Rett Syndrome and Genetic ALS with *SOD1* Mutation

February 27, 2018

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Executing on Our Strategy: Expanding Beyond SMA

Rett syndrome (*MECP2*) and ALS (*SOD1*) are rare, life-threatening, neurological monogenic diseases that have significant unmet need and limited treatment options – none addressing the root cause

Licensed preclinical data from NCH generated by Chief Scientific Officer, Dr. Brian Kaspar, that demonstrate promising efficacy and safety

Obtained exclusive worldwide rights to AAV9 for Rett syndrome (*MECP2*) and a genetic form of amyotrophic lateral sclerosis caused by mutations in the superoxide dismutase 1 (*SOD1*) gene

AveXis intends to submit IND applications for both indications in late 2018/early 2019

AveXis will leverage its scalable manufacturing platform for these programs

Rett Syndrome

Rett syndrome (RTT) is a rare, neuro-developmental genetic disorder characterized by slowed growth; loss of normal movement and coordination; and loss of communication skills

Overview

- **Caused** by an X-linked dominant mutation in the methyl CpG binding protein 2 (*MECP2*) gene in 90-95% of cases
  - Monogenic
- **Predominantly affects girls**; incidence of approximately one in 10,000 female births in the U.S.
- **Onset of signs and symptoms** usually occurs between 6-18 months
- **Hallmark symptoms** include hand wringing or squeezing, clapping, rubbing, washing, or hand to mouth movements
- **Disease is progressive** with significant disability that can include autistic-like behaviors, breathing irregularities, feeding and swallowing difficulties, growth retardation, and seizures

(Tarquinio *et al*. 2017)

Treatment Landscape

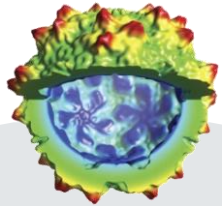
- **Median age at diagnosis** for classic Rett syndrome is approximately 2.7 years
- **Referrals to specialists** are primarily from pediatricians, neurologists and geneticists
- **Current treatments** only address associated symptoms
- **AveXis is the only company** investigating a gene therapy that addresses the root cause of the disease

Our Solution: AVXS-201

An Innovative Treatment Approach for Rett Syndrome

Gene therapy is the right approach for Rett syndrome: monogenic mutation drives the pathology

Recombinant AAV9 Capsid Shell



scAAV ITR	Minimal *MECP2* Promoter	Human *MECP2* Transgene	scAAV ITR

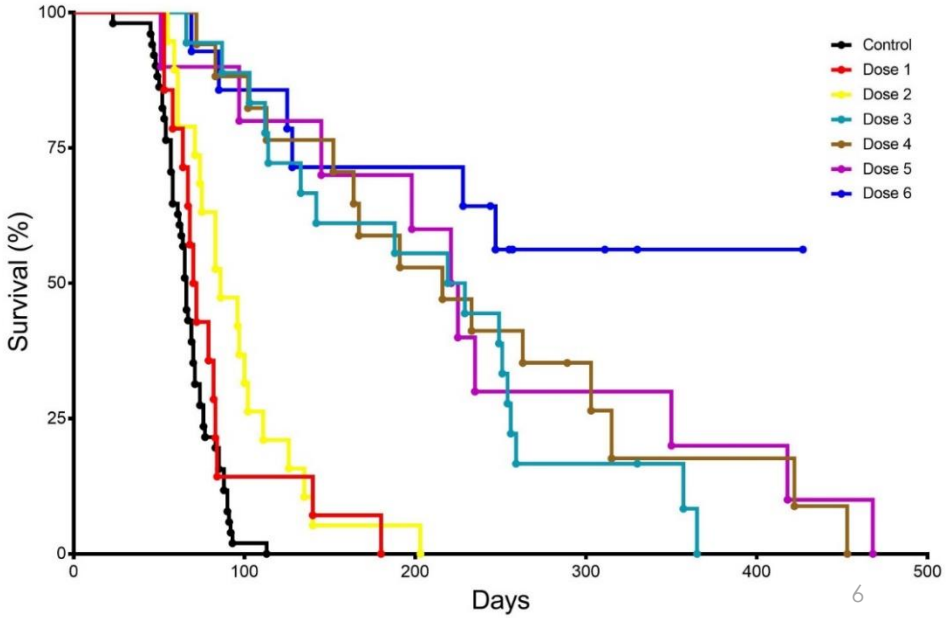
KEY COMPONENTS	PURPOSE
Recombinant AAV9 Capsid Shell	• Ability to deliver via the CSF to effectively target the brain and spinal cord
scAAV ITR (Self-complementary DNA technology)	• Enables rapid onset of effect which is key in a quickly deteriorating population
Minimal *MECP2* Promoter	• Activates the transgene in neurons and astrocytes for proper *MECP2* levels
Human *MECP2* Transgene	• Full copy of a stable, functioning *MECP2* gene that is introduced into the cell's nucleus

Rendering adapted from DiMattia et al. Structural Insight into the Unique Properties of Adeno-Associated Virus Serotype 9. J. *Virol*. June 2012.

One-time CSF Delivery of AVXS-201 Extended Survival in *MECP2* Null Rett Mice

Median survival increased from 66 days to >200 days

- 65x dose range
- Doses ascend from lowest (Dose 1) to highest (Dose 6)
- 5 of 6 doses studied significantly improved survival



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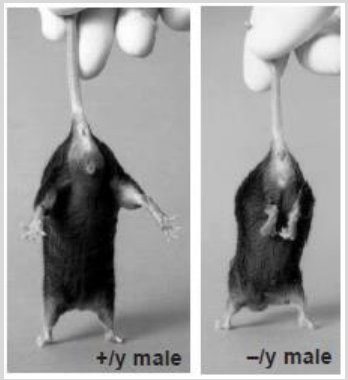
AVXS-201 Reduced Behavioral Abnormalities in Rett Mice

Reduced and maintained correction of behavioral phenotypes

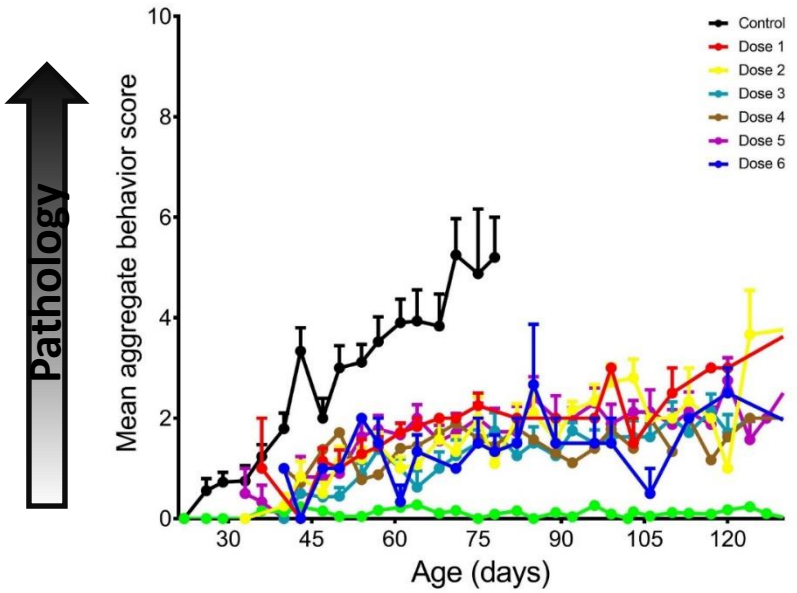
Qualitative Behavioral Scoring

Phenotypes Include:

- Tremor
- Gait
- Abnormal Respiration
- Mobility
- General Condition
- Hind limb Clasping



(Guy *et al*. 2007 Nature)



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Green line indicates Wild Type, not Rett mice

Genetic ALS with *SOD1* Mutation

Amyotrophic lateral sclerosis (ALS) is a rare, neurodegenerative genetic disorder that affects nerve cells in the brain and the spinal cord and leads to progressive degeneration of motor neurons

Overview

- **Caused by mutations in the gene** that produces the copper zinc superoxide dismutase 1 (*SOD1*) enzyme
  - Monogenic
- **Genetic (or familial) ALS affects** 1,000-2,000 in the U.S., 15 – 20% caused by mutations in *SOD1*
- **Onset** usually occurs in people between 40-70 years of age
- **Disease is progressive with significant disability** including muscle weakness resulting in loss of the ability to speak, eat, move, and eventually breathe, typically resulting in death within 3-5 years of diagnosis

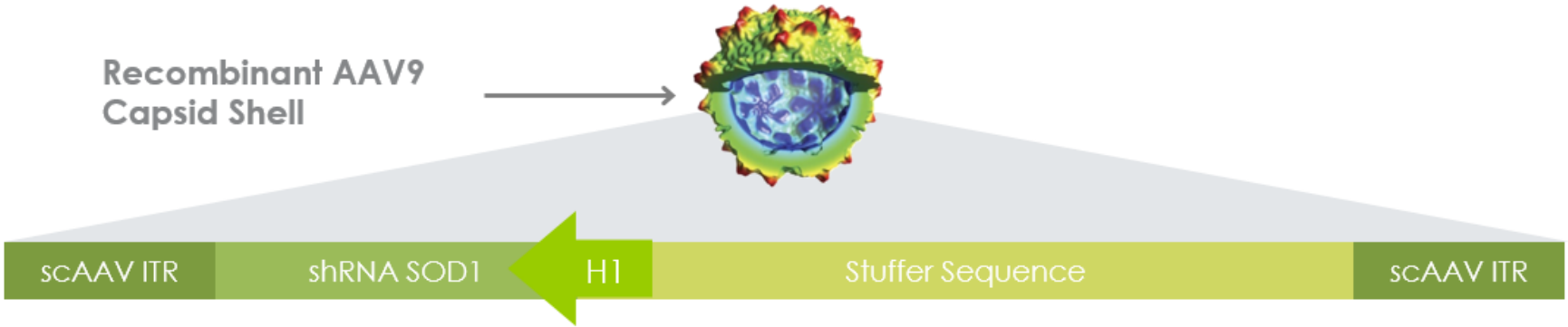
Treatment Landscape

- **Median age** at diagnosis is 55
- **Referrals to specialists** are primarily from general neurologists, with a very small number from primary care physicians
- **Current treatment** offers modest benefits but does not address the root genetic cause
- **AveXis** is investigating a gene therapy that addresses the root cause of the disease

Our Solution: AVXS-301

An Innovative Treatment Approach for Amyotrophic Lateral Sclerosis

Gene therapy is the right approach for ALS: monogenic mutation drives the pathology

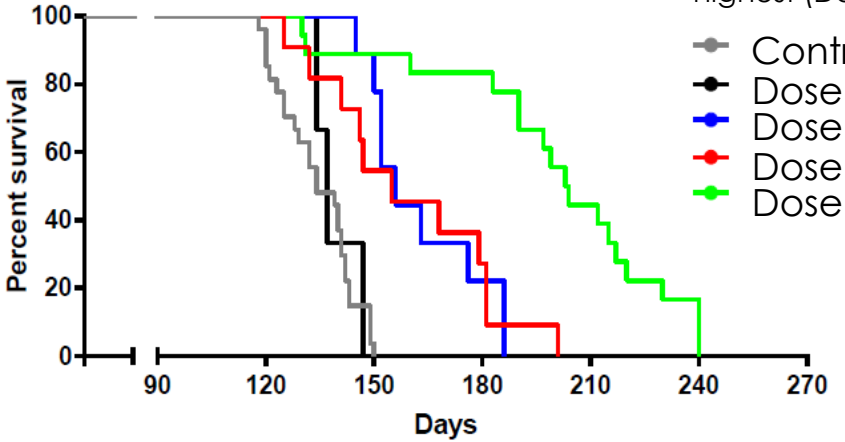


KEY COMPONENTS	PURPOSE
Recombinant AAV9 Capsid Shell	• Ability to deliver via the CSF to effectively target the brain and spinal cord
scAAV ITR (Self-complementary DNA technology)	• Enables rapid onset of effect which is key in a quickly deteriorating population
H1 promoter- shRNA *SOD1*	• Polymerase III promoter to drive expression of shRNA to suppress *SOD1*
Stuffer Sequence	• Stuffer sequence to ensure optimal vector size for proper packaging

Rendering adapted from DiMattia et al. Structural Insight into the Unique Properties of Adeno-Associated Virus Serotype 9. J. *Virol*. June 2012.

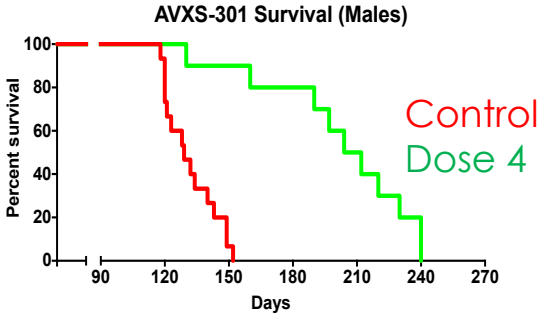
One-Time CSF Delivery of AVXS-301 Extended Survival in Male and Female ALS Model

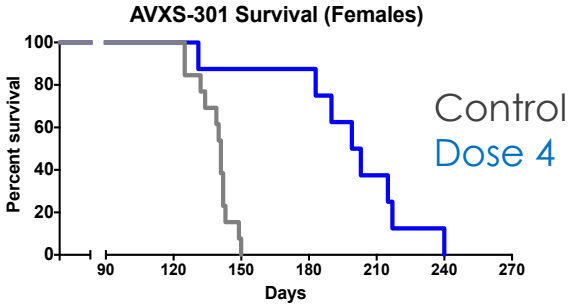
Median survival increased from ~130 days to >200 days



Doses ascend from lowest (Dose 1) to highest (Dose 4)

- Control
- Dose 1
- Dose 2
- Dose 3
- Dose 4



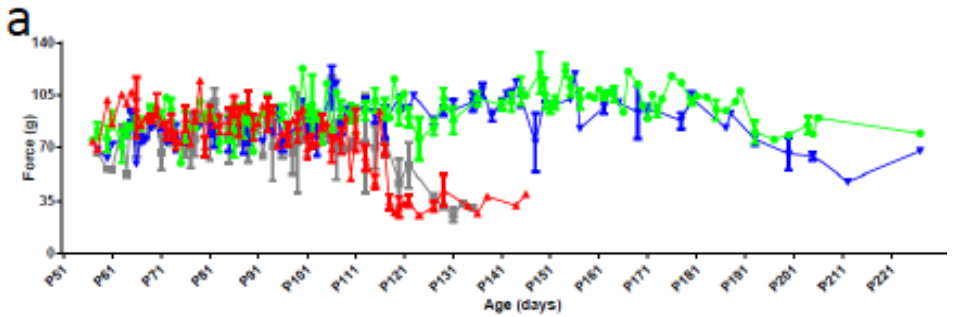


(Society of Neuroscience, 2017)

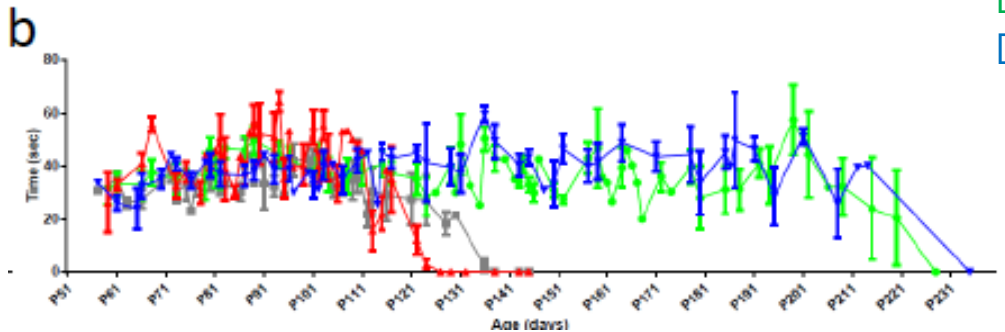
AVXS-301 Delayed Motor Impairment in ALS Mice

Maintained motor function through 200 days in male and female mice

Hind limb Grip Strength



Rotarod Performance



Control (Males)
Control (Females)

Dose 4 (Males)
Dose 4 (Females)

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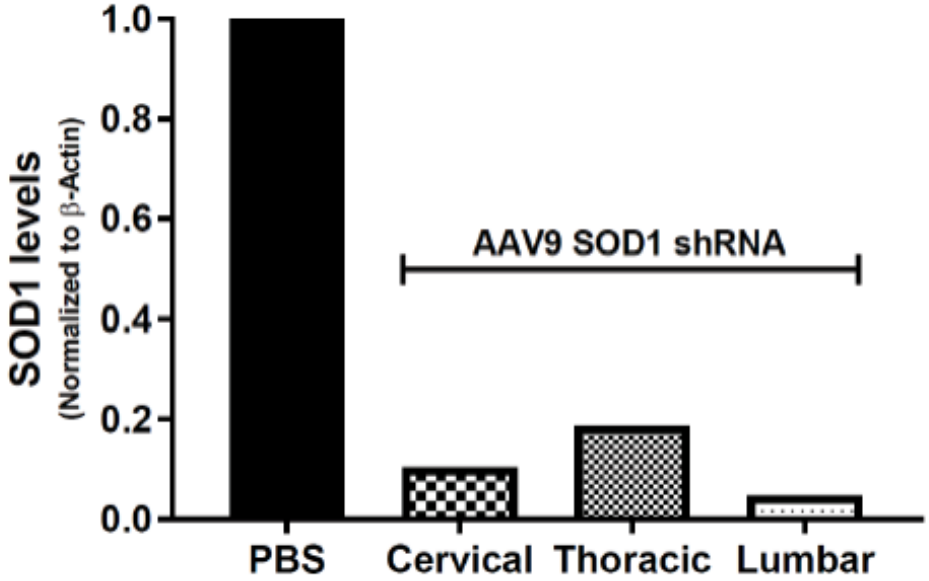
AVXS-301 Effectively Reduced *SOD1* mRNA

One-time CSF delivery of AVXS-301 in 10-year-old non-human primates reduced *SOD1*



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Preclinical Summary of AAV9 Gene Therapy for Rett Syndrome and ALS

PRECLINICAL DATA OF ONE-TIME DELIVERY OF AAV9 GENE THERAPY IN RETT SYNDROME AND GENETIC ALS DEMONSTRATED PROMISING EFFICACY AND SAFETY

- Gene therapy resulted in one of the longest living Rett syndrome and ALS mouse models reported to date, surpassing 200 days median survival
- Treated Rett syndrome mice displayed sustained reduction in behavioral abnormalities compared to untreated animals
- Treated ALS mice maintained motor function compared to untreated animals
- Safety profile in mice and non-human primates indicated gene therapy appeared to be safe and well-tolerated

Next Steps

AVEXIS INTENDS TO SUBMIT IND APPLICATIONS FOR AVXS-201 AND AVXS-301 IN LATE 2018/EARLY 2019

- AVXS-201 and AVXS-301 leverage AveXis' scalable manufacturing platform by interchanging 1 plasmid
  - Engineering runs at scale completed for AVXS-201 and AVXS-301
  - GMP campaign ongoing for AVXS-201 and scheduled for AVXS-301
- Complete remaining IND-enabling preclinical work
- KOL meetings for both AVXS-201 and AVXS-301 have occurred and clinical plans are forthcoming
- AveXis intends to submit IND applications for both indications in late 2018/early 2019

Thank You