Study NW-1029/02-08 Safety Update

Study Title:	A Multicenter, Double-Blind, Randomised, Placebo-Controlled, Extension Study to Assess Long-Term Safety and Efficacy of Two Fixed Doses of Ralfinamide (160 or 320 mg/day) in Patients with Chronic Neuropathic Low Back Pain
Name of the Test Drug/ Investigational Product:	Ralfinamide
EUDRACT Number:	2008-006159-39
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-1029/02-08
Development Phase of Study:	Phase III
Study Initiation Date (Date First Patient Screened):	20 March 2009 (first patient screened in Study NW-1029/01-08) 28 June 2009 (first patient enrolled in Study NW-1029/02-08)
Study Completion Date (Date Last Patient Completed Last Observation):	20 July 2010 (Visit 9 – post-study visit)
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

1 Synopsis

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

***Protocol Number*:** NW-1029/02-08

Development Phase: III

Study Objectives:

The objectives of this extension study were to evaluate the long-term safety and efficacy of two fixed doses of orally administered ralfinamide (160 or 320 mg/day), compared to placebo, in patients with chronic neuropathic low back pain.

Safety and tolerability were assessed by the following measures:

- Adverse events (AE)
- Vital signs (systolic/diastolic blood pressure, pulse, body weight, body temperature)
- Laboratory evaluations (blood chemistry, hematology, urinalysis)
- Electrocardiogram (ECG) – 12-lead, standard
- Physical examinations
- Neurological examinations
- Ophthalmological examinations (Details will be provided in a separate manual)
    - ***Fundus:*** A dilated fundus examination must be performed. Digital pictures are required.
    - ***Visual acuity***: The best corrected Snellen visual acuity should be determined as 20/20 equivalents.
    - ***Color vision***: Color vision should be determined for each eye separately (as an example see Appendix 6 of protocol: Farnsworth-Munsell 100 Hue Test).
    - ***Visual fields***: Automated visual fields will be charted for both eyes.
    - ***Electroretinography (ERG):*** limited to sites with an ophthalmologist experienced in working with internationally recognized methodology.
    - ***Optical coherence tomography (OCT):*** limited to sites with an ophthalmologist experienced in working with internationally recognized methodology.

The Independent Safety Monitoring Board established for the core study (NW-1029/01-08) continued to periodically review all safety data from patients enrolled in this extension study.

Efficacy:

Efficacy was to be evaluated using the 11-point Likert scales for daily pain score, effects of pain on sleep and activity, and shooting and burning pain, as well as the Visual Analogue Scale (VAS; 100-mm) for pain and the Neuropathic Pain Symptom Inventory (NPSI). However, the the efficacy analyses are ongoing and the results are not included in this **Study NW-1029/02-08 Safety Update**

All final evaluations were performed at Week 40 (end of the treatment period), or at the time of premature discontinuation, regardless of the reason for dropout, including termination of the study by the Sponsor.

Study Design and Methods

The present study was an extension to core study NW-1029/01-08, and was a multicenter, double-blind, randomised, placebo-controlled study consisting of 40 weeks of treatment to assess the long-term safety and efficacy of two fixed doses of ralfinamide (160 or 320 mg/day) versus placebo in patients with chronic neuropathic low back pain due to nerve compression. Patients were required to give informed consent for the extension study prior to entering. Only patients from the previous study (NW-1029/01-08) who wanted to continue on their current medication, were compliant with dosing in the core study, and were not experiencing any side effects or medical conditions that would have precluded their continuation on the study medication, or those who discontinued treatment, but had returned for at least one of the scheduled efficacy evaluations at Weeks 2, 4, 6, and 9 and completed the final efficacy evaluation at Week 12 (Retrieved Dropouts) were eligible for this extension study.

Upon entry into this study, patients continued to take the same treatment originally administered in the previous study NW-1029/01-08 (ralfinamide 160 or 320 mg/day, or placebo). Patients receiving the decreased dose (either 80 or 240 mg/day ralfinamide or placebo) at the time of their completion of the core study were allowed to enroll in the extension study and continue on these doses, if they met all other entry criteria.

The screening evaluations for this extension study (Visit 1) included the final (Visit 8) evaluations from the core study. Patients who gave informed consent and met all eligibility criteria entered this extension study and received their first dose of study medication in the clinic. Patients returned for scheduled evaluations at Weeks 4, 10, 16, 22, 28, 34, and 40 (or at early discontinuation), at which time safety and efficacy evaluations were performed. After the last dose of study medication, patients entered a 7-day post-study follow-up period during which adverse events (AEs) and use of concomitant medication were monitored and follow-up assessments were performed for any safety evaluations for which there were clinically significant abnormalities at Week 40 (or at early discontinuation).

During this extension treatment period, safety parameters (ECGs, laboratory tests, vital signs and ophthalmologic examinations), and key efficacy measures (Likert pain scales, VAS, NPSI) were assessed frequently throughout the study or at early discontinuation. Assessment of AEs, concomitant medication usage and compliance with study medication dosing were performed at all visits. The patients continued to maintain the eDiary as described in study NW-1029/01-08, recording daily pain assessments (11-point Likert scales, VAS), as well as use of rescue pain

medication; however, daily pain assessments were performed only during the week (7 days) preceding each scheduled office visit.

Dosing flexibility was allowed during extension treatment. Patients were to continue on the same dose of study medication they were taking in the core study, either 160 or 320 mg/day ralfinamide (or placebo), or 80 or 240 mg/day ralfinamide (or placebo), if they had required a dose reduction. For patients unable to tolerate these lower doses, a second drop-back step to 80 or 160 mg/day (or placebo) was available. To keep the dose regimen as flexible as possible, dose reductions and up-titration (if current reduced dose was well tolerated) were permitted at anytime throughout the study. Rescue pain medication (NSAIDs, including COX-inhibitors, and minor analgesics, e.g. paracetamol), may have been used at any time; narcotic analgesics, e.g. tramadol, may also have been used if necessary by patients who were not obtaining adequate pain relief from the study medication.

Early termination of the study

The results of the core study (NW-1029/01-08) obtained in early May 2010 provided no evidence of efficacy for ralfinamide in treating neuropathic low back pain. Therefore, a decision was made to stop Study NW-1029/02-08, and a letter was sent to all investigators on 10 May 2011, requesting that all patients ongoing at the time be discontinued. Final efficacy and safety evaluations were to be performed on all patients at the time of discontinuation.

Number of Patients (Planned and Analyzed)

No formal sample size estimations were performed for the extension study. Based on a drop-out rate of approximately 25% predicted in study NW-1029/01-08, it was estimated that approximately 300 patients from the core study would enter into this long-term extension study. Of the 411 patients who were randomized to treatment in the core study, 339 (82.5 %) completed the study and were eligible for participation in the extension study. A total of 267 (78.8%) of the 339 eligible patients were enrolled in the extension study, 89 (78.8%) in the ralfinamide 320 mg/day group, 80 (73.4%) in the ralfinamide 160 mg/day group, and 98 (83.8%) in the placebo group.

Statistical Analysis

No statistical analyses were performed for any of the safety variables assessed during the extension study, as only data listings were available. Key safety data were extracted from the data listings and tabulated to allow comparison among treatment groups. Additional safety information was obtained from narratives for patients who experienced SAEs or discontinued prematurely due to adverse events during the extension period.

No results for any efficacy variables are included in this abbreviated safety update.

Summary of Safety Results

- The decision by the Sponsor to prematurely terminate the extension trial allowed only 18 patients to complete the planned 52 weeks of total treatment with ralfinamide. All other patients were discontinued from treatment and completed the end of study visit.
- Serious AEs were reported in only 8 patients (320 mg/day ralfinamide – 2; 160 mg/day ralfinamide - 3; placebo – 2); all were considered "not related" to study medication. No serious TELAEs were reported.
- Only 2 patients discontinued prematurely due to adverse events, one in the 320 mg/day ralfinamide group and one in the placebo group.
- The percentage of patients with one or more newly emergent TEAEs in the extension study was similar among the 3 treatment groups (320 mg/day ralfinamide – 37.1%; 160 mg/day ralfinamide – 40.0%; Placebo – 33.7%). No pattern of adverse effects during long-term treatment with ralfinamide was observed.
    - The most common newly emergent TEAEs were diarrhea, which was reported in more patients in the 160 mg/day ralfinamide group, and pyrexia, which occurred with a similar frequency in all 3 groups.
    - The SOC with the most newly emergent TEAEs was Gastrointestinal Disorders. Diarrhea, gastritis and vomiting were reported more frequently in the 160 mg/day ralfinamide group, while nausea occurred more often in the placebo group.
    - The most common newly emergent TEAE in the Eye Disorders SOC was cataract, which was reported more frequently in the placebo group; other ocular TEAEs occurred in only a single patient in any treatment group.
    - No seizures or seizure-like TEAEs were reported for any patient.
- Overall, less than 6% of patients experienced a newly emergent laboratory TEAE. The percentage of patients with TELAEs was higher in the 320 mg/day ralfinamide group (10.1%; primarily liver function test abnormalities) than in the 160 mg/day ralfinamide (5.0%) and placebo (2.0%) groups.
- The percentage of patients with clinically notable laboratory hematology or blood chemistry values at any time in the study or at the endpoint assessment was higher in the ralfinamide groups than in the placebo group.
- Very few patients had clinically notable vital signs changes, with weight increase/decrease being the most frequent. No clinically meaningful effects of ralfinamide treatment on blood pressure or pulse were observed.
- No clinically meaningful effects were noted on any ECG parameters, including QTc interval. The proportion of patients with ECG abnormalities on treatment was higher in the placebo group than in the ralfinamide treatment groups.