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NRD.E1 a new approach to the treatment of painful diabetic peripheral neuropathy

Aim: This is a phase 2a, randomized, dose-finding clinical trial to assess efficacy and safety of NRD.E1 vs. placebo to manage painful diabetic peripheral neuropathy (PDPN).
Methods: Patients with PDPN of ≥3 months duration after at least one treatment free week (WO week) entered a 1-week single-blind (SB)-placebo run-in period followed by 3 weeks double-blind (DB) treatment period in which they were randomized in 1:1:1:1 to either NRD.E1 at 10, 40 or 150 mg per day or placebo. Pain intensity was assessed using the numerical rating scale (NRS) and a pain diary. Daily Sleep Interference Scale was completed each morning and paracetamol tablets registered. The Short-form McGill Pain Questionnaire (SF-MPQ), Patient's (PGIC) and Clinician's Global Impression of Change (CGIC) were secondary endpoints. Safety was assessed throughout the study period.
Results: 113 subjects were screened and 88 randomized (91.9% with type 2 diabetes, 55 males, age 66.6±10.27 years, diabetes duration 16.8±9.12 years, time from neuropathy diagnosis 5±4.28 years). The primary endpoint was a change from SB-placebo run-in week to week 3 in weekly mean of daily average NRS pain intensity. This endpoint did not meet the prespecified required value of p=0.016, although there was a placebo-corrected treatment effect with pain reductions at 40 mg and 150 mg/day of 0.82 (95% CI: 0.07, 1.58, p=0.034) and 0.66 (95% CI: −0.03, 1.35; p=0.061) NRS points. Moreover, post-hoc analysis showed, for the change in NRS weekly mean from the WO baseline to week 3, a placebo-corrected treatment effect of 1.46 (95% CI: 2.66, 0.26, p=0.0181) and 1.2 (95% CI: 2.29, 0.10, p=0.0329) at 40 mg and 150 m/day. Other post-hoc analysis and secondary data showed similar consistent results, i.e., 30% and 50% responder rate, maximum NRS, sleep interference, SF-MPQ, PGIC and CGIC. Treatment-emergent adverse events were reported for 49.2% of patients treated with NRD.E1 at different doses (compared to 33.3% for placebo), with 4.2% of patients requiring discontinuation. Most common side effects were headache, cough, and asthenia. No severe adverse event was reported.
Conclusions: NRD.E1 showed consistent results to treat PDPN without significant side effects. Further studies with longer duration might confirm the efficacy and safety outcomes in patients with PDPN.

Comments. This Proof of Concept, dose-finding study, despite the many limitations (recognized by the Authors) and the unmet primary outcome, introduces, on the uncrowded scene of PDPN, NRD.E1 as a new oral analgesic. Its mechanism of action would be distinct from other analgesic agents, including opioids, and regards Lyn tyrosine kinase involved in nerve injury-induced neuropathic pain. These preliminary results are encouraging with responder rate similar as the first line agents (over 40% achieved a pain reduction >50% compared to 19% in the placebo arm) and justify other studies with longer treatment period to confirm if NRD.E1 might indeed represent a novel therapeutic option for PDPN.

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Reference. Tiecke E, Rainisio M, Eisenberg E, Wainstein J, Kaplan E, Silverberg M, Hochman L, Mangialaio S. NRD.E1, an innovative non-opioid therapy for painful diabetic peripheral neuropathy-A randomized proof of concept study. Eur J Pain. 2022 Jun 7. doi: 10.1002/ejp.1989.
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