ES006	(Name not given, since no consent given)	08041 Barcelona, Spain
ES007	(Name not given, since no consent given)	08006 Barcelona, Spain
UK001	(Name not given, since no consent given)	Chesterfield S40 4TF, United Kingdom
UK002	(Name not given, since no consent given)	Bolton, BL4 9QZ, United Kingdom
UK003	(Name not given, since no consent given)	Blackpool FY3 7EN, United Kingdom
UK004	(Name not given, since no consent given)	London EC1A 7BE, United Kingdom
UK005	(Name not given, since no consent given)	Glasgow, G12 0YN, United Kingdom
UK006	(Name not given, since no consent given)	Portsmouth PO3 6AD, United Kingdom

Site number	Investigator	Site address
HR001	(Name not given, since no consent given)	31000 Osijek, Croatia
HR002	(Name not given, since no consent given)	10000 Zagreb, Croatia
HR003	(Name not given, since no consent given)	10000 Zagreb, Croatia
HR005	(Name not given, since no consent given)	47000 Karlovac, Croatia
HR006	(Name not given, since no consent given)	44000 Sisak, Croatia
IE002	(Name not given, since no consent given)	Tallaght Dublin, Ireland
IT001	(Name not given, since no consent given)	20133 Milano, Italy
IT002	(Name not given, since no consent given)	27040 Montescano, Italy
PL001	(Name not given, since no consent given)	40-635 Katowice-Ochojec, Poland
PL002	(Name not given, since no consent given)	43-100 Tychy, Poland
PL003	(Name not given, since no consent given)	40-057 Katowice, Poland
PL004	(Name not given, since no consent given)	20-022 Lublin, Poland
PL005	(Name not given, since no consent given)	40-752 Katowice-Ligota, Poland
PL006	(Name not given, since no consent given)	40-084 Katowice, Poland
PT001	(Name not given, since no consent given)	1649-028 Lisboa
PT003	(Name not given, since no consent given)	1250-203 Lisboa
RU001	(Name not given, since no consent given)	127411 Moscow, Russia
RU002	(Name not given, since no consent given)	127486 Moscow, Russia
SE001	(Name not given, since no consent given)	58185 Linköping; Sweden
SE002	(Name not given, since no consent given)	41345 Göteborg, Sweden
SI001	(Name not given, since no consent given)	1000 Ljubljana, Slovenia
SI002	(Name not given, since no consent given)	1000 Ljubljana, Slovenia
SI003	(Name not given, since no consent given)	2000 Maribor, Slovenia

5 PUBLICATION OF TRIAL RESULTS IN MEDICAL JOURNALS

The results of the KF10004/03 clinical trial have been published in the following medical journals:

Interim analysis:

Baron R, Mayoral V, Leijon G, Binder A, Steigerwald I, Serpell M. Efficacy and safety of 5% lidocaine medicated plaster (Lignocaine) in comparison with pregabalin in patients with postherpetic neuralgia and diabetic polyneuropathy – interim analysis from an open-label, two-stage adaptive, randomized, controlled trial. Clin Drug Invest 2009; 29 (4): 231 -41.

Comparative Phase:

Baron R, Mayoral V, Leijon G, Binder A, Steigerwald I, Serpell M. 5% lidocaine medicated plaster versus pregabalin in post-herpetic neuralgia and diabetic polyneuropathy: an open-label, noninferiority two-stage RCT study. Curr Med Res Opin 2009; 25 (7): 1663-76.

Combination Phase:

Baron R, Mayoral V, Leijon G, Binder A, Steigerwald I, Serpell M. Efficacy and safety of combination therapy with 5% lidocaine medicated plaster and pregabalin in post-herpetic neuralgia and diabetic polyneuropathy. Curr Med Res Opin 2009; 25 (7): 1677-87.

Sub-population of subjects with PHN:

Rehm S, Binder A, Baron R. Post-herpetic neuralgia: 5% lidocaine medicated plaster, pregabalin, or combination of both? A randomized, open, clinical effectiveness study. Curr Med Res Opin 2010; 26 (7): 1607–19.