Newron reports positive Phase II results for ralfinamide in peripheral neuropathic pain patients

-- Statistically significant and clinically relevant improvement in large trial subpopulation –

-- Phase II b/III in Neuropathic Low Back Pain planned --

Milan, Italy – April 16, 2008 - Newron Pharmaceuticals S.p.A. ("Newron"), a research and development company focused on novel CNS and pain therapies, today reports positive results from the detailed analyses of the Phase II trial of ralfinamide in patients with neuropathic pain, as presented at the American Academy of Neurology 60th Annual Meeting in Chicago. Newron also reports results from a pilot Phase II safety and tolerability study of ralfinamide in post-surgical (dental) pain.

Highlights:

- Nerve Compression and Entrapment Conditions: Aggregate prevalence of about 12% - no drugs approved for nerve compression or nerve entrapment to date
- Neuropathic Low Back Pain (associated with nerve compression syndromes): accounts for about 60% of all neuropathic pain diagnoses
- Significant and clinically relevant improvement in
  - VAS/Likert mean change and responder rates
  - Patient rated Activities of Daily Living
  - Quality of Sleep
- Future development plans discussed with major health authorities

The double-blind, randomised, placebo-controlled, multi-national study (Austria, Czech Republic, India, Italy, Poland, and UK) was performed in 272 patients with at least moderate pain of neuropathic origin, e.g. Diabetic Neuropathy, Post-herpetic Neuralgia, Post-Surgical Neuralgia, Post-compression Neuralgia, etc., diagnosed in accordance with the diagnostic criteria proposed by the International Association for Study of Pain.

In the 8 week treatment, trial patients were randomised to treatment with ralfinamide (n=177) in a dose range of 80 to 320 mg/day, or placebo (n=95). The primary efficacy measure was the change in patient rated visual analogue scale (VAS) of the severity of pain compared to baseline; secondary efficacy measures included the patient rated Likert Pain Scale (LPS), responder rates for the VAS and the LPS, burning/shooting pain as well as impact of treatment on sleep disruption and daily life activities. Safety and tolerability of treatments were judged by assessment of drop-out rate, side effects, ECG, laboratory changes, eye examinations, blood pressure and pulse.

Study Results
Preliminary results for the overall population as announced in 2007 demonstrated that ralfinamide was well tolerated with no evidence of any statistically significant or clinically relevant pattern of adverse change compared with placebo. In this population, treatment with ralfinamide was associated with clinically relevant and statistically significant benefit compared with placebo as judged by results of analyses of mean change from baseline as well as responder rates on the VAS and LPS.

The trial had been designed to include patients with multiple forms of peripheral neuropathic pain (PNP) conditions to allow analyses to determine if the multiple mechanisms of action of ralfinamide would show a unique benefit in any specific neuropathic pain condition. Review of the trial population indicated that the largest group of patients included was experiencing neuropathic pain due to Nerve Compression/Nerve Entrapment (NCET).

- Effects of Ralfinamide in patients with pain due to NCET:

  NCET conditions were the cause of pain in 96 patients (49 females), of whom 57 were treated with ralfinamide and 39 with placebo.

  Treatment with ralfinamide, compared to placebo was demonstrated to be highly efficacious as judged by the reduction in the intensity of pain as measured by the VAS and LPS in analyses of mean change from baseline, as well as responder rates in all patients with NCET included in the trial (ITT population).

  In the group of patients that were included in the trial after the re-start of the study, the therapeutic benefit of ralfinamide in patients with NCET was demonstrated by the clinically relevant (50% reduction from baseline) and statistically significant difference in responder rates for the VAS [risk difference (95% CI) 27.4%, (6.7, 48.1) p=0.018], and the LPS [risk difference (95% CI) 20.2%, (-0.2, 40.7) p=0.07], 50% or greater reduction from baseline in disruption of sleep [risk difference (95% CI) 26.2%, (4.8, 47.6) p=0.026], and daily life activities [risk difference (95% CI) 21.4%, (0.1, 42.8) p=0.064].

Ravi Anand, Newron's CMO, commented, "These results are very exciting as they demonstrate benefits of ralfinamide in a large population of patients for whom no other neuropathic pain treatments have been shown to be effective. Using a high threshold to determine the clinical relevance of the benefit, i.e., 50% reduction of pain, large differences between ralfinamide and placebo were noted. Based on the magnitude of the reduction in pain, significant benefits were also noted in the quality of sleep, daily activities, and type of pain. The robustness of the effect was noted across different analyses populations. As these data were derived from almost 100 patients with NCET, the results can be considered predictive for future trials. As a large number of these patients were experiencing low back pain due to a neuropathic component, the benefits demonstrated suggest that ralfinamide may provide a unique therapeutic benefit for patients with Neuropathic Low Back Pain (NLBP)."

Results from a pilot Phase II Safety and Tolerability Study with Ralfinamide in Post Surgical (Dental) Pain

Newron also reports results from a Phase II, pilot, randomised, placebo-controlled, double-blind, parallel-group, multi-centre study, designed to determine the safety, tolerability and preliminary evidence of preventive analgesic efficacy of orally administered ralfinamide at a dose range of 320/480 mg per day, compared to placebo, in patients with third molar, post-extraction, dental pain. 202 patients were screened and 187 randomised (1:1) to ralfinamide or placebo. Patients received 5 days of pre-treatment with ralfinamide at 320 mg/day or placebo prior to the day of molar-extraction surgery. On the day of surgery, patients received a total daily dose of ralfinamide at 480 mg or placebo. On the two days following surgery, patients received treatment at 320 mg/day of ralfinamide or placebo.

13 patients (5 ralfinamide, 8 placebo) discontinued from the study prematurely; no differences between treatments in reasons for discontinuation were detected. The starting dose of ralfinamide of 320 mg/day (no titration) was well tolerated as was the maximal dose of 480 mg/day given on the day of the surgery. No statistically significant or clinically relevant difference between ralfinamide and placebo was detected in incidence, types, and severity of adverse events as reported by patients or detected through results of vital signs, laboratory, or ECG examinations.

72% of ralfinamide and 77% of placebo patients required rescue with analgesic pain medication following the surgery; there were no differences in either the number of patients requiring rescue or the time to rescue between the two treatments. Almost 70% of the patients receiving ralfinamide rated their Global Assessment as Response to Therapy (PGART) at 6 hours post surgery as "good/very good/excellent", while the corresponding number was 56.6% for placebo. This difference did not reach statistical significance.

The trial provided important information on the tolerability and safety of ralfinamide that will help design future trials. For example, unlike other neuropathic pain agents, ralfinamide was well tolerated and safe when given at the therapeutic dose of 320 mg/day. Patients with NP conditions may expect to gain early analgesic benefit due to the high therapeutically effective starting dose of 320 mg/day. The efficacy data indicate that pre- and post-surgery administration of ralfinamide in this pilot study in humans did not replicate the effects noted in the pre-clinical animal model. The mechanisms evaluated in this experiment do not have any bearing on the pathways through which ralfinamide produces its therapeutic effects in patients with neuropathic pain conditions as demonstrated in the large placebo control study described above.

Luca Benatti, Newron's CEO, said, "We are very encouraged by the results obtained in the neuropathic pain trial. This is a market worth approximately $5.5 bn in annual sales but currently poorly served by limited treatments. Ralfinamide's demonstration of significant efficacy, not only in the overall study population but most importantly in the sub-indication of NLBP for which no compound is currently approved, is an exciting potential growth driver for Newron. The positive safety data we have gathered from the post surgical (dental) pain pilot study again demonstrates ralfinamide's excellent safety

profile. Given the very positive feedback on our proposed plans by a number of health authorities in Europe and North America, we are now planning the next development phase for ralfinamide which is expected to be a Phase II b/Phase III study in patients with Neuropathic Low Back Pain, anticipated to start towards the end of 2008."

Conference call for analysts

Newron management will be available to discuss the results in further detail during a conference call for analysts today at 12:00 CET. The poster and presentation presented at the AAN conference is available to download from:
http://www.newron.com/presentationandfactsheet.asp

Dial-in details:

Time	12:00 CET
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About ralfinamide

Ralfinamide is a unique New Chemical Entity that is believed to mediate analgesic and anti-inflammatory effects through the modulation of ion channels implicated in pain and the inhibition of substance P.

About Nerve Compression and Nerve Entrapment

Within the large symptomatic neurological disease generally known as Neuropathic Pain a substantial role is played by painful conditions caused by compression or entrapment of the nerve. Compressive diseases are classified under several definitions however a limited number i.e. radiculopathy, lumbar spinal stenosis, spondylosis and sciatic nerve compression, can be considered as the most representative in terms of numbers and social impact. Typical syndromes under nerve entrapment conditions are the carpal tunnel, the tarsus tunnel and the ulnar tunnel syndromes.

Epidemiology of Nerve Compression

According to a study (Tarulli AW and Raynor EM, 2007), the prevalence of lumbo-sacral radiculopathy is approximately 5% distributed equally in men and women. This percentage is confirmed by a recent review (Rutkove S, UpToDate Inc., 2008) which gives a range of 4 – 6% prevalence for this condition. However in other studies (Chau R et al. , 2007) radiculopathy is estimated to affect up to 7.6% of the population in a given year, of which 1/3 suffer from persistent pain. Lumbo-sacral radiculopathy belongs to the larger definition of Low Back Pain (LBP). 85% of Americans suffer LBP sometime during their lives and, after the common cold, LBP is the most frequent cause of lost workdays in adults (Orthoinfo.aaos.org, 2006). In the United States and Europe the neuropathic component of LBP represents about 50% of all subtypes of neuropathic pain affecting patients (Datamonitor, 2006) and its diagnosis rate within neuropathic pain is at about 60% (IMS Health, 2008). Lumbo-sacral radiculopathy represents from 4% (Jarvik JG and Deyo RA, 2002) to 10% (Bennet at al., 1998) of LBP. This range seems to be confirmed by a review (Medical-Library.org, 2008) for which 5-10% of the causes of low back pain are due to lumbar radiculapathies. Lumbar spinal stenosis is present in 5 of every 1,000 Americans over the age of 50 and mainly because of degenerative processes leads to radiculopathy or neurogenic claudication (Szpalsky and Gunzburg, 2004). Current estimates indicate that 70 million Americans are older than 50 years. This number is estimated to grow by 18 million in the next decade alone, suggesting that the prevalence of spinal stenosis will increase (Hsiang J., 2006). Lumbar spondilosis, a non-specific aging phenomenon, is present in 27-37% of the asymptomatic population. In the United States more than 80% older than 40 years have lumbar spondilosis. Usually it produces no symptoms however nerve compression syndromes and spinal stenosis are frequent complications (Rothschild BM, 2007).

Epidemiology of Nerve Entrapment

Carpal Tunnel Syndrome (CTS) affects 3.75% of Americans (McCabe SJ et Al., 2007) and high rates have been reported in persons who perform certain repetitive wrist motions such as frequent computer users (Natahel H, 2004). In about 6% of diagnosed entrapment syndromes, patients were found to have the

combined presence of CTS, ulnaris and supinator syndromes (Weitbrecht W and Navickine E). Ulnar nerve entrapment is the second most frequent entrapment neuropathy in the upper extremity (Tidy C, Patient.Co.UK, 2007). Nerve entrapment syndromes rank third amongst the diagnoses made for neuropathic pain (IMS Health, 2008).

About Newron Pharmaceuticals
Newron Pharmaceuticals S.p.A. (www.newron.com) is a biopharmaceutical company focused on novel therapies for diseases of the Central Nervous System and pain. Newron is undertaking phase III trials with safinamide for the treatment of Parkinson's disease (PD) in conjunction with its partner, Merck Serono, which has exclusive worldwide rights to develop, manufacture and commercialize the compound in PD, Alzheimer´s disease, and other therapeutic applications. Newron is conducting phase II trials with ralfinamide for the treatment of neuropathic and post surgical (dental) pain. In February 2008, Newron signed an agreement providing for the acquisition of 100% of the issued share capital of Hunter-Fleming, a private UK bio-pharmaceutical company developing new medicines to treat neurodegenerative and inflammatory disorders. Newron is headquartered in Bresso, near, Milan, Italy. The company is listed at SWX Swiss Exchange, trading symbol NWRN.

For more information, contact:

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