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Novaremed announces publication of Phase 1 and Phase 2a study data with NRD.E1 demonstrating the potential of this investigational non-opioid pain treatment

- *Three Phase 1 studies displayed favorable pharmacokinetics and good tolerability of NRD.E1 after oral administration*
- *The Phase 2a, proof of concept study demonstrated clinically meaningful reductions in pain across primary and secondary endpoints and a benign side effect profile*
- *In summary, data from these 4 studies now published demonstrate the potential of NRD.E1 as an innovative non-opioid treatment option for patients with painful diabetic peripheral neuropathy (PDPN)*
- *Based on available data, the National Institutes of Health (NIH) in the US has selected and included NRD.E1 to the NIH-HEAL Initiative® under which the NIH sponsors and executes a Phase 2b trial with study recruitment starting in 3Q 2022*

Basel, Switzerland, June 23, 2022 – Novaremed AG, a privately held clinical-stage biopharmaceutical company focused on innovative non-opioid treatment options for chronic pain management announces the simultaneous publication of data from three Phase 1 studies in *Clinical Pharmacology in Drug Development* and one Phase 2a, placebo-controlled, dose-finding, proof of concept study in *European Journal of Pain* with the Company's lead investigational drug candidate NRD.E1, an innovative non-opioid therapy for painful diabetic peripheral neuropathy.

"We are delighted with the publication of our Phase 1 and Phase 2a studies which collectively demonstrate the drug candidate's potential as an innovative non-opioid treatment option for patients with chronic pain," said **Eva Tiecke, PhD, Chief Scientific Officer and Head of R&D of Novaremed** and lead author of both publications. "In the Phase 2a proof of concept study, the primary endpoint showed a clinically relevant placebo-corrected treatment effect in pain reductions at 40 and 150 mg/day of 0.82 Numerical Rating Scale points, p = 0.034 and 0.66, p= 0.061, respectively, though it narrowly missed the pre-specified value of p = 0.016 due to multiplicity. Overall, the study showed robust results given the consistent performance across multiple endpoints. Based on the data now published in peer-reviewed journals, we are encouraged about the potential of NRD.E1 to address the high unmet medical need for a non-opioid agent to treat chronic pain."

In three Phase 1 studies NRD.E1 was well tolerated as single dose up to 1200 mg and repeated doses of 300 mg/day for five consecutive days. The studies revealed dose-dependent absorption, small increased exposure to NRD.E1 at peak when administered with food and no relevant accumulation after oral administration. The Phase 2a study was a randomized, double-blind, placebo-controlled, dose-finding, proof-of-concept study in 88 patients with PDPN. The study investigated NRD.E1 at 10, 40, or 150 mg/day or placebo over a 3-week treatment period. Primary, pre-specified secondary and post-hoc secondary endpoints analyses consistently demonstrate a clinically meaningful reduction in pain. NRD.E1 was safe and well tolerated.

References:

[1] Tiecke E., Rainisio M., Guentert T., Müller S., Hochman L., Kaplan E., Mangialaio S. (2022). First-in-human single-ascending-dose, multiple-dose and food interaction studies of NRD.E1, an innovative non-opioid therapy for painful diabetic peripheral neuropathy. *Clinical Pharmacology in Drug Development (CPDD)* (https://accp1.onlinelibrary.wiley.com/doi/10.1002/cpdd.1103).

[2] Tiecke E., Rainisio M., Eisenberg E., Wainstein J., Kaplan E., Silverberg M., Hochman L., Mangialaio S. (2022) NRD.E1, an innovative non-opioid therapy for painful diabetic peripheral neuropathy – a randomized proof of concept study. *European Journal of Pain* (https://onlinelibrary.wiley.com/doi/10.1002/ejp.1989).

About the Phase 1 program with NRD.E1

The publication in *Clinical Pharmacology in Drug Development* reports the results of three Phase 1 studies with NRD.E1. The first study was a first-in-human, randomized, placebo-controlled single-ascending-dose study, where NRD.E1 was administered to healthy male subjects in single dosages ranging from 300 mg to 1200 mg. The second study was a randomized, placebo-controlled multiple-dose study, where healthy male subjects received 300 mg of NRD.E1 once daily (o.d.) for five consecutive days. The third study was an open-label food interaction study in healthy men and women following a cross-over design, where NRD.E1 was administered under fed and fasted conditions at 40 mg. The studies revealed dose-dependent absorption, slight increased exposure to NRD.E1 at peak when administered with food and no relevant accumulation after o.d. multiple administration. All three Phase 1 studies consistently showed rapid absorption of orally administered NRD.E1 followed by fast elimination, mainly via metabolization (glucuronidation), and small secondary increases in plasma concentrations. NRD.E1 was well tolerated, with no subject discontinuation due to treatment-emergent adverse events in any study.

About the Phase 2a study with NRD.E1 in patients with painful diabetic peripheral neuropathy (PDPN)

The Phase 2a study now published in the *European Journal of Pain* was a randomized, dose-finding, proof-of-concept study in patients with PDPN of ≥3 months duration. After at least one treatment-free week (the wash-out [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.

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 in pain reductions at 40 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 analysis assessing the change from WO baseline to Week 3 in weekly mean of daily average NRS for pain intensity showed placebo-corrected treatment effects of 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 and 50% responder rates and numbers needed to treat (NNT)), sleep interference, Short-form McGill pain questionnaire (specially pain intensity assessed on Visual Analog Scale), and 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 2 patients and more frequently on NRD.E1 than placebo.

About peripheral neuropathy and associated neuropathic pain

Peripheral nerve injury from various etiologies may ultimately result in chronic and severe intractable neuropathic pain. Painful diabetic peripheral neuropathy (PDPN) and chemotherapy-induced peripheral neuropathy (CIPN) are frequent complications of diabetes and cancer treatment and represent the most common forms of neuropathic pain with a high unmet medical need. Worldwide, two-thirds or an estimated 8.1 million diabetes patients with PDPN requiring treatment do not obtain substantial pain relief with current therapies. Currently, over 80% or about 3.1 million cancer patients receiving neurotoxic chemotherapy develop CIPN, which is a leading cause for therapy reduction and/or discontinuation, as well as having a significant impact on patients' quality of life. Many of the currently available products for the treatment of chronic neuropathic pain have limited efficacy and are often not well tolerated. The increasing prevalence of diabetes and cancer as well as the limitations of the available therapies make the prevention and treatment of chronic neuropathic pain a condition of high unmet medical need.

About NRD.E1 and the treatment of chronic pain

NRD.E1, an orally active small molecule with a novel mechanism of action and patent protection until 2040, is Novaremed's lead compound currently being developed to treat PDPN.

On the basis of the results now published, NRD.E1 was selected by the NIH as the only oral agent to be included in the NIH-HEAL (Help End Long-term Addiction) program. The NIH will sponsor and execute by the and conducted by EPPIC-Net (Early Phase Pain Investigation Clinical Network) a 12-week, double-blind, placebo-controlled Phase 2b study in patients with moderate to severe PDPN in the US. Novaremed has an open IND and received Fast Track Designation from the FDA for NRD.E1.

About NIH, NIH-HEAL and EPPIC-Net

The US National Institutes of Health (NIH), the largest biomedical research agency in the world, has established the *NIH HEAL Initiative®* to address the opioid crisis. HEAL programs include those focused on identifying, developing, and testing new non-addictive pain therapies. The *EPPIC-Net (Early Phase Pain Investigation Clinical Network)* is part of the NIH HEAL Initiative and seeks to enhance the treatment of acute and chronic pain and reduce reliance on opioids by accelerating early-phase clinical trials of non-addictive treatments for pain. For more information: https://heal.nih.gov

About Novaremed

Novaremed AG, a privately held clinical-stage biopharmaceutical company, is developing a pipeline of innovative medications for chronic pain management to address the high unmet medical need for better pain relief and as an alternative to opioids. Its lead product is NRD.E1, an orally active non-opioid small molecule with a novel mechanism of action, has FDA Fast Track Designation and IND-approval to proceed with a Phase 2b clinical trial for the treatment of painful diabetic peripheral neuropathy (PDPN). The earlier stage pipeline addressing chronic pain includes the development candidates MP-101 (early clinical development stage), and MP-103 (preclinical stage), targeting the unmet medical need of prevention and treatment of chemotherapy-induced peripheral neuropathy (CIPN).

Novaremed Ltd (Israel) and Metys Pharmaceuticals AG (Switzerland) are fully owned subsidiaries of Novaremed AG, domiciled in Basel (Switzerland). For more information: www.novaremed.com.

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