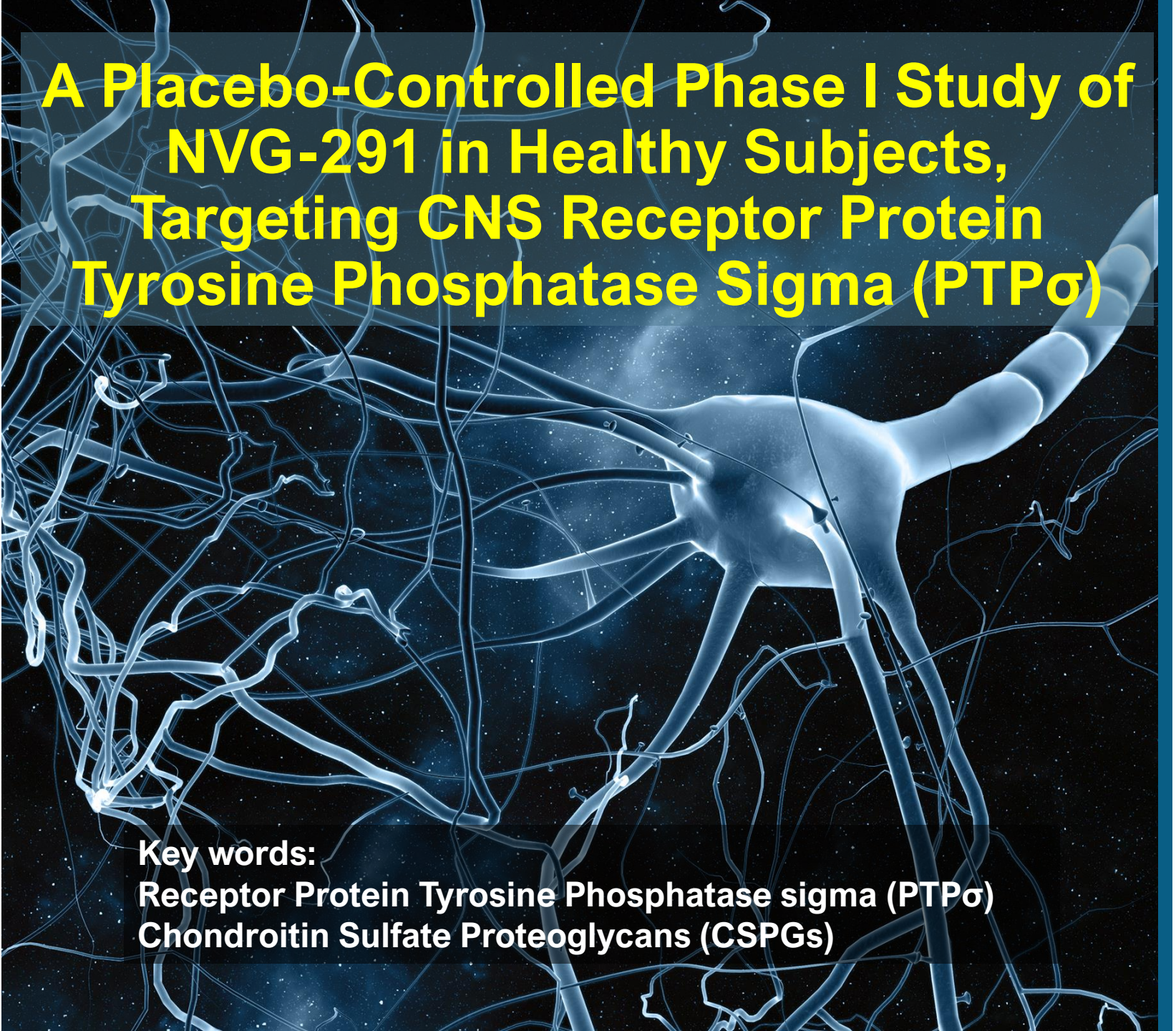
A Placebo-Controlled Phase I Study of NVG-291 in Healthy Subjects, Targeting CNS Receptor Protein Tyrosine Phosphatase Sigma (PTPσ)



Key words:
Receptor Protein Tyrosine Phosphatase sigma (PTPσ)
Chondroitin Sulfate Proteoglycans (CSPGs)

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Disclosures:

All authors are employees or consultants of NervGen

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Disclosure Statement

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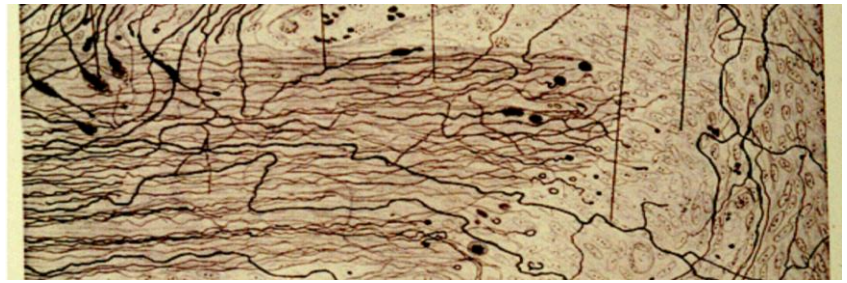
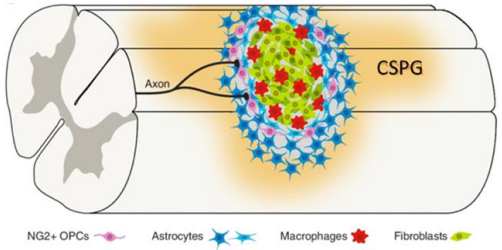
Timeline of Important Discoveries Relevant to Chondroitin Sulfate Proteoglycans (CSPGs) and PTPσ

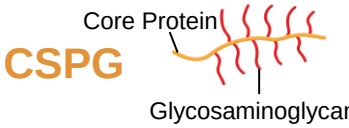


Limited axonal regrowth through glial scar identified by *Ramon y Cajal* as clue to basis for lack of repair in spinal cord injury (SCI)[1]

1900

The glial scar[14]





CSPGs found to be upregulated in the glial scar after SCI and to inhibit neurite outgrowth *in vitro*[2]

Improved outcomes in animal models of SCI following injection of chondroitinase-ABC into SCI lesion[7]

PTPσ identified as receptor mediating inhibitory effects of CSPGs[9]

Efficacy in SCI model using NVG-291-R *(rodent analogue)*[13]

1st human subject receives NVG-291

2022

1985 | 1989 | 1993 | 1997 | 2001 | 2005 | 2009 | 2013 | 2017 | 2021

CSPGs identified in human perineuronal net (PNN)[3]

CSPGs found in plaques, neurofibrillary tangles of **Alzheimer's disease**[4]

CSPGs identified in brains of patients with **Parkinson's disease, diffuse Lewy body disease, Pick's disease, progressive supranuclear palsy, Huntington's disease**[5]

CSPGs identified in demyelinating lesions of **multiple sclerosis**[6]

CSPGs of the PNN regulate critical periods of plasticity[8]

PTPσ expressed by neurons, oligodendrocytes (OLG), OLG precursors, astrocytes, neural stem cells, microglia; **when activated, PTPσ inhibits** axonal sprouting, synaptic plasticity, OLG precursor differentiation, remyelination[10,11,12]

Demonstration of NVG-291 in CNS of rat within 1 hour of SQ administration[13]

NervGen formed

Phase 1 study complete

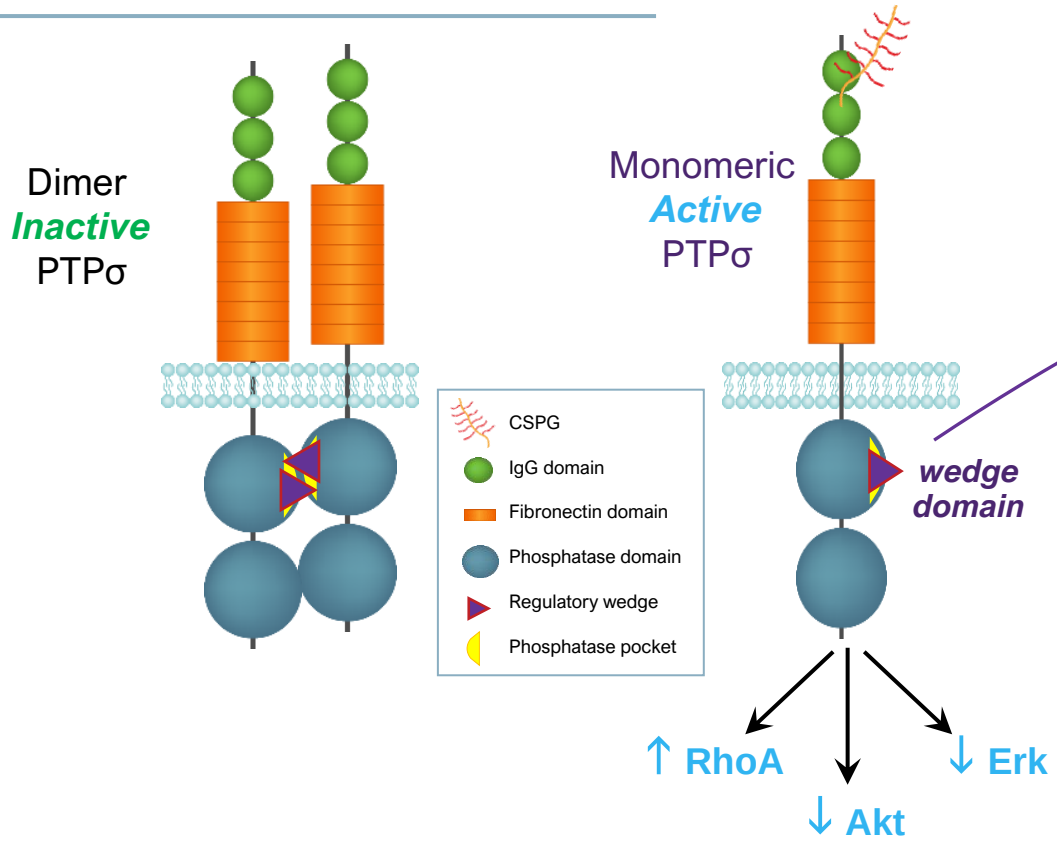
TODAY

PTPσ: Receptor Protein Tyrosine Phosphatase sigma
CSPGs: Chondroitin Sulfate Proteoglycans

1. Ramon y Cajal, Oxford UP, 1928
2. Snow et al., Exp. Neurol, 1990
3. Bertolotto et al., J Neurosci Res, 1991
4. DeWitt et al., Exp. Neurol., 1993
5. DeWitt et al., Brain Research 1994
6. Sobel and Ahmed, J Neuropathol Exp Neurol, 2001
7. Bradbury et al., Nature, 2002
8. Pizzorusso et al., Science 2002
9. Shen et al., Science 2009
10. Kirkham et al., BMC Neurosci, 2006
11. Luo et al., Nature Comm, 2018
12. Dyck et al., J Neuroinflamm, 2018
13. Lang et al., Nature 2015
14. Tran et al., Physiol Rev, 2018

NVG-291, A Peptide Mimetic of the PTPσ Wedge Domain

Reverses CSPG-Mediated Inhibition of Repair



NVG-291: **"TAT" tag (10 amino acids)** + **PTPσ *wedge domain* (25 amino acids)**

HIV transactivator of transcription (TAT) sequence - enables translocation across cell membranes

Mimetic of the intracellular ***wedge domain*** of PTPσ, which regulates its phosphatase activity

- **NVG-291-*R*** = *rodent* version of **NVG-291** (differ by 1 amino acid)
- In different animal models of CNS damage, NVG-291-R has demonstrated the ability to overcome the inhibitory effects of CSPGs
  - Reversing intracellular signaling changes induced by CSPGs
  - Promoting
    - Axonal Regeneration
    - Remyelination
    - Plasticity
  - Enabling functional recovery

CNS Injury (upregulation of **CSPGs)**

	Vehicle	***+ NVG-291***
Intracellular signaling	↑ RhoA ↓ Akt ↓ Erk	↓ RhoA ↑ Akt ↑ Erk
Biological effects	↓ axonal growth ↓ remyelination ↓ plasticity	↑ axonal growth ↑ remyelination ↑ plasticity

↑ activation
↓ deactivation

PTPσ: Receptor Protein Tyrosine Phosphatase sigma
CSPGs: Chondroitin Sulfate Proteoglycans

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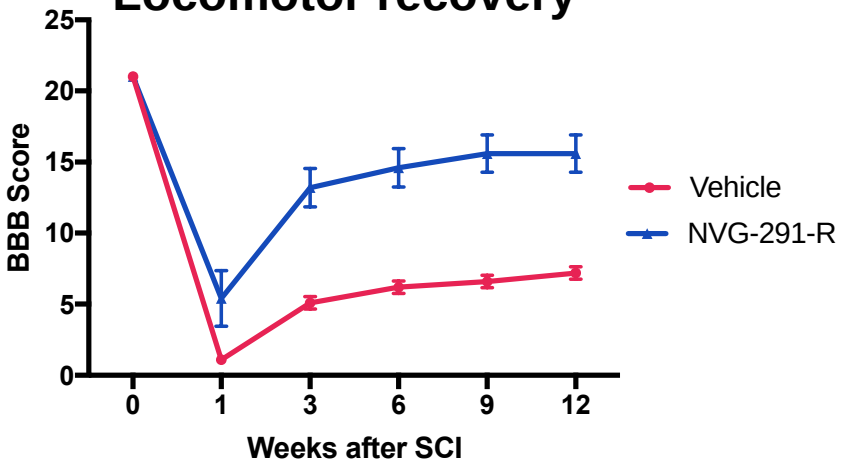
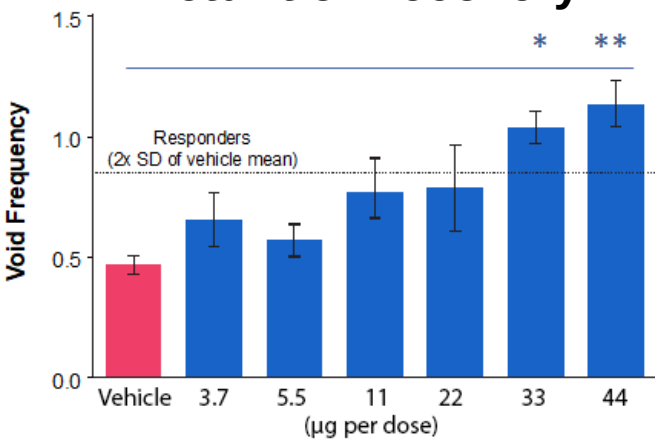
NVG-291-R Improves Functional Recovery in Animal Models of CNS Damage

Spinal Cord Injury

Locomotor recovery

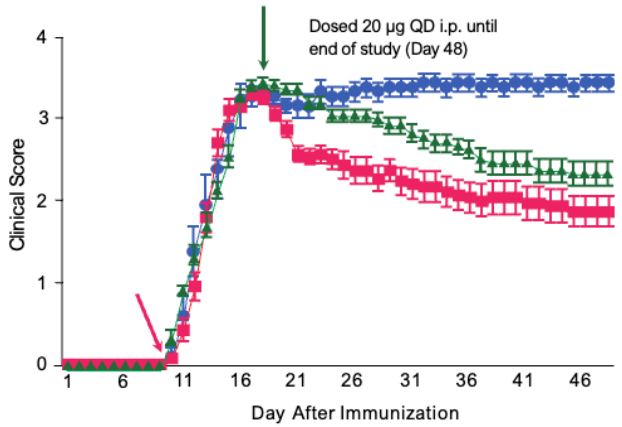


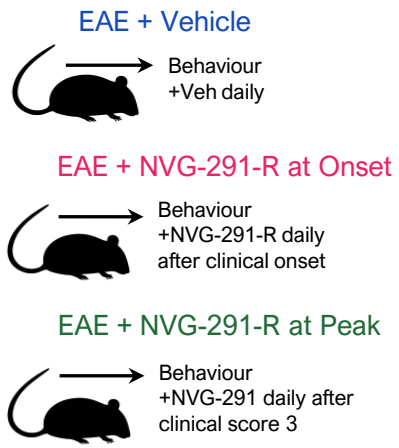
Micturition recovery



CNS Demyelination

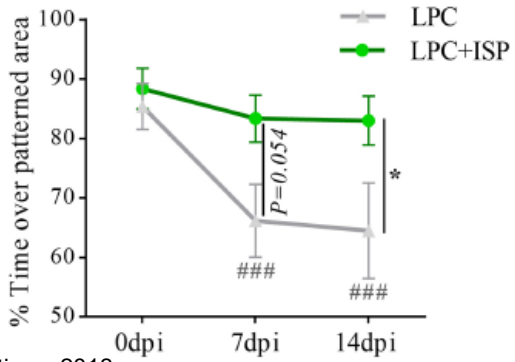
Improvement in EAE clinical scores





Visual recovery in optic chiasm lesion

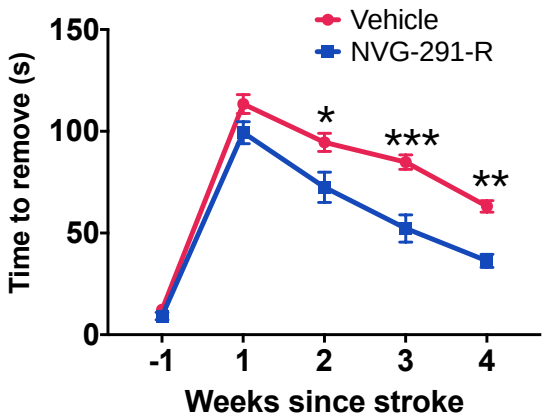
Visual Cliff Test



Stroke

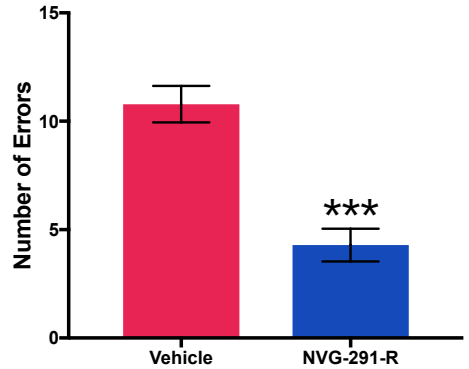
Sensorimotor Recovery

Adhesive Removal Test



Cognitive recovery

Barnes Maze



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Rink et al., Exp Neurol 2018
Lang et al, Nature 2015

Luo et al, Nature Communications, 2018
Niknam et al, Molecular and Cellular Neuroscience, 2019

Unpublished data provided by Dr. Agnes Luo, University of Cincinnati

Phase 1 Placebo-Controlled Study in Heathy Adult Subjects

- Randomization ~4:2 (NVG-291:placebo)
- Objectives:
  - **Primary**: Safety/tolerability
  - **Secondary**: Pharmacokinetic (PK) profile

Part 1 Single Ascending Dose (SAD) Single SC inj.		
	Dose level #	Dose (mg/kg)
1 NVG-291 1 Placebo	1	**0.032**
4 NVG-291 2 Placebo	2	**0.096**
4 NVG-291 2 Placebo	3	**0.192**
4 NVG-291 2 Placebo	4	**0.384**
4NVG-291 2 Placebo	5	**0.576**
7 NVG-291 4 Placebo	6	**0.864**

+ 8 NVG-291 treated subjects - CSF analysis

Part 2 Multiple Ascending Dose (MAD) Daily SC inj. x 14 days	
	*3 Cohorts (mg/kg)
4 NVG-291 2 Placebo	**0.384**
4 NVG-291 2 Placebo	**0.576**
4 NVG-291 2 Placebo	0.864

+ 8 NVG-291 treated subjects - CSF analysis

Effective doses:

peripheral nerve injury: **0.01 mg/kg**

CNS demyelination: **0.01 – 0.05 mg/kg**

spinal cord injury: **0.01 – 0.32 mg/kg**

Phase 1 MAD dose levels exceed the corresponding doses found to be efficacious in animal models

For example, 0.864 mg/kg dose level:
>2x highest efficacious dose
>100x lowest efficacious dose in animal studies

SC = subcutaneous
NVG-291 administered as 20 mg/mL solution

Results: SAD *Unblinded* Adverse Events and Pharmacokinetic Profile

	NVG-291 Cohorts						Pooled NVG-291	Pooled Placebo
	1	2	3	4	5	6		
	0.032 mg/kg	0.096 mg/kg	0.192 mg/kg	0.384 mg/kg	0.576 mg/kg	0.864 mg/kg		
	N=1	N=4	N=4	N=4	N=4	N=7	N=24	N=13
Subjects with >=1 TEAE	1 (100%)	4 (100%)	4 (100%)	4 (100%)	4 (100%)	7 (100%)	24 (100%)	7/13 (54%)
General Disorders and administration conditions	1 (100%)	4 (100%)	4 (100%)	4 (100%)	4 (100%)	7 (100%)	24 (100%)	7 (54%)
Injection site erythema	1 (100%)	4 (100%)	4 (100%)	4 (100%)	4 (100%)	7 (100%)	24 (100%)	6 (46%)
Injection site pain	1 (100%)	1 (25%)	4 (100%)	1 (25%)	2 (50%)	7 (100%)	16 (67%)	1 (8%)
Injection site pruritus	0	1 (25%)	1 (25%)	0	2 (50%)	2 (29%)	6 (25%)	0
Injection site edema	0	0	0	0	2 (50%)	0	2 (8%)	0
Injection site paresthesia	0	1 (25%)	0	0	0	1 (14%)	2 (8%)	0
Injection site swelling	0	0	0	1 (25%)	0	1 (14%)	2 (8%)	0
Injection site bruising	0	0	0	0	1 (25%)	0	1 (4%)	1 (8%)
Injection site mass	0	0	0	0	1 (25%)	0	1 (4%)	0
Fatigue`	0	0	0	0	0	0	0	1 (8%)
Nervous system Disorders	0	1 (25%)	1 (25%)	1 (25%)	1 (25%)	3 (43%)	7 (29%)	4 (31%)
Headache	0	1 (25%)	1 (25%)		1 (25%)	2 (29%)	6 (25%)	2 (15%)
Dizziness	0	0	0	0	0	2 (29%)	2 (8%)	1 (8%)
Head discomfort	0	0	0	0	0	1 (14%)	1 (4%)	0
Presyncope	0	0	0	0	0	1 (14%)	1 (4%)	0
Lethargy	0	0	0	0	0	0	0	1 (8%)
Other								
Rash macular	0	1 (25%)	0	0	0	0	1 (4%)	0
Skin odor abnormal	0	0	0	0	0	1 (14%)	1 (4%)	0
Diarrhea	0	0	0	0	0	1 (14%)	1 (4%)	0
Upper respiratory tract infection	1 (100%)	0	0	0	0	0	1 (4%)	0
Nasal congestion	0	0	0	1 (25%)	0	0	1 (4%)	0
Rhinorrhea	0	0	0	0	0	0	0	1 (8%)
Cough	0	0	0	0	0	0	0	1 (8%)
Muscle spasms	0	0	0	0	1 (25%)	0	1 (4%)	0
Oropharyngeal discomfort	0	0	0	0	0	0	0	1 (8%)
Dysmenorrhoea	0	0	0	0	0	0	0	1 (8%)

Note: Table does not include singular AEs related to blood draws or IV catheters

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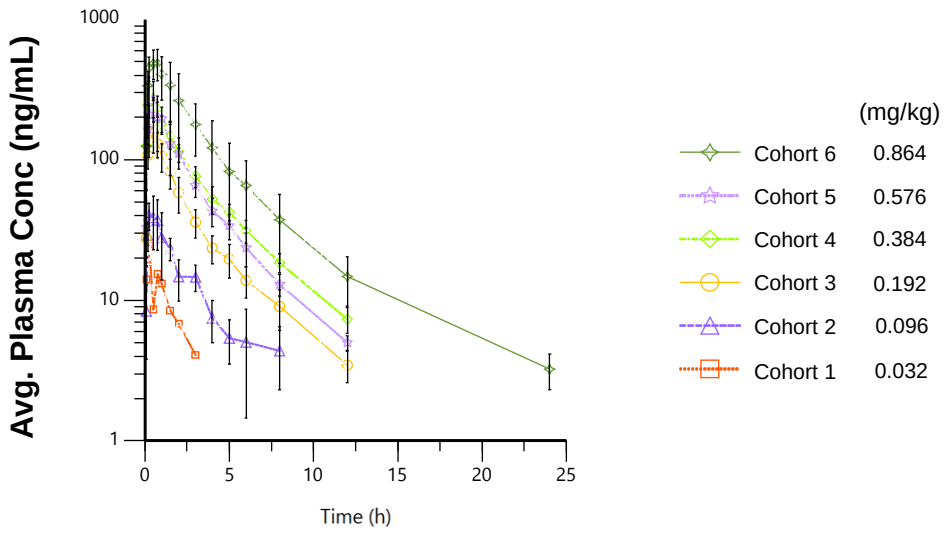
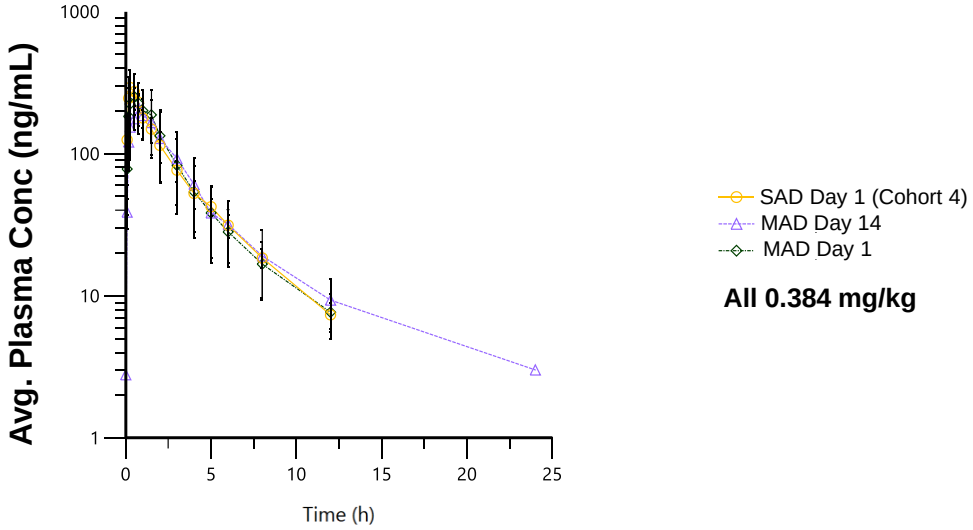
Results: SAD/MAD Pharmacokinetic Profiles

SAD (Unblinded) and MAD (Blinded) Adverse Events

Pharmacokinetic data, SAD



Pharmacokinetic data, SAD/MAD



Reproducibility of PK profiles

- *Unblinded* analysis of SAD cohort 1-6
  - Most common AE: injection site-related
  - No serious AEs
  - No clinically significant effect on vital signs, ECGs, laboratory studies
- *Blinded* analysis of MAD cohort 1*
  - Most common AE: injection site-related
  - No serious AEs
  - No clinically significant effect on vital signs, ECGs, laboratory studies

C_{max} is achieved quickly (<1 hour) with longer half-life than observed in nonclinical animal species
PK data is preliminary
*Unaudited data

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Summary and Conclusions

- Accumulation of CSPGs is a fundamental response to nervous system damage, inhibits neural repair
  - PTPσ binds to CSPGs and mediates inhibition of neural repair
- NVG-291 is a first-in-class PTPσ mimetic that modulates the PTPσ-CSPG mechanism
- Extensive data from multiple animal models of nervous system damage demonstrate improved recovery following treatment with NVG-291-R
  - Promotes axonal regeneration, remyelination, plasticity
- Phase 1 SAD dosing in healthy subjects was well tolerated, with good pharmacokinetic properties
  - Exposures exceed the (human dose equivalent) target efficacy range from preclinical studies
  - Most common AE: injection site related events (all mild); no SAEs
- MAD is ongoing
  - In MAD Cohort 1, NVG-291 was well tolerated when administered as a daily subcutaneous injection x 14 days
    - Most common AE: injection site related events (all mild); no SAEs
  - Final MAD and CSF cohort results expected mid-2022
- Phase 1 study results will enable dose selection for Ph1b/2 trials starting in 2022
  - Spinal cord injury
  - Alzheimer's disease
  - Multiple sclerosis