CONNECT: A 16-week Placebo-controlled Phase 1b/2a Study of NVG-291: Results for the Chronic Cohort

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June 3, 2025

Disclosures:
DM, JT, MD, TF: Employees and shareholders of NervGen
EG: Employee and shareholder of DP Clinical
JG, BC, MP, LJ, SK, BK, DL: : No relevant disclosures

Support provided by Wings for Life

Hypotheses: Clinical Translation of NVG-291

1

NVG-291 may be effective in individuals with **“subacute” and/or “chronic” SCI**

2

Successful translation more likely in a **motor incomplete** population

3

NVG-291 treatment may improve **connectivity**; monitor motor recovery using **electrophysiological** and **clinical measures**

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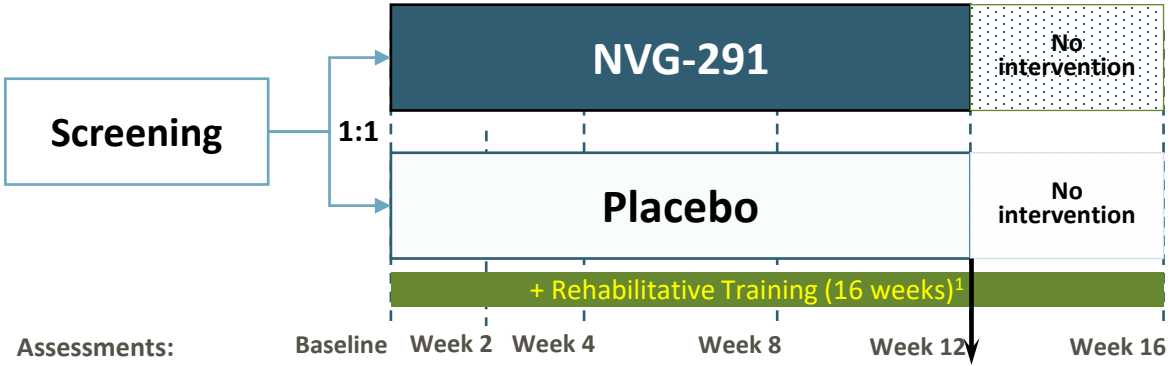
Trial NVG-291-201
Design



www.connectscistudy.com
clinicaltrials.gov NCT05965700

Two Cohorts (~20 subjects)
- Chronic: 1-10 years post-injury
- Subacute: 20-90 days post-injury

Key Eligibility Criteria (Chronic)
- Age 18-75
- Traumatic cervical SCI (NLI C7 or higher)
- Motor incomplete, defined by:
  - GRASSP qualitative prehension score
  - WISCI II ≤14
  - Able to initiate ≥1 step
- MEP in ≥1 first dorsal interosseus (FDI) *AND* ≥1 tibialis anterior (TA)

Single site - SRALab, Chicago, IL - to reduce variability of electrophysiological measurements

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Trial NVG-291-201
Key Endpoints (Chronic SCI Cohort, N=20)

- **[1,2]Co-Primary Endpoints**

  Change in normalized motor evoked potential (MEP) amplitude (corticospinal contribution) following electrical stimulation of either

  1) *First dorsal interosseus (FDI)* ***OR***
  2) *Tibialis anterior (TA)*

- **[2]Secondary Endpoints**
  - Change in **GRASSP** version 2 score
  - Change in **9-HPT** time (sec)
  - Change in **pinch** dynamometry force (Newtons)
  - Change in upper extremity motor score (**UEMS**)
  - Change in lower extremity motor score (**LEMS**)
  - Change in **10mWT** time (m/sec)

Statistical analysis:

- Assuming treatment effect on MEPs is similar to that observed with electrical stimulation studies, with 8 subjects per arm this study will have ≥80% power to detect a difference (α = 0.025, Student t-test 2-sided)
- Both co-primary endpoints tested using an α of 0.025
- **Study considered positive if at least one co-primary endpoint achieves *p*-value < 0.025**

- No hierarchy
- Looking for trend(s) in one or more endpoints
- Nominal p-values reported

1. If two resting MEPs are present in the FDI (or TA) of a given subject at baseline, the mean change will be evaluated; If only one resting MEP is present, the change on that side will be evaluated.
2. Given multiple postbaseline assessment timepoints, a linear mixed effects (LME) model used for analysis.

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Baseline Demographic/Clinical Characteristics			NVG-291 (N=10)	Placebo (N=10)
Age (years)		**Mean (SD)**	43.0 (19.7)	50.3 (15.0)
Sex		*N* (% male)	8 (80%)	9 (90%)
Ethnicity	Not Hispanic Or Latino	*N* (%)	9 (90.0%)	10 (100%)
Race	Black or African American	*N* (%)	1 (10.0%)	0
	White	*N* (%)	8 (80.0%)	10 (100%)
Time since SCI (years)		Mean (SD)	3.13 (2.36)	3.79 (2.99)
Cause of Injury	Fall	*N* (%)	1 (10.0%)	2 (20.0%)
	Sport	*N* (%)	6 (60.0%)	3 (30.0%)
	Transport	*N* (%)	3 (30.0%)	4 (40.0%)
	Other		0	1 (10%)
Neurological level of injury		*N* (%) C2	2 (20.0%)	0
		N (%) C3	2 (20.0%)	3 (30.0%)
		N (%) C4	3 (30.0%)	4 (40.0%)
		N (%) C5	3 (30.0%)	0
		N (%) C6	0	2 (20.0%)
		N (%) C7	0	1 (10.0%)
AIS		*N* (%) C	5 (50.0%)	2 (20.0%)
		N (%) D	5 (50.0%)	8 (80.0%)
WISCI II score		Mean (SD)	7.8 (5.45)	10.1 (2.08)
GRASSP v2 total score		Mean (SD)	105.6 (36.7)	119.4 (23.3)
GRASSP v2 quantitative prehension		Mean (SD)	17.3 (8.9)	22.3 (6.8)
9-HPT (sec)		Mean (SD)	[1]147.6 (98.8)	[2]144.3 (97.5)
Pinch dynamometry force (Newtons)		Mean (SD)	30.7 (29.9)	34.5 (23.3)
UEMS		Mean (SD)	32.3 (11.0)	37.3 (6.8)
LEMS		Mean (SD)	31.4 (14.2)	34.8 (6.4)
10mWT (m/sec)		Mean (SD)	[3,4]0.37 (0.55)	[3]0.27 (0.14)
FDI-MEP amplitude, % of M-Max		Mean (SD)	6.2 (8.2)	6.5 (5.7)
TA-MEP amplitude, % of M-Max		Mean (SD)	6.4 (4.9)	7.0 (4.1)

Secondary Outcome measures

Indicators of "severity"

1. N=5 in NVG-291 group unable to complete ***9-HPT*** at baseline:
   a) 2 unable to complete on either side (300 sec imputed)
   b) 3 subjects unable to complete on one side)
2. N=4 in placebo group unable to complete ***9-HPT*** on one side at baseline
3. Median 10mWT: 0.124 m/sec (NVG-291), 0.232 m/sec (Placebo)
4. N=2 (20%) in NVG-291 group unable to complete ***10mWT*** at baseline

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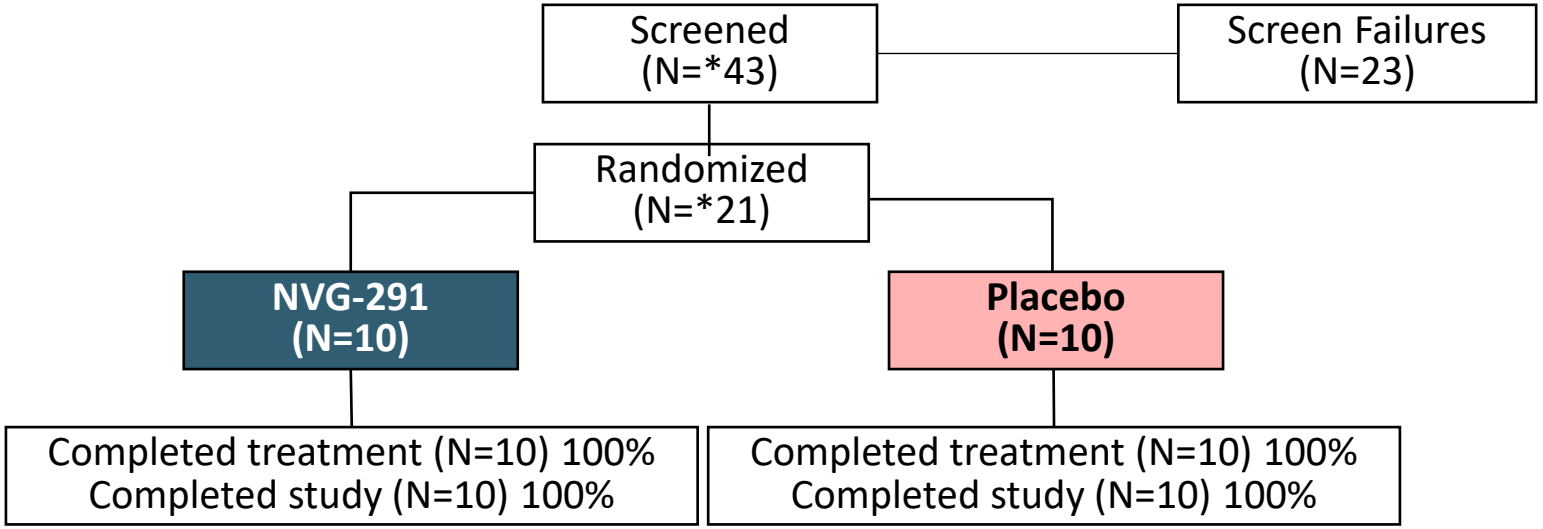
Disposition and Compliance



Treatment compliance:	NVG-291	Placebo
Mean (SD)	99.8 (0.38)	99.1 (1.93)
Range	98.8 – 100.0	94.1 – 100.0

*1 subject randomized (not treated), withdrew, rescreened and was enrolled.
1 subject screen failed, rescreened and was enrolled.

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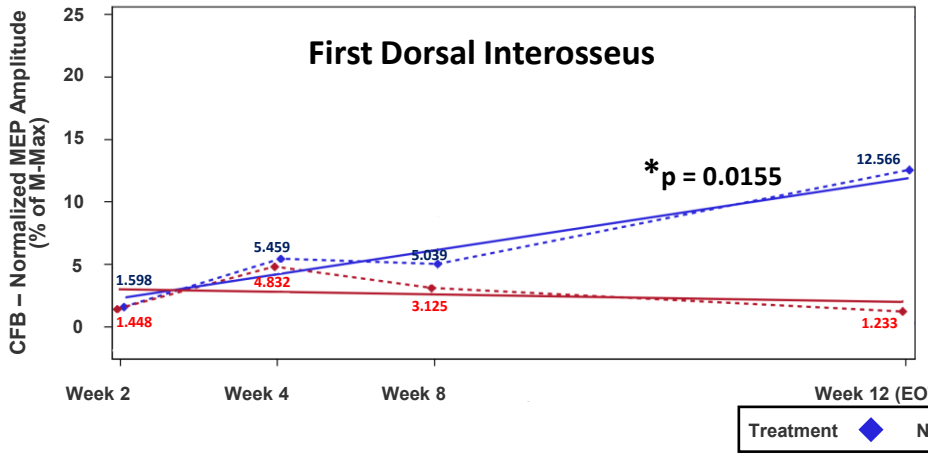
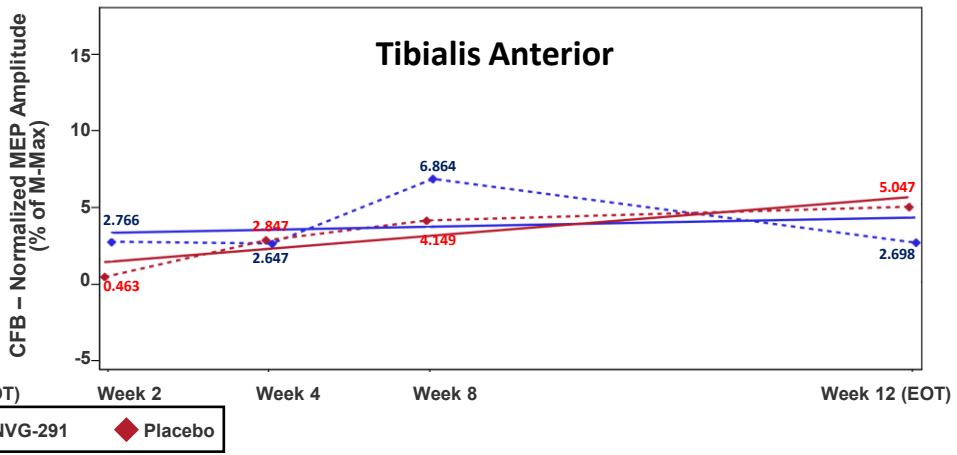
Co-Primary Endpoints

Change from Baseline to Week 12 in Normalized MEP Amplitude (% of M-max)





Treatment ◆ NVG-291 ◆ Placebo

Baseline (actual)	6.207 (8.22)	6.527 (5.74)	
Week 12 (actual)	18.773 (22.77)	7.760 (6.73)	
Mean Change (LME)	11.418	1.988	9.430
95% CI	(5.831, 17.005)	(-3.620, 7.596)	(1.512, 17.348)
p-value LSM			0.0209
p-value LME			***0.0155**

Baseline (actual)	6.385 (4.86)	7.029 (4.12)	
Week 12 (actual)	9.083 (6.58)	12.076 (6.41)	
Mean Change (LME)	4.288	5.433	-1.144
95% CI	(-0.133, 8.710)	(0.994, 9.872)	(-7.415, 5.126)
p-value LSM			0.7132
p-value LME			0.3126

***Change in FDI-MEP amplitude statistically significant vs. placebo**

CFB = Change from Baseline; EOT = End of Treatment; MEP = Motor Evoked Potential; M-max = Maximum motor response; LSM = Least-square means; LME = Linear Mixed Effects Model
LME model contains CFB as dependent variable and fixed effects for intercept, baseline result, Treatment, Week (study day/7), and Treatment x Week interaction with random intercept
The actual mean CFB values are displayed as dotted lines and diamonds with 95% confidence interval
The regression line of CFB values are displayed as solid lines

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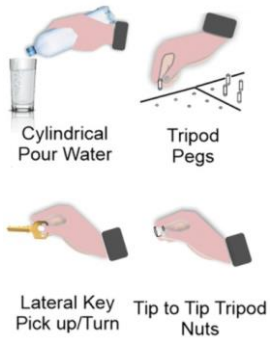
Secondary Endpoints: Positive Trends Toward Improvements on GRASSP

Change in Score	NVG-291	Placebo	NVG-291 - Placebo	*p*-value (LME)	Min-Max
GRASSP Total Score Change	8.9	4.1	+4.7	0.2678	0-188
Quantitative prehension	**3.1**	**1.0**	**+2.2**	**0.1416**	**0-40**
Qualitative prehension	2.3	0.8	+1.6	0.3403	0-24
Strength	2.3	2.6	-0.3	0.8793	0-100
Sensation	0.8	0.1	+0.7	0.4283	0-24

Improvements on GRASSP **Quantitative Prehension Performance**

Actual Values	NVG-291	Placebo	NVG-291 - Placebo
Baseline (SD)	17.3 (8.92)	22.3 (6.83)	
Week 12 (SD)	21.0 (7.42)	22.7 (6.20)	
Mean change from baseline (SD)	**+3.7 (4.35)**	**+0.4 (2.12)**	**+3.3 (1.53)**
Median	+3.0	0.0	
P-value t-test			0.0447



https://www.liebertpub.com/cms/10.1089/neu.2021.0500/asset/images/neu.2021.0500_figure2.jpg

LME: Linear Mixed Effects Model

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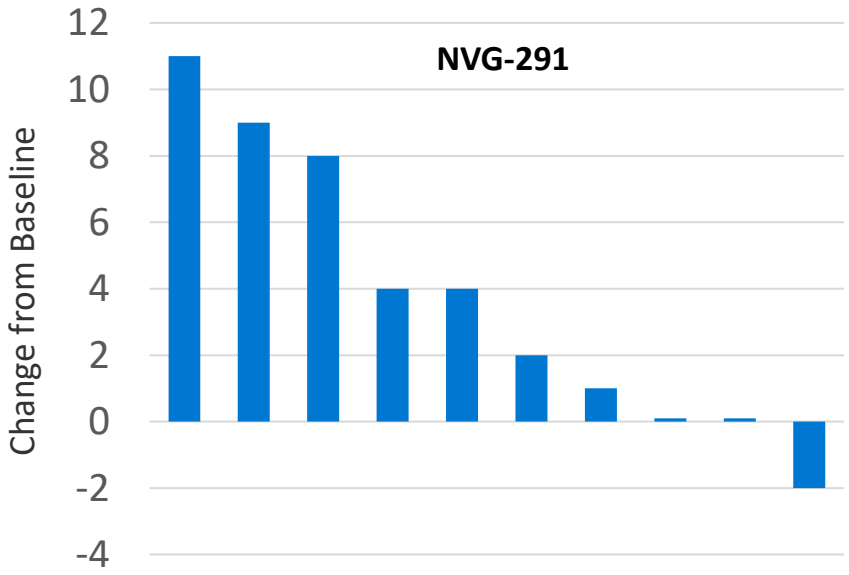
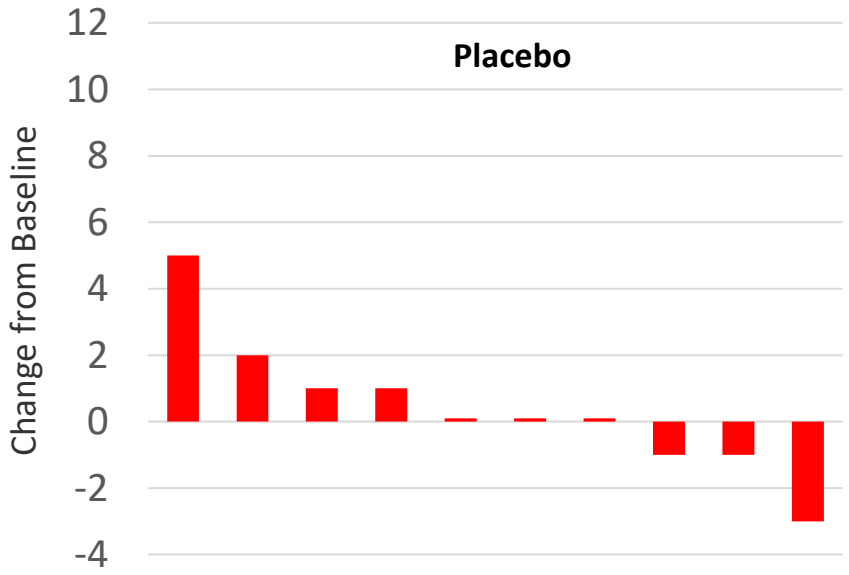
Improvements on GRASSP Quantitative Prehension Performance (QtP)





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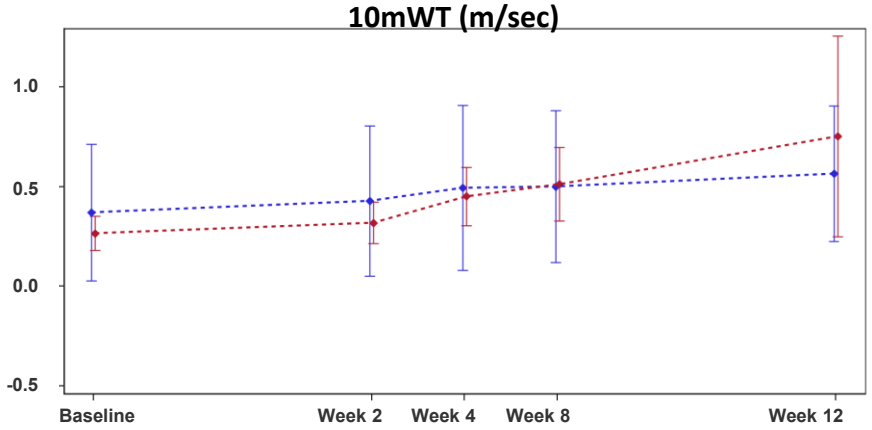
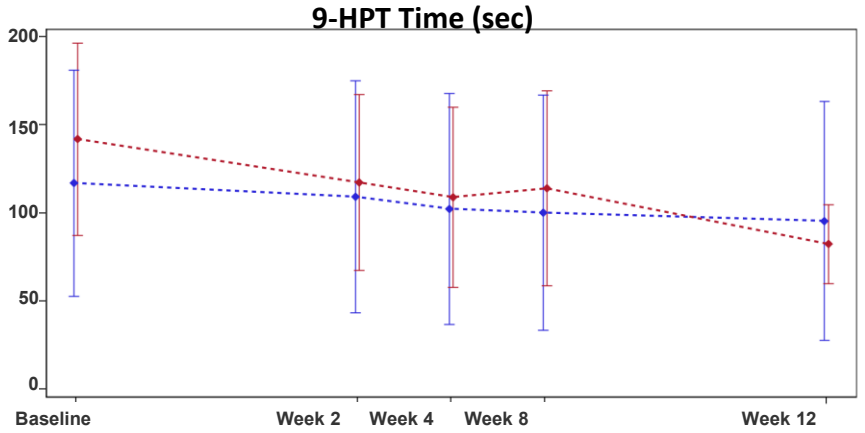
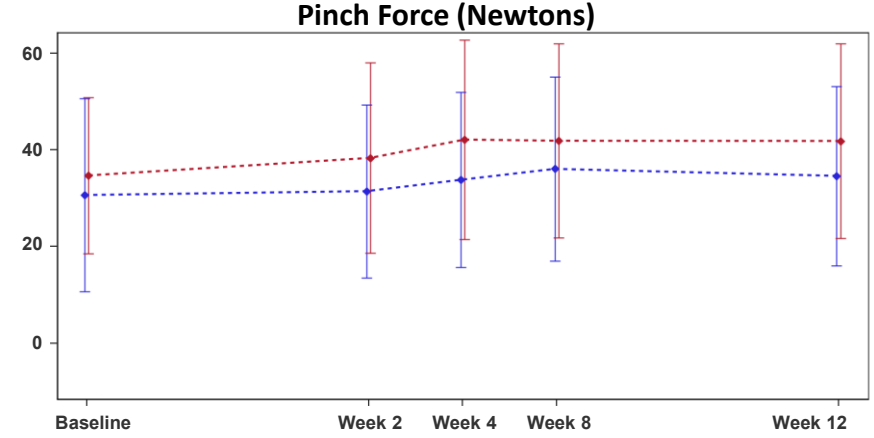
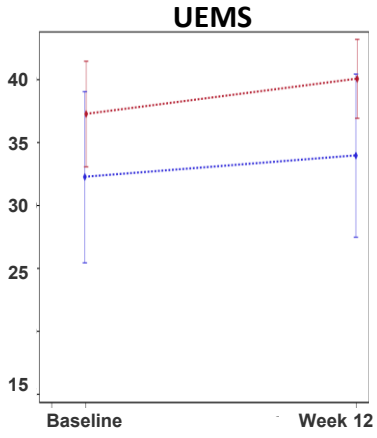
Other Secondary Endpoints:

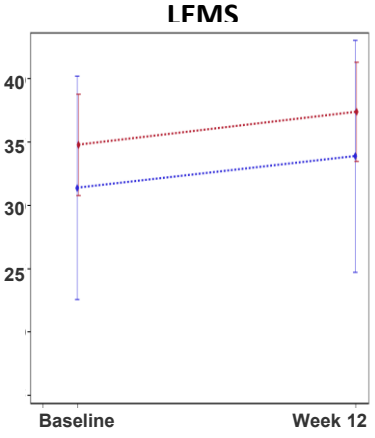
10mWT, 9-HPT, Pinch Force, UEMS, LEMS











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Treatment Emergent AEs (TEAEs) Occurring During Treatment Period

N (%) of Subjects with at least 1 TEAE	NVG-291 (N=10)	Placebo (N=10)
All TEAEs	10 (100%)	8 (80.0%)
Injection site reaction (ISR)-related TEAEs	9 (90.0%)	3 (30.0%)
Fatigue	1 (10.0%)	2 (20.0%)
Nausea	2 (20.0%)	1 (10.0%)
Urinary tract infection	3 (30.0%)	0
Nasopharyngitis	1 (10.0%)	1 (10.0%)
Urinary incontinence	2 (20.0%)	0
TEAE leading to treatment discontinuation	0	0
*Serious TEAE (SAE)	0	1 (10%)

All ISR TEAEs mild or moderate

*SAE: "Bowel obstruction due to internal hernia defect": Subject with worsening nausea, constipation and abdominal pain due to small bowel obstruction, requiring surgical closure of internal hernia – considered unrelated to IP (likely related to prior gastric bypass)

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Summary and Conclusions

- Co-primary endpoint achieved
  - **A statistically significant (*p*=0.0155) 3-fold increase in mean normalized FDI MEP amplitude following NVG-291 treatment**
  - Change in TA MEP amplitude not statistically significant
- Secondary endpoints
  - **Positive trend for efficacy on GRASSP** (in particular, quantitative prehension performance)
    - 5/10 subjects with QtP change ≥4 for NVG-291 (vs. 1/10 for placebo)
  - Based on *initial topline analyses*, no clear separation from placebo on:
    - 9-HPT, pinch force, UEMS/LEMS, 10mWT
    - Additional analyses forthcoming
- NVG-291 was safe and well tolerated and had high treatment compliance

Conclusions: 1) NVG-291 promotes motor recovery in a chronic cervical motor incomplete population
2) Next steps: Phase 3 planning, align with regulatory authorities

Support provided by Wings for Life

Wings for Life Spinal Cord Research Foundation

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