

ORIGINAL ARTICLE

NRD.E1, an innovative non-opioid therapy for painful diabetic peripheral neuropathy—A randomized proof of concept study

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Abstract

Background: Painful diabetic peripheral neuropathy (PDPN) affects up to 26% of patients with diabetes mellitus, with major impacts on their general health and well-being. Most available drugs fail to deliver acceptable pain reduction in the majority of patients and are often poorly tolerated. NRD.E1 is a novel product that has shown anti-nociceptive preclinical effects and good tolerability in healthy volunteer studies.

Methods: This phase 2a, randomized, dose-finding, Proof of Concept study enrolled patients with PDPN of ≥ 3 months duration. After at least one treatment-free week (WO week), 88 patients entered a 1-week single-blind (SB)-placebo run-in period, followed by 3 weeks' double-blind (DB) treatment, during which they received NRD.E1 at 10, 40 or 150 mg/day or placebo.

Results: The primary endpoint (change from SB-placebo run-in week to week 3 in weekly mean of daily average numerical rating scale [NRS] pain intensity) showed clinically relevant placebo-corrected treatment effect 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, respectively, though did not meet the pre-specified value of $p = 0.016$ required due to multiplicity. An additional *post hoc* endpoint looking at the change from WO baseline to week 3 in weekly mean of daily average NRS showed the placebo-corrected treatment effect was 1.46 (95% CI: 0.26, 2.66), and 1.20 (95% CI: 0.10, 2.29) NRS points, respectively. Secondary and *post hoc* analyses of NRS pain data (including 30 & 50% responder rate and NNT), sleep interference, Short-form McGill pain questionnaire (especially pain intensity assessed on Visual Analogue Scale), Patient's and Clinician's Global Impression of Change showed effects consistent with the primary findings. NRD.E1 was well tolerated, with only headache reported in more than two patients and more frequently on NRD.E1 than placebo.

Conclusions: The data suggest that NRD.E1 potentially represents a novel non-opioid therapeutic option for patients with PDPN, with at least similar efficacy and better tolerability than available therapies, justifying its further evaluation in larger-scale confirmatory studies.

Significance: NRD.E1 is a novel non-opioid therapeutic which is being developed for the treatment of PDPN. In this randomized, controlled, dose-finding, Proof of Concept study, NRD.E1 induced a clinically relevant pain reduction and it was well tolerated. Available data suggest that NRD.E1 has at least similar efficacy and better tolerability than the currently available therapies, potentially offering a promising new therapeutic option to patients with PDPN and possibly other neuropathic pain indications.

1 | INTRODUCTION

Painful diabetic peripheral neuropathy (PDPN) is a complication that affects up to 26% of patients with diabetes mellitus (DM), a disease that represents a growing global health problem (Ziegler & Fonseca, 2015). Patients with PDPN experience burning, stabbing or electric shock-type pain, usually without allodynia or hyperalgesia (Sheehan, 2009), which can have a major impact on their general health and well-being, day-to-day functioning, sleep and quality of life (Davies et al., 2006; Jensen et al., 2007).

The management of patients with PDPN remains a major challenge, since most available drugs (antidepressants, anticonvulsants, opioids) fail to achieve an acceptable reduction in pain in the majority of treated patients (Snedecor et al., 2014; Ziegler & Fonseca, 2015). Drugs commonly used for PDPN are often not well tolerated due to central nervous system (CNS) or gastrointestinal (GI) side effects (Finnerup et al., 2015).

Many treatments for PDPN (*tricyclic antidepressants* and classical opioids) are used off-label and/or have a poor safety profile, being associated with a risk for abuse, physical dependence and withdrawal symptoms upon discontinuation (Finnerup et al., 2015; Pop-Busui et al., 2017).

Overall, irrespective of the treatment, only about one-third of patients are likely to achieve more than 50% pain relief (Jensen et al., 2006). Inadequate response and poor tolerability to drug treatments constitute an unmet need in patients with PDPN. No novel treatment has been approved by a regulatory agency for more than a decade.

NRD135S.E1 (NRD.E1) is an orally available small molecule that has shown dose-dependent anti-nociceptive effects in several rodent models for both acute and chronic pain, including streptozotocin-induced diabetic neuropathy, Chung's spinal nerve ligation, tail flick, hot plate and formalin injection (S. Melin, E. Tiecke, N. Pessah, H. Shirin, E. Kaplan, unpublished data).

The mechanism of action of NRD.E1 is hypothesised to be through modulation of the phosphorylation of Lyn tyrosine kinase, a critical step in the mediation of nerve injury-induced P2X4 receptor upregulation in neuropathic pain (Tsuda et al., 2008). Importantly, NRD.E1 does not appear to act directly through any of the mechanisms, receptors, enzymes or channels known to be associated with pain and abuse-liability, including opioid receptors (S. Melin, E. Tiecke, N. Pessah, H. Shirin, E. Kaplan, unpublished data).

Clinical studies conducted in healthy, adult males evaluated the safety, tolerability and pharmacokinetic profiles of orally administered NRD.E1 as single ascending doses (300–1200 mg) and five repeated daily doses of 300 mg. NRD.E1 was well tolerated at all doses tested: no maximum tolerated dose, adverse drug reactions or any potential safety signals were identified. The pharmacokinetic profile supported the development of NRD.E1 as an orally dosed therapy for PDPN (Tiecke et al., 2022).

The combined preclinical and healthy volunteer study findings provided the basis and justification for the design and conduct of this Proof of Concept (PoC), dose-finding study (NRD135S.E1-201), which explored the efficacy, safety and tolerability of NRD.E1 in patients with PDPN.

2 | METHODS

2.1 | Study design and participants

NRD135S.E1-201 was a phase 2a, randomized, double-blind (DB), placebo-controlled, dose-finding trial to assess the safety, tolerability and efficacy of NRD.E1 in patients with PDPN. It was conducted at 10 sites in Israel between May 2015 and May 2016. Patients were males and females (of non-childbearing potential), >18 years of age, who had type 1 or type 2 DM stable for ≥ 3 months prior to study

entry (defined as stable hypoglycaemic medication with no change of insulin $\pm 20\%$, and glycated haemoglobin [HbA1c] $< 9\%$ at screening). They also had to have a documented clinical diagnosis of peripheral neuropathy (PN), confirmed by formal chart review according to prespecified criteria relating to peripheral neuropathy, neurological examination and investigations, prior to enrolment. At screening, their pain should have been ongoing for ≥ 3 months, with an daily average pain intensity of four to nine on the 11-point numerical pain rating scale (NRS). The pain was then scored to Douleur Neuropathique 4 criteria (Bouhassira et al., 2005), and required to have ≥ 4 positive items. Patients with evidence of polyneuropathy other than DPN, severe pain associated with conditions other than PDPN, or receiving any treatment for PDPN (anti-epileptic, anti-depressant, anti-inflammatory or opioids) that could not be withdrawn for the duration of the study were excluded. Regardless of whether they had been receiving prior pain medication or not, after screening all patients underwent a 7-day treatment-free wash-out (WO) week (referred to as WO week in this paper). Following the WO week, eligible patients (with a weekly mean of daily average pain intensity of four to nine on the NRS) were randomized 1:1:1:1 (in blocks of 4) to either NRD.E1 at 10, 40 or 150 mg or placebo using a computer-generated schedule provided by Syntax for Science SL (Mallorca, Spain). After randomization, all patients entered a 7-day single-blind (SB)-placebo run-in period, followed by 3 weeks' DB treatment, without any further patient selection (Figure 1). Blinding was maintained through the use of identical capsules, containers and labels that did not reveal treatment allocation. Study medication was administered orally, once daily (OD) in the morning.

The dose of 40 mg was selected based on the rat-equivalent doses that indicated efficacy in the rat streptozotocin model for diabetic neuropathic pain, which is seen as predictive of response in humans. The additional doses were selected as four times lower (10 mg) and ~four times higher (150 mg), to provide a wide dose range. The human doses were well below the no observed adverse effects level in animals and all three doses were below the dose explored in the multiple dose human pharmacology study, in which daily doses of 300 mg of NRD.E1 were well tolerated.

The use of paracetamol 500 mg tablets (up to 3000 mg/day) was permitted as rescue medication throughout the study.

No important changes to the study design (such as eligibility criteria) were made during the study conduct.

The SB-placebo run-in, which is common in other placebo-effect prone indications, was not used to exclude potential placebo responders but aimed at reducing variability and improve assay sensitivity. It is, however, uncommon in pain indications and it was not used in the clinical trials of any of the treatments approved for use in PDPN.

2.2 | Assessments

The change from baseline (BL) week to week 3 in weekly mean of the daily average pain intensity (using a 24-h recall period), as measured on the NRS, was analysed using two approaches: the SB-placebo week BL was used for the primary analysis and the WO week BL was added *post hoc* as an additional endpoint, in order to allow comparison of the study results with published data.

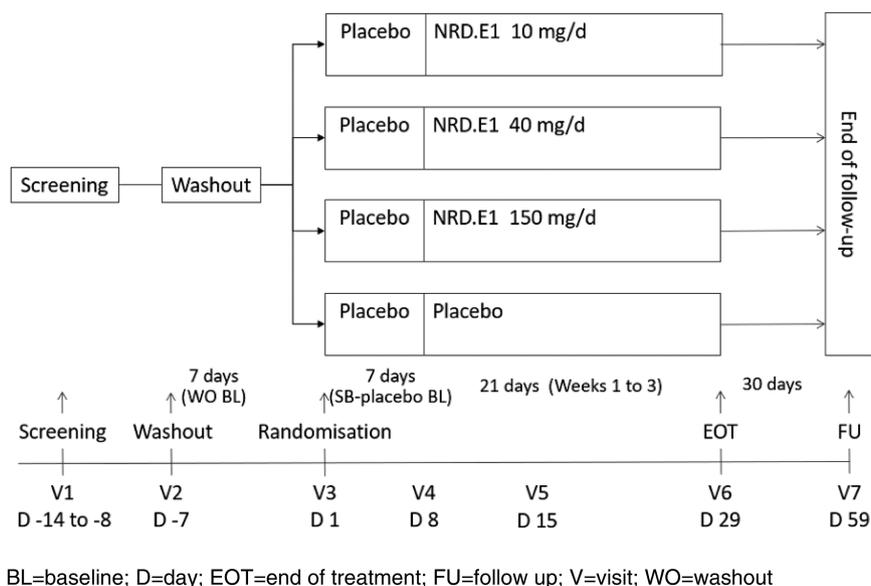
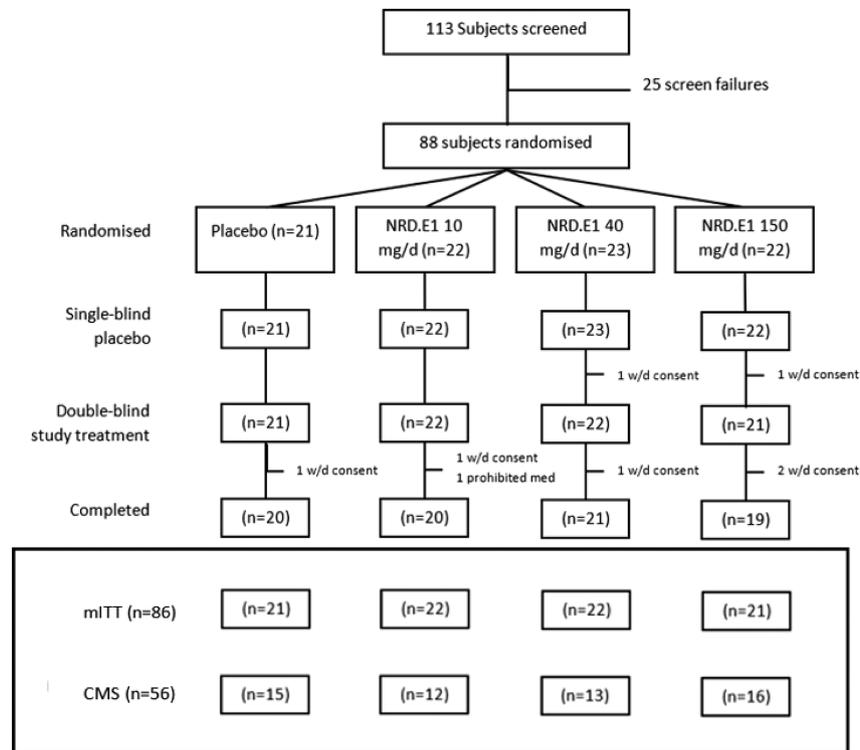


FIGURE 1 Study design. BL, baseline; D, day; EOT, end of treatment; FU, follow up; V, visit; WO, washout



CMS=sub population of mITT patients who had confirmed moderate or severe pain – a *post-hoc* analyses set;
mITT=modified intent to treat; n=number of patients

FIGURE 2 Patient disposition. CMS, sub population of mITT patients who had confirmed moderate or severe pain—a *post hoc* analyses set; mITT, modified intent to treat; n, number of patients.

Patients completed paper diaries with NRS pain scores every day, in the evening for the average and maximum daily pain intensity throughout the WO week (days –7 to –1), the SB-placebo run-in week (days 1 to 7) and DB (days 8 to 29) periods. The Daily Sleep Interference Scale (DSIS) score was completed each morning of the SB-placebo run-in week and DB (days 1 to 29) periods. The number of 500 mg tablets of paracetamol taken each day was documented by the patient in the patient diary from days 1 to 29. The Short-form McGill Pain Questionnaire (SF-MPQ; [Melzack, 1987]) was assessed before and at the end of the DB study period. Patient's and Clinician's Global Impression of Change (PGIC and CGIC) were evaluated at the end of the DB dosing period. Safety (including adverse events [AEs], laboratory tests, vital signs, electrocardiography, physical examinations and concomitant medications) was assessed throughout the study. Patients were contacted by phone 30 days after the last administration of study medication to record AEs and medication use during the follow-up period.

The trial (NCT02345291) was carried out in accordance with current standards of Good Clinical Practice and the Declaration of Helsinki. The trial protocol and all amendments were approved by the national regulatory authority and appropriate ethics body for each participating

institution. All patients provided written informed consent before enrolment.

2.3 | Statistical analyses

Assuming a normal distribution in all study groups and a common standard deviation of 2.5 NRS points, 21 patients/group would provide >90% power to detect an effect size of three NRS points for the observed most effective dose versus placebo at a two-sided significance level of 0.016. Assuming the exclusion of 8% of randomized patients from the main analysis set, 92 enrolled patients (23/group) were needed.

The null hypotheses (that none of the three active treatment doses differ from placebo in the primary efficacy endpoint), were tested by means of a two-sample Student's *t*-test using the Bonferroni-Holm procedure to address the multiplicity of hypotheses at the two-sided type I error of 0.05. Missing data for the week 3 mean of daily average pain intensity were imputed by last observation carried forward. Standardized effect sizes were computed as Cohen's *d* (Cohen, 1998).

The primary analysis was conducted using the SB-placebo run-in as the BL. However, since SB-placebo

TABLE 1 Summary of demographics and baseline characteristics, mITT set

	Placebo N = 21	NRD.E1 10 mg N = 22	NRD.E1 40 mg N = 22	NRD.E1 150 mg N = 21	All patients N = 86
Sex (n [%])					
Female	10 (47.6%)	7 (31.8%)	7 (31.8%)	7 (33.3%)	31 (36.0%)
Male	11 (52.4%)	15 (68.2%)	15 (68.2%)	14 (66.7%)	55 (64.0%)
Age (years)					
Mean (SD)	67.5 (9.28)	68.8 (8.12)	68.5 (9.44)	61.7 (12.82)	66.6 (10.27)
Median (Q1, Q3)	67.0 (61.0, 75.0)	68.5 (63.0, 76.0)	68.0 (62.0, 77.0)	63.0 (59.0, 68.0)	67.0 (61.0, 73.0)
Min, max	52.0, 86.0	54.0, 81.0	50.0, 85.0	19.0, 88.0	19.0, 88.0
BMI (kg/m ²)					
Mean (SD)	30.8 (3.29)	31.0 (6.29)	30.5 (4.94)	31.2 (4.28)	30.8 (4.77)
Median (Q1, Q3)	30.8 (28.0, 32.9)	29.9 (27.9, 35.0)	29.7 (27.2, 32.4)	29.9 (27.7, 34.4)	29.9 (27.7, 33.7)
Min, Max	26.0, 37.7	19.3, 44.8	20.9, 42.6	25.4, 41.7	19.3, 44.8
Time from diabetes diagnosis (years)					
Mean (SD)	19.7 (10.68)	17.4 (8.63)	15.3 (10.41)	14.8 (5.63)	16.8 (9.12)
Median (Q1, Q3)	16.1 (11.8, 25.4)	16.0 (11.0, 18.8)	12.1 (9.9, 18.3)	15.5 (11.2, 16.5)	15.3 (10.9, 20.2)
Min, Max	6.7, 51.5	7.1, 41.4	2.5, 52.0	4.7, 25.7	2.5, 52.0
Type of diabetes (n [%])					
Type I	5 (23.8%)	–	1 (4.5%)	1 (4.8%)	7 (8.1%)
Type II	16 (76.2%)	22 (100%)	21 (95.5%)	20 (95.2%)	79 (91.9%)
Time from neuropathy diagnosis (years)					
Mean (SD)	5.5 (5.44)	6.4 (4.80)	3.9 (2.49)	4.3 (3.68)	5.0 (4.28)
Median (Q1, Q3)	2.9 (2.0, 6.8)	5.7 (2.4, 9.9)	3.5 (1.7, 5.5)	3.7 (2.6, 5.2)	3.9 (1.9, 6.3)
Min, Max	0.1, 20.5	0.3, 16.2	0.5, 9.0	0.4, 17.0	0.1, 20.5

Abbreviations: Max, maximum; Min, minimum; mITT, modified intent to treat; N, number of patients; Q, quartile; SD, standard deviation.

run-in is unusual in this indication and has not been used in clinical studies of the standard of care therapies, *post hoc* efficacy analyses were undertaken to allow the comparison of key outcomes with published data. Most of the published data use a treatment-free week (and not an SB placebo run-in week) as baseline for the analysis of the primary endpoint. The WO week in this study was a treatment-free week and a true washout for only 29% of patients. For these patients a 1 week WO was too short to ensure a complete WO for all possible treatments, however, if any pre-existing treatment was still partially effective, this would have lowered the baseline pain, thus making it more difficult to show an effect. These analyses were appropriate as no further patient selection was performed during or after the SB-placebo run-in week. Based on these considerations the *post hoc* endpoint for the change from the WO week BL to week 3 in weekly mean of daily average NRS was completed.

Additional *post hoc* analyses were performed on the responder rate; that is, patients who had at least a 30% or 50% decrease from BL (either the SB-placebo week or

the WO week) in the weekly mean of average pain intensity. The NNT for a 30% and a 50% decrease from the SB-placebo week BL and from the WO week were provided for each NRD.E1 treatment group. These thresholds were selected in line with the preference of the American Diabetes Association and Food and Drug Administration (Pop-Busui et al., 2017) and the Special Interest Group on Neuropathic Pain of the International Association for the Study of Pain (Finnerup et al., 2018).

The main and subgroup analyses of efficacy were performed on the mITT. In line with the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) on chronic pain trials (Dworkin et al., 2012), it is planned to improve assay sensitivity of the upcoming NRD.E1 clinical trials by enrolling PDPN patients who have at least an NRS score ≥ 5 at BL. Thus, further *post hoc* analyses produced outputs using the WO week as BLs for the sub-population of mITT patients who had confirmed moderate or severe (CMS) pain at the respective BLs, that is, an NRS score ≥ 5 at screening (or, if taking medication for neuropathic pain, an NRS score ≥ 4 at screening) and an NRS score ≥ 5 for the WO week.

TABLE 2 Summary of the mean (95% CI) changes from the WO week and from the SB-placebo baseline week to week 3 in the weekly mean of daily average pain intensity as measured on the NRS – mITT and CMS sets

	Placebo N = 21	NRD.E1 10 mg N = 22	NRD.E1 40 mg N = 22	NRD.E1 150 mg N = 21
mITT (n = 86), n	21	22	22	21
SB-placebo week BL	5.21 (4.27, 6.14)	4.36 (3.68, 5.05)	4.32 (3.49, 5.15)	4.44 (3.75, 5.13)
Chg from SB-placebo week BL	0.16 (−0.67, 0.35)	−0.58 (−1.56, 0.40)	−0.98 (−1.57, −0.39)	−0.82 (−1.32, −0.32)
Treatment effect	—	−0.42 (−1.50, 0.66)	−0.82 (−1.58, −0.07)	−0.66 (−1.35, 0.03)
p-value <i>t</i> -test*	—	0.4377	0.0339	0.0609
Standardized effect size		−0.24 (−0.86, 0.38)	−0.67 (−1.29, −0.05)	−0.60 (−1.22, 0.03)
WO week BL	5.93 (5.27, 6.59)	5.19 (4.70, 5.68)	5.68 (5.02, 6.34)	5.70 (5.17, 6.23)
Chg from WO week BL	−0.89 (−1.64, −0.13)	−1.41 (−2.42, −0.40)	−2.35 (−3.31, −1.38)	−2.08 (−2.92, −1.25)
Treatment effect	—	−0.52 (−1.76, 0.71)	−1.46 (−2.66, −0.26)	−1.20 (−2.29, −0.10)
p-value <i>t</i> -test*	—	0.3969	0.0181	0.0329
Standardized effect size		−0.26 (−0.88, 0.35)	−0.75 (−1.37, −0.14)	−0.68 (−1.31, −0.06)
CMS (n = 56), n	15	12	13	16
WO week BL	6.59 (5.97, 7.22)	5.96 (5.39, 6.54)	6.52 (5.68, 7.35)	6.12 (5.60, 6.64)
Chg from WO week BL	−0.46 (−1.37, 0.44)	−2.15 (−3.67, −0.63)	−3.13 (−4.45, −1.81)	−2.25 (−3.26, −1.24)
Treatment effect	—	−1.69 (−3.29, −0.09)	−2.66 (−4.15, −1.18)	−1.78 (−3.09, −0.48)
p-value <i>t</i> -test*	—	0.0393	0.0011	0.0091
Standardized effect size		−0.84 (−1.64, −0.04)	−1.40 (−2.18, −0.62)	−1.00 (−1.74, −0.27)

Note. Values are the number of patients and mean (95% CI). Missing values were substituted using LOCF.

Abbreviations: BL, baseline; Chg, change; CI, confidence interval; CMS, confirmed moderate or severe (pain); LOCF, last observation carried forward; mITT, modified intent-to-treat; N, number of patients; NRS, numerical rating scale; SB, single-blind; WO, washout.

*p-values are not corrected for multiplicity.

Most secondary and exploratory endpoints were analysed in the same manner as the primary endpoint (e.g. SF-MPQ scores without imputation for missing values, as only a single post-BL assessment was available). The CGIC and PGIC data were summarized by category and study group). For the maximum pain, WO week and SB-placebo week baseline were available. For all other endpoints, only SB-placebo (week) was collected.

Safety and tolerability data were analysed on the DB safety analysis set (patients who started DB and had at least one safety assessment thereafter) and summarized in a descriptive manner.

3 | RESULTS

3.1 | Patient disposition, demographics and disease baseline characteristics

A total of 113 patients with PDPN were screened and eligible patients underwent the 7-day treatment-free WO period, which acted as a real washout for the 25 patients who had been receiving any pain-relieving medication (antiepileptics, antidepressants and analgesics, including

NSAIDs, paracetamol and opioids). Eighty-eight patients were then randomized to one of the four dosing groups for the 4-week study medication period, comprising the 7-day SB-placebo run-in period and the 3-week DB dosing period (Figures 1 and 2). Two patients withdrew consent during the SB-placebo run-in period, and 86 patients received DB study medication (Figure 2).

Patients had a median age of 67 years (range 19.0–88.0 years), all patients were Caucasian, the majority were male (64.0%) and the median body mass index (BMI) was 29.9 kg/m² (range 19.3–44.8). The majority of patients had type 2 DM (91.9%), and the median time since diabetes and neuropathy diagnoses was 15.3 and 3.9 years, respectively (Table 1). The majority of patients (61 [69.3%]) were not under treatment for their neuropathic pain at enrolment. Those treated for their neuropathic pain were distributed 10/21 (47.5%), 5/22 (22.7%), 5/22 (22.7%) and 5/21 (23.8%) for placebo, 10 mg, 40 mg and 150 mg groups, respectively.

3.2 | Efficacy

In the mITT population (N = 86), placebo-corrected treatment effects indicated pain reduction in the weekly mean

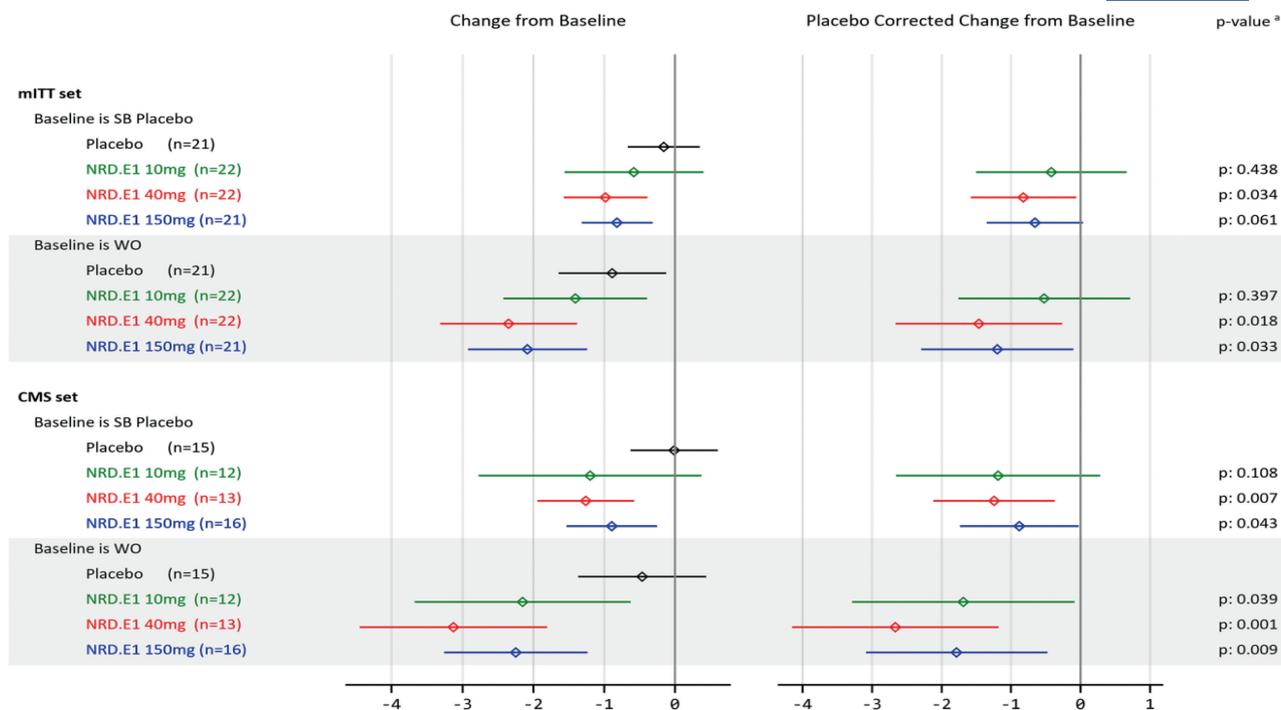


FIGURE 3 Change in weekly average NRS from SB-placebo and WO baselines to week 3 (Forest plot)—mITT and CMS sets. CMS, confirmed moderate or severe; mITT, modified intent to treat; NRS, numerical rating scale; SB, single-blind; WO, washout. ^aNumerical uncorrected *p*-value for difference from placebo.

of daily average pain intensity, from the SB-placebo run-in week to DB treatment week 3: -0.42 (95% CI: $-1.50, 0.66$; $p = 0.438$) NRS point for 10 mg, -0.82 (95% CI: $-1.58, -0.07$; $p = 0.034$) for 40 mg, and -0.66 (95% CI: $-1.35, 0.03$; $p = 0.061$) for 150 mg. These did not meet the pre-specified value of $p = 0.016$ required for the primary endpoint due to multiplicity (Table 2). Consistent with the higher weekly mean of daily average pain intensity reported for the WO week BL than the SB-placebo week BL (mostly due to the correction for the placebo effect), changes from the WO week to week 3 (placebo-corrected treatment effects) were greater than from the SB-placebo run-in week leading to a placebo-corrected treatment effect of -0.52 (95% CI: $-1.76, 0.71$), -1.46 (95% CI: $-2.66, -0.26$), and -1.20 (95% CI: $-2.29, -0.10$), respectively. For both the 40 and 150 mg treatment groups, the standardized effect size (SES) were -0.67 (95% CI: $-1.29, -0.05$) and -0.60 (95% CI: $-1.22, 0.03$), respectively, from SB week and -0.75 (95% CI: $-1.37, -0.14$) and -0.68 (95% CI: $-1.31, -0.06$), respectively, from WO week, that is, exceeding the -0.30 reduction which is considered of clinically relevant magnitude (Smith et al., 2020).

The IMMPACT initiative on chronic pain trials (Dworkin et al., 2012), recommends enrolling patients who have at least an NRS score ≥ 5 at baseline, to improve assay sensitivity of the clinical trials. Thus, further post hoc analyses were conducted on the CMS

subpopulation, using the WO periods as baseline. In the CMS population ($N = 56$), clinically relevant reductions in the weekly mean of daily average pain intensity were also seen from WO week to treatment week 3 in the placebo-corrected treatment effects for all three active treatment groups: -1.69 (95% CI: $-3.29, -0.09$), -2.66 (95% CI: $-4.15, -1.18$), and -1.78 (95% CI: $-3.09, -0.48$), respectively, corresponding to SES of -0.84 (95% CI: $-1.64, -0.04$), -1.40 (95% CI: $-2.18, -0.62$), and -1.00 (95% CI: $-1.74, -0.27$).

Baseline and week 3 average weekly pain intensity levels, treatment effects and SES for the mITT and CMS populations using both BLs, by treatment allocation, are presented in Table 2 and Figure 3.

To allow comparison of the results with historical/published data of other therapies, additional *post hoc* analyses were performed on the primary variable (e.g. subgroups, responder analysis, NNT) for the changes to week 3 from the WO week. Findings are summarized in Table 3. Sensitivity analyses were performed to confirm the results of the primary analyses (Figures S1–S8).

Responder rates (30% and 50% response) for both the mITT and CMS population using the WO week BL were higher in the NRD.E1 treatment groups compared to placebo. In the mITT population, NNT values for 30% response of 8.10 (95% CI: 2.46, -6.30), 2.85 (95% CI: 1.58, 13.92), 4.20 (95% CI: 1.90, -20.0) and for 50% response 12.15 (95% CI: 3.00, -5.94),

	Placebo	NRD.E1 10 mg	NRD.E1 40 mg	NRD.E1 150 mg
mITT, <i>n</i>	21	22	22	21
SB-placebo week BL				
30% decrease	3 (14%)	7 (32%)	11 (50%)	7 (33%)
50% decrease	1 (5%)	3 (14%)	5 (23%)	3 (14%)
NNT (95% CI)				
30% decrease		5.7 (2.4, -14.2)	2.8 (1.6, 10.0)	5.3 (2.3, -16.5)
50% decrease		11.3 (3.9, -12.3)	5.6 (2.7, -56.4)	10.5 (3.7, -12.5)
WO week BL				
30% decrease	6 (29%)	9 (41%)	14 (64%)	11 (52%)
50% decrease	4 (19%)	6 (27%)	10 (45%)	9 (43%)
NNT (95% CI)				
30% decrease		8.1 (2.5, -6.3)	2.9 (1.6, 13.9)	4.2 (1.9, -20.0)
50% decrease		12.2 (3.0, -5.9)	3.8 (1.9, -300.9)	4.2 (2.0, -31.2)
CMS, <i>n</i>	15	12	13	16
WO week BL				
30% decrease	3 (20%)	7 (58%)	10 (77%)	9 (56%)
50% decrease	1 (7%)	4 (33%)	7 (54%)	7 (44%)
NNT (95% CI)				
30% decrease		2.6 (1.4, 25.9)	1.8 (1.1, 3.8)	2.8 (1.5, 21.7)
50% decrease		3.8 (1.8, -35.2)	2.1 (1.3, 5.8)	2.7 (1.6, 10.3)

Note. When the CI spans over infinity, the upper limit is negative.

Abbreviations: %, responder rate; BL, baseline; CI, confidence interval; CMS, confirmed moderate or severe (pain); mITT, modified intent to treat, *n*, number of patients; NNT, number needed to treat; NRS, numerical rating scale; pts, patients; SB, single-blind; WO, washout.

3.78 (95% CI: 1.88, -301), 4.20 (95% CI: 1.96, -31.2) across the 10, 40 and 150 mg doses, respectively. In the CMS population NNT values for 30% response of 2.60 (95% CI: 1.37, 25.85), 1.75 (95% CI: 1.14, 3.79), 2.75 (95% CI: 1.47, 21.65) and for 50% response 3.75 (95% CI: 1.78, -35.2), 2.11 (95% CI: 1.29, 5.78), 2.69 (95% CI: 1.55, 10.31) across the 10, 40 and 150 mg doses, respectively (Table 3). Secondary and exploratory endpoints showed changes consistent with those seen with the primary endpoint. Overall, greater improvements compared to placebo were noted with the 40 and 150 mg doses of NRD.E1 for maximal NRS pain intensity (placebo corrected treatment effect from WO week BL -1.57 (-95% CI: 2.93, -0.20) and -1.34 (95% CI: -2.51, -0.17), respectively, and from SB-placebo week BL -0.84 (95% CI: -1.77, 0.10) and -0.49 (95% CI: -1.14, 0.16), respectively). Sleep interference (placebo corrected treatment effect from SB-placebo week BL was -0.48 (95% CI: -1.43, 0.47) and -0.94 (95% CI: -1.78, -0.09), respectively) and in the McGill questionnaire pain intensity as measured on Visual Analogue Scale (VAS) (mean treatment effect from start of SB-placebo visit -17.3 (95% CI: -29.2, -5.5) and -9.6 (95% CI: -19.0, -0.1), respectively) (Figures 4 and 5, and Tables S1-S3).

Only patients receiving NRDE1 reported “very much improved” and only patients receiving placebo reported “much

TABLE 3 Numbers of patients with 30% or 50% decrease from both the SB-placebo run-in and WO baselines to week 3 in the weekly mean of daily average pain intensity as measured on the NRS and NNT—mITT and CMS sets

worse” as global impression of change (PGIC). Both observations were reflected also in the assessment of global impression of change performed by the Clinician (CGIC) (Figure 6).

The data on mean rescue medication use were not interpretable, since a single outlying patient in the placebo group decreased his intake of paracetamol from 42 tablets/week during the SB-placebo run-in to 0 during weeks 2 and 3. No differences were observed in the median consumption of rescue medication among different arms. Moreover, due to the limited use of rescue medication medians and quartiles estimates do not allow a correct interpretation of these data.

3.3 | Safety

An overview of the incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), AEs leading to discontinuation of study treatment and deaths are provided in Table 4. During DB study treatment, TEAEs were reported for 12 (54.5% of patients), 11 (50.0%) and 9 (42.9%) patients on NRD.E1 10, 40 and 150 mg/day, respectively, and for 7 (33.3%) patients on placebo (Table 4).

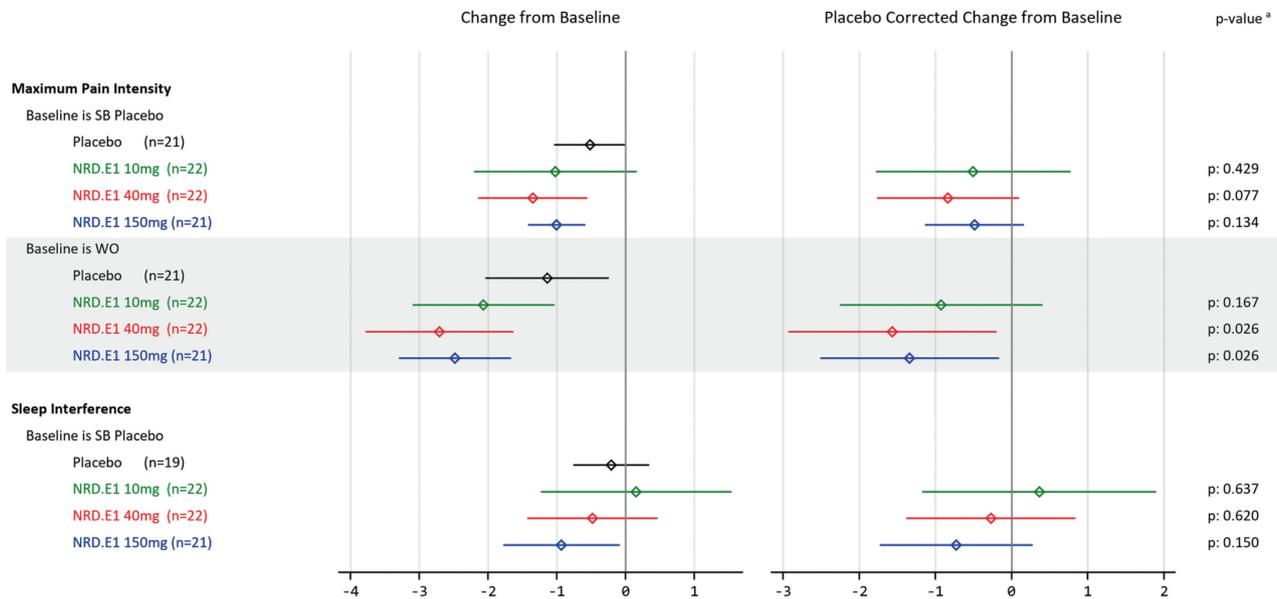
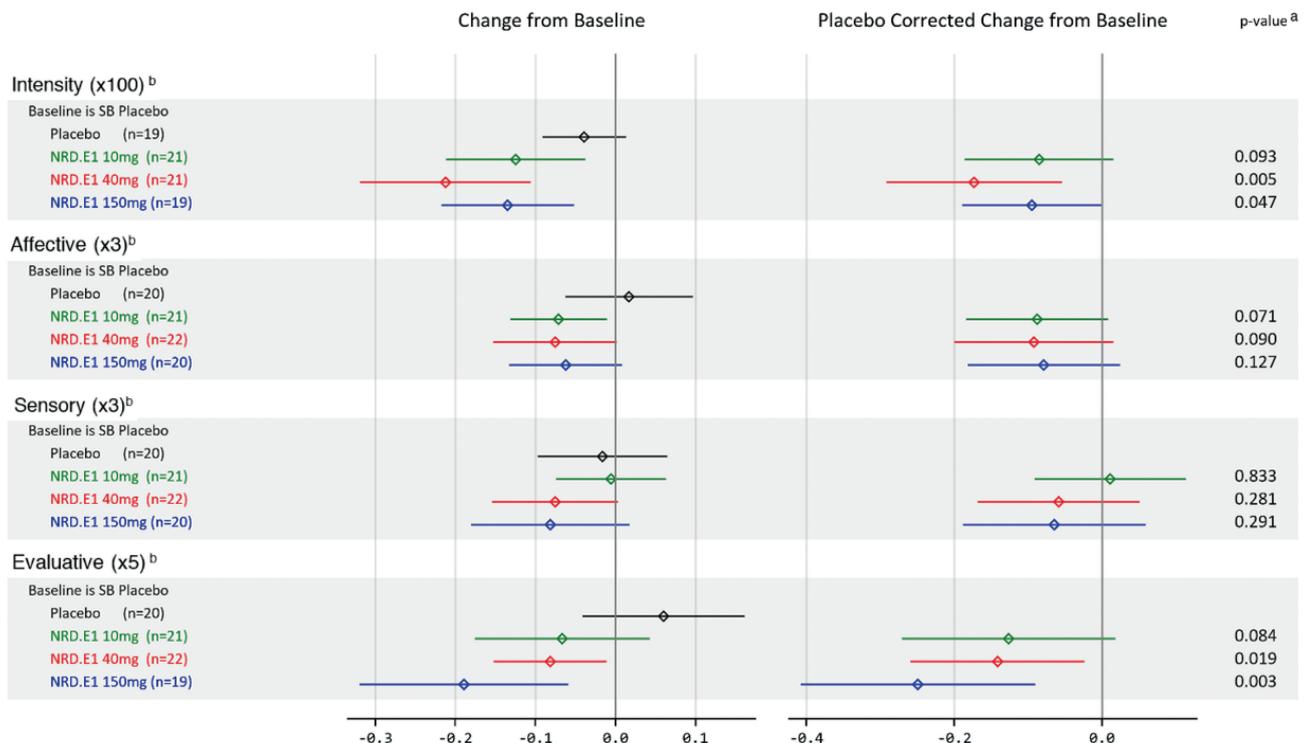


FIGURE 4 Maximum pain intensity and daily sleep interference scale from SB-placebo and WO baselines to week 3 (Forest plot)—mITT set. CMS, confirmed moderate or severe; mITT, modified intent to treat; n, number of patients; SB, single-blind; WO, washout.

^aNumerical uncorrected *p*-value for difference from placebo.



a. Numerical uncorrected *p*-value for difference from placebo

b. Scores are standardized to the scale's maximum

BL=baseline; CMS=confirmed moderate or severe; mITT=modified intent to treat; n=number of patients; WO=washout.

FIGURE 5 McGill questionnaire from SB-placebo to week 3 (Forest plot)—mITT set. Numerical uncorrected *p*-value for difference from placebo. Scores are standardized to the scale's maximum. mITT, modified intent to treat; n, number of patients; SB, single-blind.

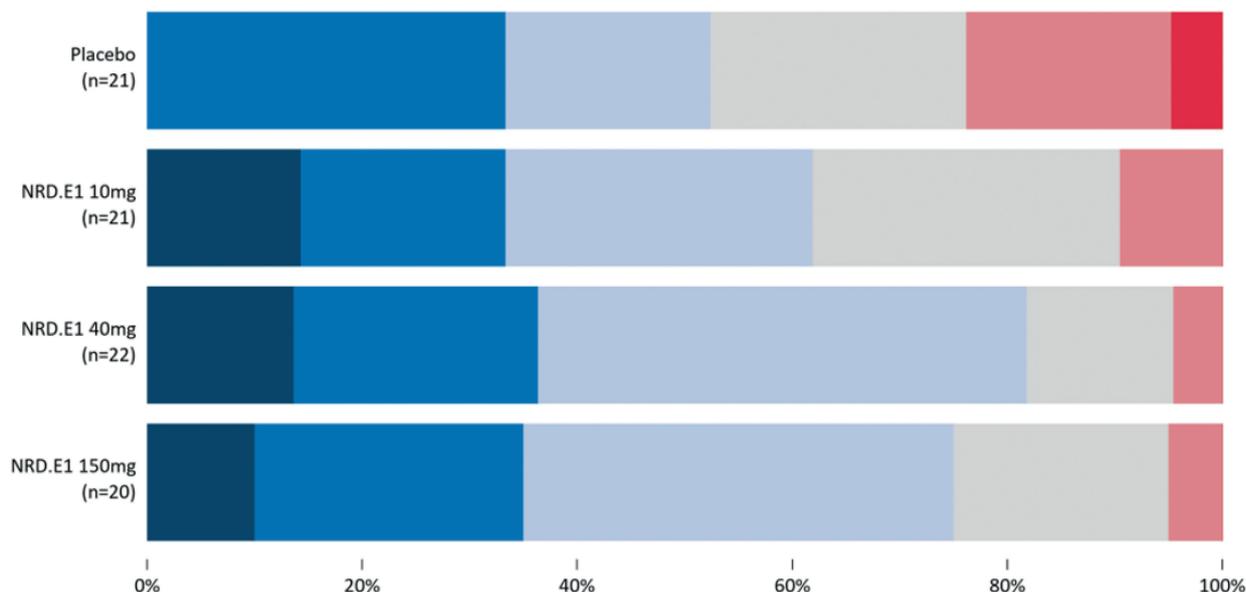
The differences between any NRD.E1 treatment group and placebo were mainly due to the incidence of headache, which was the only TEAE reported for more than

two patients on active treatment and as occurring more frequently on NRD.E1 than placebo (1/22, 3/22 and 4/21 patients on NRD.E1 10, 40 and 150 mg/day, respectively,

and 1/21 patient on placebo). Headache was the only TEAE considered treatment-related in more than one patient and appearing to be possibly related to the NRD.E1 dose level. Cough occurred in two patients on NRD.E1 150 mg/day and none on placebo, and all other events occurred in no more than a single patient per NRD.E1 group (Table 5).

Most of the TEAEs were mild, occurring in 8 (36.4%), 10 (45.5%) and 8 (38.1%) patients on NRD.E1 10, 40 and 150 mg/day, respectively, and 6 (28.6%) patients on placebo. Moderate TEAEs occurred in 5 (22.7%), 1 (4.5%) and 0 patients on NRD.E1 10, 40 and 150 mg/day, respectively, and 2 (9.5%) patients on placebo. No TEAEs were severe.

Patients' Global Impression



Clinicians' Global Impression

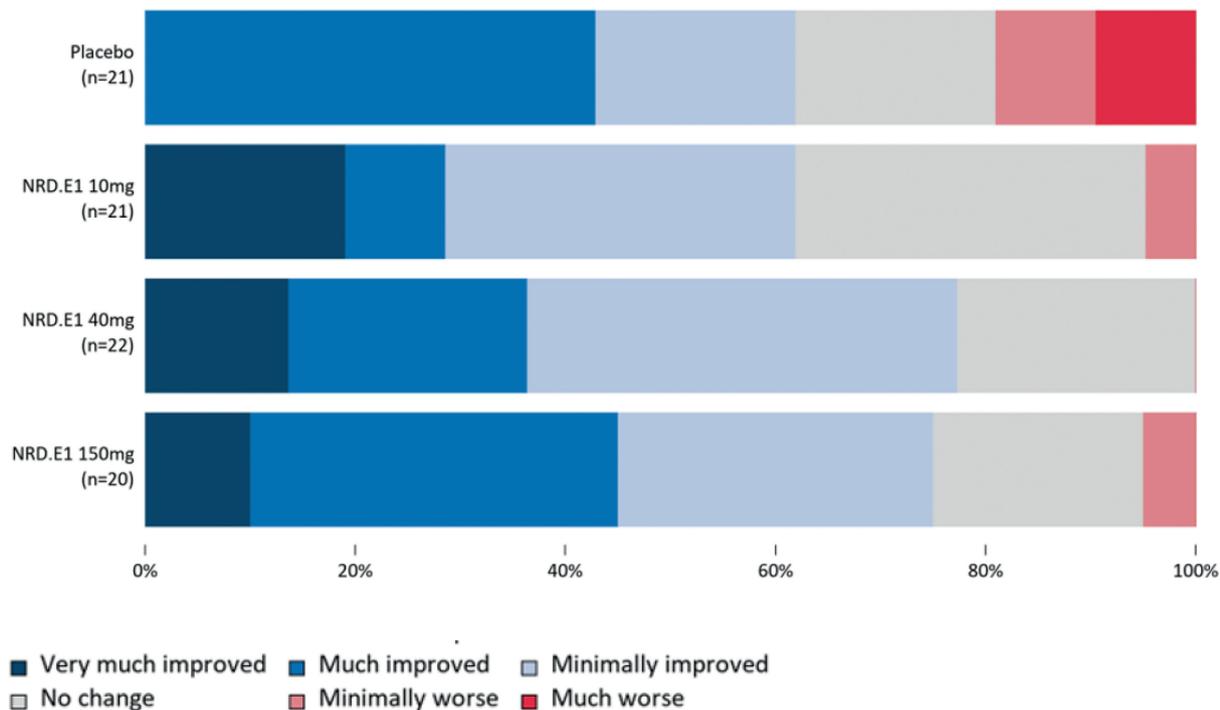


FIGURE 6 Patients' and clinicians' global impressions of change from SB-placebo to week 3—mITT set. mITT, modified intent to treat; n, number of patients; SB, single-blind.

TABLE 4 Summary of TEAEs during the DB treatment period—DB safety set

Evaluation, <i>n</i> (%)	Placebo, <i>n</i> (%) (<i>N</i> = 21)	NRD.E1 10 mg, <i>n</i> (%) (<i>N</i> = 22)	NRD.E1 40 mg, <i>n</i> (%) (<i>N</i> = 22)	NRD.E1 150 mg, <i>n</i> (%) (<i>N</i> = 21)	All NRD.E1, <i>n</i> (%) (<i>N</i> = 65)
Patients with TEAE	7 (33.3)	12 (54.5)	11 (50)	9 (42.9)	32 (49.2)
Patients with drug-related TEAE	1 (4.8)	2 (9.1)	1 (4.5)	3 (14.3)	6 (9.2)
Deaths	–	–	–	–	–
SAE	–	–	–	–	–
Patients with TEAE as primary reason leading to discontinuation	–	–	–	–	–
Patients with TEAE associated with discontinuation	1 (4.8)	–	1 (4.6)	2 (9.5)	3 (4.6)

Abbreviations: AE, adverse event; DB, double-blind; *N*, total number of patients; *n*, number of patients with events; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

No SAEs were reported during the DB study period and there were no marked laboratory abnormalities.

Of the 86 randomized patients who started the DB study period, six were prematurely discontinued. One patient (10 mg arm) was discontinued due to the use of a prohibited medication for pain due to a humeral fracture. One patient (10 mg arm) withdrew consent because his condition got worse. In the other four patients (1 after 11 days of placebo, 1 after 12 days of 40 mg and 2 after 7 and 16 days, respectively, of 150 mg) the reason for withdrawing consent was associated with TEAEs. However, in three of these, the associated TEAE was assessed as not related to the study drug by the investigator and was not assessed as directly leading to discontinuation.

One patient (NRD.E1 at 150 mg) experienced eight AEs of nausea (×2), eructation (×2), vomiting, diarrhoea, headache and dizziness (all of mild intensity), which began during the SB-placebo run-in and continued intermittently through the DB study period. Patient withdrew consent after 16 days of the DB study period and the AEs resolved during follow-up; five of these were assessed as being related to study treatment.

Mean and median changes from baseline in haematological, biochemical and urinary variables, as well as in vital signs, heart rate and PR, QRS and QT intervals were small, not clinically relevant and did not appear related to NRD1.E1 treatment. No patient had a >60 ms increase or an increase to >500 ms in QT interval at any time point during the study.

Overall, NRD.E1 was well tolerated at all doses tested over a period of 3 weeks.

4 | DISCUSSION

Management of PDPN remains an unmet medical need since two-thirds of patients requiring treatment do not see

worthwhile benefit from available therapies due to lack of efficacy or tolerability related mainly to acute CNS and GI adverse reactions.

This PoC study was conducted to provide the first efficacy data for NRD.E1 in the treatment of PDPN. Treatment with NRD.E1 40 and 150 mg daily for up to 3 weeks was associated with a clinically relevant placebo-corrected treatment effect from SB-placebo week BL of -0.82 (95% CI: $-1.58, -0.07$), and -0.66 (95% CI: $-1.35, 0.03$) NRS points, respectively. The analysis of the primary endpoint ($p = 0.034$) did not reach the prespecified $p = 0.016$, however, data from secondary endpoints showed consistent results. Furthermore, when looking at the *post hoc* endpoint for the change from WO week BL to week 3 in weekly mean of daily average NRS, to allow comparison of the study results with published data, the placebo-corrected treatment effect was 1.46 (95% CI: $-2.66, -0.26$), and 1.20 (95% CI: $-2.29, -0.10$) NRS points, respectively.

This study was underpowered, as it was powered on achieving an over-optimistic 3-point mean reduction in pain NRS score to allow a small independent pharmaceutical company to conduct a PoC study with very limited resources. In PoC studies, the primary evidence sought is to determine if there is an indication of a clinically relevant treatment effect across a range of parameters and is less focused upon reaching statistical significance with the primary endpoint. This thinking is in line with the American Statistical Association's 'Statement on p-Values: Context, Process and Purpose' (Wasserstein & Lazar, 2016) where this approach is viewed as appropriate for this kind of study.

NRD.E1 showed consistent effects with the primary findings across secondary endpoints based on NRS pain data (including 30% & 50% responder rate and NNT), maximum NRS, sleep interference, Short-form McGill pain questionnaire (especially pain intensity assessed on Visual Analogue Scale), PGIC and CGIC. The consistent efficacy data from this PoC study suggest that further studies on

TABLE 5 Summary of TEAEs occurring in at least two patients in at least one arm during DB treatment period, by frequency—DB safety set

Preferred term	Placebo (N = 21) n (%)		NRD.E1 10 mg (N = 22) n (%)		NRD.E1 40 mg (N = 22) n (%)		NRD.E1 150 mg (N = 21) n (%)		All NRD.E1 (N = 65) N (%)	
	All causality	Drug-related	All causality	Drug-related	All causality	Drug-related	All causality	Drug-related	All causality	Drug-related
All SOCs										
Total patients with at least one TEAE	7 (33)	1 (4.8)	12 (54.5)	2 (9.1)	11 (50.0)	1 (4.5)	9 (42.9)	3 (14.3)	32 (49.2)	6 (9.2)
Headache	1 (4.8)	1 (4.8)	1 (4.5)	-	3 (13.6)	-	4 (19)	3 (14.3)	8 (12.3)	3 (4.6)
Cough	-	-	-	-	-	-	2 (9.5)	-	2 (3.0)	-
Asthenia	3 (14.3)	1 (4.8)	-	-	1 (4.5)	-	-	-	1 (1.5)	-

Abbreviations: DB, double-blind; N, total number of patients; n, number of patients with events; SOC, system organ class; TEAE, treatment-emergent adverse event.

NRD.E1 might confirm the outcomes and enable the delivery of a much-needed therapeutic option to patients and the community.

The IMMPACT initiative on chronic pain trials (Dworkin et al., 2012), recommends enrolling patients who have at least an NRS score ≥ 5 at baseline, to improve assay sensitivity of the clinical trials. Thus, further post hoc analyses were conducted on the CMS subpopulation, using both the SB-placebo run-in and the WO periods as baseline.

In both the mITT and CMS populations, NRD.E1 produced pain reductions (weekly mean of daily average NRS) over a period of 3 weeks at doses of 40 and 150 mg/day that substantially exceed the suggested standardized effect size threshold for clinical relevance of -0.30 proposed by (Smith et al., 2020). In the CMS population, even the 10 mg dose induced a clinically relevant effect.

In the mITT, using the WO baseline, over 50% of patients receiving 40 or 150 mg/day achieved a pain reduction $>30\%$ (compared to 29% in the placebo arm) and over 40% achieved a pain reduction $>50\%$ (compared to 19% in the placebo arm). The NNT derived from these response rates for the 40 mg and 150 mg/day doses were estimated to be 2.85 and 4.20, respectively, for a 30% reduction and 3.78 and 4.20, respectively, for a 50% reduction. Such effects would compare favourably to the efficacy and NNT (based on 30% and 50% response in weekly average NRS) estimates of the best currently available pharmacological therapies like pregabalin 3.3–8.3; gabapentin 3.3–7.2; duloxetine 3.8–11; amitriptyline 2.1–4.2 or tramadol 3.1–6.4 (Pop-Busui et al., 2017).

In the CMS population, using the WO baseline, 56%–77% of patients receiving NRD.E1 achieved a pain reduction $>30\%$ (compared to 20% in the placebo arm) and 33%–54% achieved a pain reduction $>50\%$ (compared to 7% in the placebo arm).

Limitations of the study were the relatively modest (low moderate range) pain severity at baseline, as well as the relative lack of homogeneity in baseline pain severity data, with the placebo-treated group having a higher mean NRS score at SB-placebo baseline of 5.21 compared to the 4.36, 4.32 and 4.44 means in the 10, 40 and 150 mg NRD.E1 groups. Furthermore, the washout period of 1 week (which was a true washout for 29% of patients) was short for some of the previous pain medications used—however, the potential residual effect of the previous pain medication would have made the baseline pain lower. This would have made it more difficult to detect the treatment effect of NRD, as more patients in the placebo arm had taken previous pain medication than in the NRD arm (10/21 vs. 5/22, 5/22 and 5/21, respectively). For all of these limitations, sensitivity analyses including a mixed model for repeated measures and multiple imputation of

missing or biased data, with adjustment for baseline covariates including the baseline score, confirmed the results (see Supplemental Data).

It was noted that the NRS pain scores at the SB-placebo baseline for the placebo group were higher than those for the NR.D.E1 groups (by between 0.77 and 0.89), although that difference was smaller at the WO baseline (between 0.23 and 0.74). Nevertheless, the study still provided extremely robust and consistent findings across the range of parameters evaluated as illustrated by the SES from SB BL and from WO BL of -0.67 and 0.75 for 40mg, respectively, and -0.60 and -0.68 for 150mg, respectively. Sensitivity analyses using adjustment by the baseline values (both WO and SBP) in addition to other baseline covariates fully confirmed the outcome.

A further limitation is the short (3-week) treatment period, which was dictated by the preclinical safety data available at the time. However, after 3 weeks, the pain scores already showed a clinically relevant change, and the IMMPACT recommendations assert that although early response (e.g. at 4 weeks) is not a guarantee of sustained response, there have been few (if any) examples of such analgesic effects being transitory (Gewandter et al., 2014).

The compound was well tolerated at all doses, with no indication of the acute adverse effects in the CNS (such as somnolence, dizziness, light-headedness) and GI tract (such as nausea, vomiting and constipation) that frequently limit the utility of established therapies. However, the relatively short duration of the study must be recognized as a limitation of the study with respect to both longer-term tolerability and efficacy findings.

In conclusion, the available clinical data suggest that NR.D.E1 is a potential, novel, non-opioid therapeutic option for patients with PDPN, with at least similar efficacy and better tolerability than available therapies. The study provides a clear indication that the product has potential in the management of PDPN and possibly other chronic pain indications and warrants further evaluation in larger-scale confirmatory studies.

AUTHOR CONTRIBUTIONS

Novaremed were accountable for all aspects of the work including financial support, conception and design. All authors reviewed and discussed the results, commented on the manuscript and approved the final version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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CONFLICT OF INTEREST

Eva Tiecke (corresponding author), Sara Mangialaio, Maurizio Rainisio, Eli Kaplan, Liat Hochman and Michal Silverberg are current or former employees of Novaremed. Elon Eisenberg discloses advisory board activity for Novaremed. Julio Wainstein received consultancy fees from Novaremed.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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