Novaremed is developing NRD.E1, an innovative non-opioid therapy for Diabetic Neuropathic Pain

Results from a proof of concept study

Abstract ID 825910

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Background

Diabetic Neuropathic Pain (DNP) is chronic pain caused by diabetes-induced damage to the nerves. More than 15 million patients experience a DNP that requires treatment and substantially impairs their quality of life[1].

Existing treatments for DNP have strong limitations:

- First line therapy (pregabalin, gabapentin, duloxetine and TCA) control the disease in not more than 30% of the patients[2] either because of lack of efficacy or lack of tolerability.
- Treatment with opioids is often associated with major safety concerns (abuse, physical dependence, respiratory and CNS depression).

NRD135S.E1 (NRD.E1)

- New Chemical Entity, small orally available molecule.
- Mechanism of action different to that of approved pain therapies†.
- Working hypothesis: NRD.E1 is a Lyn kinase modulator.
- Efficacious in several pre-clinical models for acute or chronic pain.
- Very good tolerability/safety profile in 13 week toxicology studies (rats and dogs).

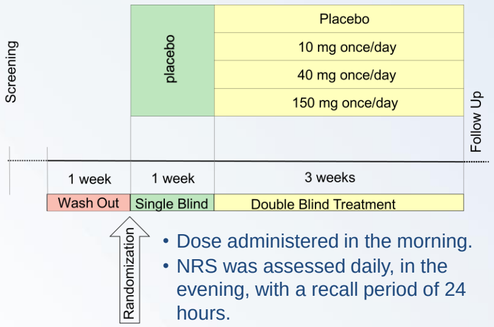
NRD.E1 was assessed in a Proof of Concept study in patients with Diabetic Neuropathic Pain.

Methods

Patient population: moderate and severe DNP at screening (i.e. patients who reported pain intensity of 4-9 on Numerical Rating Scale (NRS; single 11-point numeric scale).

Study design: randomized, double-blind, placebo-controlled dose-finding trial of 3-week duration.

Figure 1 Study Design



- Dose administered in the morning.
- NRS was assessed daily, in the evening, with a recall period of 24 hours.

†no inhibition of binding or enzyme activity at any existing therapeutic target for pain, including opioid, proteins related to serotonin and noradrenalin reuptake, GABA receptor function, NMDA receptor functions, P2X receptors and other neurotransmitters, voltage gated ion channels (Ca2+ and K+, Na+), transient receptor potential channels (e.g., TRPA1-ankirin ion channels), receptors for acetylcholine (M1), dopamine and cannabinoids.

Endpoints

1. Change from baseline to week 3 in weekly average of daily pain intensity measured by NRS.
2. Responders rate on weekly average of daily NRS (30% and 50% reduction from baseline to Week 3).

N.B: two baselines were used: Single Blind Placebo Run-in week (endpoint 1 was the primary endpoint) and Wash-out week (analysis used by all competitors in the past).

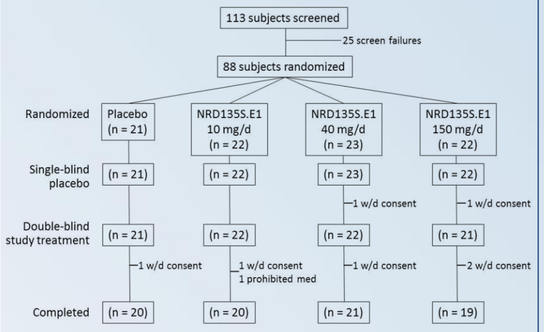
Analysis sets

a. Modified Intent-To-Treat set (mITT) i.e. all patients who received at least one dose of study drug in double blind and had at least one NRS assessment (primary analysis).
b. patients with confirmed moderate/severe DNP, i.e. patients who had an NRS at Screening either ≥ 5 or (≥ 4 and receiving pain medications) AND NRS at Washout ≥ 5.

Results

88 patients were enrolled into the study in 10 centers in Israel.

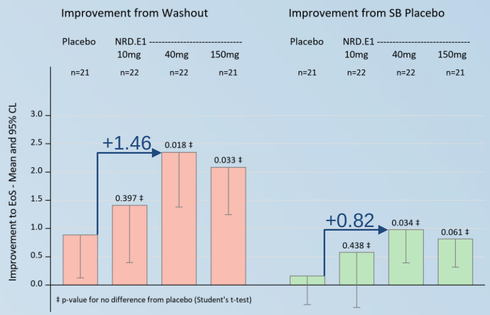
Figure 2. Patient Disposition



Efficacy Summary

Figure 3. Change from Washout and SB Placebo Week to EoS in Weekly Average NRS

a) mITT Set



b) Confirmed Moderate/Severe Pain

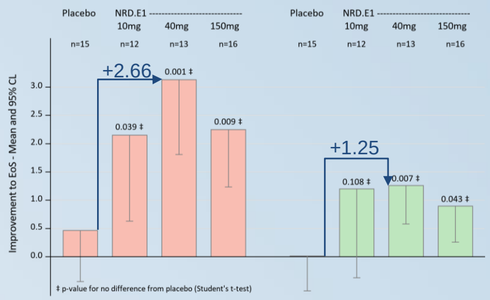
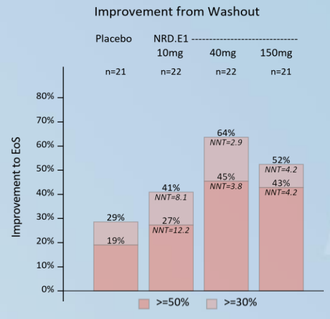
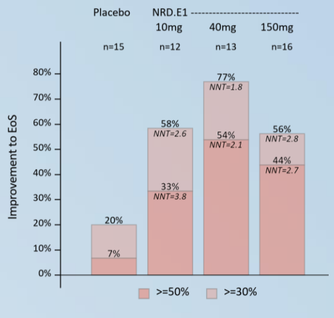


Figure 4. Responder Rate and NNT§ in Change to W3 in Weekly Average NRS

a) mITT Set



b) Confirmed Moderate/Severe Pain



§ *Number Needed to Treat* (NNT) is the number of patients that need to be treated to obtain one more success than with placebo. It is a common way to communicate the effectiveness of a treatment.

Safety Summary

No deaths and no serious adverse events during DB treatment.

No severe AEs.

No dose-relation.

4 premature discontinuations due to AE.

- All these AEs resolved and only in one subject they were considered drug-related by the investigator

Laboratory tests, vital signs, body temperature, ECG variables and physical examination: no safety signal identified.

Table 1: ***Drug Related Adverse Events (DRAEs) during Double Blind Treatment Period***

	Placebo	NRD.E1		
	N=21	10mg N=22	40mg N=22	150mg N=21
Pts with at least one AE	7	12	11	9
Pts with at least one DRAE	1	2	1	3
DRAE occurring in more than one* patient on NRD.E1				
Headache	1			3

*DRAE occurring in single patient receiving NRD.E1 (and not in placebo) included in 10 mg: Blood TG Increase and Ventricular Extrasystoles; in 40 mg: Blood LDH Increase; in 150 mg Dizziness, Eructation, Nausea and Vomiting

NRD135S.E1 Efficacy Similar to or Better than Approved Therapies *(including opioids)*

Figure 5: Placebo corrected improvement on NRS[34]

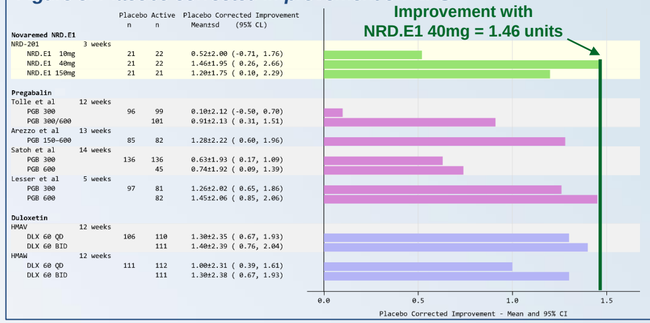
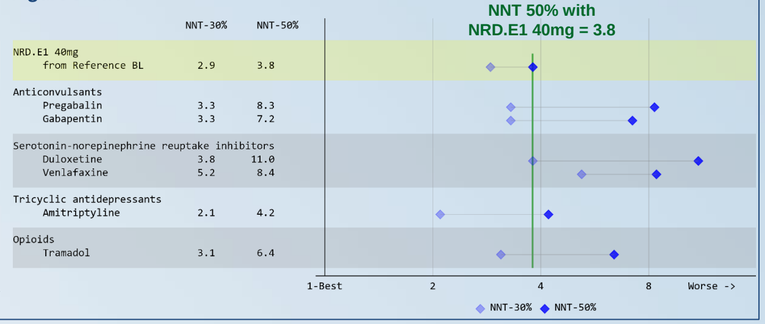


Figure 6: NNT [567]



Conclusions

- NRD.E1 was efficacious and well tolerated:
  - Clinically relevant reduction in DNP after 3 weeks of treatment with 40 and 150 mg.
  - Well tolerated over 3 weeks at all tested doses up to 150 mg/day.
- NRD.E1 is anticipated to be an innovative therapy for diabetic neuropathic pain.
- NRD. E1 will be further evaluated in Phase 2 trial of 3 months duration.
  - Minimal safety margin with selected dose is 190- fold.
- IND opened by FDA since June 2020.

References

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Disclosures

Sara Mangialaio (corresponding author) , Maurizio Rainisio, Eli Kaplan, Liat Hochman, Michal Silverberg and Eva Tiecke are employees or consultants of Novaremed. Elon Eisenberg discloses advisory board activity for Novaremed.

Source of Financial Support for the Project

Since its inception in 2008, Novaremed AG has been financially supported by angel investors and non-dilutive grant funding. To date, Novaremed has raised CHF23.6 M from these sources.

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