Phase II Randomized, Double-Blind, Parallel Group, Dose-Ranging, Placebo-Controlled Study to Assess the Safety and Efficacy of NB-01 (DA-9801) for Diabetic Neuropathic Pain

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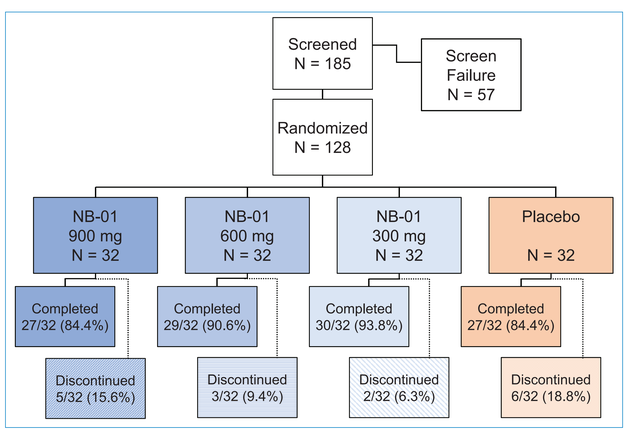
Background and Aims

Painful diabetic neuropathy affects up to 30% of individuals with diabetes. Despite the availability of approved medications to treat the pain, many patients experience inadequate pain relief, troublesome side-effects or both. NB-01 (previously known as DA-9801) is composed of extracts of 2 botanical raw materials: Dioscorea Rhizome (DR) and Dioscoreae Nipponicae Rhizoma (DNR) in a ratio of 3.5:1. In preclinical studies, this combination of DR and DNR in NB-01 increases the levels of NGF, decreases advanced glycation end-products, and decreases inflammatory markers including TNFα and IL-6. These changes may prevent nerve cell death, promote nerve regeneration, and result in reduced pain associated with diabetic neuropathy. NB-01 was well tolerated in a Phase 2a safety study conducted in Korea. The primary objective of this second Phase 2 study was to evaluate the efficacy of NB-01 in reducing pain in DPN. The secondary objective was to assess safety and tolerability of NB-01 in DPN.

Methods

This multicenter, randomized, double-blind, dose-ranging, placebo-controlled, safety and efficacy study was conducted in 16 sites in the USA. 185 subjects were screened for this study. 128 subjects who had provided informed consent were enrolled. Eligible subjects were randomized to treatment with NB-01 100 mg, 200 mg, 300 mg or placebo, all taken TID before meals for 12 weeks, for a total daily dose of 300 mg, 600 mg or 900 mg, respectively (32 per treatment group).

Figure 1. Subject Disposition



Methods (continued)

Key Inclusion / Exclusion Criteria

Inclusion:

- Men and women aged 18-75
- Type I or II diabetes with HbA1c ≤ 12%
- Diabetic neuropathic pain in the lower extremities for at least 3 months
- Score ≥ 4 on the pain diagnostic questionnaire Douleur Neuropathique 4 Questions (NP4)
- Pain score ≥4 on the 11-point numerical rating scale (NRS) after a 2-week wash-out of pain medications

Exclusion:

- Neuropathic pain caused by a condition other than diabetes
- BMI ≥ 37 kg/m^2

Study Endpoints

Primary Endpoint:

- Improvement from Baseline in the 11-point pain NRS (clinic visit pain score)

Secondary Endpoints:

- Proportion of subjects with at least 30% improvement in the pain NRS
- Proportion of responders in the Patient Global Impression of Improvement (PGI-I)
- Average weekly rescue medication use

Table 1. Baseline Pain Score

Parameter	Statistic	NB-01 900 mg n=32	NB-01 600 mg n=32	NB-01 300 mg n=32	Placebo n=32
NRS Score	n	32	32	32	32
	Mean (SD)	6.5 (1.54)	6.6 (1.54)	6.6 (1.43)	6.2 (1.93)
	Median	6.5	7.0	7.0	6.0
	Min - Max	4.0 – 10.0	4.0 – 10.0	4.0 – 10.0	3.0 – 10.0

Table 2. Baseline NP4 Score

Parameter	Statistic	NB-01 900 mg n=32	NB-01 600 mg n=32	NB-01 300 mg n=32	Placebo n=32	Total n=128
Total Neuropathic Pain Score	n	32	32	32	32	128
	Mean (SD)	7.3 (1.4)	7.0 (1.4)	7.3 (1.4)	7.0 (1.0)	7.1 (1.3)
	Median	7.5	7.0	7.5	7.0	7.0
	Min - Max	4.0 – 9.0	5.0 – 9.0	4.0 – 10.0	5.0 – 9.0	4.0 – 10.0

Results

Clinically meaningful and statistically significant reductions were observed in the primary endpoint (improvement in clinic visit pain score of the 0-10 pain NRS) in the 300 mg and 600 mg daily dose groups. Reduction from baseline was 2.7, 3.1, 3.2 and 2.2 in the 900 mg , 600 mg , 300 mg and placebo groups, respectively.

Secondary endpoints (% change from baseline, 30% responder rate, global impression of improvement) were consistent with the primary endpoint.

NB-01 was well tolerated with an incidence of AEs in active treatment groups similar to that in the placebo group. There were no SAEs related to study treatment (2 SAEs were not related).

Figure 2. Improvement in Clinic Visit Pain Score Significant for 600 mg and 300 mg Daily Dose

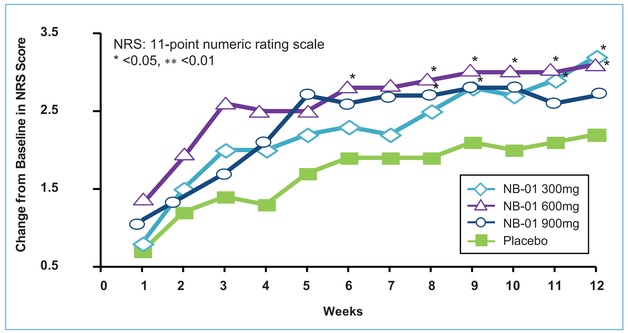


Table 3. Responders (30% and 50% improvement in Clinic Visit Pain Score)

	DA-9801 300 mg (N=32)	DA-9801 600 mg (N=32)	DA-9801 900 mg (N=32)	Placebo (N=32)
30% Responders/Total (%) at Week 12	20/30 (66.7%)	21/31 (67.7%)	16/28 (57.1%)	16/29 (55.2%)
50% Responders/Total (%) at Week 12	15/30 (50.0%)	16/31 (51.6%)	13/28 (46.4%)	11/29 (37.9%)

Table 4. Incidence of Adverse Events Similar to Placebo

	NB-01						Placebo	
	900mg (N=32)		600mg (N=32)		300mg (N=32)		(N=32)	
	Subjects N (%)	AE Number	Subjects N (%)	AE Number	Subjects N (%)	AE Number	Subjects N (%)	AE Number
Any AE	21 (65.6)	43	18 (56.3)	58	22 (68.8)	47	19 (59.4)	46
Severe AE	2 (6.3)	3	2 (6.3)	4	2 (6.3)	2	4 (12.5)	4
Related AE	6 (18.8)	11	4 (12.5)	12	9 (28.1)	13	7 (21.9)	14
Serious AE (SAE)	0 (0.0)	0	2 (6.3)	2*	0 (0.0)	0	3 (9.4)	3

* not related

Incidence of AEs was similar to placebo. Most of the AEs were mild to moderate and not related to treatment.
The most common AEs were infections not related to study treatment

Conclusions

- Treatment with NB-01 for 12 weeks provided statistically significant and clinically meaningful improvement in pain scores
- NB-01 was well tolerated with an incidence of mostly mild to moderate adverse events that was similar to placebo

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