# Efficacy and safety of Ralfinamide in an 8-week, randomised, double-blind, placebo controlled, international trial in patients with Neuropathic Pain (NP)

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## Abstract

**Objective:** To assess safety/tolerability and efficacy of ralfinamide (80 to 320mg/day), in patients with moderate NP of various aetiologies in accordance with IASP criteria.

**Design/Methods:** Safety was determined by drop-out rate, AEs, ECG, laboratory, and vital signs. Efficacy was assessed through changes in the severity of pain (VAS, 11-point Likert scale). Ralfinamide was dosed at 40 mg BID with weekly increases to 80 and 160 mg BID contingent on tolerability.

**Results:** 272 patients were enrolled (RAL=177; PLA=95); 78 discontinued prematurely (RAL 31.2%; PLA 23.2 %): no significant difference in reasons for discontinuation between groups was noted. The highest dose of Ralfinamide (320mg) was reached and maintained in 75% of patients. The most frequent (5%) AEs were: headache (RAL 7.3%; PLA 10.5%), nausea (5.1%; 10.5%), abdominal pain (4.5%; 5.3%), dizziness (3.4%; 8.4%), dyspepsia (2.8%; 7.4%), and vomiting (2.8%; 5.3%). There were no differences in vital signs and laboratory results between groups. Least Square, mean changes for ralfinamide over placebo in ITT-LOCF analysis in VAS (-5.2; 95%CI -11.0, 0.5; p=0.075) and Likert (-0.68; 95%CI -1.18,-0.17; p=0.008) indicate efficacy of ralfinamide in NP patients. Differences in Responder (50%) Rates for the VAS (11%; 95%CI 0.7, 21.3; p=0.048) and Likert (11.8%; 95%CI 2.1, 21.4; p=0.027) indicate that the analgesic effect of ralfinamide is of therapeutic relevance. In addition, ralfinamide showed significant benefit for disturbed sleep (p=0.026), and a trend for daily activity and shooting pain.

**Conclusions/Relevance:** Ralfinamide was well tolerated and showed statistically significant and clinically relevant efficacy in patients with different forms of peripheral NP.

## Background

Neuropathic pain is a chronic, frequently progressive condition that accompanies an injury to nervous system; the most common NP conditions are estimated to affect more than 31 million patients in US, Europe and Japan.[1] Following peripheral nerve injury, changes occur in nerve excitability, sustained by alteration in the function and pattern of ion channels such as sodium channels, that contribute to the abnormal spontaneous firing after injury, and calcium channels associated with neurotransmitter release in spinal cord. In addition, after nerve injury, anatomical and neurochemical changes occur also within the central nervous system that can persist long after the injury has healed [2].

Ralfinamide is an alpha-aminoamide derivative that blocks different targets important in pain control (Na+/Ca++ channels and NMDA receptors), modulates substance P and glutamate release and shows analgesic activity in animal models of pain. Studies in rodents showed that ralfinamide has preemptive and palliative analgesic effects in a model of chronic pain after neurectomy.

This study was performed in patients with peripheral neuropathic pain (PNP) of various etiologies diagnosed in accordance with IASP criteria. The study was interrupted by the sponsor when 62 patients had been randomised due to the occurrence of retinal degeneration in albino rats; treatment was terminated in 21 (ralfinamide 16 and placebo 5) ongoing patients. The study was reinitiated following discussions with regulatory authorities, approval of a protocol amendment to exclude high ocular risk patients, institution of ocular monitoring, and resolution of the toxicology issue (limited to albino rats).

The inclusion of numerous PNP etiologies was designed to allow post hoc analyses to determine if ralfinamide showed a distinct therapeutic benefit in any of the major subcategories of PNP, provided the overall analyses in all patients (all PNP diagnosis) showed a statistically significant difference; these analyses would determine the indication for ralfinamide in further PNP disease.

## Methods

**Objective:** To determine the safety/tolerability and efficacy of ralfinamide (80-320 mg/day) given b.i.d. compared to placebo in patients diagnosed with PNP conditions.

- Primary safety objective: to define the maximum tolerated dose (MTD); this was to be based on the proportion of patients reaching and maintaining the highest dose of 320 mg/day (8 tablets/day or matching placebo).
- Primary efficacy measure: mean change on the VAS
- Secondary objectives: change on the 11-point Likert pain scale, responder rates on the VAS, and Likert, impact on sleep, daily activities, and effect on types of pain (allodynia, hyperalgesia, shooting pain) from the Patient Diary

**Design:** Double-blind, randomised (2:1 ralfinamide to placebo), International, 8-week trial.

**Study treatment:** Ralfinamide was initiated at 40 mg bid, with weekly increases to 80 mg and 160 mg bid contingent on tolerability; dose reductions were allowed in case of intolerance. Patients randomised to placebo received matching tablets.

Inclusion criteria:

- Age 18-85 years; fecund women were included only if practicing adequate contraception and if a pregnancy test was negative
- Pain associated with PNP condition (IASP criteria) of at least 3 months duration prior to screening
- Intensity of pain (at least moderate) measured as ≥ 40 mm on the 100 mm patient rated VAS at screening and at baseline
- Presence of stimulus evoked pain (hyperalgesia, allodynia), or shooting pain
- Inform consent in writing

**Exclusion criteria:**

- Patients with central, psychogenic or migrating pain, or severe trophic changes in joints, or pain due to other conditions that was as severe as the NP
- Patients managed with other NP treatment
- Patients whose NP was due to infectious (other than PHN), proliferative, or metabolic conditions (other than diabetes)
- Patients with severe and/or unstable medical conditions

**Analyses:** Safety analyses were performed in the ITT population. Overall efficacy analyses were performed in the ITT population (ALL-LOCF); to account for the patients whose treatment was terminated due to the interruption of the study in 21 patients, and the resulting bias, analyses were repeated as a Modified Population-LOCF (MPOP-LOCF) on those patients included in the trial subsequent to the interruption (N=209)

## Results

The demographic characteristics and the types of PNP conditions are shown in table 1.

**Table 1: Demographic data and types of NP**

| | Ralfinamide | Placebo |
|---|---|---|
| Age in years: mean (SD) | 58.1 (11.43) | 56.7 (9.76) |
| Gender (male): number (%) | 94 (53.4) | 52 (54.7) |
| Body weight in kg: mean (SD) | 75.6 (14.76) | 76.5 (15.8) |
| Race number (%) | | |
| • Caucasian | 140 (79.5) | 73 (76.8) |
| • Asian | 36 (20.5) | 21 (22.1) |
| PNP Diagnosis | | |
| • NCET | 59 (33.4%) | 38 (41.1%) |
| • Diabetic neuropathy | 44 (24.9%) | 21 (22.1%) |
| • Ischemic nerve disease | 10 (5.6%) | 5 (5.3%) |
| • Traumatic neuropathy | 27 (15.2%) | 10 (10.6%) |
| • PHN | 13 (7.3%) | 7 (7.4%) |
| • Other | 24 (13.6%) | 13 (13.7%) |

NCET: Nerve Compression or Entrapment

## Safety:

Study disposition:

**Table 2: Study Disposition**

| Screened | n=386 | |
|---|---|---|
| **Treatment Groups** | **Ralfinamide (n=177)** | **Placebo (n=95)** |
| Premature Termination | N= 56 (31.8%) | N= 22 (23.2%) |
| • Sponsor action[1] | 16 (9%) | 5 (5.3%) |
| • Protocol deviation | 7 (4%) | 3 (3.2% |
| • Lack of efficacy | 4 (2.3%) | 1 (1.1%) |
| • Consent withdrawn | 14 (7.9%) | 5 (5.3%) |
| • Loss to follow up/other | 3 (1.7%) | 3 (3.2%) |
| • SAEs | 1 (0.6%) | 1 (1.1%) |
| • Due to AEs (not rated serious) | 11 (6.2%) | 4 (4.2%) |

[1]= treatment was terminated in these patients by the sponsor due to toxicology finding; study was reinitiated later after resolution of the issue.

MTD: The MTD could not be established in this trial as the vast majority (> 75%) of patients (excluding those whose treatment was terminated prematurely by the sponsor) reached and maintained the 320 mg/day dose; similar numbers were noted in the placebo patients.

AEs: Most frequent AEs (≥ 5%) are shown in the table 3.

**Table 3: Most Frequent AEs (≥ 5%)**

| Adverse Events (Preferred Terms) | Ralfinamide (n= 177) | Placebo (n= 95) |
|---|---|---|
| Headache | 13 (7.3%) | 10 (10.5%) |
| Nausea | 9 (5.1%) | 10 (10.5%) |
| Dyspepsia | 5 (2.8%) | 7 (7.4%) |
| Abdominal Pain | 8 (4.5%) | 5 [1 SAE] (5.3%) |
| CPK increase | 4 (2.3%) | 5 (5.3%) |
| Dizziness | 6 (3.4%) | 8 (8.4%) |
| Pruritus | 3 (1.7) | 5 (5.3%) |
| Retinal disorder | 4 (2.3%) | 5 (5.3%) |
| Vomiting | 5 (2.8%) | 5 (5.3%) |

Other Safety Findings: No statistically significant or clinically relevant findings were noted in results of vital signs, ECG, or Laboratory examinations. Results of ocular examinations rated by an independent, blinded neuro-ophthalmologist consultant are shown in the Table 4.

**Table 4: Results of Ocular Examination**

| Change from Baseline to Endpoint | Ralfinamide[1] | Placebo[1] |
|---|---|---|
| Patients with 1 New Abnormality | 13 (11.5%) | 7 (10.4%) |
| • Visual acuity | 1 (0.9%) | 0 |
| • Visual fields left eye | 10 (9.1%) | 2 (3%) |
| • Visual fields right eye | 7 (6.4%) | 4 (6.1%) |
| • Fundoscopy left eye | 1 (0.9%) | 2 (3%) |
| • Fundoscopy right eye | 0 | 2 (3%) |

[1]= 113 patients in the ralfinamide and 67 in the placebo group underwent ocular examination

## Efficacy

The mean change from baseline to end of treatment for the patient rated VAS and Likert scales for the all patients randomised and who had a post baseline value (ALL-LOCF) and for all patients who were enrolled following the restart of the study (Modified Population-LOCF) populations for mean change and responder rates is shown in table 6 and 7.

**Table 6: Differences in the Mean Change for the VAS and Likert**

| | | ALL-LOCF | | MPOP-LOCF | |
|---|---|---|---|---|---|
| | | Ralfinamide (n=169) | Placebo (n=92) | Ralfinamide (n=126) | Placebo (n=74) |
| VAS Ancova | Change Vs Baseline (±SD) | -18.1 (24.54) | -12.5 (20.13) | -20.1 (25.74) | -10.4 (20.62) |
| | Treatment Difference* (95% CI) | -5.2 (-11.0, 0.5) | | -8.1 (-14.9, -1.4) | |
| | p-value | 0.075 | | 0.0187 | |
| Likert (Pain) Ancova | Change Vs Baseline (±SD) | -1.7 (2.09) | -0.97 (1.85) | -1.8 (2.22) | -0.84 (1.96) |
| | Treatment Difference* (95% CI) | -0.7 (-1.18, -0.17) | | -0.93 (-1.5, -0.3) | |
| | p-value | 0.008 | | 0.0026 | |
| Daily Diary Sleep Ancova | Change Vs Baseline (±SD) | -1.27 (2.06) | -0.67 (2.09) | -1.5 (2.14) | -0.44 (2.13) |
| | Treatment Difference* (95% CI) | -0.57 (-1.06, -0.08) | | -0.95 (-1.5, -0.37) | |
| | p-value | 0.024 | | 0.0014 | |
| Daily Diary Activity Ancova | Change Vs Baseline (±SD) | -1.3 (2.37) | -0.8 (2.04) | -1.55 (2.51) | -0.72 (2.17) |
| | Treatment Difference* (95% CI) | -0.49 (-1.04, 0.06) | | -0.76 (-1.4, -0.10) | |
| | p-value | 0.079 | | 0.024 | |

* Difference in LS Mean

**Table 7: Differences in the Responder Rate Analyses for the VAS and Likert**

| | | ALL-LOCF | | MPOP-LOCF | |
|---|---|---|---|---|---|
| | | Ralfinamide (n=169) | Placebo (n=92) | Ralfinamide (n=126) | Placebo (n=74) |
| VAS | Responder Rate 50% n (%) | 48 (28.4) | 16 (17.4) | 40 (31.7) | 12 (16.2) |
| | Risk Difference (95% CI) | 11.0 (0.7, 21.3) | | 15.5 (3.8, 27.2) | |
| | p-value | 0.048 | | 0.016 | |
| Likert (Pain) | Responder Rate 50% n (%) | 43 (25.7) | 13 (14.0) | 34 (27.4) | 11 (14.7) |
| | Risk Difference (95% CI) | 11.8 (2.1, 21.4) | | 12.8 (1.5, 24.0) | |
| | p-value | 0.027 | | 0.037 | |
| Daily Diary Sleep | Responder Rate 50% n (%) | 46 (27.7) | 13 (14.0) | 37 (30.1) | 9 (12.00) |
| | Risk Difference (95% CI) | 13.7 (3.9, 23.5) | | 18.1 (7.1, 29.0) | |
| | p-value | 0.011 | | 0.003 | |
| Daily Diary Activity | Responder Rate 50% n (%) | 47 (28.1) | 17 (18.3) | 39 (31.4) | 14 (18.7) |
| | Risk Difference (95% CI) | 9.9 (-0.5, 20.3) | | 12.8 (0.8, 24.8) | |
| | p-value | 0.079 | | 0.024 | |

**Analyses in subcategory of PNP**

Efficacy analyses were repeated in the largest subgroup of PNP patients included in the trial i.e., patients with pain due to Nerve Compression or Entrapment (NCET). The etiological diagnosis included in this subgroup of patients is shown below in table 8.

**Table 8 – Nerve Compression and Entrapment Syndromes; Distribution of Sub-diagnosis by Treatment**

| Neuropathic Pain Diagnosis | Ralfinamide | Placebo |
|---|---|---|
| Compression radiculopathy | 32 | 17 |
| Sciatic NC | 1 | 1 |
| Radial tunnel compression syndrome | 1 | 0 |
| Carpal tunnel syndrome | 18 | 13 |
| Median nerve entrapment | 0 | 1 |
| Cubital tunnel syndrome | 1 | 1 |
| Tarsal tunnel syndrome | 0 | 3 |
| Meralgia paresthtica | 2 | 0 |
| Other syndromes | 5 | 3 |
| Total | 60 | 39 |

The results for the VAS and Likert scales (including pain, sleep, daily activities items) for the ALL-LOCF and the MPOP-LOCF populations for mean change and responder rates in NCET patients is shown below in tables 9 and 10 respectively.

**Table 9: Mean Change in NCET patients (VAS and Likert for ALL-LOCF and the MPOP-LOCF Populations)**

| | | NCET-ALL-LOCF | | NCET-MPOP-LOCF | |
|---|---|---|---|---|---|
| | | Ralfinamide (n=57) | Placebo (n=39) | Ralfinamide (n=42) | Placebo (n=28) |
| VAS Ancova | Change Vs Baseline (±SD) | -24.91 (24.59) | -14.42 (19.85) | -25.0 (25.66) | -12.2 (20.5) |
| | Treatment Difference* (95% CI) | -9.5 (-19.0, 0.03) | | -10.5 (-21.9, 0.86) | |
| | p-value | 0.051 | | 0.069 | |
| Likert (Pain) Ancova | Change Vs Baseline (±SD) | -2.24 (2.23) | -1.28 (1.68) | -2.27 (2.38) | -1.18 (1.86) |
| | Treatment Difference* (95% CI) | -0.85 (-1.67, -0.03) | | -0.95 (-1.92, 0.03) | |
| | p-value | 0.042 | | 0.057 | |

**Table 10: Responder Rates in NCET patients (VAS and Likert for ALL_LOCF and the MPOP-LOCF Populations)**

| | | NCET-ALL-LOCF | | NCET-MPOP-LOCF | |
|---|---|---|---|---|---|
| | | Ralfinamide (n=57) | Placebo (n=39) | Ralfinamide (n=42) | Placebo (n=28) |
| VAS | Responder Rate 50% n (%) | 26 (45.6) | 8 (20.5) | 19 (45.2) | 5 (17.9) |
| | Risk Difference (95% CI) | 25.1 (7.0, 43.2) | | 27.4 (6.7, 48.1) | |
| | p-value | 0.012 | | 0.018 | |
| Likert (Pain) | Responder Rate 50% n (%) | 24 (42.1) | 7 (17.9) | 16 (38.1) | 5 (17.9) |
| | Risk Difference (95% CI) | 24.2 (6.6, 41.7) | | 20.2 (-0.2, 40.7) | |
| | p-value | 0.013 | | 0.07 | |
| Daily Diary Sleep | Responder Rate 50% n (%) | 27 (47.4) | 10 (25.6) | 20 (47.6) | 6 (21.4) |
| | Risk Difference (95% CI) | 21.7 (2.9, 40.6) | | 26.2 (4.8, 47.6) | |
| | p-value | 0.032 | | 0.026 | |
| Daily Diary Activity | Responder Rate 50% n (%) | 25 (43.9) | 9 (23.1) | 18 (42.7) | 6 (21.4) |
| | Risk Difference (95% CI) | 20.8 (2.3, 39.2) | | 21.4 (0.1, 42.8) | |
| | p-value | 0.036 | | 0.064 | |

## Conclusions

Ralfinamide was extremely well tolerated and did not show any clinically relevant or statistically significant changes for a wide variety of safety and tolerability assessments. The ALL-LOCF analyses demonstrated that ralfinamide showed clinically relevant reduction of pain as assessed by the VAS and Likert scales; significant benefit was also demonstrated for pain, sleep, and impact in daily life activities using the daily pain diary.

Analyses performed in patients with pain due to NCET syndromes demonstrated clinically meaningful and statistically significant benefit. No NP agent has previously been shown to be effective in this very large subpopulation (60% of NP diagnosis) of NP patients. The multiple pharmacological actions of ralfinamide may explain this unique benefit. Future studies in patients with chronic Neuropathic Low Back Pain (NLBP) syndromes, the most prevalent nerve compression conditions, are currently being planned.

**REFERENCES**

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Presented at the 60th Annual Meeting of the American Academy of Neurology, Chicago, April 15 2008, PO3.179.