Preclinical pharmacology and toxicology of intrathecally infused AAV9-hABCD1, a gene therapy candidate for AMN, in non-human primates

V Vasireddy, SwanBio Therapeutics, Philadelphia, PA, USA

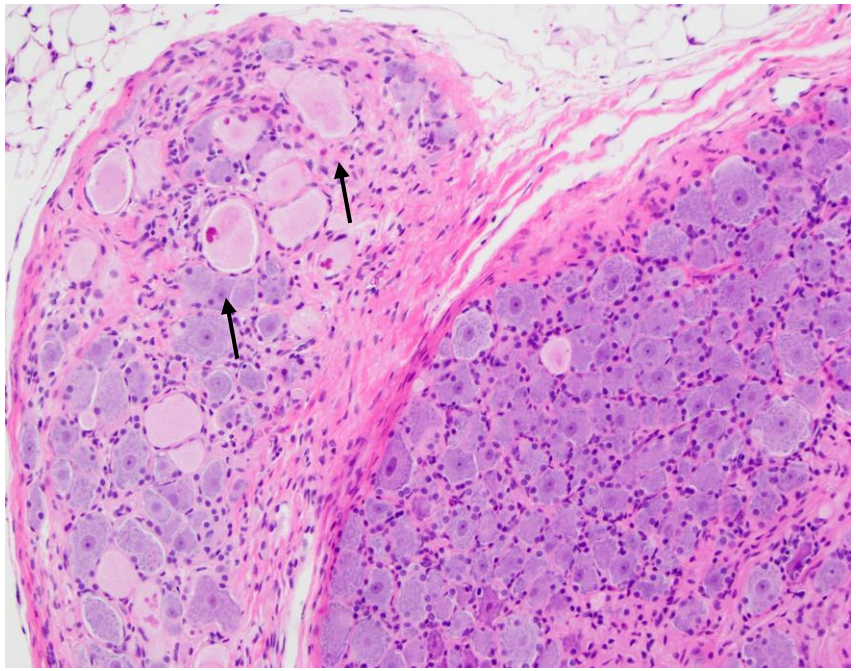
Co-authors: SW Clark, M Cartwright, K Kozarsky, DW Anderson

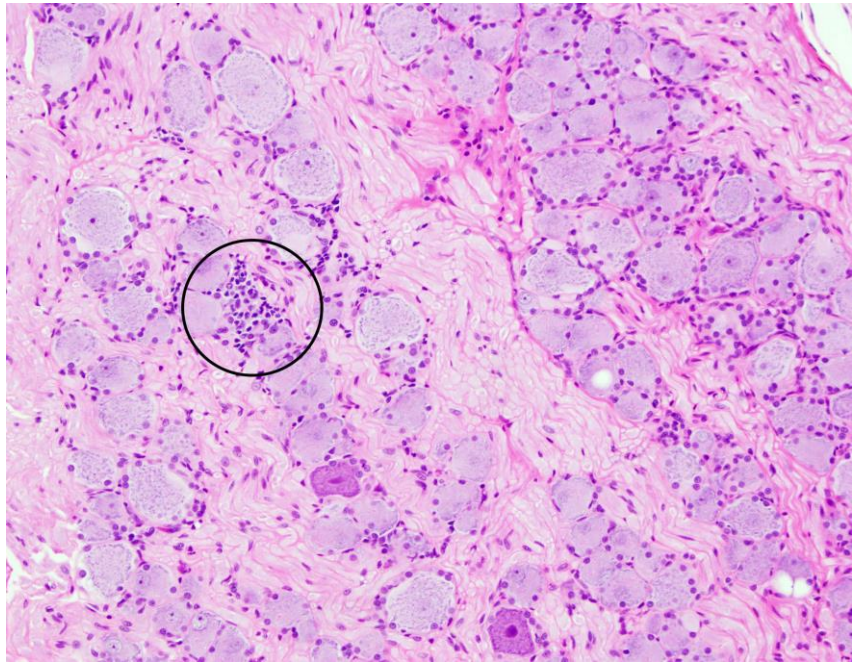
Disclosures

- **V Vasireddy** – employee, stock/shareholder: SwanBio Therapeutics
- **SW Clark** – employee, stock/shareholder: SwanBio Therapeutics
- **M Cartwright** – consultancy: SwanBio Therapeutics
- **K Kozarsky** – employee, stock/shareholder: SwanBio Therapeutics
- **DW Anderson** – employee, stock/shareholder: SwanBio Therapeutics

Preclinical Histopathology of SBT101 in NHPs at 13 Weeks

- SBT101-related neuronal necrosis (minimal to moderate), characterized by:
  - nerve cell bodies with a loss of Nissl substance and darkly eosinophilic staining cytoplasm, often irregularly bordered and shrunken in size (black arrows)
  - several-layer-thick ring of mononuclear cells at their outer margins (black circle)

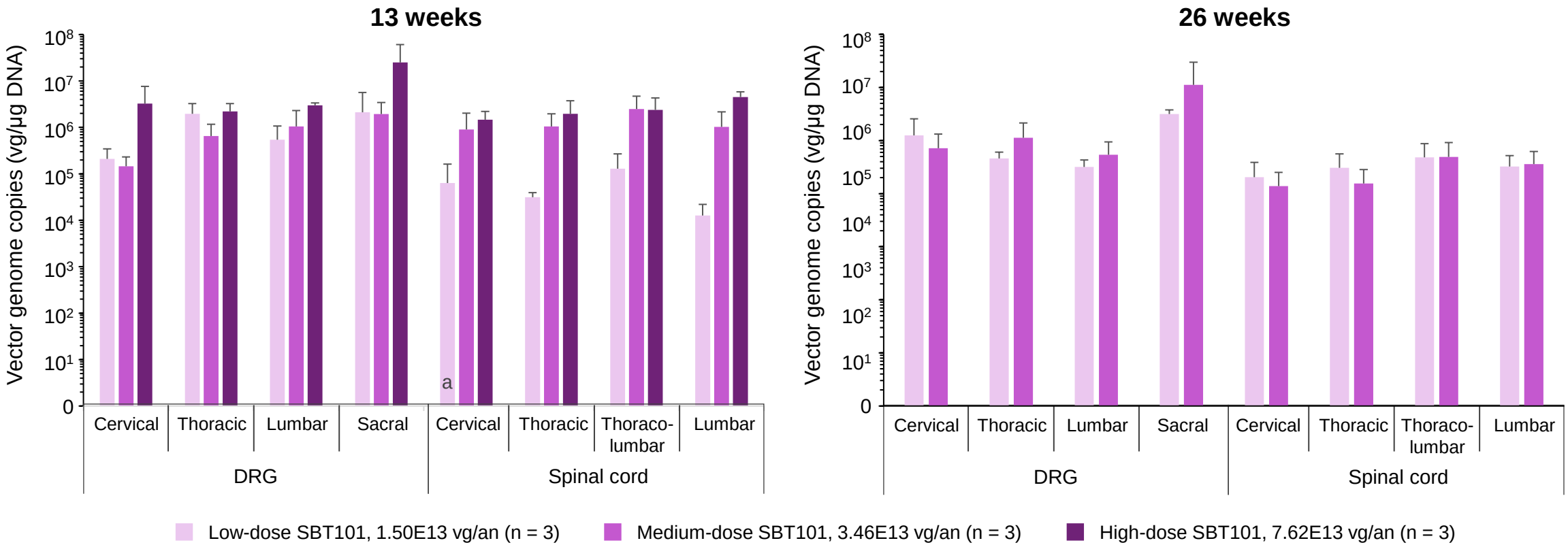




NHP, non-human primate

AAV9 Vector Genome Distribution in DRG and Spinal Cord

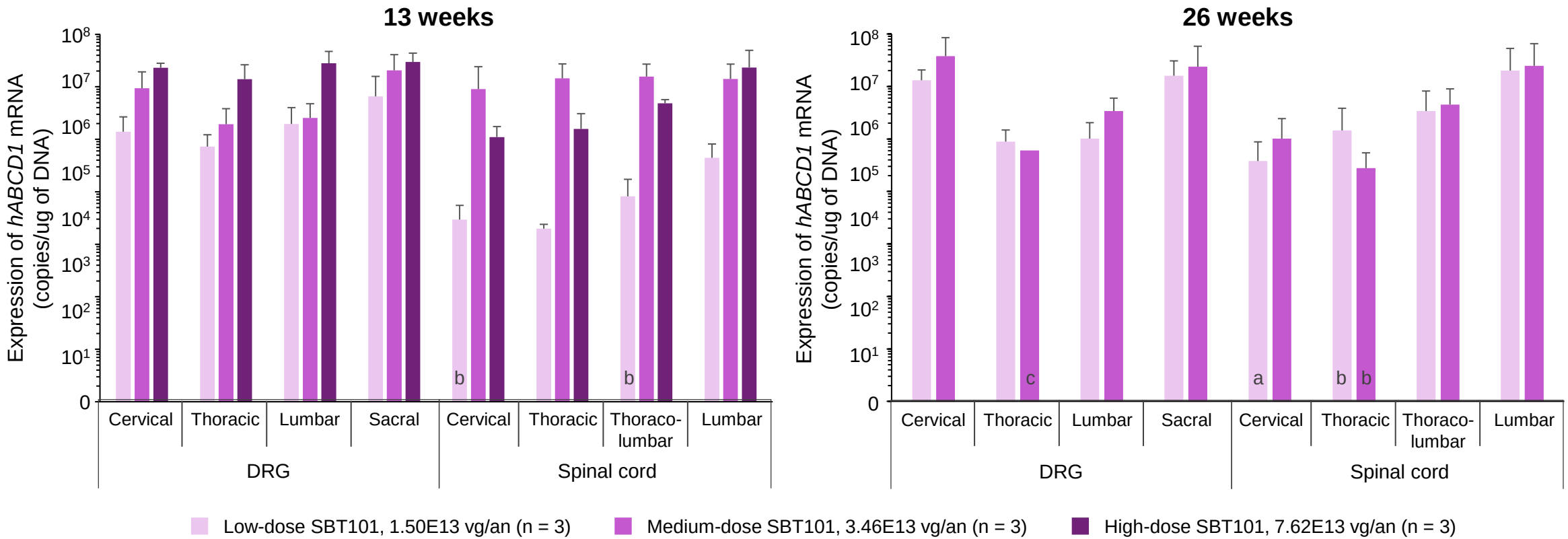
- Efficient transduction of target tissues (DRG and spinal cord) was observed up to 26 weeks post dosing with SBT101



Data represent mean ± standard deviation. [a]One NHP had a measure below the LOQ
Vector copies were below the LOD for all controls (placebo; n = 3): data not plotted. No data available for high-dose SBT101 at 26 weeks
an, animal; DRG, dorsal root ganglion; LOD, limit of detection; LOQ, limit of quantification; NHP, non-human primate; vg, vector genome

hABCD1 mRNA Expression

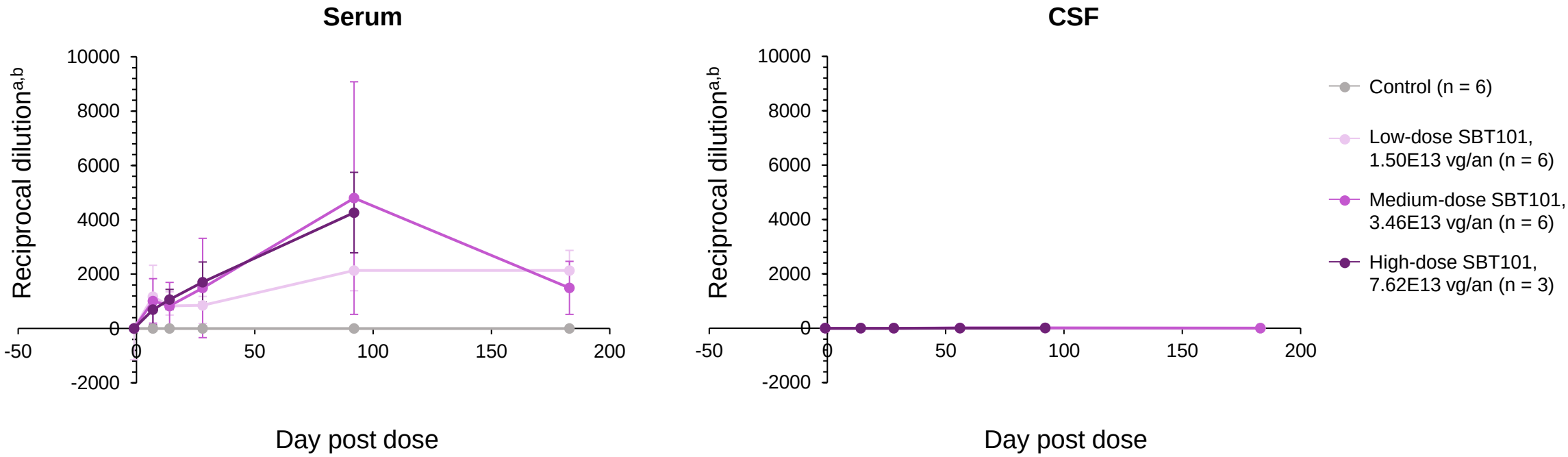
- Detectable hABCD1 mRNA expression was observed in target tissues (DRG and spinal cord)



Data represent mean ± standard deviation. [a]One NHP had a measure below the LOD; [b]One NHP had a measure below the LOQ; [c]n = 1
All controls measured below the LOD (placebo; n = 3): data not plotted. No data available for high-dose SBT101 at 26 weeks. ABCD1, ATP-Binding Cassette sub-family D Member 1; an, animal; ATP, adenosine triphosphate; DRG, dorsal root ganglia; LOD, limit of detection; LOQ, limit of quantification; NHP, non-human primate

AAV9 NAbs in Serum and CSF

- AAV9 NAbs in serum were first detected on day 7 and remained elevated through day 183, but were not dose dependent
- AAV9 NAbs in CSF were first detected on day 56; however, these were transient and not dose dependent



Data represent mean ± standard deviation. [a]Plotted values are the serum reciprocal dilution at which relative luminescence units were reduced 50% compared to virus control wells (no test sample); EC50 in HEK cells. [b]LOD = 1:5 dilution. There were no data for high-dose SBT101, and data for low- and medium-dose SBT101 were based on n = 3. At day -1, there was no CSF sample for 5 of 6 control animals, and 1 of 6 animals receiving medium-dose SBT101. AAV, adeno-associated virus; an, animal; CSF, cerebrospinal fluid; EC50, half maximal effective concentration; HEK, human embryonic kidney; LOD, limit of detection; NAb, neutralising antibody

Conclusions

- IT administration of SBT101 NHPs resulted in detectable tissue-specific transduction of vector genomes and expression of *ABCD1* mRNA
- Axonal degeneration and neuronal necrosis were observed via histopathologic examination, but these were minimal to moderate changes, and there were no clinical or neurobehavioral observations that correlated with the microscopic observations
  - These histopathological findings are consistent with those typically observed for AAV9
- In conclusion, these results provide evidence that delivery of SBT101 at doses predicted to be clinically relevant in patients with AMN has a relatively unremarkable safety profile in NHPs

AAV, adeno-associated virus; *ABCD1*, ATP-Binding Cassette sub-family D Member 1; AMN, adrenomyeloneuropathy; ATP, adenosine triphosphate; NHP, non-human primate; vg, vector genome

Acknowledgements

- The authors thank Dr David Gothard of Oxford PharmaGenesis, Oxford, UK, for providing medical writing support, which was sponsored by SwanBio in accordance with Good Publication Practice (GPP3) guidelines

Funding

- This study was funded by SwanBio Therapeutics Ltd

Thank you for listening