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NVG-291 Phase 1 Results and Phase 2 Study Design in Individuals with Relapsing-remitting Multiple Sclerosis

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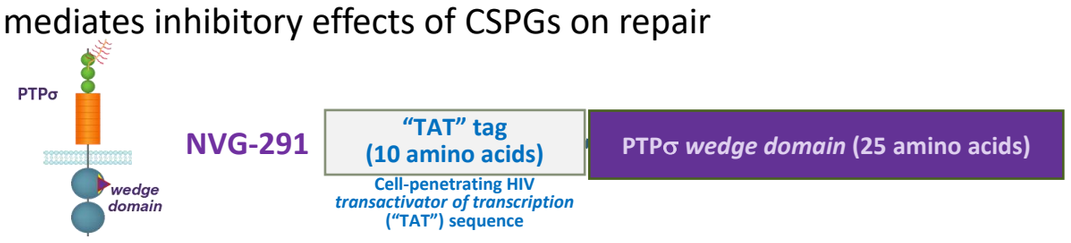
Background

- Chondroitin sulfate proteoglycans (**CSPGs**) accumulate at sites of CNS damage (including MS lesions); acutely, CSPGs "wall off" injury; later, CSPGs inhibit neural repair
- Protein tyrosine phosphatase sigma (**PTPσ**) is a CSPG receptor that mediates inhibitory effects of CSPGs on repair

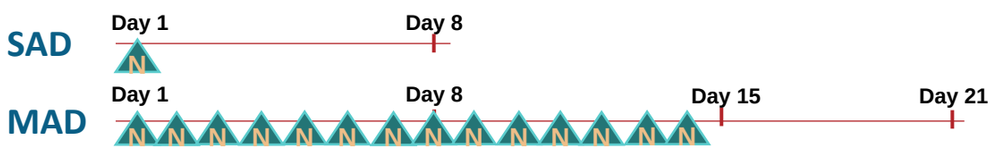


- **NVG-291**, a subcutaneously (SC) administered peptide mimetic of the wedge domain of PTPσ, promotes neural repair in several animal models of nervous system damage (e.g. EAE, lysolecithin)
  - Evidence of enhanced remyelination, oligodendrocyte precursor migration/differentiation, axonal regeneration and neuroplasticity
- **Hypothesis**: NVG-291 treatment will promote neural repair in individuals with relapsing-remitting multiple sclerosis (RRMS), as measured by clinical assessment tools and brain MRI

Methods

- Phase 1 trial in healthy volunteers: placebo-controlled, randomized, triple-blind study evaluating safety, tolerability, pharmacokinetics (PK)
- Part 1 Single Ascending Dose (SAD); Part 2 Multiple Ascending Dose (MAD) (**Figure 1**)
  - SAD: 6 dose cohorts (24 NVG-291, 13 Placebo); single subcutaneous dose (**0.032 mg/kg to 0.864 mg/kg**)
  - MAD: 3 dose cohorts (approximately 18 subjects); 14 daily SC doses (**0.384 mg/kg to 0.864 mg/kg**)
- The doses tested exceed the human equivalent doses that showed efficacy in animal models: 11 – 500 μg/day in rats (human equivalent range **0.007 – 0.32 mg/kg**)

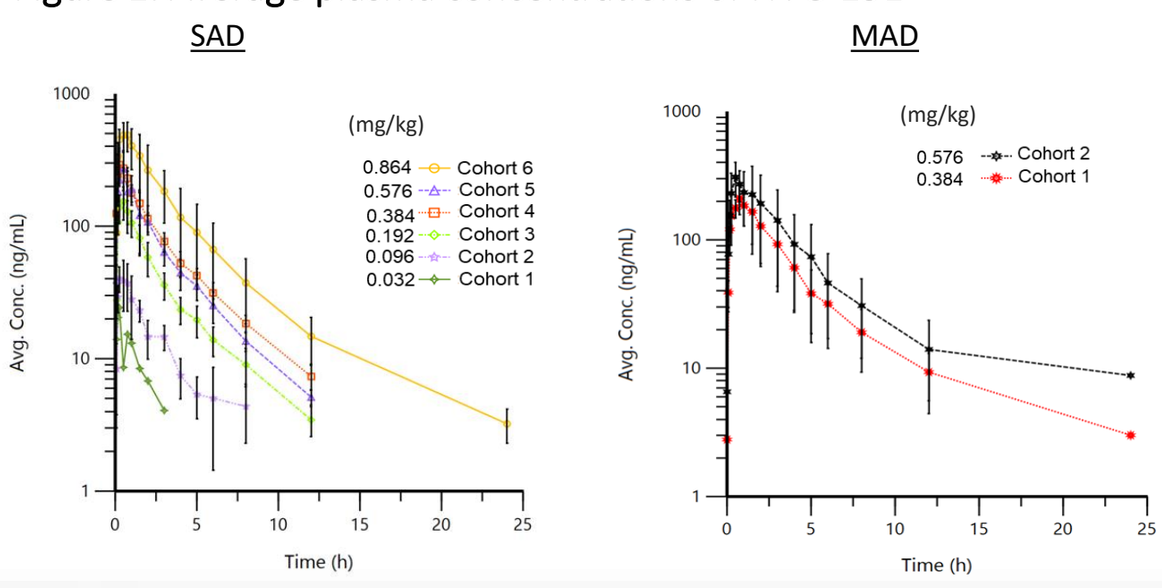
Figure 1. Phase 1 Trial dosing schedule



Results

- NVG-291 was safe and well tolerated through 6 completed SAD and 2 completed MAD cohorts
- Currently enrolling MAD dose cohort 3
- Most common adverse event (AE): injection site-related (all mild; more common in pooled NVG-291 group)
- No other AE clearly increased in the NVG-291 group vs. placebo
- No effects on vital signs, electrocardiograms (ECG)
- A single serious AE (MAD cohort 3): mild increase of troponin resulting in overnight hospitalization, without ECG changes; discharge diagnosis bronchitis (subject completed treatment; treatment remains blinded)
- Reproducible PK, with maximum plasma concentration < 1 hour; longer half-life than observed in nonclinical animal species (**Figure 2**)

Figure 2. Average plasma concentrations of NVG-291



Discussion

- Results to date from the Phase 1 trial are supportive of proceeding to a Phase 2 clinical trial in MS (**Figure 3**)

Primary objective

- To evaluate NVG-291's effect on short distance speed of ambulation (responder analysis) in an enriched population with ambulatory impairment

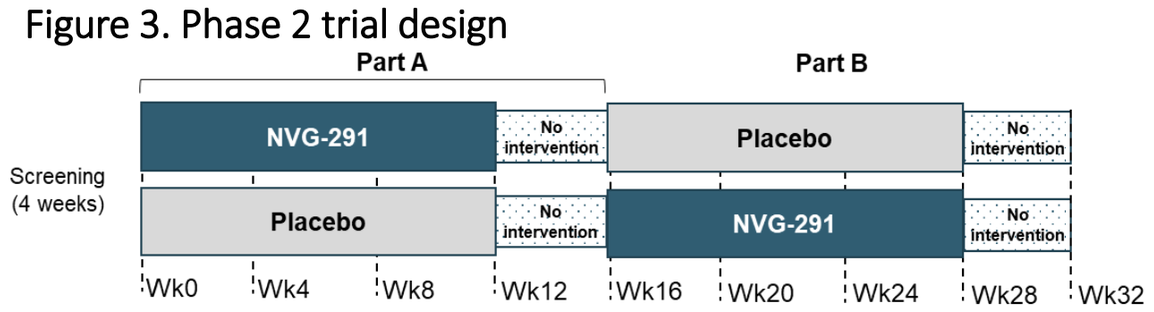
Primary endpoint

- Percentage of subjects whose timed 25-foot walk test (T25FW) at week 12 improves at least 20% compared with baseline

Key eligibility criteria

- RRMS
- Age 18 - 45
- EDSS 3.0 - 5.5
- Baseline T25FW 8-30 sec
- Disease duration ≤ 15 years
- On approved disease-modifying therapy for at least 6 months

Figure 3. Phase 2 trial design



- Multicenter (15-20 sites), randomized (1:1 NVG-291 [fixed dose] or placebo SC daily) 32-week study (N~84)
- Weeks 1-12 and 16-28: 12-week blinded treatment periods
- Primary analytic approaches:
  - Part A placebo-controlled period: NVG-291 vs. placebo (weeks 1-12)
  - "Delayed start": *Combined* Parts A + B NVG-291 groups (weeks 1-12, 16-28) vs. Part A placebo group (weeks 1-12)
  - ➢ Rationale for a young RRMS population: Higher remyelination potential (compared to older, progressive populations)
  - ➢ Rationale for *no intervention* periods: i) Assesses durability of NVG-291 effect; ii) Reduces placebo effect (e.g. week 16, 32 assessments)
  - ➢ Rationale for 2-part design: i) Enables "delayed start" analysis (effectively increasing *N* of NVG-291 treated subjects); ii) Assesses durability of NVG-291 effect; iii) Facilitates recruitment

Secondary outcome measures

- MS Walking Scale-12 (MSWS-12) v. 2.0
- 2-minute walk test (2MWT)
- MRI brain lesional myelin content, as assessed by magnetization transfer ratio
- Safety and tolerability of NVG-291

Exploratory outcome measures

- 9-hole peg test (9-HPT)
- Symbol digit modality test (SDMT)
- CANTAB (Cambridge Neuropsychological Test Automated Battery) modules:
  - PAL Paired associates learning
  - RVP Rapid visual information processing
  - RTI Reaction time task
- Modified Fatigue Impact Scale (MFIS)
- Low-contrast (2.5% Sloan chart) letter acuity (LCLA)
- Expanded disability status scale (EDSS)
- Advanced structural imaging (MRI)
  - Intra- and extralesional magnetization transfer ratio, tissue-based radial diffusivity, apparent fiber density
- Plasma and CSF (substudy) biomarkers, including Nf-L, GFAP

Sample Size estimation

- Assumptions related to the primary endpoint are derived from Phase 2/3 results of extended release 4-aminopyridine (dalfampridine)*
  - Assuming 8% of placebo subjects and 35% of NVG-291 subjects achieve ≥ 20% improvement from baseline in T25FW at week 12, the study will have 80% power to detect a difference favoring NVG-291 treatment, with an α of 0.10 (1-sided)
  - Power is greater for "delayed start" analysis

*Goodman et al., 2008; Goodman et al., 2009; Goodman et al., 2010

Conclusion

Results of the Phase 1 study will establish the safety, tolerability, and PK of NVG-291 to support advancement to a Phase 2 clinical trial in patients with RRMS in 2023

Disclosures DDM and JT are employees and shareholders of NervGen; JC has been local principal investigator for commercial trials funded by: Actelion, Novartis and Roche; has taken part in advisory boards/consultancy for Azadyne, Janssen, Merck, NervGen, Novartis and Roche; and received support from the National Institute for Health Research (NIHR), UK MS Society, Canadian MS Society, US National MS Society and the Rosetrees Trust; JAC received personal compensation for consulting for Biogen, Convelo, EMD Serono, Gossamer Bio, Mylan, and PSI; and serving as an Editor of *Multiple Sclerosis* Journal; AVDW received unrestricted research grants from Merck, Roche and Biogen and received speaker's honoraria from Merck, Biogen, Novartis and Roche; RTN has consulted for Abata Therapeutics, Banner Life Sciences, BeiGene, Biogen, Bristol Myers Squibb, Celltrion, Genentech, Genzyme, Janssen, GW Therapeutics, Horizon Therapeutics, Lundbeck, NervGen, TG Therapeutics.