Clinical Study Report

Study Title:	Efficacy and Safety of Two Fixed Doses (160 Or 320 mg/day) of Ralfinamide in Patients with Chronic Neuropathic Low Back Pain. A Multicenter, Double-Blind, Randomised, Placebo-Controlled, 12-Week Study with Long-Term Extension
Name of the Test Drug/Investigational Product:	Ralfinamide
EUDRACT Number:	2008-006176-30
Indication:	Neuropathic Low Back Pain
Study Design	Double-blind, placebo-controlled, parallel-group, multicenter, multinational
Name of the Sponsor:	Newron Pharmaceuticals SpA.
Protocol Number:	NW-1029/01-08
Development Phase of Study:	Phase III
Study Initiation Date (Date First Patient Screened):	20 March 2009
Study Completion Date (Date Last Patient Completed Last Observation):	11 March 2010
Name and contact of Sponsor Signatory:	Ravi Anand, MD, Chief Medical Officer Newron Pharmaceuticals SpA. Via Ludovico Ariosto 21, 20091 Bresso (MI), Italy Tel: +39 0261034600 Fax: +39 0261034635
Good Clinical Practice (GCP) Statement:	This study was conducted in accordance with good clinical practices.
Date of Report:	09 August 2011, Final

2. SYNOPSIS

Name of Sponsor/Company: Newron Pharmaceuticals SpA.		*(For National Authority Use Only)*
Name of Finished Product: Ralfinamide		
Name of Active Ingredient: Ralfinamide		

Title of Study:

Efficacy and Safety of Two Fixed Doses (160 Or 320 mg/day) of Ralfinamide in Patients with Chronic Neuropathic Low Back Pain. A Multicenter, Double-Blind, Randomised, Placebo-Controlled, 12-Week Study with Long-Term Extension.

Study Number:

NW-1029/01-08

Investigators:

See Appendix 16.1.4.

Study Centers:

The study was conducted at 56 study centers: 5 in Germany, 24 in India, 4 in Italy, 13 in Poland, 8 in Romania, and 2 in the UK. The following additional centers were approved to start, but did not screen or enroll any patients: 1 in Germany, 1 in India, 2 in Poland, and 1 in the UK.

Publication (Reference):

There were no publications based on this study.

Study Period (Date First Patient Screened—Date Last Patient Completed Last Observation): 20 March 2009 – 11 March 2010	**Study Phase of Development:** 3

Objectives:

The objectives of this study are to evaluate the efficacy, safety and tolerability of two doses of orally administered ralfinamide, compared to placebo, in patients with chronic neuropathic low back pain.

Methods:

This was a randomised, placebo-controlled, double-blind, parallel-group, multi-centre, multi-national, Phase III trial, comparing two doses of ralfinamide (160 and 320 mg/day, p.o.) versus placebo in patients with chronic neuropathic low back pain. Patients were randomized 1:1:1 to one of the two doses of ralfinamide or placebo.

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Summary of study design

Screening/Run-In Period	**Baseline**	**Randomised Treatment Period**	**Post study Period**
Week -1	Week 0	Weeks 1-12	Week 13
Days -7 to -1	Day 0/1	Days 1-84	Days 85-91
Screening evaluations performed; inclusion/ exclusion criteria evaluated and patients given eDiary to complete at home for 7 days	Baseline evaluations (Day 0); patients meeting entry criteria randomised to treatment and started on Dose Level 1 (Day 1); patients dispensed medication	Efficacy and safety evaluations performed; final evaluations at Week 12 (or at early discontinuation). Dose reduction permitted if Dose Level 1 not tolerated	Week without study medication. Follow up on any abnormal findings from previous visit; assess adverse events and concomitant medication use

This study was performed in patients with neuropathic low back pain, of at least moderate severity, associated with nerve compression in accordance with:

- the taxonomy of the diagnostic criteria documented in the International Association for the Study of Pain (IASP) Classification of Chronic Pain (Merskey and Bogduk, eds., 1994): pain provoked by a lesion of the peripheral nervous system, and
- the diagnostic criteria to identify neuropathic pain components in patients with low back pain in accordance with the Pain Detect Questionnaire (PD-Q; Freynhagen et al. 2006).

The study was to be performed in a minimum of 20 centres in 4-8 countries.

Potential patients had to provide informed consent prior to initiation of screening procedures; this includes washout of prohibited concomitant medications, which may have begun prior to the Screening visit on Day -7 (Visit 1). At screening, the demographic data, prior and concomitant medications and medical history information were collected, and rating of the Michigan Neuropathy Screening Instrument (MNSI) was performed for patients with a diagnosis of diabetes, based on medical history or laboratory evaluations. In addition, the following safety evaluations were performed: vital signs, 12-lead electrocardiogram (ECG), clinical laboratory tests (blood chemistry, hematology, urinalysis, virology, and pregnancy test and assessment of post-menopausal status for women <50 years of age), Beck Depression Inventory (BDI), and physical, neurological and ophthalmological examinations. Assessment of inclusion/exclusion criteria was to be performed based on the above information. Patients were monitored for the occurrence of any AEs beginning at the time of signing the Informed Consent form and continuing until the end of their participation in the trial.

Patients were required to discontinue all approved therapies for neuropathic pain (eg. pregabalin, gabapentin, duloxetine, carbamazepine, etc.) prior to screening, according to the guidelines specified in the protocol. Patients receiving continuous treatment with opioids, tricyclic antidepressants, anti-epileptics, or beta-blockers as analgesics, were required to discontinue this medication prior to initiating the screening period. Specific exceptions to these requirements were allowed as per the protocol.

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During the one-week screening/run-in period eligible patients were required to maintain a daily electronic diary (eDiary), completing the Visual Analogue Scale (VAS; 100-mm) and the 11-point Likert-type scales for the daily pain score and assessment of the impact of pain on sleep and activities of daily living. At screening Day -4 (Visit 2) patients with abnormal laboratory test results at Visit 1 were asked to return for an office visit and have the clinical laboratory tests repeated. Those patients with normal screening laboratory values were contacted by telephone to assess their compliance with the patient diary recording procedures and were questioned about the occurrence of any adverse events or use of concomitant medication. If the patient was having difficulty completing the diary or had experienced any adverse events requiring follow-up, the patient may have been asked to return for an office visit.

The patients enrolled in the trial underwent examinations of localization of symptoms (including potential projection area), muscle strength and flexibility at screening to further characterize the population.

Following baseline safety and efficacy evaluations on Day 0, patients meeting all inclusion and none of the exclusion criteria were randomized to treatment and enrolled in the 12-week treatment period. Patients were started on placebo or a dose of 160 or 320 mg/day ralfinamide (Dose Level 1). Drop-back doses (Dose Level 0) of placebo, or 80 or 240 mg/day ralfinamide, respectively, were available for patients who were unable to tolerate the starting dose.

All patients were required to complete a daily eDiary, in which they rated the severity of their pain and associated symptoms and answered a question regarding their ability to do their work or participate in their usual occupational activities. During the initial treatment period, efficacy was assessed at Baseline and at Weeks 2, 4, 6, 9 and 12 (or at early discontinuation), using an 11-point Likert scale (daily pain score) as the primary measure to assess pain. Secondary and other efficacy measures performed at Baseline and Weeks 2, 4, 6, 9 and 12 included the following: VAS for rating pain (daily in eDiary); 11-point Likert-type scales for assessing sleep and activity (daily in eDiary), and the Patient's Global Impression (PGI) of change in pain (post-baseline). In addition, the Clinical Global Impression (CGI) of pain severity and change in pain (post-baseline), as well as the ratings of shooting and burning pain, using 11-point Likert-type scales, were performed by the investigator and reported in the eCRF. The Neuropathic Pain Symptom Inventory (NPSI), and the Work Productivity and Activity Impairment (WPAI) questionnaire were performed by the patient only at Baseline and Week 12 (or at early discontinuation).

Measurement of vital signs and 12-lead standard ECGs was performed at Baseline and all scheduled visits. At the Baseline visit, Days 0 and 1 coincided, and the vital signs and ECG evaluations were done prior to the first dose of study medication, which was administered in the clinic, and repeated at 3 hr post-dose. The change in patient's mood, as measured by the Beck Depression Inventory (BDI), was evaluated only at Baseline (Day 0) and at Week 12 (or at early discontinuation). Clinical laboratory tests were performed during the Screening period at Day -7, and repeated at Day -4 if abnormalities were noted at Day -7, and at Weeks 2, 6 and 12 (or at early discontinuation). Physical, neurological and ophthalmological examinations and a urine pregnancy test (women of child-bearing potential only; could have been performed more frequently, based on local requirements) were performed only at Week 12 (or at early discontinuation). Information on adverse events, use of concomitant medication and compliance with study medication dosing was collected throughout the 12-week treatment period.

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Upon completion of 12 weeks of treatment, eligible patients had the option of continuing in a 40-week, double-blind extension treatment period (Study NW-1029/02-08), during which they were to remain on the same dose level of study medication at which they completed the 12-week study. Patients who did not continue in the extension treatment period had their study medication discontinued and entered a 7-day post-study follow-up period during which adverse events and use of concomitant medication were monitored. It was recommended that clinical laboratory tests be done for all patients; follow-up assessments were performed for any other safety evaluations (e.g., vital signs, ECG, ophthalmological examination) for which there were clinically significant abnormalities at Week 12.

At Baseline (Day 0/1) and during visits at Weeks 2, 6 and 12, blood samples for the measurement of plasma concentrations of ralfinamide and its main metabolites were collected prior to dosing. A second sample was taken 3 hr post-dose at Baseline (Day 0/1), and at random time points post-dose during visits at Weeks 2, 6 and 12. If use of prohibited concomitant medication was suspected, PK plasma samples may also have been used for random drug testing.

Rescue pain medication was allowed to be prescribed by the physician, if needed at any time during the trial, for patients whose pain was not adequately controlled by the study medication. The rescue pain medications allowed were NSAIDs, including COX-inhibitors, or mild analgesics (e.g., paracetamol). If a patient was unable to take these medications, or if they provided inadequate pain relief, narcotics (e.g. tramadol) were also permitted. **The date on which the rescue medication was administered was to be recorded, and a complete pain assessment (11-point Likert scales and VAS) done prior to the administration of this rescue medication.** These assessments served as the final efficacy evaluations for analysis purposes for patients who required repeated use of rescue medication, defined as dosing on more than 2 consecutive days during the treatment period. In addition, the time from initiation of treatment to the first use and cumulative number of days of usage of rescue pain medication were to be analyzed as one of the secondary efficacy parameters.

Number of Patients (Planned and Analyzed):

It was planned that a total of 390 patients (130 per treatment group) were to be randomized to treatment so that minimally 98 patients per group would complete the study. Assuming a screen failure rate of 30% it was estimated that 560 patients would need to be screened. Overall, 591 patients were screened and 411 were randomized to treatment (136 to ralfinamide 320 mg/day, 136 to ralfinamide 160 mg/day and 139 to placebo) and 339 (82.5%) completed the study. A total of 411 patients comprised the intent-to-treat (ITT) population and 410 patients comprised the safety population, as one randomized patient was discontinued before receiving study medication.

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Diagnosis and Main Criteria for Inclusion:

Male and female (non-fecund or practicing a double contraception method) patients, ages 18-85 (inclusive), were eligible for enrolment in the trial. To be included, all patients had to give informed consent in writing and have a diagnosis of neuropathic low back pain (NLBP) according to the following criteria:

- Onset of pain > 3 months, but <3 years prior to Screening, based on medical history,
- Pain intensity at least moderate (> 40 mm) on the VAS at screening and each of 5-7 days before baseline,
- Current neuropathic pain due to a lesion of the peripheral nervous system and directly related to a neurological disease, meeting diagnostic criteria of the IASP Classification of Chronic Pain (supported by radiologic data if needed),
- Neuropathic nature of low back pain confirmed by a score > 18 on the Pain Detect Questionnaire (PD-Q),
- Cutaneous and sensory testing confirms involvement of dermatomes corresponding to L1-S1,
- NLBP is caused by compression radiculopathy or post-traumatic/post-surgical lumbar radiculopathy.

Patients with other causes of peripheral or central neuropathic pain due to metabolic (e.g. diabetes – confirmed by MNSI > 2), infectious, or proliferative diseases, or other severe pain conditions were excluded.

Patients with the following medical conditions were to be excluded from the study: significant cardiovascular conditions (e.g. 2^{nd}.or 3^{rd} degree A-V block, uncontrolled atrial fibrillation, myocardial infarction within 3 months of screening,); concomitant diseases that could interfere with the study drug; a history or current diagnosis of hepatitis B or C; a history of psychosis or current Axis I diagnosis; a neoplastic disorder (in remission < 1 year); clinically significant uncontrolled gastrointestinal, renal, hepatic, endocrine, or pulmonary diseases; seizure disorders; severe postural hypotension; hypersensitivity to drugs similar to ralfinamide. Patients with clinically significant abnormalities on medical history, physical examination, ECG or laboratory tests were to be excluded. Specific exclusion criteria related to ophthalmologic history comprised the following: albino patients, family history of hereditary retinal disease, progressive and/or severe diminution of visual acuity, i.e. 20/70, retinitis pigmentosa, retinal pigmentation due to any cause, any active retinopathy or ocular inflammation (uveitis), moderate or severe diabetic retinopathy, or moderate proliferative retinopathy.

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Test Product, Dose and Mode of Administration, Batch Numbers:

Test product: rafinamide, 80-mg tablets

Route and mode of administration: oral

Dose and dosage schedule:

Dose Level 1 (Starting dose):

- Ralfinamide 320 mg/day (160 mg [2 x 80-mg], b.i.d.) for 12 weeks, unless dose reduction to Dose Level 0 is necessary, due to tolerability issues.
- Ralfinamide 160 mg/day (80 mg [1 x 80-mg + 1 x placebo], b.i.d.) for 12 weeks, unless dose reduction to Dose Level 0 is necessary, due to tolerability issues.

Dose Level 0 (Drop-back dose):

- High dose: Ralfinamide 240 mg/day (AM: 160 mg [2 x 80-mg]; PM: 80 mg [1 x 80-mg + 1 x placebo])
- Low dose: Ralfinamide 80 mg/day (AM: 80 mg [1 x 80-mg + 1 x placebo]; PM: placebo [2 x placebo])

Batch Numbers: 08RV01, 09RV01

Duration of Treatment:

Up to 12 weeks of treatment in the initial study (NW-1029/01-08), with an additional 40 weeks of treatment in the optional extension study (NW-1029/02-08), for a total of 52 weeks of treatment.

Reference Products, Dose, Mode of Administration, Batch Numbers:

Reference product: placebo, matching tablets

Route and mode of administration: oral

Dose and dosage schedule:

Dose Level 1 (Starting dose): Placebo, 2 tablets, b.i.d.

Dose Level 0 (Drop-back dose): Placebo, 2 tablets, b.i.d.

Batch Numbers: 08RP01, 09RP02

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Criteria for Evaluation - Efficacy:

The **primary efficacy variable** was the mean change from baseline to Week 12 or endpoint (in case of premature termination) on the 11-point Likert categorical scale (daily pain assessment)..

The **secondary efficacy variables** included

- "Responder" rates, based on the proportion of patients experiencing a 50% improvement from baseline to endpoint in mean pain rating on the 11-point Likert scale (daily pain assessment),
- Change from baseline in the subject's perception of the impact of pain on sleep (11-point Likert scale),
- Change from baseline in the subject's perception of the impact of pain on daily activity (11-point Likert scale)
- Total number of days without taking any additional pain medication.

Other efficacy variables that were assessed included

- Weekly pain score on the 100-mm VAS, comparing the proportion of "responders" (50% decrease in score from baseline) between treatment groups,
- Change from baseline in patient's shooting and burning pain (11-point Likert scales), as assessed by the investigator at scheduled visits,
- Clinical Global Impression of severity of pain (CGI part I; 7-point scale assessed by the investigator),
- Clinical Global Impression of change in pain from baseline (CGI part II; 7-point scale assessed by the Investigator),
- Neuropathic Pain Symptom Inventory (NPSI) total intensity score (excluding questions 4 and 7), change from baseline,
- Quality of life (QOL) assessment, based on composite score from BDI items 4, 12, 16, 17, 18, and 21 (i.e. dissatisfaction, social withdrawal, insomnia, fatigability, loss of appetite, low level of energy),
- Work Productivity and Activity Impairment Questionnaire (WPAI) items 1-4, as assessed at baseline and endpoint, and items 5 and 6 evaluated as change from baseline to endpoint,
- Patient's Global Impression (PGI) of change in pain from baseline (7-point scale assessed by the patient).

Criteria for Evaluation - Safety:

Safety variables included adverse events (AEs); clinical laboratory test results (hematology, biochemistry, and urinalysis); vital sign measurements; 12-lead ECG findings; physical, neurological, and ophthalmological examination findings; and Beck Depression Inventory (BDI) scores.

Pharmacokinetics:

Blood samples were taken at Baseline (Days 0/1) and Weeks 2, 6 and 12, or at early discontinuation, for the measurement of plasma levels of ralfinamide and its main metabolites. Plasma concentrations were determined using an LC/MS/MS method.

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Statistical Methods:

Sample Size: It was determined that a sample size of 98 patients per group (comparison of drug vs. placebo) achieves 90% power to detect a difference of 1 point in the 11-point Likert scale between the null hypothesis that both group mean changes from baseline are -0.82, and the alternative hypothesis that the mean change in the ralfinamide group is -1.82, with estimated pooled standard deviations of 2.14, and with a significance level (alpha) of 0.05, using a two-sided two-sample t-test (estimations based on Study 001). Considering a dropout rate of at least 25%, the total number of patients to be randomized was minimally 130 in each of the ralfinamide groups and the placebo group. Assuming a screening failure rate of 30%, a total of 560 patients with clinically diagnosed chronic neuropathic low back pain due to nerve compression (e.g., compression radiculopathy or post-traumatic/post-surgical lumbar radiculopathy) were to be screened to enable a randomisation of approximately 400 patients.

Subject Characteristics: The subject characteristics (age, gender, race, medical history, physical and neurological examination findings, vital signs, ECG, laboratory tests, type of neuropathic low back pain, pain ratings, etc.) of included patients at the screening visit were tabulated by subject, and summarized using descriptive statistics by treatment group and overall. Differences among treatment groups were assessed.

Interim Analysis: There was no formal interim analysis planned for this study in order to stop the trial for manifest superiority and/or futility, but only a blinded evaluation of the magnitude of the primary endpoint variance was performed when approximately two thirds of the patients (260) had completed the study, as proposed by Gould and Shih [1992]. The analysis was done using a conservative Baseline Observation Carried Forward (BOCF) method for handling missing data. Based on the results of this analysis, the sample size could have been increased, but not decreased.

Efficacy Analysis

All efficacy data were summarised by treatment group (Ralfinamide 320 mg/day; Ralfinamide 160 mg/day; or Placebo) by presenting frequency distributions and/or summary statistics. Mean scores for the VAS and the Likert scales for the daily pain score and assessments of sleep and activity were based on the average of ratings from the last 7 days prior to the scheduled visit.

Primary Efficacy Analysis

The primary efficacy variable was the change from baseline in the mean weekly pain score (11-point Likert scale). The mean weekly pain score was summarised descriptively at baseline and for each week in the study; the change in mean pain score from baseline at each week was also presented.

Two sets of analyses were performed in the Intent-to-Treat (ITT) population, in accordance with White and Pocock [1996]:

"ON Treatment" analysis. In this approach, patient's data are censored at the time the patient starts intake of 'rescue' medication that lasts for more than two consecutive days.

"ON & OFF Treatment" analysis. In this approach, all available data are analysed regardless of 'rescue' medication intake.

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The "ON Treatment" analysis was considered as the primary one, while the "ON & OFF Treatment" analysis was performed for sensitivity purposes.

The primary efficacy endpoint analysis was the change from baseline to Week 12 of the mean weekly pain score using the "ON Treatment" ITT analysis set with BOCF imputation of missing data (only in the case of premature discontinuation). A 'sequence of comparisons' approach was used in analyzing the data for the primary efficacy measure. The analysis was done in a two-step process, in which the high dose of ralfinamide (320 mg/day) was compared to placebo first. If, and only if, a statistically significant difference was noted in this analysis, the comparison between the low dose of ralfinamide (160 mg/day) and placebo was to be performed. The treatments were compared using analysis of covariance (ANCOVA) using SAS PROC GLM. The mean baseline pain score was used as a covariate. The model also included terms for treatment, centre, and treatment-by-centre interaction. If the treatment-by-centre interaction was not significant ($p > 0.10$) using a type II contrast, then it was to be removed from the final model. The type III sum of squares was used for the final model.

The results from the analysis were summarised by presenting adjusted means (Least Squares Means) for each treatment group, the estimated difference between the treatment groups along with the standard error, associated 95% confidence interval and p-value. In the event that the treatment-by-centre interaction was significant ($p < 0.10$), the treatment difference was to be estimated using a mixed linear model with treatment as fixed factor, centre and treatment-by-centre interaction as random factors (instead of fixed factors as for the primary analysis) and mean baseline pain score as covariate. If violations of the statistical assumptions were noted, then the treatments were to be compared using the ANCOVA method stated above on ranked data.

The following supportive analyses were performed in addition to the primary efficacy analysis:

"ON treatment" and "ON & OFF treatment" ITT population with conventional missing efficacy endpoint imputed by Last Observation Carried Forward (LOCF) using the same ANCOVA model and methods as outlined for the primary efficacy analysis,

Observed Cases (OC) population (no imputation) using the same ANCOVA model and methods as outlined for the primary efficacy analysis,

- Using a Mixed Linear Model with treatment, centre and visit as fixed effects and baseline as covariate and using the ESTIMATE statement to compute the treatment mean difference together with the associated two-sided 95% CI and two-sided p-value at Visit 8. Both the "ON Treatment" and "ON & OFF Treatment" ITT populations were analysed without any imputation.

Supportive analyses were to be performed for the retrieved dropout (RDO) population only if there were at least 13 RDO patients available for each treatment group.

Secondary Efficacy Analysis

The secondary efficacy analyses was evaluated in a hierarchical fashion. Each of the variables below was to be analysed sequentially, as long as a significant difference between the 320 mg/day group vs. placebo was detected. In addition, if a significant difference was detected between the placebo group and the 320 mg/day group, the analysis was to proceed to compare the placebo group to the 160 mg/day group. This approach

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avoided the need for correcting the p-value due to multiplicity of testing over endpoints and over treatment groups.

Only the "ON Treatment" analyses were carried out using the ITT population with a LOCF imputation for missing endpoints. In addition, results for the OC population were presented.

Weekly Pain Score – Responders

An additional analysis of the mean weekly pain score was performed comparing the proportion of responders (defined as a patient who experienced a decrease in score of at least 50%) between treatment groups at each of the visits between baseline and Week 12 (LOCF). Treatment groups were compared by means of a Cochran-Mantel-Haenszel (CMH) test stratified by centre using PROC FREQ. The difference between treatment groups was summarised by presenting the odds ratio, associated 95% confidence interval and p-value.

Daily Assessment of Sleep and Activity

Mean baseline and weekly scores for the Likert scales for daily assessments of the impact of pain on sleep and activity (derived from patient's eDiary) were summarised, as were the changes from baseline at each visit. The treatments were compared using ANCOVA in the same way as described for the primary efficacy variable.

Total Number of Days without Taking Additional Pain Medication

Patients using rescue pain medication while taking either ralfinamide or placebo were identified by the Sponsor prior to unblinding. The number and percentage of patients without any additional pain medication was presented along with descriptive statistics for the number of days without any additional pain medication. A logistic regression analysis with treatment and center as categorical factors in the model was performed using as response variable for each randomised patient the number of days without intake of any additional analgesic (non-study) medication over the total number of days the patient stays on study. Tests for treatment differences in proportions were performed and the odds ratios along with 95% confidence intervals for the treatment differences to placebo was displayed.

Other Efficacy Analyses

This set of efficacy analyses were carried out using the ITT population with LOCF imputation for 'conventional' missing data. Only the "ON Treatment" analyses were performed.

Visual Analogue Scale (VAS)

The mean values for the VAS were summarised descriptively at baseline and for each week in the study, as well as the change from baseline at each week. The treatments were compared using an ANCOVA in the same way as described for the primary efficacy variable.

A responder analysis was performed to determine the number of patients in each treatment group who improved on the VAS by at least 50%. The treatments were compared by means of a CMH test stratified by centre using PROC FREQ. This was performed using the CMH test with each Ralfinamide dose group versus placebo. The differences between treatment groups were summarised by presenting the odds ratios, associated 95% confidence intervals and p-values.

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Burning and Shooting Pain

Scores for the Likert scales for burning and shooting pain at baseline and scheduled assessments were summarised, as were the changes from baseline. The treatments were compared using ANCOVA in the same way as described for the primary efficacy variable.

Clinical Global Impression (CGI) of Severity and Change from Baseline

The ratings for the CGI – severity of pain were summarised for each visit in the study. The analysis of the CGI - severity of pain was based on the change from baseline to Week 12 (LOCF). The treatments were compared using analysis of covariance (ANCOVA), with the baseline score as a covariate in the same way as described for the primary efficacy variable. The number and percentage of patients who improved by 0, 1, or 2 categories in the severity ratings were presented by visit.

The ratings for the CGI - change in pain from baseline were presented for each post-baseline visit. Descriptive statistics were given for the 7-point scores and in addition frequency tables for the seven categories. The number and percentage of patients who improved in the CGI – change in pain (categories of 0, 1 and 2) and those who showed no change or worsening (categories of 3 to 6) were presented by visit.

Neuropathic Pain Symptom Inventory (NPSI)

Questions 1-3, 5, 6, and 8-12 of the NPSI were summarised descriptively at baseline and at endpoint (Week 12 or early discontinuation), as well as the change from baseline at endpoint. The total scores were calculated as the sum of scores for questions 1-3, 5, 6, and 8-12. Questions 4 and 7, which relate to pain duration and number of pain attacks, were presented as frequency tables.

Quality of Life (derived from BDI)

To assess the quality of life functioning, a BDI sub-score, the sum of items 4, 12, 16, 17, 18, 21 (i.e. dissatisfaction, social withdrawal, insomnia, fatigability, loss of appetite, low level of energy) was calculated for each patient. Descriptive statistics were presented for this sub-score and the change from baseline by visit. The treatments were compared for the change from baseline using the Wilcoxon rank sum test.

Work Productivity and Activity Impairment (WPAI)

Question 1 (categories "No" and "Yes") were summarised descriptively by a frequency table. Questions 2 to 6 were summarised by descriptive statistics. The treatments were compared for Questions 5 to 6 using an ANCOVA with baseline score in the same way as described for the primary efficacy analysis.

Patient's Global Impression (PGI)

The PGI assessments were summarised descriptively for each post-baseline visit. Descriptive statistics were presented for the 7-point score, and in addition a frequency table was given for the seven categories. A comparison of the distribution of categorical ratings of change was done using the CMH test.

Time to return to work or usual occupational activity

At baseline patients were asked whether they could perform their daily work or usual occupational activity. In the eDiary the following question was presented: "Did you return to work or to your usual occupational activity?

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Yes / No". These data were collected, but no formal analysis was planned.

Safety Analysis

The safety population consisted of all patients who received at least one dose of the study medication and had a subsequent safety assessment. Patients were assigned to the study treatment group as per treatment received.

Adverse events from the pre-treatment and treatment phases were analysed separately. The treatment emergent AEs were summarized by preferred term (MedDRA) and by body system. Overall incidences of AEs, including 95% confidence intervals, were calculated, and a comparison made between treatment groups in the incidence of treatment-emergent AEs, Serious AEs and AEs leading to premature discontinuation.

Changes from baseline in vital signs, ECG parameters, and clinical laboratory tests were described. Differences between the treatment groups were summarized in a descriptive manner. "Shift tables" were used to evaluate categorical (below, within or above normal range) changes in clinical laboratory parameters by examining the proportion of patients whose test values are outside the specified range at their final visit or changed at the final assessment. In addition, the proportion of patients experiencing clinically notable abnormalities in vital signs and laboratory tests were compared among treatment groups. "Shift tables" of the change in ECG status (normal, abnormal – insignificant, abnormal – significant) from Screening were presented. An evaluation of the QTcB interval (Bazett's correction) on the ECG was performed, with the number/percentage of patients with values or changes from baseline that are above normal (i.e. value >450 ms; change >30 ms) or considered notable (i.e. value >500 ms; change >60 ms) being determined for each group. Descriptive statistics were provided for results from the physical, neurological, and ophthalmological examinations. For the ophthalmological examination, descriptive results for assessments of visual acuity, intraocular pressure, color vision testing, standard eye examination, slit lamp examination, visual field test, and fundus examination were provided and compared among groups. In addition, a frequency table was provided for the evaluation of the clinical global impression of change in the eye examination from Visit 1 (Screening) to Visit 8 (Week 12 or endpoint), performed by the central reader (no change/improved, worsened, unassessable, not done).

Beck Depression Inventory (BDI)

The two versions of the BDI (BDI-Ia and BDI-II) used in the study were analyzed separately. The overall score from the BDI (sum of the 21 items) was summarised by treatment group at baseline and change from baseline at each visit in the study was presented. The analysis of the BDI was based on the change from baseline to Week 12 (LOCF) in the overall score. The treatments were compared using ANCOVA, with the baseline score being used as a covariate.

Pharmacokinetic Analysis

The pharmacokinetic analysis based on plasma levels of ralfinamide and its main metabolites was performed by an external vendor and summarized in a separate report.

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SUMMARY OF RESULTS

EFFICACY RESULTS

Primary Efficacy Endpoint

All 3 treatment groups showed improvement (reduction in score) on the primary efficacy measure, i.e. the change from baseline to Week 12 (endpoint) in the mean weekly pain score (rated by the patient using an 11-point Likert scale in the eDiary). However, there was no statistically significant difference between either the 320 mg/day or 160 mg/day ralfinamide treatment groups and the placebo group in the analysis of the primary efficacy endpoint, which was performed using ANCOVA for the "ON treatment" ITT analysis set, with BOCF imputation for missing values.

Supportive analyses of the mean weekly pain score for the "ON treatment" analysis set using ANCOVA for the ITT population with LOCF imputation or the OC population, as well as analyses using mixed linear and mixed linear repeated measures models, showed similar results. Analyses performed for the "ON & OFF treatment" analysis set, which included data from patients while taking rescue pain medication, as well as analyses by region (Europe and India), also did not show any significant effects of ralfinamide, compared to placebo, on the primary efficacy measure.

Secondary Efficacy Endpoints

No statistically significant differences were observed between either of the ralfinamide groups and the placebo group in the analyses of the following secondary efficacy measures:

- Mean Weekly Pain Score Responders: There were no differences among groups in the proportions of patients showing ≥50% improvement from baseline on the 11-point Likert scale, compared using the CMH test for the ITT-LOCF and OC populations;
- Daily Assessment of Sleep and Activity: ANCOVA analyses on ITT-LOCF and OC populations indicated no effect of ralfinamide on the impact of pain on sleep or daily activities assessed by the patients using 11-point Likert scales in the eDiary;
- Total Number of Days without Taking Additional Pain Medication: A logistic regression analysis showed no difference between either of the ralfinamide groups and the placebo group in the mean number of days without taking additional pain medication.

Other Efficacy Endpoints

No statistically significant differences were observed between either of the ralfinamide groups and the placebo group in the analyses of the following other efficacy measures:

- VAS (recorded in patient diary): Mean changes from baseline to Week 12 (endpoint) in mean weekly VAS score were compared using ANCOVA on the ITT-LOCF population;
- VAS Responders: Proportions of patients showing ≥50% improvement from baseline to Week 12 (endpoint) on the VAS were compared using the CMH test;

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- Assessment of Burning and Shooting Pain: Mean changes from baseline to Week 12 (endpoint) in ratings of burning and shooting pain, performed by the Investigator using 11-point Likert scales, were compared using ANCOVA on the ITT-LOCF population;
- CGI – Severity of Pain (performed by the Investigator): Mean changes from baseline to Week 12 (endpoint) in the rating of the CGI-Severity, compared using ANCOVA on the ITT-LOCF population, as well as the proportions of patients with an improvement of 0, 1 or ≥2 points from baseline at endpoint were similar among the 3 groups;
- CGI – Change in Pain from Baseline (performed by the Investigator): Proportions of patients rated as improved (scores of 0, 1, or 2) vs. those showing no change (score of 3) or worsening (scores of 4, 5 or 6) were similar among the groups (compared using the CMH test); a logistic regression analysis evaluating the distribution of scores across all 7 categories also did not reveal any effect of treatment.
- WPAI (performed by the patient): No beneficial effects of ralfinamide treatment were noted on the patients' ability to work, work productivity (for those patients who were working), or ability to perform daily activities.
- PGI (performed by the patient): Mean ratings of the PGI, assessing change in pain from baseline to Week 12 (endpoint), showed that ~70% of patients in each group rated their pain as improved (minimally, much or very much); the proportion of patients showing improvement vs. those showing no change or worsening were compared among groups using the CMH test.

No formal analyses were performed for the following efficacy measures; however, descriptive statistics did not indicate any meaningful differences among treatment groups:

- NPSI (performed by the Investigator): Similar mean reductions from baseline in total scores from items 1-3, 5, 6 and 8-12, reflecting improvement in individual neuropathic pain symptoms, were noted in all 3 groups; the distribution of ratings at endpoint among the different categories for items 4 and 7, evaluating pain duration and number of pain attacks, respectively, also did not differ among groups.
- Quality of Life (derived from the BDI): A similar mean decrease (improvement) from baseline was noted in the quality of life sub-score from the BDI (sum of items 4, 12, 16, 17, 18 and 21) in all 3 groups.

SAFETY RESULTS

Ralfinamide at doses of 160 and 320 mg/day (80 and 160 mg b.i.d., respectively) was well tolerated in this population of patients with NLBP, as evident from the results for the following safety variables:

- Over 95% of patients in each of the ralfinamide treatment groups remained at their starting (target) dose throughout the study.
- The proportion of patients experiencing any treatment emergent AE (TEAE) was higher in the placebo group (59.4%) than in the 320 mg/day (50.0%) and 160 mg/day (55.9%) ralfinamide groups.
- The proportions of patients experiencing the most common TEAEs (i.e. dyspepsia, diarrhoea, nausea, headache, dizziness, pyrexia, cataract and cough) were generally similar across treatment groups and did not

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indicate any pattern of treatment-related effects. Gastrointestinal Disorders occurred more frequently in ralfinamide-treated patients, while Nervous System Disorders were reported more frequently in the placebo group. The proportion of patients with Eye Disorders was lowest in the 320 mg/day ralfinamide group. No seizure or 'seizure-like' event was reported for any patient in the study.

- The proportions of patients with TEAEs considered to be study drug-related were similar across all 3 treatment groups (~30%), with nausea and headache being the most common 'related' events. The proportion of patients with severe TEAEs was low (<4% in any group), and no severe TEAE was reported for more than one patient in any group.
- One death occurred in the study: a 67-year-old, male, Asian patient receiving 320 mg/day ralfinamide had a cerebellar hemorrhage leading to death; this event was considered 'not related' to the study medication.
- A total of 7 serious AEs were reported in the study, 4 in the 320 mg/day group, 1 in the 160 mg/day ralfinamide group and 2 (in a single patient) in the placebo group. All of the events in ralfinamide-treated patients were considered 'not related'.
- Treatment emergent clinical laboratory AEs (TELAEs) were reported more frequently for patients in the 320 mg/day ralfinamide group (19.1% of patients), compared to the 160 mg/day (8.1%) and placebo (11.6%) groups, and were judged to be study-drug related in a greater percentage of patients in the high dose ralfinamide group. Individual TELAEs occurring in a greater percentage of patients in the 320 mg/day ralfinamide group were increases in ALAT, ASAT, hepatic enzymes and blood CPK, as well as 'liver function test abnormal'. The proportion of TELAEs considered 'clinically notable' was small in each group, and no serious TELAEs were reported. Despite the higher incidence of notable LFT abnormalities in the 320 mg/day ralfinamide group, most of these were transient, and, importantly, there were no concomitant increases in bilirubin levels, indicating that there is a low likelihood of hepatocellular injury. In addition, these LFT elevations were not accompanied by any TEAEs, e.g. loss of appetite, that would be indicative of an effect on liver function, except in one patient [Pt. 83001].
- Only 11 patients discontinued treatment prematurely due to TEAEs (n=9) or TELAEs (n=2); the percentage of patients withdrawing due to an AE was slightly higher in the 320 mg/day ralfinamide group (4.4%), compared to the 160 mg/day ralfinamide (1.5%) and placebo (2.2%) groups.
- Results of clinical laboratory tests did not reveal any effects of ralfinamide treatment on hematology, renal function, biochemistry, or urinalysis parameters; however, an apparent dose-dependent mean increase from baseline was noted for ALAT, ASAT and GGT in ralfinamide-treated patients, compared to placebo. This effect of ralfinamide on liver function tests was reflected in a greater percentage of patients in the 320 mg/day ralfinamide group having clinically notable values (2 [1.5%] patients for each parameter) at endpoint for ALAT, ASAT and GGT, compared to the other two treatment groups (no patients for ALAT and ASAT; one patient each for GGT).
- No effects of ralfinamide treatment were noted on any vital signs parameter, including orthostatic changes in blood pressure and pulse; the proportion of patients experiencing clinically notable vital signs values was very low and similar across treatment groups.
- Results of the physical and neurological examinations did not indicate any effects of ralfinamide treatment

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on any body system.

- No clinically relevant effect of ralfinamide treatment was observed on any ECG parameter; in particular, ralfinamide did not prolong the QTc interval. The proportion of patients that had a normal ECG at baseline and a clinically significant abnormal ECG at endpoint was low (<7%) and similar across the 3 treatment groups.
- Results of the ophthalmological examinations and interpretation by the central reader did not indicate any effect of ralfinamide treatment on ocular function; the proportion of patients that had a Clinical Global Impression of Change assessment for the eye examination at endpoint indicating worsening compared to baseline was approximately 24% overall, but similar across the 3 treatment groups. In addition, results of individual ocular tests, including assessments of visual acuity, intraocular pressure, color vision, and visual acuity, as well as standard eye, slit lamp and fundus examinations, did not indicate any treatment-related effects.
- A small improvement in depressive symptoms, assessed using the BDI-Ia, was noted at endpoint in all 3 treatment groups.

CONCLUSIONS**:**

The results of this study indicate that ralfinamide at doses of 160 and 320 mg/day had no benefit in this population of patients diagnosed with NLBP, as evident from the lack of any statistically significant effects on any of the primary, secondary or other efficacy measures used to assess pain and its associated symptoms. These results are inconsistent with the effects shown in animal pharmacology models, including those for neuropathic pain, as well as with the results of the placebo-controlled Phase II trial in patients with mixed neuropathic pain syndromes. Improvement from baseline with ralfinamide treatment was noted for almost all efficacy measures; however, the level of benefit was comparable to that of the placebo group.

Both doses of ralfinamide were well tolerated in this patient population, and the adverse event profile was generally similar to placebo. No clinically meaningful effects of ralfinamide were observed on vital signs, ECGs, physical examinations or tests of ocular function. No laboratory test abnormalities related to ralfinamide treatment were noted, except for elevations in liver enzymes for the high dose (320 mg/day), which were largely asymptomatic, mostly transient and unaccompanied by changes in bilirubin. The safety and tolerability profile for ralfinamide would not preclude administering ralfinamide in long-term studies in patients, provided periodic monitoring of liver function tests is performed.

Based on the above results, ralfinamide will be evaluated in other neuropathic pain conditions in the future.

DATE OF THE REPORT:

09 August 2011, Final