Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Finalgon® ointment		**EudraCT No.:** 2011-003890-27	
Name of active ingredient: Nicoboxil/nonivamide		**Page:** 1 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 01 OCT 2013	**Trial No. / U No.:** 69.52 / U13-2315-01	**Dates of trial:** 16 OCT 2012 – 19 APR 2013	**Date of revision:** Not applicable

Title of trial:	A multi-centre, double-blind, randomised, parallel group study to assess the efficacy and safety of multiple doses of topically applied hyperemisation-inducing ointment (2 cm ointment line per application; up to 3 times daily for up to 4 days) containing 2.5% Nicoboxil/0.4% Nonivamide versus 2.5% Nicoboxil, 0.4% Nonivamide and placebo in patients 18 to 65 years of age with acute low back pain
Coordinating Investigator:	[redacted]
Trial sites:	Multicentre trial in 37 sites in Germany
Publication (reference):	Data from this trial have not been published.
Clinical phase:	III
Objectives:	The objective of this trial was to demonstrate superior efficacy of a hyperemisation-inducing ointment containing a combination of 2.5% nicoboxil and 0.4% nonivamide over ointments containing 2.5% nicoboxil alone, 0.4% nonivamide alone, and placebo for the treatment of acute low back pain in patients 18 to 65 years of age
Methodology:	Multi-centre, randomised, active- and placebo-controlled, double-blind, parallel-group 4-arm study with a treatment duration of up to 4 days
No. of patients:	
planned:	entered: 800

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Name of finished product: Finalgon® ointment		**EudraCT No.:** 2011-003890-27	
Name of active ingredient: Nicoboxil/nonivamide		**Page:** 2 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 01 OCT 2013	**Trial No. / U No.:** 69.52 / U13-2315-01	**Dates of trial:** 16 OCT 2012 – 19 APR 2013	**Date of revision:** Not applicable

No. of patients (continued): **actual:**	enrolled: 805 entered: 805 2.5% Nicoboxil/0.4% nonivamide ointment: entered: 202 treated: 202 analysed (for primary endpoint): 202 2.5% Nicoboxil ointment: entered: 201 treated: 201 analysed (for primary endpoint): 201 0.4% Nonivamide ointment: entered: 198 treated: 198 analysed (for primary endpoint): 198 Placebo ointment: entered: 204 treated: 204 analysed (for primary endpoint): 204
Diagnosis and main criteria for inclusion:	Male and female patients between 18 and 65 years old with a current diagnosis of acute low back pain with no signs of neuropathic origin and a self-rated pain score of ≥5 on a numerical rating scale (NRS; range 0 to 10)
Test product:	2.5% Nicoboxil/0.4% nonivamide ointment
dose:	2 cm of ointment for a skin area of 20 cm × 20 cm administered at baseline and after 4 hours. Further applications could be administered as needed but not earlier than 8 hours after the first application. A maximum of 3 applications per 24 hours with intervals of at least 4 hours in between was allowed.
mode of admin.:	Topical
batch no.:	11170
Reference therapy 1:	2.5% Nicoboxil ointment
dose:	2 cm of ointment for a skin area of 20 cm × 20 cm administered at baseline and after 4 hours. Further applications could be administered as needed but not earlier than 8 hours after the first application. A maximum of 3 applications per 24 hours with intervals of at least 4 hours in between was allowed.
mode of admin.:	Topical
batch no.:	11192

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Name of finished product: Finalgon® ointment		**EudraCT No.:** 2011-003890-27	
Name of active ingredient: Nicoboxil/nonivamide		**Page:** 3 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 01 OCT 2013	**Trial No. / U No.:** 69.52 / U13-2315-01	**Dates of trial:** 16 OCT 2012 – 19 APR 2013	**Date of revision:** Not applicable

Reference therapy 2:	0.4% Nonivamide ointment
dose:	2 cm of ointment for a skin area of 20 cm × 20 cm administered at baseline and after 4 hours. Further applications could be administered as needed but not earlier than 8 hours after the first application. A maximum of 3 applications per 24 hours with intervals of at least 4 hours in between was allowed.
mode of admin.:	Topical
batch no.:	11193
Reference therapy 3:	Placebo
dose:	Not applicable
mode of admin.:	Topical
batch no.:	11195
Duration of treatment:	Up to 4 days
Criteria for evaluation:	
Efficacy:	Primary endpoint: - Pain intensity difference (PID) between baseline (pre-dose at Visit 1) and 8 hours after the first application (PID_{8h}); pain intensity (PI) was assessed by each patient on an 11-point NRS Secondary endpoints: - PID between baseline and 4 hours after the first application (PID_{4h}); PI was assessed by each patient on an 11-point NRS - PID between baseline and average pain intensity (API) on the last individual treatment day (lid, $APID_{lid}$); PI was assessed by each patient on an 11-point NRS - Patient assessment of efficacy on the last individual treatment day assessed on a 4-point verbal rating scale (VRS) Other endpoints included the time to onset of pain relief within 8 hours after the first application as assessed by each patient on a 7-point VRS, the final overall investigator assessment of efficacy on a 4-point-VRS, and the mobility score on each treatment day as assessed by each patient on a 4-point VRS.

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Name of finished product: Finalgon® ointment		**EudraCT No.:** 2011-003890-27	
Name of active ingredient: Nicoboxil/nonivamide		**Page:** 4 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 01 OCT 2013	**Trial No. / U No.:** 69.52 / U13-2315-01	**Dates of trial:** 16 OCT 2012 – 19 APR 2013	**Date of revision:** Not applicable

Safety:	Determination of safety was mainly based on the incidence of adverse events (AEs), the patient tolerability assessment on each treatment day, and the investigator final tolerability assessment, both assessed on a 4-point VRS.
Statistical methods:	The efficacy of the combination of nicoboxil and nonivamide compared to nicoboxil alone, nonivamide alone, and placebo was tested at the level of $\alpha = 0.05$ (2-sided). Primary endpoint: For the analysis of the PID_{8h}, a generalised linear repeated measures model using all available longitudinal pain intensity observations at each post-dose time point up to 8 hours with adjustment for the continuous covariate baseline PI and including the fixed effects of treatment, centre, time, and treatment-by-time interaction was used. Adjusted mean least square means were calculated together with 95% confidence intervals (CIs). Secondary endpoints: For the PID_{4h}, the primary analysis was used. For the $APID_{lid}$, an analysis of covariance (ANCOVA) that included the continuous covariate of baseline PI and the fixed effects of treatment and centre was used. For the analysis of the patient assessment of efficacy on the last individual treatment day, ordinal logistic regression with adjustment for the covariate baseline PI and including the fixed effects of treatment and centre was performed. Other endpoints: For the time to onset of pain relief, a Kaplan-Meier analysis was performed and the log rank test stratifying for the variable baseline PI was used. For the analysis of the final overall investigator assessment of efficacy, ordinal logistic regression with adjustment for the covariate baseline PI and including the fixed effects of treatment and centre was performed. For the analysis of the mobility score, a repeated ordinal logistic regression model with adjustment for the covariate baseline PI and including the fixed effects of treatment, centre, time, and treatment-by-time interaction was used. Safety endpoints: For the analysis of the patient assessment of tolerability at the end of each treatment day, a repeated measures ordinal regression model with adjustment for the covariate baseline PI and including the fixed effects of treatment, centre, time, and treatment-by-time interaction was used, and for the analysis of the final overall investigator assessment of tolerability, an ordinal regression model with adjustment for the covariate baseline PI and including the fixed effects of treatment and centre was calculated. For all other safety endpoints, descriptive statistics were performed.

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Name of finished product: Finalgon® ointment		**EudraCT No.:** 2011-003890-27	
Name of active ingredient: Nicoboxil/nonivamide		**Page:** 5 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 01 OCT 2013	**Trial No. / U No.:** 69.52 / U13-2315-01	**Dates of trial:** 16 OCT 2012 – 19 APR 2013	**Date of revision:** Not applicable

SUMMARY – CONCLUSIONS:

Efficacy results:

A total of 805 patients were enrolled, randomised, and treated with either a combination of nicoboxil and nonivamide (202 patients), nonivamide alone (198 patients), nicoboxil alone (201 patients), or placebo (204 patients). Of the treated patients, 28.2% discontinued prematurely (nicoboxil/nonivamide: 16.3%, nonivamide: 23.2%, nicoboxil: 30.8%, placebo: 42.2%). The most frequent reason for premature discontinuation was lack of efficacy (nicoboxil/ nonivamide: 7.4%, nonivamide 17.7%, nicoboxil: 29.9%, placebo: 41.2%). Overall, the demographic profile was similar between the treatment groups. About half of the patients were male (51.8%) and half were female (48.2%), almost all patients were White (98.9%), and the mean age was 40.5 years (standard deviation 13.57 years). Mean baseline PI was 6.6 on an 11-point NRS ranging from 0 ('no pain') to 10 ('worst pain possible').

Primary endpoint

In terms of the adjusted mean PID_{8h}, the combination of nicoboxil and nonivamide was shown to be superior over nicoboxil alone and over placebo but not over nonivamide alone. From baseline to 8 hours after the first application, the intensity of low back pain (adjusted mean PID_{8h}) was most effectively lowered by the combination of nicoboxil/nonivamide (-2.410), followed by nonivamide (-2.252), nicoboxil (-1.428), and placebo (-1.049). The observed treatment differences were statistically significant and in favour of nicoboxil/nonivamide compared to nicoboxil ($p<0.0001$) and placebo ($p<0.0001$) but did not reach statistical significance compared to nonivamide ($p = 0.4171$). Sensitivity analyses of the primary endpoint using the per-protocol set and subgroup analyses by gender confirmed the results of the primary analyses.

Secondary endpoints

From baseline to 4 hours after the first application, intensity of low back pain (adjusted mean PID_{4h}) was most effectively lowered by nicoboxil/nonivamide (-1.699), followed by nonivamide alone (-1.641), nicoboxil alone (-0.968), and placebo (-0.650). The treatment differences in favour of nicoboxil/nonivamide were statistically significant compared to nicoboxil ($p<0.0001$) and placebo ($p<0.0001$) but did not reach statistical significance compared to nonivamide ($p = 0.7037$).

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Name of finished product: Finalgon® ointment		**EudraCT No.:** 2011-003890-27	
Name of active ingredient: Nicoboxil/nonivamide		**Page:** 6 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 01 OCT 2013	**Trial No. / U No.:** 69.52 / U13-2315-01	**Dates of trial:** 16 OCT 2012 – 19 APR 2013	**Date of revision:** Not applicable

Efficacy results (continued):

From baseline to the last individual treatment day, average pain intensity (adjusted mean $APID_{lid}$) was most effectively lowered by nicoboxil/nonivamide (-3.540), followed by nonivamide alone (-3.074), nicoboxil alone (-2.371), and placebo (-1.884). The treatment differences in favour of nicoboxil/nonivamide were statistically significant compared to all 3 reference therapies (nonivamide: $p = 0.0259$, nicoboxil: $p<0.0001$, placebo: $p<0.0001$).

For the patient assessment of efficacy on the last individual treatment day, the combination of nicoboxil and nonivamide was shown to be statistically significantly better than each individual drug and placebo (nonivamide: odds ratio [OR] = 1.594 [95% CI 1.104, 2.303], $p = 0.0129$; nicoboxil: OR = 3.620 [95% CI 2.469, 5.308], $p<0.0001$; placebo: OR = 7.385 [95% CI 4.943, 11.032], $p<0.0001$). The proportion of patients who assessed the efficacy on their last individual treatment day as 'very good' or 'good' was highest in the nicoboxil/ nonivamide group (~68%), followed by the nonivamide group (~60%), the nicoboxil group (~43%), and the placebo group (~27%).

Other endpoints

Based on the median category of time to onset of pain relief, the combination of nicoboxil/nonivamide showed a trend to an earlier onset of pain relief (1 to 2 h) compared to the other treatments (nonivamide: 2 to 4 h, nicoboxil: 4 to 8 h, placebo: >8 h); the difference in favour of nicoboxil/nonivamide was statistically significant compared to nicoboxil ($p<0.0001$) and placebo ($p<0.0001$) but not compared to nonivamide ($p = 0.3828$). The final overall investigator assessment of efficacy was statistically significantly better for nicoboxil/nonivamide in comparison to each individual drug and placebo (nonivamide: OR = 1.571 [95% CI 1.092, 2.260], $p = 0.0150$; nicoboxil: OR = 4.320 [95% CI 2.969, 6.285], $p<0.0001$; placebo: OR = 8.860 [95% CI 5.967, 13.155], $p<0.0001$). In terms of the mobility score, patients of the nicoboxil/nonivamide group assessed the improvement of their mobility as statistically significantly better compared to nicoboxil ($p\leq0.0025$) and placebo ($p<0.0001$) on all 4 treatment days and compared to nonivamide on Day 1 ($p = 0.0435$) only. On all 4 treatment days, the proportion of patients who assessed the improvement of their mobility as 'very good' or 'good' was numerically highest in the nicoboxil/nonivamide group, followed by the nonivamide group, the nicoboxil group, and the placebo group.

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Name of finished product: Finalgon® ointment		**EudraCT No.:** 2011-003890-27	
Name of active ingredient: Nicoboxil/nonivamide		**Page:** 7 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 01 OCT 2013	**Trial No. / U No.:** 69.52 / U13-2315-01	**Dates of trial:** 16 OCT 2012 – 19 APR 2013	**Date of revision:** Not applicable

Safety results:

All of the 805 patients randomised in this trial were treated (nicoboxil/ nonivamide: 202 patients, nonivamide: 198 patients, nicoboxil: 201 patients, placebo: 204 patients). Treatment duration ranged in all treatment groups from 1 to 4 days; median exposure was 4 days in the nicoboxil/nonivamide group and 3 days in the other treatment groups. The proportion of patients who stayed on treatment for 4 days was highest in the nicoboxil/nonivamide group (52.5%), followed by the nicoboxil group (49.3%), the nonivamide group (47.0%), and the placebo group (44.1%).

The overall occurrence of AEs was highest for nicoboxil/nonivamide (13.9%), followed by nonivamide alone (9.1%), nicoboxil alone (5.5%), and placebo (4.4%). The most frequently reported AEs overall included feeling hot (nicoboxil/nonivamide: 3.5%, nonivamide: 2.5%, nicoboxil: 0.5%, placebo: 0) and burning sensation (nicoboxil/nonivamide: 3.0%, nonivamide: 1.0%, nicoboxil: 1.0%, placebo: 0), which were most commonly reported under treatment with nicoboxil/nonivamide, followed by nonivamide alone, nicoboxil alone, and placebo. The same order of AE frequency applied to AEs assessed as being drug-related by the investigator (nicoboxil/nonivamide: 8.9%, nonivamide: 5.6%, nicoboxil: 4.0%, placebo: 0.5%). Overall, feeling hot, burning sensation, and erythema were the most frequently reported drug-related AEs. Other significant AEs (based on ICH E3) and AEs leading to discontinuation were reported by 13 patients (6.4%) on nicoboxil/nonivamide, 10 patients (5.1%) on nonivamide, none of the patients on nicoboxil, and 1 patient (0.5%) on placebo. Feeling hot was the most frequently reported AE that led to discontinuation overall. There was 1 patient (0.5%) in the nonivamide group with a not drug-related SAE that required hospitalisation. In the 3 other treatment groups, no SAEs occurred.

Blood pressure and pulse rate were similar between the treatment groups at baseline and at the end of the study.

For most of the patients who were still on treatment, tolerability of all treatments was rated by the patients at the end of each treatment day and by the investigators at the end of the trial as 'very good' or 'good'. However, in terms of patient and investigator assessments of tolerability, placebo ($p \leq 0.0002$) and nicoboxil ($p \leq 0.0098$) were assessed as statistically significantly better compared to nicoboxil/nonivamide, whereas nonivamide ($p \geq 0.4249$) was assessed as similar compared to the combination of nicoboxil and nonivamide.

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Name of finished product: Finalgon® ointment		**EudraCT No.:** 2011-003890-27	
Name of active ingredient: Nicoboxil/nonivamide		**Page:** 8 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 01 OCT 2013	**Trial No. / U No.:** 69.52 / U13-2315-01	**Dates of trial:** 16 OCT 2012 – 19 APR 2013	**Date of revision:** Not applicable

Conclusions:

The topically applied combination of the hyperemisation-inducing drugs nicoboxil and nonivamide was effective and well tolerated as short-term (up to 4 days) treatment for acute low back pain in adult patients. Nicoboxil/ nonivamide applied up to 3 times/day was shown to be superior over nicoboxil alone and placebo in its ability to reduce pain intensity from baseline to 8 hours after the first application (primary endpoint). The combination reduced pain intensity from baseline to 4 hours after the first application (secondary endpoint) statistically significantly more than nicoboxil alone and placebo and reduced pain intensity from baseline to the average score on the last individual treatment day (secondary endpoint) statistically significantly more than each of its individual drugs or placebo. In terms of the clinical relevance of the pain intensity reductions that were achieved by the combination of nicoboxil and nonivamide, these represent a 'minimum clinical benefit' after 4 hours, a 'moderate clinical benefit' after 8 hours, and a 'substantial clinical benefit' on the last individual treatment day. Patients assessed the efficacy of the combination on their last individual treatment day (secondary endpoint) as significantly better than the efficacy of each individual drug or of placebo. In line and related to the mechanism of action of hyperemisation-inducing drugs, the reported frequency of drug-related AEs, which were all non-serious, was higher for the nicoboxil/ nonivamide combination than for each individual drug or placebo. The most frequent drug-related AEs of nicoboxil/nonivamide were expected and are listed in the current label of Finalgon® ointment as undesirable effects.