



2020
VIRTUAL

SMA RESEARCH



MEETING



PROGRAM AND ABSTRACT GUIDE

UNITED, AT HOME
#VIRTUALSMACONFERENCE

JUNE 11-12, 2020



Make today a
breakthrough.

Dear Researchers & Clinicians,

Welcome to the virtual edition of the anticipated 24th Annual Spinal Muscular Atrophy (SMA) Researcher Meeting. As you know, due to the COVID-19 pandemic, Cure SMA made the difficult decision to cancel our scheduled in-person meeting. While we are disappointed to not gather in one place, the health and safety of our attendees is our top priority. We are very pleased you have chosen to join us in this first-ever virtual meeting, and we hope you find it to be both informative and helpful.

One of the most unique and valued components of our annual meeting is the ability for researchers and families to interact. While this is more difficult due to current circumstances, we highly encourage you to participate in the Friday Night Celebration on June 12th at 7 p.m. CT. At this time, we are asking virtual attendees of both the Annual SMA Conference and the Research & Clinical Care Meeting to think about what represents “unity” for you, then share this symbol on your social channels (Facebook, Twitter, Instagram) using the #SMAConferenceAtHome and #CureSMA. We want to show that while we are apart, we are all connected in the fight against SMA.

The Cure SMA mission is to lead the way to a world without SMA. We fund and direct comprehensive research that drives breakthroughs in treatment and care, and we provide individuals and families the support they need today. We believe that hosting and financially supporting this meeting helps achieve this mission by promoting a more motivated, collaborative, and productive SMA research community. Our specific virtual meeting goals are:

- Providing an open venue for the sharing of new, unpublished data.
- Fostering research collaborations among attendees.
- Creating a sense of community among SMA researchers.
- Integrating new researchers and drug companies into the SMA community.

As mentioned above, a critical element of our annual research meeting is to foster collaboration. To that end, we encourage all participants to reach out to speakers and fellow researchers if they hear data in these sessions that may be relevant to their work.

We would also like to take this opportunity to thank the Cure SMA Scientific Advisory Board (SAB) for their time and effort in organizing this meeting. Their help is invaluable. The SAB includes Elliot Androphy, M.D.; Arthur Burghes, Ph.D.; Thomas Crawford, M.D.; Stephen J. Kolb, M.D., Ph.D.; Adrian Krainer, Ph.D.; Umrao Monani, Ph.D.; Samuel Pfaff, Ph.D.; Katherine Klinger, Ph.D.; Christine DiDonato, Ph.D.; and Charlotte Sumner, M.D. We also extend our gratitude to Kathryn Swoboda, M.D., who recently stepped down from our SAB after many years of service. We thank her for her devotion and contributions to Cure SMA and the SMA community at large.

Finally, Cure SMA thanks all of you for your ongoing commitment to SMA research. We know that each participant in the SMA research community plays an essential role in our mission of a world without SMA.

Sincerely,



Jill Jarecki, PhD
Cure SMA Chief Scientific Officer



Jacqueline Glascock, PhD
Cure SMA Research Programs Director

JOIN US!

FOR AN END-OF-CONFERENCE
CELEBRATION

To cap off the 2020 Virtual SMA Conference week, we want to see the full SMA community come together and show how we are “United, At Home.”

Friday, June 12th at 7:00 p.m. CT

What represents “unity” for you? Share this symbol with us on your social channels.

cure
SMA



#SMAConferenceAtHome and #CureSMA

THURSDAY

JUNE 11, 2020

Basic and Clinical Research
12:00 PM – 4:00 PM (CT)

Welcome Jackie Glascock, Ph.D. Director of Research Programs, Cure SMA	12:00 PM to 12:05 PM
Gain of Toxic Function by Long-Term SMN Overexpression in the Mouse Motor Circuit Meaghan Van Alstyne	12:05 PM to 12:20 PM
Degeneration of Proprioceptive Synapses Precedes p53-Dependent Motor Neuron Death in Different Mouse Models for SMA Jannik Maximilian Büttner	12:20 AM to 12:35 PM
Impact of Neuregulin 1 Type III Overexpression on Motor Axon Development in SMA Model Mice Jeffrey Petigrow	12:35 AM to 12:50 PM
Motor Transmission Defects with Sex Differences in a New Mouse Model of Mild SMA Marc-Olivier Deguise	12:50 AM to 1:05 PM
Targeting Muscle Stem Cells to Treat SMA Sean Buchanan	1:05 PM to 1:20 PM
Identification of Functional SMNs and Suppressors of the Nonfunctional SMNE134K Anton Blatnik	1:20 PM to 1:35 PM
SMN-Primed Ribosomes Modulate the Translation of Transcripts Related to SMA Ewout Groen	1:35 PM to 1:50 PM
Minor snRNA Gene Delivery Rescues the Loss of Proprioceptive Synapses on SMA Motor Neurons Christian Lorson	1:50 PM to 2:05 PM
ZPR1: An Alternative SMN-Dependent Modifier for the Rescue of SMA Laxman Gangwani	2:05 PM to 2:20 PM
BREAK	2:20 PM to 2:45 PM
Fast-to-Slow Remodeling and Lower Oxidative Capacity of Upper Arm Muscles in SMA Type 3 and 4 Laura E. Habets	2:45 PM to 3:00 PM
NMJ Transmission Failure in Adults with SMA W. David Arnold	3:00 PM to 3:15 PM
Nusinersen Does Not Mitigate Spine Pathoanatomy in SMA Patients Michael Troy	3:15 PM to 3:30 PM
Baseline Plasma Phosphorylated Neurofilament Heavy Chain Level Predicts Sitting in Nusinersen-Treated Individuals with Infantile-Onset SMA Charlotte Sumner	3:30 PM to 3:45 PM
Continued Nusinersen Treatment Reduced Caregiver Impact and Improved Health Related Quality of Life Among Children with Later-Onset SMA: Results from the SHINE Study Jacqueline Montes	3:45 PM to 4:00 PM

FRIDAY

JUNE 12, 2020

**Clinical Drug Development
12:00 PM – 3:05 PM (CT)**

MEETING AGENDA

Welcome Jill Jarecki, Ph.D. Chief Scientific Officer, Cure SMA	12:00 PM to 12:05 PM
Clinical Development of SRK-015, a Fully Human Anti-ProMyostatin Monoclonal Antibody, for the Treatment of Later Onset SMA George Nomikos	12:05 PM to 12:20 PM
A Phase 2 Study to Evaluate the Efficacy and Safety of SRK-015 in Patients with Later-Onset SMA (TOPAZ): An Introduction Amy Place	12:20 AM to 12:35 PM
FIREFISH Part 2: Efficacy and Safety of Risdiplam (RG7916) in Infants with Type 1 SMA Laurent Servais	12:35 AM to 12:50 PM
SUNFISH Part 1: 24-month Safety and Exploratory Outcomes of Risdiplam (RG7916) Treatment in Patients with Type 2 or 3 SMA John Day	12:50 AM to 1:05 PM
JEWELFISH: Safety and Pharmacodynamic Data in Non-Naive Patients with SMA Receiving Treatment with Risdiplam Claudia Chiriboga	1:05 PM to 1:20 PM
Onasemnogene Abeparvovec Gene Therapy in Presymptomatic SMA: SPR1NT Study Update Kevin Strauss	1:20 PM to 1:35 PM
Onasemnogene Abeparvovec Gene Therapy for SMA Type 1: Phase 3 Study (STR1VE-US) Update John Day	1:35 PM to 1:50 PM
One-Time Administration of AVXS-101 IT for SMA: Phase 1/2 Study (STRONG) Richard Finkel	1:50 PM to 2:05 PM
Nusinersen Effect in Infants Who Initiate Treatment in a Presymptomatic Stage of SMA: NURTURE Results Kathryn Swoboda	2:05 PM to 2:20 PM
Prospective Open-Label Study of Nusinersen Treatment for Adults with Spinal Muscular Atrophy Part 1: Ambulatory Adults with SMA Part 2: Non-Ambulatory Adults with SMA Bakri Elsheikh	2:20 PM to 2:35 PM
Escalating Dose and Randomized, Controlled Study of Nusinersen in Participants with SMA; Study Design and Updated Enrollment for the Phase 2/3 DEVOTE (232SM203) Study to Explore High Dose Nusinersen Richard Finkel	2:35 PM to 2:50 PM
Preliminary Results of the Spinraza in Adults with SMA (SAS) Study Craig Zaidman	2:50 PM to 3:05 PM

WHEN A CHILD HAS A LIFE-THREATENING GENETIC CONDITION, IT'S NOT JUST A DISEASE. IT'S DEVASTATING.

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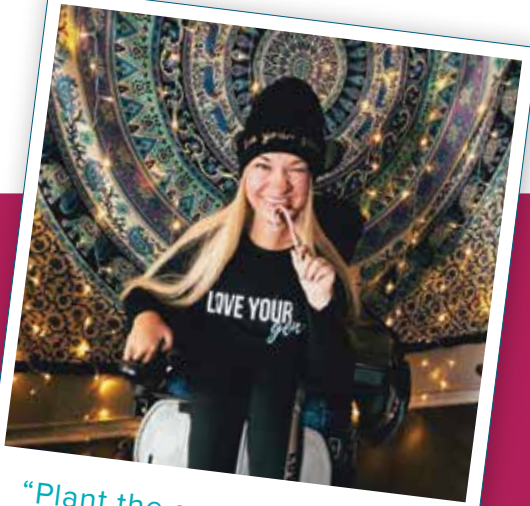
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Enrollment in the TOPAZ trial has been completed and we look forward to keeping the SMA community updated on our progress.



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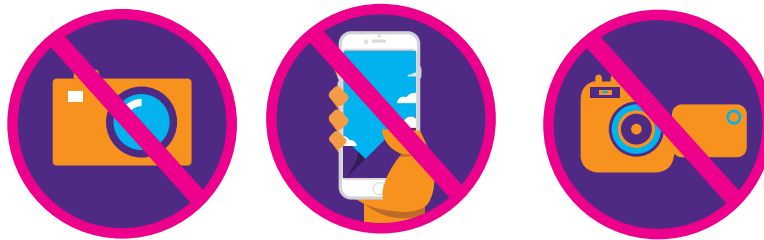


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BASIC AND CLINICAL RESEARCH ABSTRACTS



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GAIN OF TOXIC FUNCTION BY LONG-TERM SMN OVEREXPRESSION IN THE MOUSE MOTOR CIRCUIT

Meaghan Van Alstyne 1,2,3, Ivan Tattoli 1,2, Nicolas Delestree 1,2, Yocelyn Recinos 1,4, Eileen Workman 1,2, Lamya S. Shihabuddin 5, Chaolin Zhang 1,4, George Z. Mentis 1,2,3, Livio Pellizzoni 1,2,3

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2. Department of Pathology and Cell Biology, Columbia University, New York (NY), USA
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4. Department of Systems Biology, Columbia University, New York (NY), USA
5. Neuroscience Therapeutic Area, Sanofi, Framingham (MA), US

Background: SMA is a neurodegenerative disease characterized by motor dysfunction and skeletal muscle atrophy. FDA-approved therapies increase SMN expression through antisense oligonucleotides that correct SMN2 splicing and gene replacement with AAV9-SMN. Moreover, FDA approval is pending for orally bioavailable small molecules that promote SMN2 splicing. At a time when SMN-inducing therapies with different mechanisms of action are available, it is critical to compare and contrast their benefits and potential liabilities. In this respect, unlike the correction of SMN2 splicing, the potential for SMN expression well beyond physiological levels is a unique feature of AAV9-SMN gene therapy. However, the biology of SMN overexpression is poorly understood and the long-term safety of AAV9-SMN is unknown.

Results: This study stemmed from the unexpected observation of late-onset toxicity associated with intracerebroventricular delivery of AAV9-SMN in mouse models and aimed to determine the underlying mechanisms. We found that long-term, AAV9-mediated overexpression of SMN leads to motor deficits in a dose-dependent manner as assayed by a battery of behavioral tests. This toxicity is characterized by late-onset impairment of sensory-motor connectivity in both wild-type and 'rescued' SMA mice, affecting the same group of spinal motor circuit neurons that are particularly vulnerable to SMN deficiency in SMA. Importantly, none of these effects were observed in mice injected with equivalent doses of AAV9-GFP. At the cellular level, the exceedingly high levels of SMN expression in motor neurons and proprioceptive neurons that is associated with AAV9-SMN gene delivery in combination with their post-mitotic nature induces dramatic and progressive cytoplasmic aggregation. This is concomitant with the sequestration of SMN's endogenous substrates in the cytoplasmic aggregates and consequent disruption of snRNP biogenesis and function. Accordingly, RNA sequencing revealed splicing dysregulation consistent with reduced availability of nuclear snRNPs and widespread transcriptional abnormalities in dorsal root ganglia (DRG) that are specifically associated with AAV9-mediated SMN overexpression. Furthermore, pathway analysis to identify downstream pathogenic cellular processes revealed strong induction of genes associated with inflammation and the innate immune response, which could contribute to observed AAV9-SMN dependent DRG pathology including synaptic loss and neuronal death.

Conclusions: Our findings reveal toxic gain of function mechanisms by which AAV9-mediated SMN overexpression leads to inhibition of its normal activity in RNA processing and consequent induction of SMA-like functional abnormalities at the molecular, cellular, and morphological level. Unlike known acute toxicity of high systemic doses of AAV9 in target organs such as the liver, these deleterious effects are slow-progressing, SMN-dependent, and neuron-specific. In addition to uncovering a new facet of SMN biology, this study provides a mechanistic framework to explain the recently reported DRG toxicity of AAV9-SMN in non-human primates that led the FDA to halt intrathecal clinical trials of Zolgensma in SMA patients, linking neuronal toxicity not to the biology of AAV9 viral capsids but of SMN itself.

Acknowledgements: N/A

DEGENERATION OF PROPRIOCEPTIVE SYNAPSES PRECEDES P53-DEPENDENT MOTOR NEURON DEATH IN DIFFERENT MOUSE MODELS FOR SPINAL MUSCULAR ATROPHY

Jannik M. Büttner ¹, Josiane K. Sime Longang ¹, Katharina Apel ¹, Florian Gerstner ¹, Eva Janzen ², Brunhilde Wirth ^{2,3}, Christian M. Simon ¹

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2. Institute of Human Genetics, Center for Molecular Medicine Cologne, Institute for Genetics, University of Cologne, Cologne, Germany
3. Center for Rare Diseases Cologne, University Hospital of Cologne, Cologne, Germany

Background: Patients with SMA suffer from muscle atrophy, neuronal death and impairment of the motor circuit which are closely recapitulated in SMA mouse models. Novel cellular pathomechanisms for motor circuit dysfunction have been recently discovered in the most frequently used SMA-Delta7 mouse model. Motor neurons exhibit selective death and dysfunction depending on the muscles they innervate, with proximal muscles being more affected than distal muscles. It has been shown that proprioceptive synaptic loss leads to motor neuron dysfunction, whereas motor neuron death is mediated by the cell autonomous activation of the p53 pathway. The next step to identify patient-relevant outcomes of the motor circuit pathology found in SMA-Delta7 mice is their validation in other SMA mouse models.

Results: In order to validate the importance of recent findings in the SMA-Delta7 mouse model for patients with different types of SMA, we compared those results with the motor circuit pathology of two commonly used mouse models: a severe (Taiwanese) and an intermediate (Smn2b) form of SMA. First, we compared the temporal progression of motor neuron death and loss of proprioceptive synapses within a vulnerable and a resistant lumbar spinal cord segment with the degree of NMJ denervation in their corresponding innervated muscles. Confocal analysis revealed that NMJ denervation and proprioceptive loss precede motor neuron death in all three SMA models. Strikingly, while the onset and degree of motor neuron loss and NMJ denervation vary significantly, 70% of proprioceptive synapses are consistently lost in all SMA mouse models, which lead to a functional impairment of the motor circuit measured by electrophysiological recordings of the intact spinal cord. This results in a reduction of the potassium channel Kv2.1 incorporated in the membrane of SMA motor neurons, which is required for their ability of repetitive firing, suggesting that degeneration of proprioceptive synapses leads to reduced firing in motor neurons across different SMA mouse models. Next, we investigated the mechanisms of motor neuron death. Interestingly, the accumulation and, most importantly, phosphorylation of p53 which trigger motor neuron degeneration in SMA-Delta7 mice, correlates with the temporal progression of motor neuron loss in all SMA models, which can be prevented by pharmacological inhibition of p53. This proposes a common p53 dependent mechanism for motor neuron death in SMA.

Conclusions: Here, we show that different SMA mouse models exhibit a variable degree of selective motor neuron death and NMJ denervation. In contrast, significant early proprioceptive synaptic de-generation is constant among all mouse models, suggesting central synaptic loss as a key component for motor circuit pathology in SMA mice and patients. Furthermore, we establish a common p53-dependent mechanism to trigger selective death of vulnerable motor neurons, which might be helpful as complementary SMN-independent strategies for SMA patients.

Acknowledgements: Support: DFG SI1969/2-1 and SMA Europe (CMS). DFG Wi-945/14-2, Wi-945/17-1, RTG 1960 (BW), and CMMC C16 (BW).

IMPACT OF NEUREGULIN 1 TYPE III OVEREXPRESSION ON MOTOR AXON DEVELOPMENT IN SMA MODEL MICE

Cera Hassinan 1, Jeffrey Petigrow 1, Lingling Kong 1, Michelle Harren Chan-Cortes 1, Jannick Büttner 2, Christian M. Simon 2, Charlotte Sumner 1

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2. Carl-Ludwig-Institute for Physiology, Leipzig University, Leipzig Germany

Background: We have previously demonstrated that Type I SMA patients and severe SMA model mice have severe impairments of motor axon radial growth and Schwann cell ensheathment beginning prenatally that are followed by early postnatal motor unit degeneration. Neuregulin 1 type III (NRG1-III) expressed on the surface of axons and interacting with ErbB2/3 receptors on Schwann cells is critical for axon ensheathment and myelination. In this study, we characterized the expression levels of NRG1-III in SMA patient tissues and in severe SMA mice and determined the impact of NRG1-III overexpression on motor axon development and disease outcomes in SMA Δ 7 mice.

Results: NRG1-III, but not NRG1-1 mRNA levels were reduced in Type I SMA patient spinal cord tissues and in symptomatic SMA mouse spinal cords. IHC showed a reduction in NRG1 staining in both human and mouse SMA ventral roots and in mouse spinal cords at symptomatic disease stages. In order to evaluate the effect of overexpression of NRG1-III on SMA disease pathogenesis, we bred mice expressing NRG1-III driven by the Thy1 promoter to SMA Δ 7 mice. We confirmed that both WT and SMA carrying the Thy1-NRG1-III allele overexpress NRG1-III in spinal cord tissues by immunoblotting. Both WT and SMA mice overexpressing NRG1-III showed slower weight gain and acquisition of time to right compared to non-NRG1-III overexpressing littermates indicating some general toxicity related to NRG1 overexpression. The characterization of the effects of NRG1-III overexpression on motor axon development are ongoing, but initial examination shows no change in L1 ventral root size or myelinated axon number; however there is an increase in myelin sheath thickness. Electron microscopic analysis of motor axon development at different time points is ongoing. Morphological and biochemical assessment of axonal degeneration are also ongoing.

Conclusions: Overexpression of NRG1-III early postnatally did not improve body weight, motor function, or survival of SMA mice despite an increase in myelin sheath thickness. These studies suggest that improving myelination alone is not sufficient to meaningfully impact the SMA disease phenotype.

Acknowledgements: This work was funded by the NIH R01NS106875.

MOTOR TRANSMISSION DEFECTS WITH SEX DIFFERENCES IN A NEW MOUSE MODEL OF MILD SPINAL MUSCULAR ATROPHY

Marc-Olivier Deguise 1,2,3, Yves De Repentigny 1, Alexandra Tierney 1, Ariane Beauvais 1, Jean Michaud 4, Lucia Chehade 1,2,3, Mohamed Thabet 2, Brittany Paul 1,3, Aoife Reilly 1,2,3, Sabrina Gagnon 1, Jean-Marc Renaud 2,3, Rashmi Kothary 1,2,3,5

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Background: Mouse models of mild spinal muscular atrophy (SMA) have been extremely challenging to generate. In pre-clinical models, SMN depletion causes an SMA phenotype in a very narrow range of SMN level, leading to an all-or-nothing phenomenon. As such, the mice are either very sick and severe, or almost unaffected. This paucity of model systems has limited our understanding of pathophysiological events in milder forms of the disease and of the effect of SMN depletion during aging. Having such a model will allow us to understand therapeutic requirement throughout the life of less affected SMA individuals.

Results: A mild mouse model of SMA, termed *Smn2B^{-/-};SMN2^{+/-}*, was generated by crossing *Smn^{-/-};SMN2* and *Smn2B/2B* mice. The *Smn2B^{-/-};SMN2^{+/-}* mice have normal survival, and mild but sustained motor weakness that appear more prominent in males. Motor neuron loss is not observed in the lumbar region as determined by cresyl violet and ChAT staining. Similarly, axon number in the sciatic nerve was unchanged. However, denervation and neuronal/neuromuscular junction (NMJ) transmission defects were identified through nerve-muscle electrophysiology and NMJ staining, where defects were more prominent in the male mice. Additionally, neurogenic muscle atrophy was readily observed, again with a higher prevalence in male mice. Increased centrally located nuclei, intrinsic contractile and relaxation muscle defects were also identified in both female and male mice, with some male predominance. Next, extra-neuronal pathology was investigated. There were no histological disturbances or doppler perfusion defects in the spleen. Similarly, there was no change in liver histology and triglyceride content. Lastly, there was no functional cardiac deficit as determined by echocardiogram.

Conclusions: The *Smn2B^{-/-};SMN2^{+/-}* mouse provides a model of mild SMA, displaying some hallmark features including reduced weight, sustained motor weakness, electrophysiological transmission deficit, NMJ defects, and muscle atrophy. Early and prominent increase in central nucleation and intrinsic electrophysiological deficits demonstrate the potential role played by muscle in SMA disease. The use of this model will allow for the understanding of the most susceptible pathogenic molecular changes in motor neurons and muscles, investigation of the effects of SMN depletion in aging, sex differences and most importantly will provide guidance for the currently aging SMA patients treated with the recently approved genetic therapies.

Acknowledgements: This work was supported by Cure SMA/Families of SMA Canada (grant KOT-1819 and KOT-2021); Muscular Dystrophy Association (grant 575466); and Canadian Institutes of Health Research (grant PJT-156379).

TARGETING MUSCLE STEM CELLS TO TREAT SPINAL MUSCULAR ATROPHY

Sean M. Buchanan, Rebecca M. Gibbs, Feodor D. Price, Lee L. Rubin

Department of Stem Cell & Regenerative Biology, Harvard University, Cambridge, MA

Background: Although the motor unit consists of both the motor neuron and the muscle that it innervates, muscle is often overlooked in the pathology and therapeutic development for motor neuron disorders. Treatments that enhance muscle's capacity for repair, and especially those that target the satellite cell, the adult stem cell responsible for the growth and regeneration of skeletal muscle, might reduce the atrophy, fibrosis and loss of strength characteristic of SMA and other diseases. Using genetic approaches, stem cell-based models and small molecule screening, we have revealed muscle-specific defects that result from the loss of SMN protein and identified compounds and therapeutic targets that can enhance satellite cells' ability to repair damaged muscle.

Results: We and others have shown that in SMA, skeletal muscle is not only affected by the loss of motor neurons, but has intrinsic defects in its development, growth and regeneration after damage. Here we have further explored the effects of SMN mutations on the satellite cell itself. We find that when SMN protein levels are reduced in *in vitro* and *in vivo* mouse models of SMA, satellite cells show profound defects in their ability to proliferate and to properly differentiate into fused myotubes, even when SMN expression is only lowered specifically in satellite cells. We also tested our findings in myogenic cells derived from SMA patient iPS cells. Again, mutations in SMN1, or reduction of SMN protein levels by siRNA, lead to impairments in the capacity to form myotubes. We next worked to identify novel therapies and therapeutic targets that might improve muscle growth and regeneration in SMA patients. Intriguingly, muscle from SMA patients still contains at least some satellite cells. Small molecule screens carried out using FACS purified mouse satellite cells identified multiple compounds and candidate drug targets that can enhance satellite cell proliferation, improve muscle regeneration, increase bodyweight and improve behavior in a mouse model of SMA. These results point towards novel inroads to treating SMA, potentially used in combination with SMN-elevating therapeutics.

Conclusions: Skeletal muscle represents a critical, but overlooked, tissue in neuromuscular disorders. In SMA patients, muscle is impaired both from the loss of innervation from motor neurons, and from muscle-intrinsic defects resulting from the loss of SMN protein. Novel therapies that target muscle stem cells to enhance their repair and regenerative abilities represent a completely novel strategy to treating these types of diseases. Importantly, these approaches may be complementary to drugs that act on SMN protein levels or on motor neurons themselves, and they may be necessary to restore function and quality of life to patients who have already experienced muscle atrophy.

Acknowledgements: This work was funded by grants from Frequency Therapeutics, Atlas Venture and the NINDS.

IDENTIFICATION OF FUNCTIONAL SMNS AND SUPPRESSORS OF THE NONFUNCTIONAL SMNE134K

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2. Salk Institute for Biological Studies, Howard Hughes Medical Institute, La Jolla CA, United States
3. Department of Gene Therapy, The Research Institute at Nationwide Children's Hospital, Columbus OH, United States
4. Department of Biochemistry, Theodor-Boveri-Institute at the Biocentre, University of Wurzburg, Wurzburg, Germany

Background: SMA is caused by mutation or deletion of SMN1 and retention of SMN2 leading to SMN deficiency. How SMN deficiency results in motor neuron loss and SMA is unknown. Many molecular pathways have been shown to be affected by SMN deficiency, however whether this is due to direct SMN involvement and whether these affected pathways are critical to SMA pathogenesis is unclear. To determine which pathways are important to SMA, we developed a cell line which can be conditionally deleted for wild-type SMN through removal of *Smn* exon 7 by Cre-recombinase. Deletion of wtSMN always results in lethality in these cells and thus can be used to determine what SMN alleles are functional. Nonfunctional SMN alleles can be used to mine for suppressors which will identify critical pathways involved in SMA.

Results: Our cells have been used to assay whether loss of function mutations in SMN1 have function in the absence of SMN2. We report missense mutants SMNA2G, D44V, A111G, E134K, and T274I do not rescue survival in cells lacking wtSMN. To date no missense alleles have partial function in mammals, but instead work in concert with the wtSMN produced from SMN2. Given SMN forms an oligomeric complex, we asked if two different SMN mutants interact to produce a functional oligomer. We analyze this effect in our cells, finding complementation between different SMN alleles to occur between several combinations indicating the oligomer is the functional unit of SMN in the cell. Furthermore, we have used the E134K mutation in a screen for suppressors. While the E134K mutation never rescues deleted SMN cell lines, ENU mutagenesis yielded 5 lines which do survive. Genome sequencing identified 4 mutations in known SMN interactors. One candidate is a mutation in an Sm protein. Upon reintroduction into the SMNE134K cell line, we confirmed expression of this Sm mutant suppresses lethality when wtSMN is deleted. The Sm mutant does not rescue cell viability in complete absence of SMN. In vitro assembly assays indicate that, in the presence of the Sm suppressor mutant, E134K assembles snRNPs more efficiently than conditions using wtSMN and Sm. This suggests the Sm mutant is specific to E134K loss of function and implicates Sm assembly as a critical function affected by the E134K mutation. We are testing whether introduction of the Sm suppressor via scAAV9 rescues electrophysiology and survival in SMNE134K SMA mice. These results will identify how rescue of Sm assembly affects SMA pathogenesis.

Conclusions: We have created a novel system to identify functional and nonfunctional SMNs using cell survival as the primary readout upon deletion of wtSMN. We have provided further evidence the oligomer is the functional unit of SMN in the cell by showing coexpression of two nonfunctional SMN missense mutants can rescue cell survival. We have identified Sm assembly as a critical pathway affected by the SMNE134K mutation through a suppressor screen yielding mutation in an Sm protein. Carrying these experiments forward into SMNE134K SMA mice, we will test how rescue of Sm assembly contributes to SMA pathogenesis. In summary, we have created a pipeline capable of discerning which molecular pathways are affected by SMN1 missense mutations and which of these pathways are critical to SMA pathogenesis.

Acknowledgements: This work was supported by CureSMA, the Marshall Heritage Foundation, and the National Institute of Child Health & Human Development.

SMN-PRIMED RIBOSOMES MODULATE THE TRANSLATION OF TRANSCRIPTS RELATED TO SPINAL MUSCULAR ATROPHY

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Background: The cellular roles of the survival motor neuron (SMN) protein have been studied extensively and, consequently, many molecular pathways have been implicated in the pathogenesis of SMA. However, the exact mechanisms leading to motor neuron degeneration remain elusive. Recent work by several groups has implicated defective protein translation as a central pathway in SMA pathogenesis. Specifically, we have shown previously that genome-wide defects occur in mRNA recruitment onto polysomes in SMA, but how SMN is linked to these defects remains to be investigated.

Results: Here, we demonstrate that SMN binds directly to ribosomes and that this interaction is tissue dependent. SMN-primed ribosomes regulate a set of mRNAs which are enriched in IRES-like sequences in the 5'UTR and rare codons at the start of their coding sequence. Loss of SMN at early stages of SMA induces translational defects in vivo, including ribosome depletion at rare codons. These defects cause ribosome depletion from mRNAs bound by SMN-primed ribosomes and translational impairment of proteins involved in motor neuron function and stability, including acetylcholinesterase. When we further characterized these defects, we found that changes at the translational level lead to modified expression and localization of acetylcholinesterase in a mouse model of SMA.

Conclusions: Thus, SMN plays a crucial role in the regulation of ribosome fluxes along a specific subset of mRNAs which encode proteins relevant to SMA pathogenesis.

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MINOR SNRNA GENE DELIVERY RESCUES THE LOSS OF PROPRIOCEPTIVE SYNAPSES ON SMA MOTOR NEURONS

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Background: Spinal muscular atrophy (SMA) is an inherited neuromuscular disorder caused by reduced expression of the survival motor neuron (SMN) protein. SMN has key functions in multiple RNA pathways, including the biogenesis of small nuclear ribonucleoproteins (snRNPs) that are essential components of both major (U2-dependent) and minor (U12-dependent) spliceosomes. Here we investigated the specific contribution of U12 splicing dysfunction to SMA pathology through selective restoration of this RNA pathway in mouse models of varying phenotypic severity.

Results: We show that viral-mediated delivery of minor snRNA genes specifically improves select U12 splicing defects induced by SMN deficiency in cultured mammalian cells as well as in the spinal cord and dorsal root ganglia of SMA mice without increasing SMN expression. This approach resulted in a moderate amelioration of several parameters of the disease phenotype in SMA mice including survival, weight gain and motor function. Importantly, minor snRNA gene delivery improved aberrant splicing of the U12 intron-containing gene *Stasimon* and rescued the severe loss of proprioceptive sensory synapses on SMA motor neurons, which are early signatures of motor circuit dysfunction in mouse models.

Conclusions: Taken together, these findings establish the direct contribution of U12 splicing dysfunction to synaptic deafferentation and motor circuit pathology in SMA.

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ZPR1: AN ALTERNATIVE SMN-DEPENDENT MODIFIER FOR THE RESCUE OF SPINAL MUSCULAR ATROPHY

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Background: Spinal muscular atrophy (SMA) is a neuromuscular disorder caused by homozygous mutation or deletion of the survival motor neuron 1 (SMN1) gene. A second copy SMN2 is similar to SMN1 but produces ~10% SMN protein because of a single-point mutation that causes splicing defects. SMA is caused by chronic low levels of SMN and is characterized by degeneration of motor neurons leading to muscle atrophy and death. Chronic low levels of SMN cause accumulation of pathogenic R-loops and DNA damage leading to genomic instability and neurodegeneration in SMA. Severity of SMA disease correlates inversely with SMN levels. The SMN2 gene is a promising target to produce higher levels of SMN by enhancing its expression. Mechanisms that regulate expression of SMN genes are largely unknown.

Results: In this study, we investigated the function of zinc finger protein ZPR1 as a potential regulator of the SMN genes expression. ZPR1 is a potential candidate modifier gene, which is downregulated in SMA patients and may contribute to the severity of disease. However, whether ZPR1 overexpression will rescue SMA disease and emerge as a protective modifier of SMA remains to be examined. We investigated the effect of in vivo genetic overexpression of ZPR1 on the rescue of SMA using SMA mouse model. We also investigated the molecular mechanism of ZPR1-dependent prevention of R-loop and DNA damage accumulation and the rescue of SMA phenotype. We report that ZPR1 binds to RNA polymerase II, interacts in vivo with SMN locus and upregulates SMN2 expression in SMA mice and patient cells. Modulation of ZPR1 levels directly correlates and influences SMN2 expression levels in SMA patient cells. ZPR1 overexpression in vivo results in a systemic increase of SMN levels and rescues severe to moderate disease in SMA mice. ZPR1-dependent rescue improves growth and motor function and increases the lifespan of male and female SMA mice. ZPR1 reduces neurodegeneration in SMA mice and prevents degeneration of cultured primary spinal cord neurons derived from SMA mice. Further, we show that the chronic low levels of ZPR1 associated with SMA pathogenesis cause accumulation of transcriptional RNA-DNA hybrids (R-loops) and DNA damage leading to genomic instability in SMA mice and patient cells. Complementation with ZPR1 elevates Senataxin levels, reduces R-loop accumulation and rescues DNA damage in SMA mice, motor neurons and patient cells.

Conclusions: In conclusion, ZPR1 is critical for preventing accumulation of pathogenic R-loops and DNA damage to avert genomic instability and neurodegeneration in SMA. ZPR1 enhances in vivo SMN2 gene expression and leads to SMN-dependent rescue of severe to moderate SMA. ZPR1 represents a protective modifier and a therapeutic target for developing a new method, including scAAV9-ZPR1 based gene therapy for the treatment of milder forms of SMA.

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FAST-TO-SLOW REMODELING AND LOWER OXIDATIVE CAPACITY OF UPPER ARM MUSCLES IN SMA TYPE 3 AND 4

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Background: Exercise intolerance affects activities of daily life in patients with SMA. Several studies have found abnormalities at the level of mitochondria and capillary contacts in SMA muscle that may impair ATP balance during exercise, and so contribute to the phenotype. Here, we used in vivo 31P Magnetic Resonance Spectroscopy (MRS) to test if muscular oxidative ATP synthetic capacity is altered in SMA type 3-4. Fifteen patients and age and gender matched controls performed two bouts of dynamic arm-cycling exercise until exhaustion inside an MRI scanner. 31P MRS data were collected from the m. biceps and m. triceps muscles of the upper arm at rest, during exercise and recovery, yielding quantitative ATP metabolite (Pi and Phosphocreatine (PCr)) and pH dynamics over time for each muscle.

Results: Fifteen patients (age(y): 40 ± 17 , m/f: 5/10) with SMA type 3a (n=6), type 3b (n=8) and type 4 (n=1), and fifteen controls (age(y): 40 ± 17 , m/f: 5/10) were enrolled. Motor function and muscle strength of the patients with SMA was moderately affected (HFMSE: 38.4 ± 17.7 , MRC m. biceps: ≥ 4 , MRC m. triceps: ≥ 2). Arm-cycling endurance in patients (m. biceps: 187 ± 116 s, m. triceps: 180 ± 127 s, mean \pm SD) was shorter compared to controls (m. biceps: 441 ± 77 s, m. triceps: 431 ± 141 s). 31P MRS datasets of eleven patients and their controls have been analyzed thus far. In the majority of patients, the dominant signal in the 31P MR spectra of the m. biceps and m. triceps collected at the point of exhaustion originated from accumulated Pi in mild-to-moderately acidified slow-oxidative (SO; pH 6.8-7.2) and fast-oxidative-glycolytic (FOG; pH 6.7-6.5) myofibers. In contrast, the dominant Pi signal in 31P MR spectra of fatigued m. biceps and m. triceps of healthy controls typically originated from highly acidified fast-glycolytic (FG; pH 6.4-6.0) fibers. Post-exercise oxidative PCr recovery to resting levels was analyzed by non-linear curve fitting of exponential functions according to standard methods (Meyer, 1988). Recovery time (RT; min.) was defined as three times the time constant. RT was prolonged in five patients with SMA (m. biceps 4.6 ± 1.1 min., m. triceps: 4.7 ± 1.4 min. (mean \pm SD)) compared to 1.5-2 min. in healthy oxidative muscle fibers (Meyerspeer, 2020).

Conclusions: This is the first study that provides in vivo data on dynamic muscle fiber recruitment and oxidative metabolic function of upper arm muscles in human SMA. Our results suggest fast-to-slow remodeling of these muscles in the majority of patients with SMA, and decreased oxidative metabolic capacity in half of these patients. These findings correlate well with known symptoms of weakness and exercise intolerance, respectively, in SMA type 3 and 4. Finally, the results of this study provide a rational basis for personalized training programs and treatment strategies, which can be monitored using this non-invasive investigative platform.

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NMJ TRANSMISSION FAILURE IN ADULTS WITH SPINAL MUSCULAR ATROPHY

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Background: Spinal muscular atrophy (SMA) is an autosomal recessive motor neuron disorder caused by homozygous loss of the SMN1 gene resulting in low levels of SMN protein. Preclinical and clinical studies have shown that SMA results in altered NMJ transmission. Recent advances have led to treatment interventions that can increase SMN levels. The primary objectives of the current study were to examine the frequency of neuromuscular junction transmission abnormalities in adult participants with SMA and to explore the impact of nusinersen. Secondary objectives were to explore the relationships between clinical biomarkers and outcomes with severity of RNS decrement.

Results: Participants were enrolled as part of an ongoing study investigating the effects of nusinersen treatment in adults with SMA. Repetitive nerve stimulation (RNS) at 3 Hz was recorded from the trapezius muscle following stimulation of the spinal accessory nerve prior to and after initiation of nusinersen. CMAP amplitude decrement by >10% was considered abnormal. Other assessments included maximum voluntary isometric contraction (MVICT), Revised Upper Limb Module (RULM), forced vital capacity (FVC), and ulnar CMAP and Single Motor Unit Potential (SMUP). RNS has been performed at baseline (prior to nusinersen) in 12 adult participants with SMA, and enrollment is ongoing. Abnormal RNS was demonstrated in 8 (67%) with a mean decrement of 19±5%. No differences were noted between individuals with and without abnormal RNS, for mean age (43±13 years versus 38± years), age of onset (44±28 months versus 28±13 months), or disease duration (40±12 years versus 36±13 years). RNS was associated with CMAP($r=0.842$, $p=0.018$) and SMUP($r=0.662$, $p=0.105$); absolute FVC ($r=0.833$, $p=0.020$) and % predicted FVC($r=0.893$, $p=0.007$); MVIC for key pinch($r=0.909$, $p=0.012$), hand grip($r=0.780$, $p=0.067$), knee extension($r=0.914$, $p=0.030$), knee flexion($r=0.802$, $p=0.103$); and RULM($r=0.789$, $p=0.035$). Preliminary analysis suggests no change of % RNS decrement with nusinersen treatment.

Conclusions: Our results suggest that a high percentage of adults with SMA patients have NMJ transmission defects as measured by RNS at 3 Hz stimulation of the spinal accessory nerve. The findings of significant correlations between RNS and other measures suggest that NMJ transmission is related to disease severity and physical function. While our preliminary data suggests that NMJ transmission defects may persist despite treatment with nusinersen, this study is ongoing to further investigate this possibility. If NMJ defects are persistent following SMN-restoring therapies, modulation of NMJ transmission may be a promising target for additive pharmacological interventions.

Acknowledgements: The study is funded by Cure SMA.

NUSINERSEN DOES NOT MITIGATE SPINE PATHOANATOMY IN SPINAL MUSCULAR ATROPHY PATIENTS

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Background: SMA is a genetically-inherited, neuromuscular disorder characterized by degeneration of alpha motor neurons due to deletions or mutations in SMN1 gene resulting in nonfunctioning SMN protein. Phenotype severity depends on the number of SMN2 rescue gene copies: < 3 copies is associated with progressive muscle atrophy, respiratory dysfunction and spine/thoracic (parasol rib) deformity. Nusinersen is an antisense oligonucleotide, administered intrathecally that improves muscle strength/pulmonary function in SMA patients, depending on SMN2 copy number and age at treatment initiation. Our hypothesis is that SMA patients receiving treatment will have lower incidence, slower progression and less need for surgery for scoliosis compared to similar cohort of SMA patients not treated with Nusinersin.

Results: 87 SMA subjects were analyzed: median age @ baseline 3.9 years (range, 0.2-23.9), followed for median 7.1 years (2.1-15.3) to median age 11.6 years (3.0-36.3) (Table 1). 43 subjects (49%) were treated with Nusinersen for a median of 2.1 years (1-6.6). Baseline and follow-up radiographs of the spine and thorax were measured to document presence/progression of deformity. Owing to differences in age and phenotype between treatment groups at baseline (untreated: older, bigger Cobb), statistical analysis included younger subjects with baseline scoliosis < 40 to better match the cohorts at baseline: 39/66 (59%) treated with Nusinersen before 2018. The effect of treatment on change in curve magnitude between baseline and follow-up was evaluated using mixed model analysis that controlled for age and duration follow-up. Results No differences were detected between treatment groups with regard to progression of scoliosis, parasol rib deformity, need for respiratory assist, or need for spine surgery.

Conclusions: The benefit to SMA patients treated with Nusinersen depends on the number of SMN-2 copies and remaining neuro-motor axis growth at the time of treatment initiation. However Nusinersen did not delay or ameliorate the progression of scoliosis, parasol rib deformity, need for respiratory assist or surgical intervention.

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BASELINE PLASMA PHOSPHORYLATED NEUROFILAMENT HEAVY CHAIN LEVEL PREDICTS SITTING IN NUSINERSEN-TREATED INDIVIDUALS WITH INFANTILE-ONSET SMA

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Background: Neurofilament (NF) isoforms are major structural proteins of the neuronal cytoskeleton and are released into interstitial fluid following axonal damage or neuronal degeneration. Elevated NF levels have been detected in neurodegenerative disorders. These analyses investigated the association between plasma phosphorylated NF heavy chain (pNF-H) levels and achieving the motor milestone of sitting in nusinersen-treated individuals with infantile-onset SMA. Individuals treated with nusinersen in the Phase 3, randomized, double-blind ENDEAR (most likely to develop SMA Type I) study had the opportunity to transition to the open-label SHINE extension study (NCT02594124).

Results: Plasma pNF-H levels were measured at baseline and predose using the pNF-H SimplePlex ELLA assay (ProteinSimple). Odds ratios (OR) and area under the receiver operating characteristic (ROC) curves were used to determine any association with the Hammersmith Infant Neurological Examination Section 2 motor milestone of sitting (proper sitting [score of 2] and improvement of ≥ 1 point in sitting motor milestone score) in infants < 2 years, or the WHO motor milestone of sitting in children aged ≥ 2 years. Participants who died during the study were considered as non-responders and data imputed. The reported data are based on the 15 October 2018 SHINE data cut. Baseline log pNF-H was inversely associated with Day 302 achievement of sitting when adjusted for baseline Childrens Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) and age at first dose (explanatory variables): OR=0.024, $p=0.0128$, $n=60$. The area under the ROC curve for this analysis was 0.9499, suggesting that baseline plasma pNF-H level is a strong predictor of sitting. A significant association between baseline log pNF-H and Day 302 achievement of sitting persisted after adjusting for Day 64 plasma log pNF-H change from baseline, baseline CHOP INTEND, and age at first dose (OR=0.011, $p=0.0232$, $n=51$; area under the ROC curve, 0.9419). When adjusting for Day 183 plasma log pNF-H change from baseline, baseline CHOP INTEND, and age at first dose, the association approached the borderline of significance (OR=0.018; $p=0.0575$; $n=44$). The area under the ROC curve was 0.9683, suggesting a strong association with these explanatory variables, however. Additional analyses will be presented.

Conclusions: Baseline plasma pNF-H is a good predictor of early sitting among nusinersen-treated ENDEAR/SHINE participants; lower baseline pNF-H is associated with achievement of sitting. Further analyses are warranted to evaluate plasma pNF-H as a biomarker in SMA.

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CONTINUED NUSINERSEN TREATMENT REDUCED CAREGIVER IMPACT AND IMPROVED HEALTH RELATED QUALITY OF LIFE AMONG CHILDREN WITH LATER-ONSET SMA: RESULTS FROM THE SHINE STUDY

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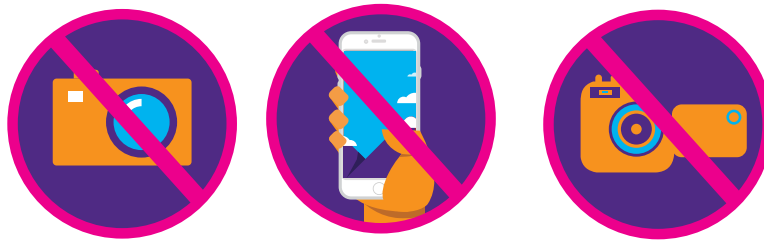
Background: In the Phase 3, randomized, double-blind, sham procedure-controlled CHERISH study (NCT02292537), nusinersen demonstrated significant and clinically meaningful improvement in motor function versus sham control in children with later-onset SMA. Within CHERISH, nusinersen was also associated with reduced caregiver impact and less decline in health-related quality of life (HRQoL) among children with later-onset SMA versus sham control. Children with later-onset SMA who completed CHERISH were eligible to enroll in the SHINE open-label extension study (NCT02594124) in which, following a protocol amendment, all participants receive nusinersen 12 mg every 4 months. The effects of longer-term treatment with nusinersen on caregiver impact and HRQoL were evaluated in SHINE.

Results: The Assessment of Caregiver Experience with Neuromuscular Disease (ACEND) and Pediatric Quality of Life Inventory (PedsQL) Generic Core and Neuromuscular Module were administered to caregivers of children with later-onset SMA in CHERISH and SHINE. Both the ACEND and PedsQL scales are scored from 0-100 and higher scores indicate reduced caregiver impact and improved HRQoL, respectively. SHINE interim data from 27 August 2019 were evaluated focusing on children with a value windowed to Day 1170. ACEND scores among caregivers improved (mean change [95% CI] from baseline of CHERISH to Day 1170) for the nusinersen treated group in CHERISH/SHINE (n=67) in five out of the seven subdomains: Feeding/Grooming/Dressing: 10.3 (5.99, 14.54), Sitting/Playing: 1.1 (-2.18, 4.45), Transfers: 3.5 (-0.68, 7.70), Mobility: 5.0 (-0.47, 10.45), and Finance: 0.7 (-3.76, 5.25). Those treated with nusinersen in CHERISH/SHINE who were younger at first dose (≥ 2 to < 3.5 y, and ≥ 3.5 to < 5 y) showed greater benefits in caregiver impact than older children (≥ 5 to < 9.5 y) in six out of seven subdomains of the ACEND. For example, mean change (95% CI) from baseline of CHERISH to Day 1170 in Feeding/Grooming/Dressing total score was 17.4 (8.90, 25.89) among ≥ 2 to < 3.5 y (n=23), 9.9 (2.94, 16.81) among ≥ 3.5 to < 5 y (n=27), and 1.3 (-3.26, 5.77) among ≥ 5 to < 9.5 y (n=17). PedsQL generic total score improved from baseline of CHERISH to Day 1170 for children treated with nusinersen in CHERISH/SHINE (n=63): mean (95% CI) change was 2.3 (-1.08, 5.72); whereas the PedsQL neuromuscular module score showed stabilization over time: -0.2 (-3.79, 3.49).

Conclusions: Continued nusinersen treatment reduced caregiver impact in CHERISH/SHINE as assessed by the ACEND. Younger participants treated with nusinersen in CHERISH/SHINE showed greater reductions in caregiver impact than older children on the majority of subdomains of the ACEND. Improved HRQoL was observed among children treated with nusinersen in CHERISH/SHINE at Day 1170, as reported on the parent proxy PedsQL Generic Core scale. In addition to significant and clinically meaningful improvements in motor function among children with later-onset SMA, nusinersen was associated with reduced impact for caregivers and improvements in HRQoL for children with later-onset SMA over 3 years as measured by the ACEND and PedsQL, respectively.

Acknowledgements: This study was sponsored by Biogen. Writing and editorial support for the preparation of this abstract was provided by Excel Scientific Solutions (Fairfield, CT, USA); funding was provided by Biogen.

CLINICAL DRUG DEVELOPMENT ABSTRACTS



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CLINICAL DEVELOPMENT OF SRK-015, A FULLY HUMAN ANTI-PROMYOSTATIN MONOCLONAL ANTIBODY, FOR THE TREATMENT OF LATER ONSET SPINAL MUSCULAR ATROPHY

George Nomikos on Behalf of the Scholar Rock Team

Scholar Rock

Background: SRK-015 is a fully human anti-proMyostatin monoclonal antibody (mAb) that selectively binds to pro-/latent myostatin with high affinity, inhibiting the proteolytic activation of the growth factor. SRK-015 is being developed for the treatment of spinal muscular atrophy (SMA) by targeting muscle atrophy and improving muscle strength, with the aim of offering clinically meaningful improvements in motor function.

Results: Pre-clinical studies demonstrated selective inhibition of myostatin activation, effectively increasing muscle mass and function in a SMA mouse model. No toxicologically significant findings were observed for SRK-015 in rats and non-human primates. A Phase 1, healthy volunteer study demonstrated a favorable safety profile of SRK-015 administered intravenously (IV) at all doses tested. The ongoing Phase 2 study evaluates the safety and efficacy of SRK-015 dosed IV every four weeks over a 12-month treatment period; Three distinct and parallel cohorts were enrolled. Cohort 1 enrolled 20 patients (5-21 years old) with ambulatory Type 3 SMA and were treated with 20 mg/kg of SRK-015 as monotherapy or in conjunction with an approved SMN up-regulator. The primary objectives are to assess safety and the mean change from baseline in the Revised Hammersmith Scale (RHS). Cohort 2 enrolled 15 patients (5-21 years old) with Type 2 or non-ambulatory Type 3 SMA, who were already treated with an approved SMN up-regulator. Patients were treated with 20 mg/kg of SRK-015. The primary objectives are to assess safety and the mean change from baseline in Hammersmith Functional Motor Scale Expanded (HF MSE). Cohort 3 enrolled 20 patients with Type 2 SMA, who were at least 2 years old and initiated treatment with an approved SMA up-regulator before turning five. Patients were randomized 1:1 to either 2 mg/kg or 20 mg/kg of SRK-015. The primary objectives are to assess safety and the mean change from baseline in HF MSE.

Conclusions: N/A

Acknowledgements: Participants in the Phase 1 and Phase 2 Trials and the Scholar Rock Myostatin Team.

A PHASE 2 STUDY TO EVALUATE THE EFFICACY AND SAFETY OF SRK-015 IN PATIENTS WITH LATER-ONSET SPINAL MUSCULAR ATROPHY (TOPAZ): AN INTRODUCTION

Amy Place, George Nomikos, Doreen Barrett, Mara Sadanowicz, Stephanie D'Eon, Tiina Xu, Guochen Song, Shaun Cote, Ryan Jarrobino, Yung Chyung

Scholar Rock

Background: SRK-015 is a fully human anti-proMyostatin monoclonal antibody that's being developed and investigated for the treatment of later-onset SMA. This Phase 2 study involves approximately 25 study sites across United States and Europe. The study purpose is to evaluate the safety and efficacy of SRK-015 on motor function in SMA patients with Types 2 and 3, aged 2 through 21 years old, for 52 weeks. All patients received SRK-015 every 4 weeks via intravenous infusion.

Results: Patients in Cohorts 1 and 2 were directly assigned to a 20 mg/kg SRK-015 dose and patients in Cohort 3 were randomized 1:1 in a double-blind manner to either 2 mg/kg or 20 mg/kg SRK-015. Cohort 1 (N=23) enrolled ambulatory Type 3 patients, at least some of whom were not receiving an approved SMA up-regulator, as well as patients receiving an approved SMA treatment that was started after the patient turned 5 years old. Cohort 2 (N=15) enrolled Type 2 and non-ambulatory Type 3 patients already receiving an approved SMA up-regulator that was started after the patient turned 5 years old. Cohort 3 (N=20) enrolled Type 2 patients, who started on an approved SMA up-regulator before the patient turned 5 years old. The primary efficacy endpoint for Cohort 1 is the change from baseline in the Revised Hammersmith Scale. The primary efficacy endpoint for Cohorts 2 and 3 is change from baseline in Hammersmith Functional Motor Scale Expanded.

Conclusions: Safety is being assessed throughout the trial by the Safety Surveillance Team. Blood samples for the measurement of SRK-015 concentrations, circulating latent myostatin concentrations, and anti-SRK-015 antibodies are being obtained. Demographic, baseline characteristics and PK/PD data will be presented.

Acknowledgements: Participants in the Phase 2 Trial and the Scholar Rock Myostatin Team.

FIREFISH PART 2: EFFICACY AND SAFETY OF RISDIPLAM (RG7916) IN INFANTS WITH TYPE 1 SPINAL MUSCULAR ATROPHY

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Background: Spinal muscular atrophy (SMA) is a severe, progressive neuromuscular disease caused by reduced levels of survival of motor neuron (SMN) protein due to deletions and/or mutations of the SMN1 gene. A second gene, SMN2, produces only low levels of functional SMN protein. Risdiplam (RG7916) is a centrally and peripherally distributed oral SMN2 pre-mRNA splicing modifier that increases the levels of functional SMN protein. FIREFISH (NCT02913482) is an ongoing, multicenter, open-label study of risdiplam in infants aged 1–7 months at enrollment with Type 1 SMA and two SMN2 gene copies.

Results: FIREFISH Part 1 (n=21) assesses the safety, tolerability, pharmacokinetics and pharmacodynamics of different risdiplam dose levels (plus exploratory efficacy outcomes). In FIREFISH Part 1 there have been no drug-related safety findings leading to withdrawal from the study following ≤ 30 (median 19) months of treatment (data-cut: 2nd July 2019). The primary objective of confirmatory Part 2 (n=41) is to investigate the efficacy of risdiplam at the dose selected in Part 1. The primary efficacy endpoint is the proportion of infants sitting without support for 5 seconds after 12 months on treatment, as assessed by Item 22 of the Gross Motor Scale of the Bayley Scales of Infant and Toddler Development, third edition. Additional secondary endpoints will also be measured. The primary endpoint of FIREFISH Part 2 at 12 months was met (data-cut: 14th November 2019). Here, we will report efficacy and safety data in participants who have received treatment with risdiplam for a minimum of 12 months at the dose selected in Part 1.

Conclusions: Part 2 of FIREFISH will provide important data on the efficacy and safety of risdiplam in infants with Type 1 SMA.

Acknowledgements: The authors would like to thank all individuals enrolled in the risdiplam studies, their families and the site staff involved. Study sponsored by F. Hoffmann-La Roche Ltd., Basel, Switzerland.

SUNFISH PART 1: 24-MONTH SAFETY AND EXPLORATORY OUTCOMES OF RISDIPLAM (RG7916) TREATMENT IN PATIENTS WITH TYPE 2 OR 3 SPINAL MUSCULAR ATROPHY (SMA)

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Background: Spinal muscular atrophy (SMA) is a severe, progressive neuromuscular disease caused by reduced levels of survival of motor neuron (SMN) protein due to deletions and/or mutations of the SMN1 gene. A second gene, SMN2, produces only low levels of functional SMN protein. Risdiplam (RG7916) is a centrally and peripherally distributed oral SMN2 pre-mRNA splicing modifier that increases the levels of functional SMN protein. SUNFISH (NCT02908685) is a multicenter, two-part, randomized, placebo-controlled, double-blind study of risdiplam (randomized 2:1, risdiplam:placebo) in a broad population of patients with Type 2 or 3 SMA, aged 2-25 years.

Results: SUNFISH Part 1 (n=51) was a dose-selection study assessing the safety, tolerability and pharmacokinetics/pharmacodynamics (PK/PD) of different risdiplam dose levels in patients with Type 2 and 3 SMA (ambulant and non-ambulant). SUNFISH Part 2 (n=180) is a confirmatory study assessing the safety and efficacy of the Part 1-selected dose level of risdiplam versus placebo in patients with Type 2 and non-ambulant Type 3 SMA. The SUNFISH Part 1 patient population had a broad range of ages and clinical characteristics (functional level, scoliosis and contractures). There have been no deaths or drug-related safety findings leading to withdrawal in SUNFISH Part 1 or 2 to date (data-cuts: 28th June 2019 and 6th September 2019, respectively). In an interim analysis of Part 1 (data-cut: 9th Jan 2019) risdiplam treatment led to a median >2-fold increase in blood SMN protein levels after 4 weeks of treatment, which was sustained for at least 12 months. Despite not being designed to detect efficacy, exploratory 32-item Motor Function Measure (MFM32) results from Part 1 indicated that treatment with risdiplam led to improvements in motor function versus natural history after all patients were treated for a minimum of 12 months with the pivotal dose (data-cut: 9th Jan 2019). Safety, tolerability and PK/PD data will be reported for the first time from all patients in Part 1 who have been treated with the pivotal dose of risdiplam for a minimum of 24 months (data-cut: 15th Jan 2020). Updated Part 1 exploratory efficacy data, including motor outcome measures, will also be presented

Conclusions: The clinical benefit of risdiplam is being assessed in Part 2 of the SUNFISH study, which met its primary endpoint of change from baseline in MFM32 scale after 1 year of treatment with risdiplam, compared to placebo (data-cut: 6th Sept 2019). The multinational SUNFISH study is the first positive placebo-controlled trial undertaken in a heterogeneous patient population with Type 2 or 3 non-ambulant SMA, aged 2-25 years. Part 1 and Part 2 of SUNFISH are ongoing globally.

Acknowledgements: The authors would like to thank all individuals enrolled in the risdiplam studies, their families and the site staff involved. Study sponsored by F. Hoffmann-La Roche Ltd, Basel, Switzerland.

JEWELFISH: SAFETY AND PHARMACODYNAMIC DATA IN NON-NAIVE PATIENTS WITH SPINAL MUSCULAR ATROPHY RECEIVING TREATMENT WITH RISDIPLAM

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Background: Spinal muscular atrophy (SMA) is a severe, progressive neuromuscular disease caused by reduced levels of survival of motor neuron (SMN) protein due to deletions and/or mutations of the SMN1 gene. A second SMN gene, SMN2, produces only low levels of functional SMN protein. Risdiplam (RG7916) is a centrally and peripherally distributed oral SMN2 pre-mRNA splicing modifier that increases the levels of functional SMN protein. JEWELFISH (NCT03032172) is a multicenter, open-label study of daily oral risdiplam in non-naïve patients with SMA, aged 6 months to 60 years. JEWELFISH participants previously received RG7800 (RO6885247), nusinersen (SPINRAZA®), olesoxime or onasemnogene abeparvovec-xioi (ZOLGENSMA®).

Results: JEWELFISH (N=174) assesses the safety, tolerability and pharmacokinetics (PK)/pharmacodynamics (PD) relationship of risdiplam. We have previously presented safety data from 45 patients with SMA (data-cut: 28th June 2019) who received risdiplam for up to 28.9 months (nine patients previously received RG7800, 24 patients received nusinersen and 12 patients received olesoxime). No drug-related safety findings leading to withdrawal were reported. In an earlier analysis of SMN protein in whole blood, while patient numbers were limited (n=18), the magnitude of SMN protein increase (>2-fold) was comparable to that in SUNFISH Part 1 (NCT02908685) in patients with Types 2 and 3 SMA who had not previously received an SMN2-targeting therapy. We will present updated data on safety and PK/PD from patients within the JEWELFISH study, including new patients, and reasons for discontinuing previous treatment regimens.

Conclusions: The JEWELFISH study is ongoing in sites across Europe and the US.

Acknowledgements: The authors would like to thank all individuals enrolled in the risdiplam studies, their families and the site staff involved. Study sponsored by F. Hoffmann-La Roche Ltd, Basel, Switzerland.

ONASEMNOGENE ABEPARVOVEC GENE THERAPY IN PRESYMPTOMATIC SPINAL MUSCULAR ATROPHY: SPR1NT STUDY UPDATE

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Background: Spinal muscular atrophy (SMA) causes loss of motor/respiratory function due to biallelic survival motor neuron 1 gene (SMN1) deletion/mutation. Copies of a similar gene (SMN2) modify disease severity. Here, we assess the safety/efficacy of onasemnogene abeparvec (formerly AVXS-101) in presymptomatic SMA patients (pts). SPR1NT (NCT03505099) is an ongoing multicenter, open-label, phase 3 study. Asymptomatic pts expected to develop SMA (2–3xSMN2, ≤6 weeks) receive a one-time IV onasemnogene abeparvec infusion and are assessed through 18/24 (2x/3xSMN2) months. Primary outcomes: sitting ≥30 seconds (2xSMN2)/standing unassisted ≥3 seconds (3xSMN2). Exploratory outcome: motor function improvement (CHOP INTEND). Safety outcomes: incidence of adverse events (AEs)/serious AEs.

Results: As of 31 Dec 2019, 30 pts were dosed (2xSMN2/3xSMN2/4xSMN2, n=14/15/1). Mean age (range) at dosing: 2xSMN2, 20.6 (8.0–34.0) days; 3xSMN2, 28.7 (9.0–43.0) days. Mean age (range) at last follow-up visit: 2xSMN2: 11.2 (6.0–18.6) months; 3xSMN2, 9.7 (3.3–15.1) months. All pts are alive and none required ventilator support as of last visit. Among 2xSMN2 pts, all have achieved CHOP INTEND scores of ≥50, which exceeds the maximal score observed in untreated pts; a mean CHOP INTEND increase of 16.3 points from baseline was observed at 6 months post-dosing; 8 pts achieved the primary endpoint of sitting (all within the WHO 1st–99th percentile; range: 5.7–11.8 months); 4 stood and walked independently (range: 12.2–18.3 months). Among 3xSMN2 pts, 10 sat independently (6.1–12.0 months); 4 achieved the primary endpoint of standing independently (9.5–12.4 months); 7 walked with assistance (12.2–15.1 months) and 3 walked alone (9.3–12.4 months). The remaining pts in both Cohorts who have not achieved these milestones have not yet passed the WHO window and are progressing toward achieving the primary endpoint by the end of the study. All pts (2x–3xSMN2) evaluated at 6 or 12 months demonstrated intact swallowing. Nearly all pts are able to feed orally without need for feeding support, and most remained within the healthy, appropriate weight range. All pts experienced ≥1 AE; treatment-related AEs were reported in 17/30 pts; 17/30 pts experienced AEs of special interest. All serious AEs resolved and were considered unrelated to onasemnogene abeparvec.

Conclusions: As of 31 Dec 2019, preliminary SPR1NT data reported that presymptomatic SMA pts dosed with one-time IV onasemnogene abeparvec continued to meet primary endpoints. Pts remained free of ventilatory support of any kind. Furthermore, age-appropriate motor milestones and intact swallowing were demonstrated. Compared with observations in the natural history, these data suggest that onasemnogene abeparvec has a significant therapeutic benefit in milestone achievements in presymptomatic pts with SMA. Reported AEs were manageable and consistent with the known safety profile of onasemnogene abeparvec.

Acknowledgements: The authors thank the investigators, site coordinators, patients, families, and caregivers. Medical writing assistance was provided by Ashfield Healthcare Communications.

ONASEMNOGENE ABEPARVOVEC GENE THERAPY FOR SPINAL MUSCULAR ATROPHY TYPE 1: PHASE 3 STUDY (STR1VE-US) UPDATE

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Background: Onasemnogene abeparvovec (formerly AVXS-101), a one-time intravenous (IV) adeno-associated virus serotype 9-based gene therapy, is designed to deliver a fully functional copy of the human survival motor neuron gene (SMN) to address the genetic root cause of spinal muscular atrophy (SMA). Here, we evaluate final data from STR1VE-US (NCT03306277), a multicenter, open-label, single-arm, single-dose, phase 3 study conducted in the United States investigating efficacy and safety of one-time IV infusion of onasemnogene abeparvovec in patients (pts) with SMA1 < 6 months (mos) of age.

Results: Study is complete, final data are presented. Co-primary endpoints: independent sitting for ≥ 30 seconds at the 18 mo visit, survival (no death/permanent ventilation) at 14 mos. Co-secondary endpoints: ability to thrive at 18 mos (tolerates thin liquids, no mechanical nutrition support, maintains weight consistent with age), independence from ventilatory support at 18 mos (based on Trilogy BiPAP usage). All 22 pts met intention-to-treat criteria (symptomatic with bi-allelic SMN1 deletions and 2 copies of SMN2 without the variant in SMN2 disease modifier. All co-primary and co-secondary endpoints were statistically superior to the Pediatric Neuromuscular Clinical Research (PNCr) database comparator. Twenty-one of 22 pts (95.5%) survived ≥ 10.5 mos without permanent ventilatory support and 20 of 22 pts (90.9%) survived event-free to 18 mos of age. For comparison, the relevant PNCr dataset showed event-free survival of 50% at 10.5 mos and 25% at 13.6 mos. Fourteen pts (63.6%) achieved the milestone of sitting independently during the study, 13 (59.0%) of whom also demonstrated this ability at the Month 18 visit. Nine of 22 pts (40.9%) maintained the ability to thrive at 18 mos of age and 15 of 22 pts (68.1%) did not require any ventilator support at any point during the study, both of which compared favorably to the PNCr dataset. Through 18 mos of age, 19 pts (86.4%) achieved motor milestones, confirmed by independent central video review. Rapid, early, and sustained improvements in CHOP INTEND were observed. The safety was generally similar to that observed in the phase 1 START study and the risk-benefit remains positive.

Conclusions: The therapeutic benefit of onasemnogene abeparvovec was demonstrated in prolonging survival independent of permanent ventilatory support, achieving the milestone of sitting independently for 30 seconds in more than 60% of treated pts, and maintaining the ability to thrive and independence from ventilatory support. Rapid and sustained improvements in CHOP INTEND scores demonstrate efficacy on motor function. No new clinical safety signals were detected. Overall, final data from the STR1VE-US study demonstrate that onasemnogene abeparvovec has significant therapeutic benefit in the treatment of pts with SMA1 and the benefit:risk profile remains favorable.

Acknowledgements: The authors thank the investigators, site coordinators, patients, families, and caregivers for their participation. Medical writing assistance was provided by Ashfield Healthcare Communications.

ONE-TIME ADMINISTRATION OF AVXS-101 IT FOR SPINAL MUSCULAR ATROPHY: PHASE 1/2 STUDY (STRONG)

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Background: Spinal muscular atrophy type 1 (SMA1) is caused by deletion/mutation of the survival motor neuron 1 gene (SMN1). AVXS-101 intrathecal (IT) addresses the genetic root cause of SMA. STRONG, a phase 1/2 study (NCT03381729), assessed the safety/tolerability, optimal dose, and efficacy of AVXS-101 IT. Patients (biallelic SMN1 loss, 3xSMN2) aged $\geq 6 < 60$ months who could sit but not stand/walk received a single, one-time AVXS-101 IT dose (dose A: 6.0×10^{13} ; B: 1.2×10^{14} ; C: 2.4×10^{14} vg). Primary endpoints: safety/tolerability, optimal dose, unsupported standing for ≥ 3 seconds ($\geq 6 < 24$ months) and change in baseline Hammersmith Functional Motor Scale Expanded (HFMSSE) score from baseline ($\geq 24 < 60$ months) at 12 months post-dose.

Results: As of 31 May 2019, 31 patients were enrolled (dose A, complete: $n=3$, $\geq 6 < 24$ months; dose B, complete: $n=13$, $\geq 6 < 24$ months; $n=12$, $\geq 24 < 60$ months; dose C, ongoing: $n=3$). As of 8 March 2019 ($n=30$ patients), no fatal treatment-emergent adverse events (TEAEs) have occurred; 7 serious TEAEs occurred in 4 patients. As of 31 May 2019, HFMSSE increased a mean 5.9 points from baseline at most recent visit in patients $24 < 60$ months (mean [range] duration of follow-up, 9.3 [7.211.9] months). Six of 12 patients (50%) aged ≥ 24 and < 60 months demonstrated ≥ 3 -point increase in baseline HFMSSE at 1 month after dosing. Eighteen motor milestones were gained following treatment in patients $\geq 6 < 24$ months; 2 stood independently, 1 walked alone. In patients $\geq 24 < 60$ months, 3/12 (25%) gained motor milestones following treatment; 1 walked with assistance. End of study data from the first 2 cohorts will be presented.

Conclusions: Dose A and B cohort interim data from the ongoing, multicenter, STRONG study demonstrate signs of efficacy (motor milestones and functional achievements) in sitting but non-ambulatory patients with SMA. No dose-limiting toxicity was observed, permitting dose-escalation of AVXS-101 IT; safety profile remains favorable and consistent with known AEs associated with onasemnogene abeparvovec.

Acknowledgements: The authors thank the investigators, site coordinators, patients, families, and caregivers. Medical writing assistance was provided by Ashfield Healthcare Communications.

NUSINERSEN EFFECT IN INFANTS WHO INITIATE TREATMENT IN A PRESYMPTOMATIC STAGE OF SMA: NURTURE RESULTS

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Background: Nusinersen is the first approved treatment for spinal muscular atrophy (SMA). The objective is to present interim results from the ongoing NURTURE study (NCT02386553) examining the efficacy and safety of intrathecal nusinersen initiated in presymptomatic infants with two or three SMN2 copies. Enrolled infants were ≤ 6 weeks at first dose, clinically presymptomatic, and genetically diagnosed with SMA. The primary endpoint is time to death or respiratory intervention (≥ 6 hours/day continuously for ≥ 7 days or tracheostomy).

Results: NURTURE has enrolled 25 infants (two copies SMN2, $n = 15$; three copies, $n = 10$). As of 29 March 2019, the median age at last visit was 34.8 (range 25.7–45.4) months. All infants were alive and none required permanent ventilation. Four infants (all with two SMN2 copies) required respiratory intervention over the course of the study, with all cases initiated during an acute reversible illness. Median time to death or respiratory intervention could not be estimated because of too few events. All 25 infants achieved the World Health Organization (WHO) motor milestone of sitting without support, 23/25 (92%) achieved walking with assistance, and 22/25 (88%) were walking alone. Most children achieved these motor milestones (21/25 [84%] sitting without support, 15/23 [65%] walking with assistance, and 16/22 [73%] independent walking) within the 99th percentile age window established by the WHO for healthy children. Nearly all children reached the maximum score on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) scale. Phosphorylated neurofilament heavy chain (pNF-H) levels rapidly declined during the loading phase of nusinersen and then stabilized. Plasma pNF-H levels at Day 64 were significantly correlated with the WHO motor milestone walking alone age (Spearman's $r = 0.64$; $p = 0.0025$; $n = 20$). No new safety concerns were identified. Results from a new, Spring 2020 interim analysis, including additional assessments, will be presented.

Conclusions: These data demonstrate the continued benefit to infants who initiated nusinersen before symptom onset, emphasizing the value of newborn screening and early treatment.

Acknowledgements: Study sponsored by Biogen (Cambridge, MA, USA); writing and editorial support for abstract preparation was provided by Excel Scientific Solutions (Fairfield, CT, USA); funding was provided by Biogen.

PROSPECTIVE OPEN-LABEL STUDY OF NUSINERSEN TREATMENT FOR ADULTS WITH SPINAL MUSCULAR ATROPHY

PART ONE: AMBULATORY ADULTS WITH SPINAL MUSCULAR ATROPHY

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Background: Nusinersen is an intrathecally administered antisense-oligonucleotide that modulates the splicing of the SMN2 pre-messenger RNA. Several studies have demonstrated favorable benefit: risk profile and clinically-meaningful responses in the pediatric SMA patients. There is limited data regarding the safety and efficacy of nusinersen treatment in adults with SMA, the best outcome measures to track response to treatment and the effects of increased SMN protein levels on motor unit number and size. Aims of this study were to determine the following in ambulatory- adults with SMA: 1. Safety and tolerability of intrathecal nusinersen treatment, 2. Efficacy of nusinersen to improve muscle strength and physical function, and 3. Effects of nusinersen treatment in adulthood on motor unit physiology.

Results: Fifteen ambulatory- adults with SMA met enrollment criteria (age 18 or older, genetically-confirmed 5q SMA, three or more copies of the SMN2 gene, and the ability to ambulate thirty feet without assistance at baseline) and were enrolled in the study. Participants were assessed at baseline (prior to first dose of nusinersen), 2, 6, 10, and 14 months. The primary outcome assessment was change from baseline in muscle strength quantified by a Maximal Voluntary Isometric Muscle Contraction average score derived from five muscle groups bilaterally (elbow flexor, elbow extensor, knee flexor, knee extensor, and handgrip). Secondary outcomes included the change from baseline in the 6-MWT distance, HFMSE, SMA-FRS, ulnar CMAP, average SMUP, MUNE, absolute FVC and percent predicted FVC. Safety outcomes included the number of participants who experience Adverse Events and Serious Adverse Events, clinically significant vital sign or laboratory parameter abnormalities. The most common side effects included headache and back pain, but overall the procedures and treatments were well tolerated. No serious adverse events reported. None of the participants had clinically significant abnormalities of vital signs or laboratory parameters or discontinued treatment. For analyses of nusinersen treatment effect on primary and secondary outcomes, data from thirteen patients were included for analyses (6 women, 7 men; mean age: $37\hat{A}\pm 11$, range: 18-59 years) based on having post-treatment assessments for at least 10 months following treatment initiation. Final study data analyses for primary and second outcome measures is underway and will be presented.

Conclusions: The majority of prior studies investigating the effect of nusinersen in SMA have focused on pediatric and infant populations. The results of the current study demonstrate that nusinersen treatment is safe and well tolerated in ambulatory adults with SMA. Final study data analyses will be presented regarding the impact of nusinersen on muscle strength, physical function, and motor unit physiology. These data will provide insight into the effects of nusinersen treatment on ambulatory adults with SMA.

Acknowledgments: The Study is funded by Biogen and Cure SMA.

PROSPECTIVE OPEN-LABEL STUDY OF NUSINERSEN TREATMENT FOR ADULTS WITH SPINAL MUSCULAR ATROPHY

PART TWO: NON-AMBULATORY ADULTS WITH SPINAL MUSCULAR ATROPHY

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Background: Nusinersen is an intrathecally administered antisense oligonucleotide that modulates the splicing of the SMN2 pre-messenger RNA. Nusinersen treatment has a favorable benefit: risk profile and clinically-meaningful responses in the pediatric SMA patients. There is limited data regarding the safety and efficacy of nusinersen treatment of adults with SMA. It is also unclear which outcome measures are optimized for tracking treatment response in non-ambulatory adults with SMA. Aims of this study were to determine the following in non-ambulatory adults with SMA: 1. Efficacy, safety and tolerability of intrathecal nusinersen treatment, 2. Role of different outcome measures to track treatment response and 3. Effects of nusinersen treatment in adulthood on motor unit physiology.

Results: 25 participants met enrollment criteria (age 18 or above, genetic confirmation of 5q SMA, inability to walk independently, and insurance treatment approval or enrollment in drug free program) and were enrolled. Assessments were performed baseline, 2, 6, 10 and 14 months. The primary outcome assessment was change from baseline in forced vital capacity. Additional secondary outcomes included change from baseline in the RULM, HFMSE, the modified SMA-FRS, ulnar CMAP amplitude, and ulnar MUNE. Safety outcome include the number of participants that experience Adverse Events and Serious Adverse Events, clinically significant vital sign or laboratory parameters abnormalities. All participants had scoliosis. Fluoroscopy guided C1-C2 lateral approach was used for participants with prior spinal fusion. Five participants were hospitalized during the course of the study for pneumonia. Two participant sustained injuries (rotator cuff injury and distal leg fracture) during transfer independent of the treatment. Other noted adverse events included headache, back pain, cervical injection site pain, and upper respiratory and urinary tract infections. Overall the procedures and treatments were well tolerated. No participant had clinically significant vital signs or laboratory parameters abnormalities or discontinued treatment. Forced vital capacity measurement was feasible in all participants. However, HFMSE and RULM testing was not feasible in 14 and 6 participants respectively. Study completion is anticipated in May 2020. Twenty participants (12 women, 8 men; mean age 39.7 ± 13.7 years of age range, 21-64) are anticipated to have completed at least 10 months of follow up assessments.

Conclusions: The results of this study confirm that nusinersen treatment is safe and well tolerated in non-ambulatory adults with SMA. C1/C2 lateral approach is a viable alternative for intrathecal drug delivery for patients with difficult intrathecal access due to spinal fusion. In adults with SMA, commonly used outcome measures are frequently inadequate or not feasible. Therefore, this study may provide insight into improved methods for tracking disease status and treatment response. Results will be presented regarding the effects of nusinersen on ventilatory and motor function in non-ambulatory adults with SMA.

Acknowledgements: The study is funded by Cure SMA.

ESCALATING DOSE AND RANDOMIZED, CONTROLLED STUDY OF NUSINERSEN IN PARTICIPANTS WITH SPINAL MUSCULAR ATROPHY (SMA); STUDY DESIGN AND UPDATED ENROLLMENT FOR THE PHASE 2/3 DEVOTE (232SM203) STUDY TO EXPLORE HIGH DOSE NUSINERSEN

Richard S. Finkel 1, John W. Day 2, Monique M. Ryan 3, Eugenio Mercuri 4, Darryl C. De Vivo 5, Samuel Ignacio Pascual Pascual 6, Jacqueline Montes 5, Juliana Gurgel-Giannetti 7, Nancy Mitchell-Sweeney 8, Richard Foster 9, Peng Sun 8, Daniela Ramirez-Schrempf 8, Boris Kandinov 8, Wildon Farwell 8, on behalf of the DEVOTE Study Group

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Background: This abstract describes the design of the 3-part, Phase 2/3 DEVOTE study (NCT04089566) that will examine the safety and efficacy of nusinersen administered intrathecally at higher doses in participants with 5q spinal muscular atrophy (SMA). Part A is an open-label safety evaluation of later onset SMA participants. After Part A safety evaluation, Part B will enroll ~125 participants with infantile-onset or later-onset SMA and is a pivotal, double blind, active controlled randomized trial. After Part B safety evaluation, Part C will enroll ~20 participants of any age and any SMA type.

Results: Part A includes later onset SMA participants (n=6, age 2-15 years, inclusive; SMA onset age >6 months) who will receive three 28 mg loading doses at 14-day intervals followed by two 28 mg maintenance doses every 4 months. Part B will enroll with infantile-onset (age ≤7 months at informed consent; 2 SMN2 copies; SMA onset age ≤6 months) or later-onset SMA (age 2 to < 10 years; SMA onset age >6 months; sat but not walking independently; Hammersmith Functional Motor Scale - Expanded [HFMSSE] score ≥10 to ≤54). Part B participants will be randomized (1:2 ratio) to the approved dose or two 50 mg loading doses 15 days apart with 28 mg maintenance doses every 4 months thereafter. Part C will enroll participants of any age and any SMA type on approved nusinersen dose ≥1 year who will receive one 50 mg loading dose with 28 mg maintenance doses every 4 months thereafter. The primary objective is to evaluate the clinical efficacy of nusinersen administered at higher doses. Key endpoints include, for infantile-onset SMA: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND), Hammersmith Infant Neurological Examination (HINE) Section 2 motor milestones and event-free survival; for later-onset SMA: HFMSSE, Revised Upper Limb Module (RULM), and World Health Organization (WHO) motor milestones. Secondary and exploratory endpoints include safety and tolerability, biomarker assessment, quality of life, and pharmacokinetics. Updated enrollment data will be presented.

Conclusions: Enrollment anticipated to begin in Q1 2020 with a target enrollment of ~150 participants from approximately 50 centers globally.

Acknowledgements: Writing and editorial support for the preparation of this abstract were provided by Excel Scientific Solutions (Fairfield, CT, USA); funding was provided by Biogen.

PRELIMINARY RESULTS OF THE SPINRAZA IN ADULTS WITH SPINAL MUSCULAR ATROPHY (SAS) STUDY

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Background: The safety and efficacy of Spinraza (nusinersen) has not been extensively studied in adults with spinal muscular atrophy. The Spinraza in Adults with SMA (SAS) study is a prospective, multicenter longitudinal observational study of safety and effectiveness in adults age 18-70 years with SMA Type II/III who are initiating treatment with nusinersen.

Results: At time of this interim analysis (24 January 2020), 24 patients (11 female), age 20-59 years, 5 with SMA II, 19 with SMA III, (n=2/10/12 with 2/3/4 smn2 copies) have enrolled across nine sites in the United States and Canada. 10 patients (3 ambulatory) have ≥ 6 (range 6-14) months follow up and are included in this interim analysis. In these patients, in comparison to baseline: four patients improved (≥ 3 points) in the Revised Hammersmith Scale and none declined ≥ 3 points (range -1 to 8) at the time of their most recent follow up. All 10 patients showed stability (-2 to 2) in the Revised Upper Limb Module. The three ambulatory patients showed variable change in the 6 minute walk distance (-58 to 24 meters). Pulmonary function tests were stable (median change in the percent predicted FVC: 0.5%, MIP: -5cm H₂O, MEP 2.5 cm H₂O). Four patients showed reduced (< -10) disease burden with the SMA-Health Index outcome measure and none significantly (> 10) worsened (range -68 to 5). In all 24 enrolled patients, there have been two serious adverse events out of over 2490 cumulative days on treatment and 95 total nusinersen intrathecal injections: pancreatitis, which was possibly related to Spinraza, and pneumonia, which was not likely related. No patient has discontinued treatment.

Conclusions: Preliminary results from the SAS study suggests that Spinraza is well tolerated in adults. Strength and function are generally stable over 6-14 months and some adults show improvements, in contrast to the natural history of measurable decline over 12 months. Enrollment is ongoing, with serial assessments planned in each patient over 30 months.

Acknowledgements: Special thanks to the project manager, Heather Wilkins, M.A., for her indispensable support. This research is sponsored by Craig Zaidman (PI) and Washington University and funded by Biogen.



2021 ANNUAL SMA CONFERENCE

**JOIN US IN AUSTIN, TEXAS!
THURSDAY, JUNE 10 – SUNDAY, JUNE 13, 2021**

If the unexpected circumstances of 2020 have shown us anything, it is how impactful this one week of the year is for families, individuals, researchers, and medical professionals in the SMA community. We cannot wait to welcome you back as we gather next June in Texas. The JW Marriott Austin will host the 2021 Annual SMA Conference and SMA Research & Clinical Care Meeting. The hotel is centrally located in Austin's lively downtown neighborhood with a variety of restaurants, live music, and entertainment venues.

Cure SMA is excited to reunite the SMA community for the 2021 Annual SMA Conference in Austin, Texas from Thursday, June 10 – Sunday, June 13, 2021. Additional conference details will be announced in the upcoming months and registration will launch in the fall of 2020.

If you have any questions, please contact conference@curesma.org.

**WE LOOK FORWARD TO SEEING
YOU IN AUSTIN NEXT JUNE!**

STAY TUNED

**to the Cure SMA website for more details
on the 2021 Annual SMA Conference as they
become available.**

SMA DRUG PIPELINE

We are funding and directing research with more breadth and depth than ever before. We know what we need to do to develop and deliver new therapies, which could also work in combination, to reach our goal of treatments for all ages and stages of SMA. And we are on the verge of further breakthroughs that will continue to change the course of SMA for everyone affected, and eventually lead to a cure.

The Cure SMA Drug Pipeline is one of the primary ways we evaluate the success of our research program. It identifies the major drug programs in development and tracks their progress from basic research through FDA approval and beyond. The Cure SMA Drug Pipeline identifies several possible treatment targets:

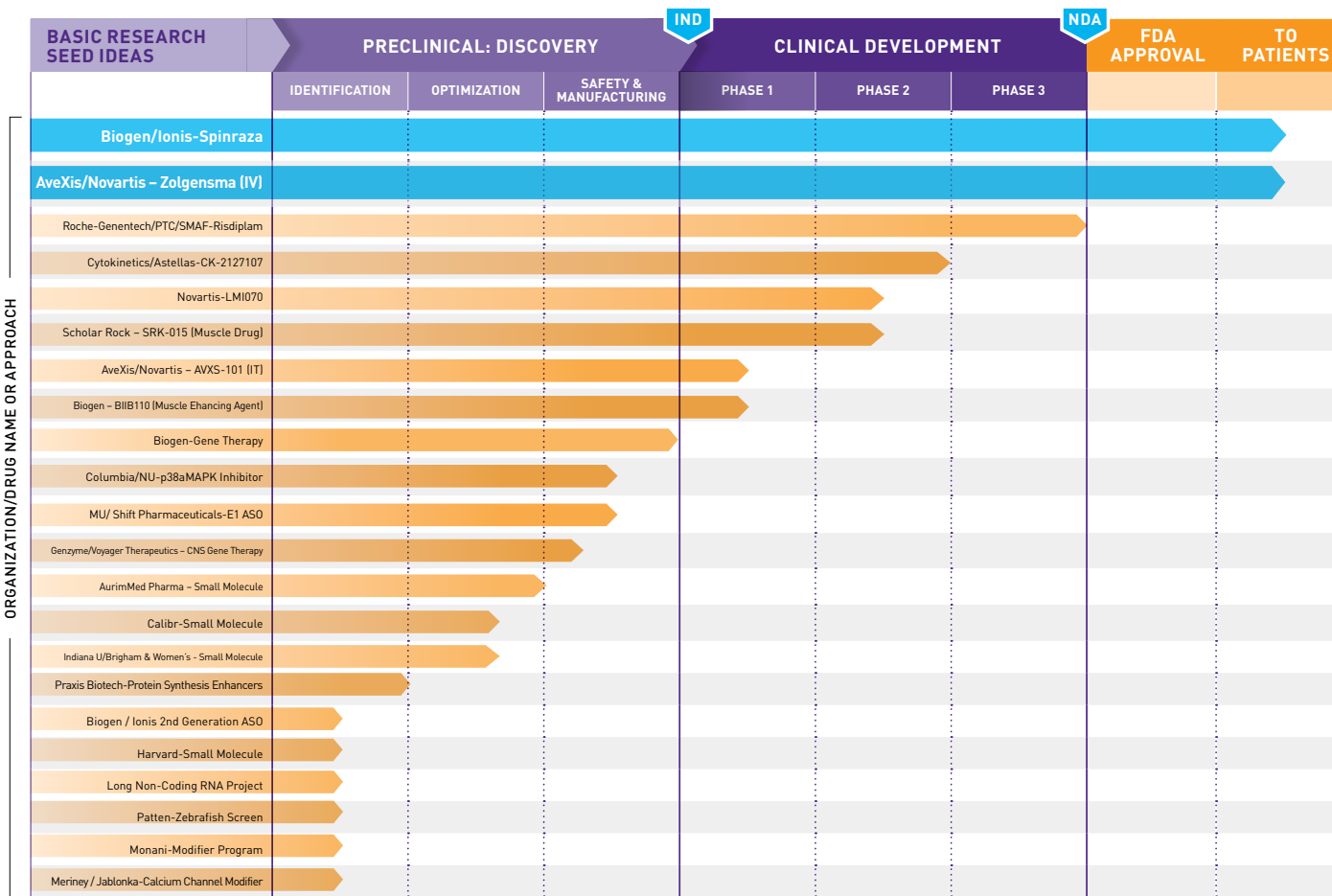
- Replacement or correction of the faulty SMN1 gene.
- Modulation of the low functioning SMN2 “back-up gene.”
- Muscle protection to prevent or restore the loss of muscle function in SMA.
- Neuroprotection of the motor neurons affected by loss of SMN protein.
- Newer approaches that identify additional systems and pathways affected by SMA.

DRUG PIPELINE



SMA DRUG PIPELINE

We're funding and directing research with more breadth and depth than ever before. We know what we need to do to develop and deliver new therapies, which could also work in combination, to reach our goal of treatments for all ages and types. And we're on the verge of further breakthroughs that will continue to change the course of SMA for everyone affected, and eventually lead to a cure.



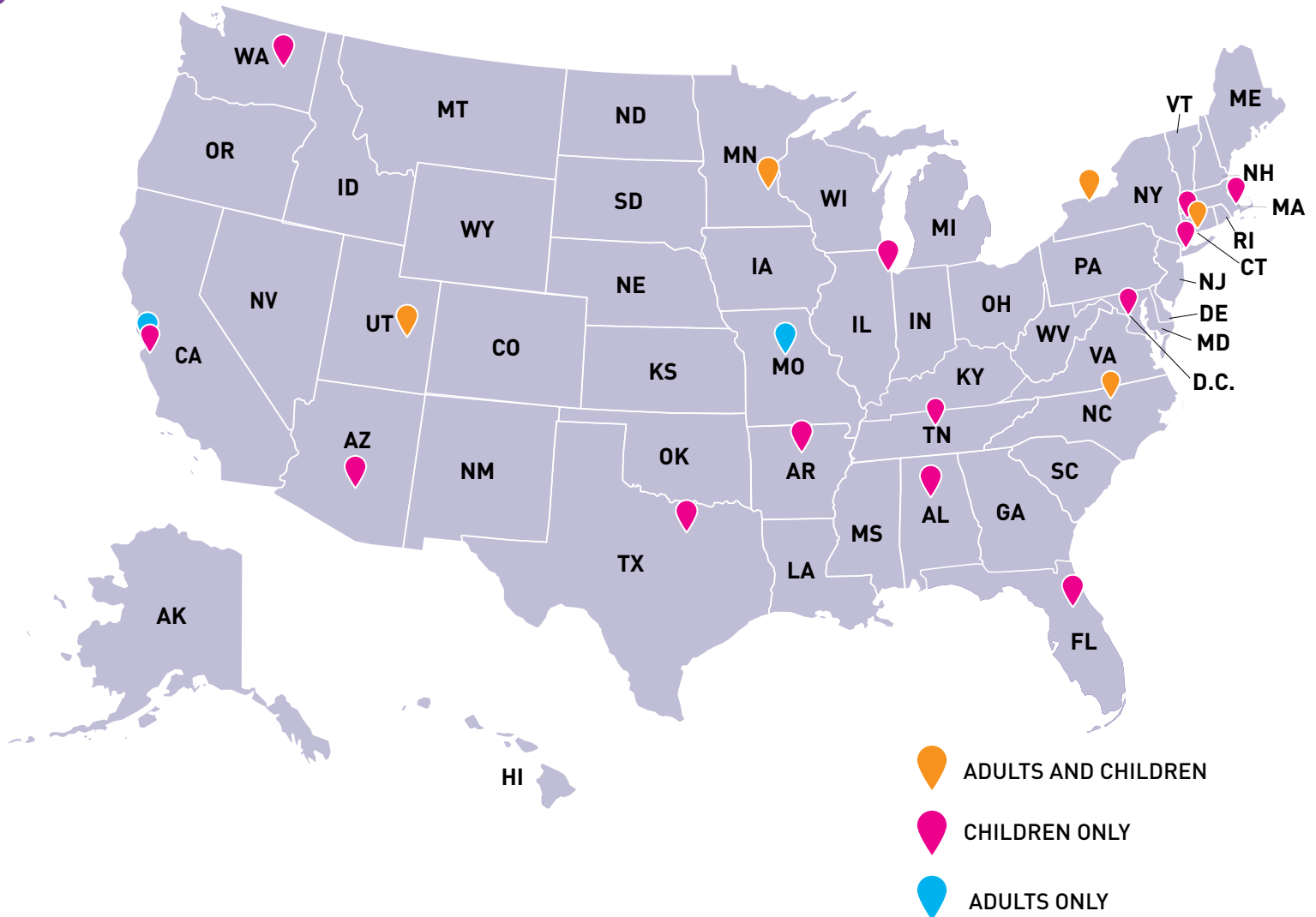
IND = Investigational New Drug NDA = New Drug Application Last updated: November 2019

CURE SMA CARE CENTER NETWORK

The Cure SMA Care Center Network is made up of clinics who are partnering with Cure SMA to share consented electronic health record data with the SMA Clinical Data Registry to achieve the following goals:

1. Quality improvement of SMA clinical care and disease management leading to creation of evidence to support a robust standard of care for SMA.
2. Standardize care across the U.S. to facilitate more rapid therapeutic development.
3. Expand clinical care center capacity to deliver new therapies to individuals with SMA, increase patient access to new treatments, and increase the number of sites for SMA clinical trials.
4. Resource for local patient services and family support and regional healthcare providers.

The Cure SMA Care Center Network now includes 20 centers geographically dispersed throughout the U.S., representing 14 pediatric centers, 2 adult centers, and 4 combined pediatric and adult centers. To date, 16 of these centers have fully integrated into the SMA Clinical Data Registry, where we have 274 patients enrolled. Patient enrollment is ongoing. The next expansion phase for the Cure SMA Care Center Network is planned for late 2020, and data collected in the SMA Clinical Data Registry will be utilized to evaluate current care practices and develop accreditation standards for the Care Centers.





EARLY ACTION, EARLY TREATMENT, SAVES LIVES.

Spinal muscular atrophy (SMA) is a rare autosomal recessive neuromuscular disease caused by deletion/mutation in SMN 1 gene, which is critical to the development of muscle mass and strength. It is characterized by progressive hypotonia and weakness. SMA puts a significant financial, logistical, and emotional strain on affected individuals and families.^{1,2} Literature reviews indicate a significant diagnostic delay in SMA, during time periods that overlap with major motor neuron loss. For instance, in individuals affected by SMA Type 1, the average age of diagnosis is documented to occur between 5.3 to 6.3 months.^{2,3} Yet, the onset of irreversible denervation occurs within the first 3 months, with loss of 90 percent of motor units occurring within 6 months of age.⁴ However, clinical and preclinical studies indicate that treatment exposure early is critical to modifying the rapid and irreversible loss of motor neurons.⁵⁻⁸

The diagnosis of SMA, especially Type 1, is a medical emergency. To promote reduction of diagnostic delays, [Cure SMA](#) launched [SMArt Moves](#), a disease awareness and educational campaign to empower parents, pediatricians, and other healthcare professionals to promptly recognize and diagnose the early signs of SMA.

Central to the SMArt Moves effort is a special section dedicated to healthcare professionals, detailing current diagnostic criteria, educational resources, and the latest treatment options and protocols. Available resources include:

- [SMA Diagnostic Toolkit](#): Summarizes clinical trial data supporting early treatment, provides a table of clinical signs and symptoms by SMA type, and features a list of disorders to consider in the differential diagnosis of SMA
- [SMA 1-Page Quick Reference Guide](#): An abbreviated version of the SMA Diagnostic Toolkit.
- [Know the Warning Signs](#): A series of videos that break down some of the hallmark symptoms of SMA.
- [SMA CME HubSpot](#): Free and accredited SMA related activities.

In addition, parents also have access to an easy-to-use website that encourages parents to trust their instincts if they suspect a motor delay, because missed milestones may be a sign of a serious medical condition like SMA. On the site, parents improve their understanding of the early signs of motor delays, watch [instructional videos](#), and download a [helpful checklist](#) to share with their doctor and help address their concerns.



What About Newborn Screening?

Cure SMA recognizes that early diagnosis and treatment occurs most effectively with universal newborn screening. SMA was added to the Recommended Uniform Screening Panel (RUSP) in July 2018. As each state works to implement SMA screening within their newborn screening panel, providers must continue to be vigilant for the early signs to optimize outcomes.

Additionally, even in states in which SMA has been added to the panel, we encourage providers to remain watchful, as approximately 3% to 5% of individuals with SMA will not be identified by newborn screening due to SMN1 point mutations. Thus, clinical evaluation and consideration of the SMA diagnosis will remain important once universal inclusion of SMA within newborn screening panels is achieved.

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