CRITICAL PATH INNOVATION MEETING (CPIM) FOR SPINAL MUSCULAR ATROPHY

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Table of Contents

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SPINAL MUSCULAR ATROPHY WITH US FDA (CDER / CBER)
04 AUGUST 2020

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Table of Contents

ADL – Activities of Daily Living

BiPAP – Bilevel Positive Airway Pressure

ClinRO – Clinician-Reported Outcome

EL-PFDD – Externally-Led Patient-Focused Drug Development

FDA – Food and Drug Administration

HRQoL – Health-Related Quality of Life

ICF – International Classification of Functioning

SMA – Spinal Muscular Atrophy

SMN1 – Survival Motor Neuron 1

Abbreviations pertaining to outcome measures

ACEND – Assessment of Caregiver Experience with Neuromuscular Disease
The ACEND was developed and validated to specifically assess caregiver impact experienced by raising children severely affected by neuromuscular diseases. While specifically developed for application to patients undergoing orthopedic surgery, it was application to those with SMA and is currently being assessed in larger patient populations (Matsumoto et al., 2011).

BSID-III – Bayley Scales of Infant and Toddler Development – Third Edition
The Bayley-III is a standardized test series of measurements used primarily to assess the development of infants and toddlers, ages 1-42 months (Bayley et al., 2006).

CHOP INTEND – Children Hospital of Philadelphia, Infant Test of Neuromuscular Disorders
The CHOP INTEND is a reliable and valid measure of motor skills in weaker patients with SMA type I and neuromuscular disorders presenting in infancy (Glanzman et al., 2010).

CHOP ATEND – Children Hospital of Philadelphia, Adult Test of Neuromuscular Disorders
The CHOP ATEND is the modified version of the CHOP INTEND specifically adapted for adults who are non-sitters. It is currently under development.

COA's – Clinical Outcome Assessments.
A COA is a measure that describes or reflects how a patient feels, functions, or survives. Types of COAs include: Patient-reported outcome (PRO) measures, Observer-reported outcome (ObsRO) measures, Clinician-reported outcome (ClinRO) measures, Performance outcome (PerfO) measures (see, [US FDA's Definition of COA](#))

FVC – Forced Vital Capacity
FVC is a test that measures the amount of air that can be forcibly exhaled from one's lungs after taking the deepest breath possible. The test is measured by spirometry.

HFMSE – Hammersmith Functional Motor Scale- Expanded
The HFMSE allows for assessment of higher functioning sitters and walkers (SMA types II and III). Ease of administration and correlation with established motor function measures and excellent validity and reliability justify use for those with SMA in clinical trials (Glanzman et al., 2011).

HINE-2 – Hammersmith Infant Neurological Examination – Part 2
The HINE is an easily performable and relatively brief clinical neurological examination for infants ages 2-24 months. The motor section Part 2 has been used to record milestone achievement in SMA (Bishop et al., 2017).

HUI – Health Utilities Index
The HUI is a rating scale used to measure general health status and health-related quality of life (Horsman et al., 2013).

MFM-32 – Motor Function Measure 32
The MFM is designed to measure functional motor abilities in neuromuscular diseases. It is validated and usable from ages 6 to 60 years old (Vuillerot et al., 2013).

MIP – Maximal Inspiratory Pressure
MIP is a static respiratory measure that can be measured to non-invasively assess respiratory muscle strength.

PedsQL – Paediatric Quality of Life Inventory
The PedsQL is designed to measure health-related quality of life dimensions specific to children ages 2 to 18 years old with neuromuscular disorders, including SMA (Varni et al., 1999).

PFT – Pulmonary Function Tests
PFTs are non-invasive tests that measure lung volume, capacity, rates of flow, and gas exchange.

PRO/PROM – Patient Reported Outcome Measure
Patient reported outcome measures are tools to directly evaluate quality of life of SMA patients. They can be helpful in investigating symptoms such as pain, fatigue, swallowing difficulties, and assessing clinical meaningfulness (Pechmann et al., 2019)

R/ULM – Revised /Upper Limb Module
The R/ULM scale shows good reliability and validity, making it a suitable tool to assess upper extremity function in the SMA population (Mazzone et al., 2016).

SMAFRS – Spinal Muscular Atrophy Functional Rating Scale
The SMAFRS is designed to assess function in ambulatory adults with SMA (Elsheikh et al., 2009).

SMA-HI – Spinal Muscular Atrophy Health Index
The SMA-HI is a patient-reported outcome measure composed of a questionnaire that assess quality of life in SMA patients ages 8-100 (Mongiovi et at., 2018).

SMAIS – Spinal Muscular Atrophy Independence Scale
The SMAIS is specifically designed for SMA type II and III individuals and measures the amount of assistance required to perform typical daily activities.

UE Fatigue Tests – Upper Extremity Fatigue Test
May include Endurance Shuttle Box and Block Test and the Nine Hole Peg Test for fatigability testing of proximal and distal arm function (Bartels, de Groot, et al., 2019).

WPAI – Workplace Productivity and Activity Impairment Questionnaire
The WPAI questionnaire is a well validated instrument to measure impairments in work and activities (Zhang et al., 2010).

EXECUTIVE SUMMARY

Cure SMA is dedicated to the treatment and care of Spinal Muscular Atrophy (SMA) by promoting research that drives breakthroughs and providing support to our 8,000 affected members and their families, while educating the public and medical community about SMA. Established in 1984 by a group of concerned parents, Cure SMA now has 36 chapters and more than 120,000 families and supporters. Cure SMA continues to be at the forefront of research, having funded over $80 MM in basic and translational research, patient focused development projects, and patient care.

Thanks to the U.S. Food and Drug Administration (FDA), many of the 10,000 Americans living with SMA now have approved treatments for their condition. The approval of SPINRAZA® (nusinersen) in December 2016 and Zolgensma (onasemnogene abeparvovec-xioi) in May 2019 have advanced targeted SMN-enhancing therapies for our community and dramatically altered the natural history of SMA. However, while the burden of disease is shifting in those patients eligible, there is still much work to do. Patients who are administered these drugs after symptom onset continue to have significant unmet medical needs.

Cure SMA also wishes to thank key regulatory leaders at FDA for granting our community the opportunity to hod a Critical Path Innovation Meeting (CPIM); a means by which key leaders at FDA may communicate with investigators, members of academia, industry/scientific consortia, patient advocacy groups, etc. to improve efficiency and success in drug development. At this CPIM and via this briefing document, Cure SMA aims to enhance FDA's understanding of what represents the most significant burdens and treatment goals of individuals with SMA. We also hope to discuss opportunities for collaboration to help address these unmet medical needs. In order to continue to advance a pipeline of therapies for SMA, we must address new scientific and regulatory issues.

 During this meeting, Cure SMA plans to address, at a high-level, the following pivotal topics,

   A. Shifting burden of SMA / continued unmet medical need amongst older patients with slower progressing disease (i.e., people with SMA types II and III);
   B. Development of novel outcomes & fit-for purpose Endpoints in SMA, particularly for adults with SMA, both in a clinical trial and real-world, clinical setting.
   C. Exploration of novel biomarkers (specifically, the already identified neurofilament levels (NF) as a marker of disease progression and/or to assess possible efficacy of a given therapeutic), in a clinical trial and real-world, clinical setting
   D. Approaches to combination therapies / exploratory study protocols. New therapeutic candidates in development, mainly those with complimentary mechanisms of action to those already approved, will be used in an additive fashion in the real-world. Also patients available to participate in future clinical trials may already be on commercially-available drugs.

To facilitate discussion, each section (I-IV) of the CPIM briefing packet will include, 1) question(s) that Cure SMA wishes to discuss with regulatory leaders at FDA (CBER/CDER) who will attend the SMA CPIM; and 2) important a brief background on SMA, and important updates on each of the above outlined community priorities. The shifting burden of SMA will be further characterized through natural history, long-term clinical trial data in SMA in children and teens and real world evidence. Additional sources include recent learning from observational studies in treated adults with SMA as well as summary results from the Cure SMA Annual Community Update Survey, completed by parents, caregivers and affected adults with SMA in the United States, from 2017-2020. This will be supplemented by patient/caregiver testimonials at the CPIM itself.

We hope that bringing the voice of the patient to FDA in this format will build upon the learnings from the April 18, 2017 externally-led Patient-Focused Drug Development meeting, which was held prior to our community's experience with the two approved therapies (see the Voice of the Patient summary report update meeting with the US Food and Drug Administrataion (FDA) here). An appendix with additional supporting materials is attached.

The Shifting Burden of SMA in a Post-Treatment Era

Overview of Opportunities to Address Unmet Medical Needs

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Background

Spinal muscular atrophy (SMA), is a rare progressive, life-threating, recessively inherited neuromuscular disease (NMD) caused by a homozygous deletion or mutation of the survival motor neuron 1 (*SMN1*) gene that lead to the degeneration of alpha motor neurons in the spinal cord and progressive muscle wasting and severe weakness (Lefebvre et al., 1995; Ogino et al., 2002; Arnold et al., 2015). SMA affects one in 11,000 infants in the United States each year and about 8 million Americans are genetic carriers. SMA has traditionally been the leading genetic cause of death in children under the age of two years (Prior et al., 2008; Sugarman et al., 2012; Verhaart).

Disease Severity and Classification (Natural History)

The severity of SMA is largely correlated with the number of copies of *SMN2*, a paralogue of the *SMN1* gene, which produces only 5-10% of functional SMN protein; the larger number of copies of *SMN2* is typically associated with a less severe phenotype. Symptom severity and survival in SMA are heterogeneous, which has resulted in the disease being traditionally classified into four primary clinical phenotypes (I-IV) based upon the age of onset (which correlates with disease severity and survival) and the highest motor milestone achieved (Zerres and Rudnik-Schöneborn, 1995; Russman, 2007; Piepers et al., 2008; Wadman et al., 2017). Without treatment, the most common and life-threatening form, SMA type I, presents in the first six months of life, and is characterized by severe hypotonia, debilitating muscle weakness, difficulties breathing, coughing and swallowing; always requiring intensive supportive care, including respiratory and feeding support. Prior to the availability of FDA-approved treatments (SPINRAZA® [nusinersen] and ZOLGENSMA® [onasemnogene abeparvovec-xioi]), infants with SMA type I, never achieved the ability to sit unaided, and most succumbed to their disease before the age of two years (Zerres and Rudnik-Schöneborn, 1995; Wirth, 2002; Oskoui, 2007; Kolb, 2017). Young children with SMA type II, typically diagnosed between 6 to 18 months, may sit or crawl but never walk. Respiratory muscle weakness is variable and hip dislocation, joint contractures, and scoliosis are common. With supportive care, life expectancy is into adulthood (Zerres et al., 1997); while children diagnosed with SMA type III are able to walk, at least for a time. Adults with SMA type IV experience symptoms in adulthood, typically after 30 years of age (Piepers et al., 2008). Natural history studies have demonstrated a slowly progressive decline of motor function across all subtypes (Wadman et al., 2018; Mercuri et al., 2019).

Burden of SMA on Patients and Caregivers (Natural History)

The complex and all-encompassing burden of SMA for patients and their families has been well characterized (Arnold et al., 2015; Qian et al., 2015; Hunter et al., 2016; Rouault et al., 2017; Cruz et al., 2018; Droege et al., 2020). Prior to the implementation of Newborn Screening for SMA, in 2018, it would begin with a prolonged and often traumatic diagnostic journey, followed by a lifetime of overwhelming physical, emotional, psychosocial, and financial strains associated with living with a severe, degenerative condition. In the absence of disease-modifying therapies, children and adults with SMA face a life of disability and uncertainty as the disease increasingly takes away their strength, energy, muscle function and the ability to perform the most basic activities of daily living.

Nearly four years after the advent of the first-ever FDA approved therapy for SMA, the burden of disease is considerable, particularly for patients who receive treatment much after symptom onset. The unmet medical needs for patients treated in adulthood or after symptom onset remains significant.

Part 1: How could new data on the existing burden of SMA, evolving phenotypes, and unmet need, (included in this briefing packet) be best utilized to inform the development of,

  a. *new endpoints to be used in future clinical trials* to support medicinal product development for the most chronically affected population? And,

  b. *new endpoints that are 'fit-for-purpose"*?

Part 2: How can we ensure that these sources of information presented here (on aspects of symptoms, impact of disease, and treatment impact/ burden), important to patients and caregivers, are collected in a way that results in their acceptability for inclusion in a filing or for label claims?

I. An Evolving SMA Treatment Landscape and Standard of Care

The natural history of SMA is dramatically changing with the advent of new therapies and approaches to treat SMA; most strikingly through newborn screening (NBS) identification (Bertini et al., 2017, De Vivo et al., 2017, Glasscock et al., 2018, De Vivo et al., 2019, Kariyawasam et al., 2019). Evidence from clinical trials in SMA, including recent long-term follow-up studies (Lowes et al., 2019, De Vivo et al., 2019) as well as, data captured through the Cure SMA Annual Community Update Survey (Belter et al., 2017-2020), has provided evidence that *the nomenclature for classifying disease severity may soon become obsolete; infants with early onset SMA, treated early or pre-symptomatically, may now surpass the expected maximum motor function achieved based on natural history. In other words, type I's may now sit, crawl, or even walk, depending on the timing of treatment (and other variables discussed later in the report).* Please refer to page 9 for a proposed new classification system for SMA (Finkel et al., 2017, Mercuri et al., 2018). The adherence to the Recommended Standards of Care, along with the administration of treatment(s), ideally, presymptomatically, or soon after symptom onset continues to be critical to achieving optimal long-term outcomes (Finkel et al., 2017, Mercuri et al., 2018; De Vivo et al., 2019).

Evidence from Clinical Trials in Infants, Children and Adults

The safety and therapeutic benefit of FDA-approved disease-modifying therapies and approaches to treat SMA-such as *SMN2* splicing modifiers (i.e., ASOs, small molecules), *SMN1* gene-replacement therapy, and others on the horizon have been established through a few Phase 1-3 trials, including double-blind randomized placebo/sham-controlled studies, with infants, children (ENDEAR and CHERISH (nusinersen), START (onasemnogene abeparvovec-xioi)), and FIREFISH and SUNFISH (Risdiplam) in children and adults with SMA (after symptom onset) and NURTURE (nusinersen), in pre-symptomatic infants (Chiriboga et al., 2016; Finkel et al., 2016, 2017; Mendell, 2017; Mercuri et al., 2018; De Vivo et al., 2019; Sturm et al., 2019). These therapies and investigational drugs, have been shown to significantly improve clinical outcomes in patients with SMA, including survival (Kaplan–Meier method) respiratory function (measured by required hours on BiPAP, or need for permanent ventilation), motor function, (as evidenced by improvements on various validated functional scales (such as the Children Hospital of Philadelphia, Infant Test of Neuromuscular Disorders (CHOP INTEND), Hammersmith Infant Neurological Examination – Part 2 (HINE-2), Gross Motor Scale of the Bayley Scales of Infant and Toddler Development – Third Edition (BSID-III), Hammersmith Functional Motor Scale-Expanded (HFMSE), Revised/Upper Limb Module (R/ULM), etc.), Motor Function Scale (MFM-32), and in health-related quality of life (HRQL) in patients and caregivers of treated patients with SMA (using scales such as PedsQL, ASCEND, WPAI, HUI6, SMAIS, etc. [Johnson, Paradis et al., 2020], Montes et al., 2020, Messina et al., 2019, Belter et al., 2019).

For the first time in the history of SMA, children who received any of these disease-modifying therapies, achieved functional and motor milestones unlike any before seen or expected, based on the natural history of SMA (regardless of type, *SMN2* copy number and age of symptom onset [Mendell et al., 2017, Mendell et al., 2017; Mercuri et al., 2018]).

Generally, the disease trajectory, including milestones reached, varied depending on timing of treatment, type of treatment, and *SMN2* copy number. Other clinically meaningful improvements have also been reported including the ability to swallow, feed by mouth (Mendell et al., 2017, Sturm et al., 2019; Servais, Darras, et al., 2020) and communicate (most relevant and clinically meaningful to type I infants; refer to VOP for SMA, p. 8-9, 43; and adults [Belter et al., 2020, Cure SMA Community Update Survey]).

Timing of treatment has been shown to be the most critical factor, coupled with SMN2 copy number, in determining long-term outcomes in treated SMA patients.

SMA Clinical Trials & Long-Term Follow-Up Studies – Results on Outcomes Based on Timing of Treatment

Performance or improvements on key measures of disease severity or progression, including survival, respiratory function, strength, ability to swallow, etc. are highly correlated with timing of treatment. Clinical studies clearly indicate that the timing of treatment is critical to modifying the rapid and irreversible loss of motor neurons which occurs within the first few of months of life (Swoboda et al., 2005). This was further supported through the ENDEAR (nusinersen) and START (onasemnogene abeparvovec-xioi) trials, (Finkel et al., 2017; Mendell et al., 2017), and most-strikingly, through the results of the NURTURE (nusinersen) study involving pre-symptomatic infants (De Vivo et al., 2018, 2019). In ENDEAR, a Phase 3, sham-controlled study, infants treated with nusinersen and disease duration of <12 weeks, had greater improvements in motor function and motor milestones than untreated patients (75% vs 0%; <0.0001). In infants with disease duration >12 weeks, the response rate (i.e., a motor milestone response, defined according to results on the Hammersmith Infant Neurological Examination) and event-free survival (time to death or the use of permanent assisted ventilation still greatly favored the nusinersen treated group (32% vs 0%; P=0.0026), but at a much lower rate (Finkel et al., 2017). At the end of the study 51% of the treated group achieved a HINE-2 motor milestone response vs. 0% in the sham-controlled group (Finkel et al., 2020).

Results of long-term follow-up studies with infants and children with SMA further show that timing of treatment continues to have an impact on long-term outcomes, both in early-onset and in later-onset SMA children. The ENDEAR-SHINE, CHERISH-SHINE (nusinersen) and START studies (onasemnogene abeparvovec-xioi) (Mercuri et al., 2018; Lowes et al., 2019; Finkel et al., 2020; Darras et al., 2020) all show greater gains/new motor function improvements, in various outcomes, in children treated earlier versus those in the sham-control group (treated after study termination). Please refer to **Table 1** for longer-term follow-up results in children treated pre-symptomatically and at various intervals, after symptom onset (**Figure 1**). Eighty-eight percent (88%) of children treated, presymptomatically, with nusinersen (n=22, NURTURE), have achieved the ability to walk independently versus 2% of those treated after symptom onset (n=1, ENDEAR).

WHO MOTOR MILESTONES	Total number of infants achieving milestone, n/N (%)	
	ENDEAR [a] (Symptomatic patients; N=61)	NURTURE [b] (Pre-symptomatic patients; N=25)
Sitting (independent: stable, pivot)	37/61 (61%)	25/25 (100%)
Hands and knees crawling	3/61 (5%)	25/25 (100%)
Standing (stands with support, unaided)	11/61 (18%)	25/25 (100%)
Walking (cruising, walking with assistance)	4/61 (7%)	23/25 (92%)
Walking independently	1/61 (2%)	22/25 (88%)

Table 1. The above data a. represents longer-term data from the Open-label ENDEAR-SHINE Extension Study; WHO Motor Milestones achieved in early-onset SMA children assigned to treatment with nusinersen, **five years** after the study initiation (data cutoff, 8/27/2019; Finkel et al., 2020, Finkel et al., 2017;). b. Phase 2, multi-center, open-label, single-arm NURTURE trial. Median 2.9 years follow-up; median age 34.8 months [25.7-45.4; in months]. As of February 2020, all patients treated (n=25; median age of 3.8 years old) were alive and remained free of permanent ventilation (De Vivo et al., 2019).

Similarly, children with later-onset, type II, SMA, who participated in CHERISH, a Phase 3, sham-controlled study, and received nusinersen after the age of 2 years, also showed clinically meaningful improvements in motor function compared to that of the sham-control group (NH) but not nearly as dramatic as those seen in the younger infants. Of note, patients in this study received a different dosing regimen than infants (with 3 initial loading doses vs. 4 administered to infants). *Overall, the greatest improvements in the HFMSE score over the 15-month period were observed in younger children and in those who received treatment soon after symptom onset* (Mercuri et al., 2017). Children treated after 5 years of age however gained no greater than 2 points, on average.
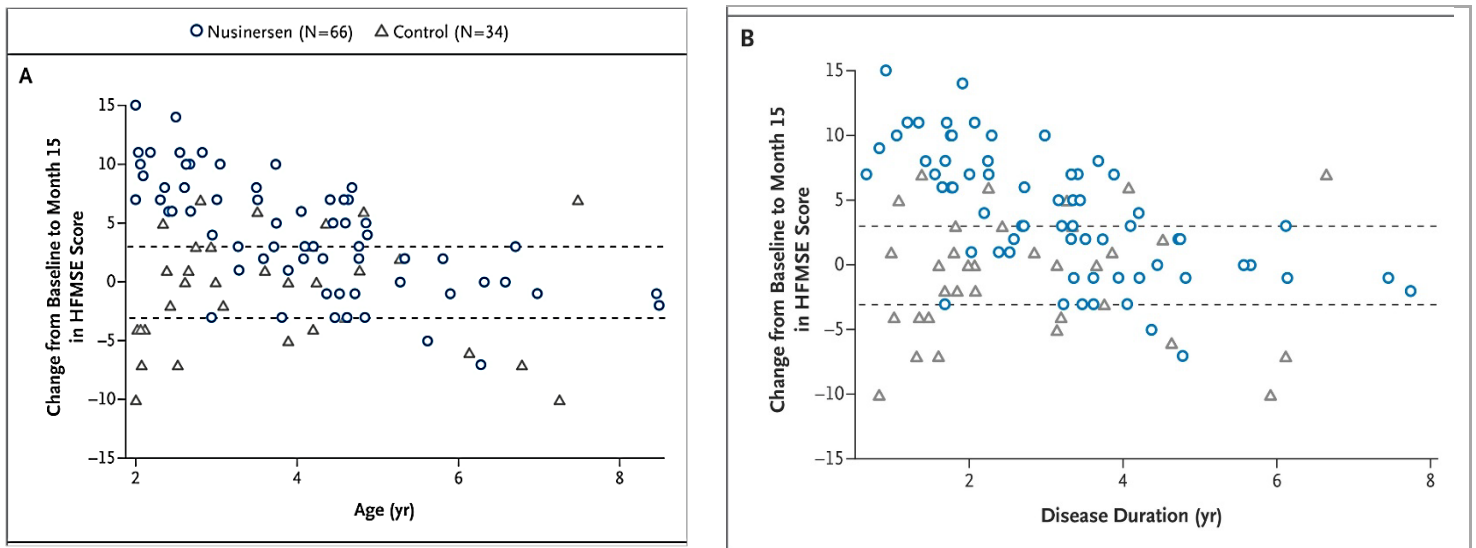
Figure 1. Change from Baseline to Month 15 in Individual HFMSE Scores According to Age and Disease Duration at Screening (Final Analysis). Shown is the change from baseline to month 15 in each child's HFMSE score according to age (Panel A) and disease duration (Panel B) at screening in the final analysis. Disease duration is a child's age at screening minus the age at symptom onset. The analyses included children in the intention-to-treat population who did not have missing data for the 15-month assessment (66 in the nusinersen group, and 34 in the control group). The dotted lines indicate a +/-**3-point** change in the HFMSE score, which is considered to be clinically meaningful (Swoboda et al., 2010).

Invariably, the degree to which trial participants demonstrated long-term improvements in motor function and various outcomes assessed was largely correlated with early exposure to the therapy; the earlier the exposure the better the long-term outcomes. This was further influenced by *SMN2* copy number (Swoboda, 2009, Wadman, 2017; Finkel et al., 2017; Mendell et al., 2017).

Data from a long-term follow-up study assessing the gene replacement therapy (AVXS-101, [onasemnogene abeparvovec-xioi]), further illustrates how age of treatment onset profoundly impacts outcome achievement (Lowes, Mendell, et al., 2019). The rapid, significant motor improvements among infants with severe SMA type I treated with AVXS-101 at an early age highlights the importance of newborn screening and early treatment. See **Figure 2**.
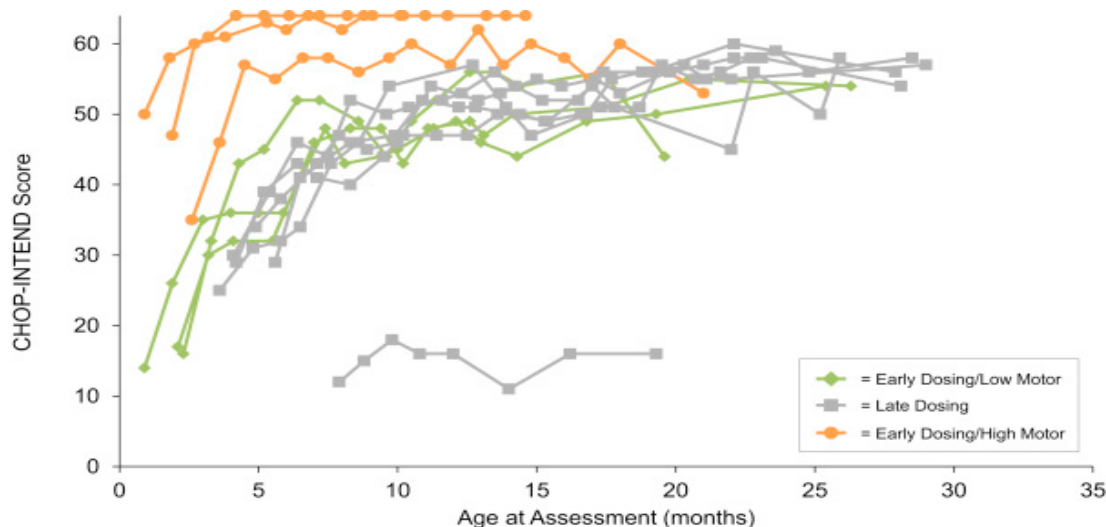

Figure 2. CHOP-INTEND assessments were conducted for each patient at each monthly visit if the participants were able to perform the assessments. Assessments were discontinued for patients who reached or exceeded a score of 60 of 64 on the CHOP-INTEND. **Green** lines: patients in the **Early** Dosing/**Low** Motor group were dosed early (less than three months), and each had a CHOP-INTEND score <20 at baseline. **Gray** lines: patients in the **Late** Dosing group were dosed at three months or greater, and five of six had CHOP-INTEND score ≥20. **Orange** lines: patients in the **Early** Dosing/**High Motor** group were dosed early (less than three months), and each had CHOP-INTEND scores ≥20 at baseline. CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders. Adapted from *New England Journal of Medicine*, Mendell J, Al-Zaidy S, Shell R, et al., Single-dose gene-replacement therapy for spinal muscular atrophy, volume 377, issue 18, pages 1713-1722, Copyright © 2017 Massachusetts Medical Society.

While the above data demonstrate a strong correlation between pre-symptomatic/early treatment and improved outcomes, *there still remains significant unmet needs for SMA patients treated after symptom onset or chronically, with more advanced symptoms that will be described in the next section*. The potential treatment gaps that may arise in infants with SMA treated presymptomatically is less well understood. The development over time of the NURTURE cohort does suggest these children follow trajectories that resemble those of normal children although not perfectly; variability is observed in the timing when certain motor milestones are reached. Children with 3 copies of *SMN2*, generally, fall closer to normal development than those with 2 *SMN2* copies. The majority of the children in this study have achieved the ability to walk. The availability of care and treatment centers for adults with SMA continues to be a priority for our community.

Impact of Treatments in Children and Teens with SMA- Long-term Clinical Trials' Data

The efficacy of nusinersen has been assessed in teens and young adults (type II and III) as part of an open-label, long-term, safety and efficacy study, SHINE (NCT02594124); with 24 participants with SMA type II (n = 10) and type III (n = 14) who transitioned from the ISIS CS2/CS12 studies.

Measures of motor function in the SHINE study analysis consisted of the Hammersmith Functional Motor Scale–Expanded (HFMSE), the Upper Limb Module (ULM), and the 6-Minute Walk Test (6MWT). Results showed that 11 patients with SMA type II and 17 with SMA type III, had improved on all measures of motor function by day 1150: HFMSE scores improved by 10.8 points for SMA type II and by 1.8 points for type III patients. Comparatively, scores on the Revised Upper Limb Module, (RULM), scores improved by 4 points for the type II patients and median (25th, 75th percentile) 6MWT distance walked increased over time by 98.0 (62.0, 135.0) meters at day 1050, in type III patients. Results also demonstrated a decrease in median fatigue of −3.8% (−19.7%, 1.4%) in types II and III SMA patients (Montes et al., 2019).
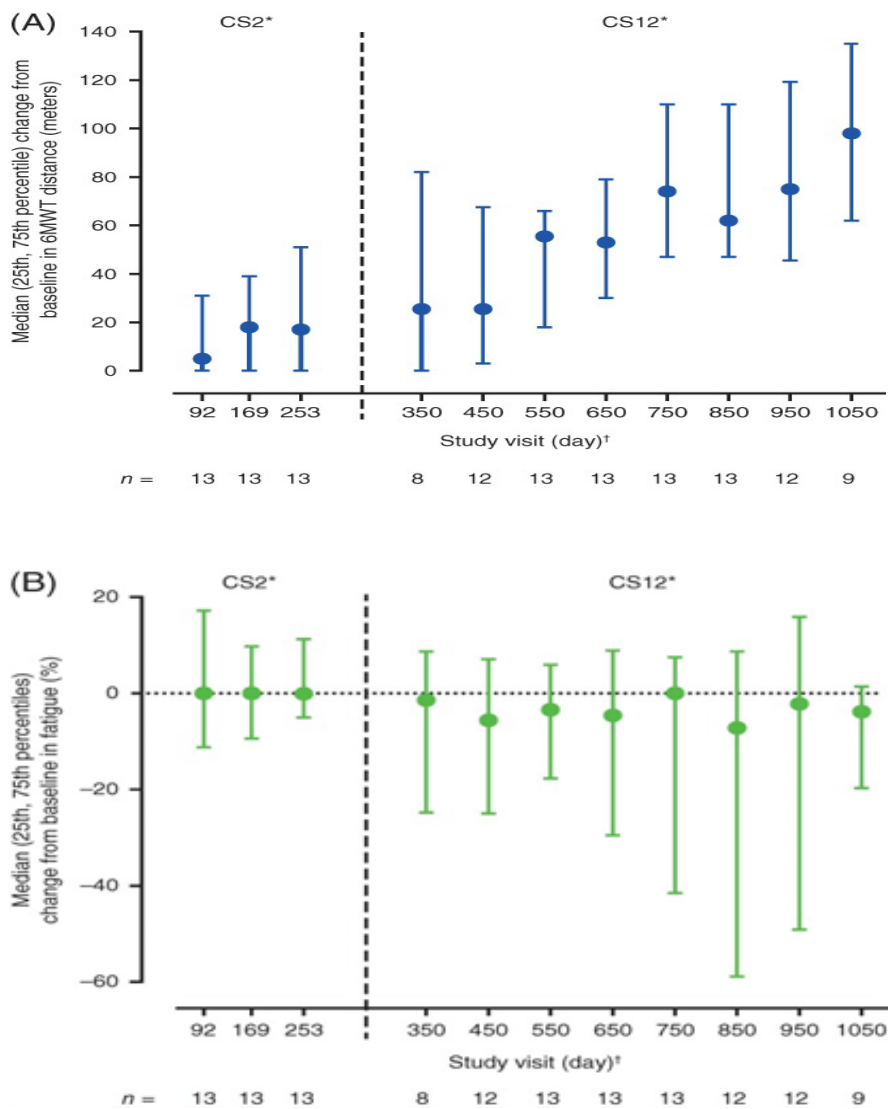

Figure 3. Median (25th, 75th percentile) change from baseline in 6MWT (A) distance and (B) fatigue over time. *Study visits up to and including day 253 occurred during the CS2 study, subsequent study visits occurred during the CS12 study. The day of the first study visit attended in the CS12 study depended upon the time between the end of the CS2 study and first dose in the CS12 study and the windowing of study visits described as follows. Median (range) time from the end of the CS2 study to first dose in the CS12 study was 118.0 (19–233) days. †Study days were derived from the first day of CS2 dosing for all CS2 and CS12 study visits and were assigned visit days as follows: study visits that took place >50 and ≤131 days from the first dose in the CS2 study were labeled day 92, visits >131 and ≤211 days from the first dose in CS2 were labeled day 169, those >211 and ≤302 days were labeled day 253, those >302 and ≤400 days were labeled day 350, and study visits >X – 50 to ≤X + 50 were labeled day X (starting at day 450 and increasing by 100 until day 1050), times between visit days were not equal, but were similar. 6MWT, 6-minute walk test.

Impact of Treatment in Adults - Real-World Evidence (RWE), Supported by Observational Studies and Clinician-Reported Data

Until recently, the effects of nusinersen in adults with chronic SMA (long history of disease) has been largely unexplored. In a first-ever, prospective observational study in adults with SMA, Walter et al., (2019) evaluated the safety and treatment effects of nusinersen in ambulatory and non-ambulatory adults (N=19), ages 18-59, with confirmed 5q-SMA, type III. Patients were treated with intrathecal loading doses at day 1, 14, 28 and 63 (mirroring the study regime in past clinical trials with nusinersen), followed by maintenance dose every four months up to 300 days.

Results indicated a moderate but clinically meaningful treatment effect in adults with long-standing SMA type III after 10 months of treatment with nusinersen, which had never been reported in the natural history of the disease (Walter et al., 2019). In this cohort, the most significant outcome measures were the 6MWT with statistically significant changes after day 180 and day 300, RULM after day 300 and peak cough flow after day 180.

Another important, real-world, observational, multi-center study was conducted in Germany by Hagenacker et al., (2020), among adults with genetically confirmed 5q-SMA, types II and III (ages, 16-69 years). About 63% were non-ambulatory and roughly 23% had undergone spinal fusion. All eligible screened patients (n=139) were evaluated on the Hammersmith Functional Motor Scale Expanded (HFMSE), Revised Upper Limb Module (RULM) and the 6MWT. Participants' baseline scores were used as the treatment comparator. This new observational cohort data demonstrates that treatment with nusinersen is safe and effective in the real-world treatment of adults with SMA. Of 139 patients who were eligible for data analysis, 124 (89%) were included in the 6-month analysis, 92 (66%) in the 10-month analysis, and 57 (41%) in the 14-month analysis while patients with missing baseline HFMSE scores were excluded from these analyses. Mean HFMSE scores were increased from baseline by a mean difference of 1.73 (95% CI, 1.05–2.41; $P <.0001$) at 6 month, 2.58 (95% CI, 1.76–3.39; $P <.0001$) at 10 months, and 3.12 (95% CI, 2.06–4.19; $P <.0001$) at 14 months with patients with missing baseline HFMSE excluded from analyses. (Hagenacker et al., 2020).

Overall, these results suggest that treatment with nusinersen, at the FDA-approved dose, can be administered safely, with efficacious results in the treatment of adults with 5q-SMA, as reflected by improvements in motor function in a real-world cohort and with clinically meaningful improvements in the ambulatory cohort (Hagenacker, Wurster et al., 2020). As one would have expected, in this study, advanced disease severity, including the presence of spinal fusion, was negatively correlated with response to treatment; such that those with lower disease severity, at baseline, exhibited the greater improvements across measures.

These are important studies for adults with SMA on a number of levels. First, and most importantly, they demonstrate that adults, with type III SMA, can be effectively treated and expect meaningful gains, in a real-world setting. Our learnings from past studies (Qian, 2015, Rouault et al., 2017), teach us that the slowing down or stopping of disease progression is highly significant to this population. Patients/caregivers polled during the externally led-Patient Focused Drug Development Meeting (EL-PFDD) for SMA, chose the option of: 'how the treatment might prevent further disease progression or improve my/my loved one's health,' as one of the top 4 factors they would consider when choosing an experimental drug (you may also refer to the Voice of the Patient Report, VOP for SMA (pp.30; 48, 49).

The importance of disease stabilization was highlighted across types and stages of SMA, particularly for those who are most chronically affected. For instance, an SMA-PFDD participant stressed that while she'd like to see improvements from a treatment,

"it is important to remember that SMA is a progressive disease. It's ugly over time. Even if the current treatment doesn't offer much in terms of strength gained, a slowing of the progression of SMA is extremely meaningful" [VOP for SMA*, p. 38]*.

Secondly, *the above results, may be pointing to the need for novel outcome measures that may hopefully allow us to capture changes in aspects of disease progression, such as respiratory function, bulbar function, etc. that are meaningful to the affected individual and may capture additional important aspects of disease.*

New 'Natural' History of SMA - Moving from SMA Phenotypes to Mobility/Functional Ability

Since the introduction of new treatments for SMA in December 2016, the disease classification by types is shifting and the course of the disease changing, particularly in children who are treated presymptomatically (Glascock et al., 2018, Belter et al., 2017-2020). The highest motor function achieved is now determined by multiple factors including: the age at diagnosis, the genetics or *SMN2* copy number, when treatment is started, and the severity of SMA symptoms at treatment start.

Infants with early onset SMA who receive treatment soon after symptom onset may now be able to hold their heads-up/achieve head control, roll independently from side to side, sit with or without support, and stand with support. Depending on how soon children are treated after symptoms emerge, a minority of children with SMA type I, have achieved the ability to walk (Mendell et al., 2020; Finkel et al., 2020, Belter et al., 2019, 2020). Based on results from the NURTURE study, we can expect most infants treated presymptomatically, with 2 or 3 copies of *SMN2,* to achieve the ability to walk unaided (88%), or with assistance (92%) (De Vivo et al., 2020). For later-onset SMA, children may achieve the ability to stand without support, walk with or without assistance (the latter being seen in a minority of patients (Chiriboga, Swoboda et al., 2016, Finkel, Mercuri et al., 2017, Mercuri, Mendell, 2017; Darras et al., 2018; Sturm et al., 2019; Servais, Darras, et al., 2019 and 2020; Finkel et al., 2020; Darras et al., 2020).

As proposed in the 2007 SMA Standard of Care Consensus Statement and continued in the updated 2018 SMA Care Recommendations publications, classification by highest motor function achieved (Non-Sitters, Sitters, and Walkers), instead of types, would now be most meaningful and provide guidelines on evaluation and rehabilitation (Wang et al., 2007, Finkel et al., 2017, Mercuri et al., 2018).

Real World Evidence on the Shifting Burden of SMA - New Features of SMA Captured Clinically

Learning about and capturing the emerging features in SMA, from infantile to later onset SMA, will require careful observation and systematic methods for capturing this information; from clinical trials to clinician-entered data to patient-reported data (PROs). Patient-reported data is critical to the collection of clinically meaningful data that comes from the patient's perspective (Tizzano et al., 2017).

Below is a non-comprehensive list of new features of SMA that have been captured as reported by clinical assessments (presented at national and international professional conferences, such as the 2020 SMA Europe International Conference, and 2020 Cure SMA Annual Conference) or have been reported through patient reported vehicles, by patients and their caregivers.

Newly Captured Effects on Motor function – Observational Studies

A one-year follow-up study in children with SMA type 1b to 3a, treated with nusinersen captured its **effects on motor, respiratory and bulbar function**, noting the following unique features such as increased motility of the

tongue and intelligibility in voice, among others, in SMA type 1b (non-sitters) (Scheijmans, 2020, SMA Europe; see **Table 2**).

Similarly, a longitudinal, real-world, data set which corroborates the previously discussed findings in adults with SMA treated with nusinersen (Day, Wolford et al., 2020, Elsheikh, Severyn et al., 2018-2020) has shown that adult SMA patients treated with Spinraza,® have reported *qualitative* improvements in 8 primary areas: **axial and limb strength, motor function, motor stamina, pulmonary function, chewing/swallowing ability, voice projection, and quality of life**. Most of these improvements (new aspects of disease phenotypes) are not all well captured in current assessments.

Adult SMA Pre- & Post-nusinersen – HFMSE (composite ordinally scored functions: 0 – 66)

$N = 37 \quad + 1.1 \text{ pts/y}$
$p = 0.08$

Natural History HFMSE >15 yo
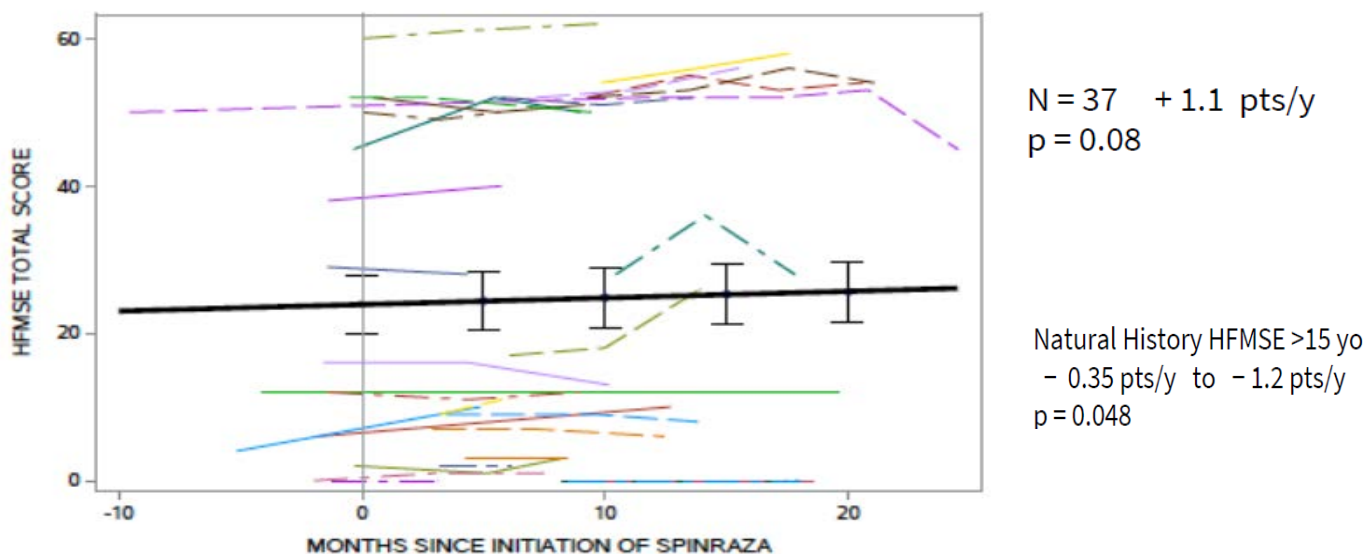$- 0.35 \text{ pts/y to } - 1.2 \text{ pts/y}$
$p = 0.048$

Figure 4. Adult SMA Pre and Post-nusinersen – HFMSE (Day, Wolford et al., 2018)

The recent learnings from longitudinal, observational studies in chronically treated adults (Osmanovic et al., 2020, Walter et al., 2019, Hagenacker et al., 2020) show clinically meaningful change for adults treated with nusinersen, though the improvements demonstrated, with gains of roughly +1 point on the HFMSE for SMA type II patients and non-ambulatory type III patients, could ideally be improved.

Given the progressive nature of SMA, even small gains or improvements are hugely important to this population. We know from previous research in SMA that disease stabilization, particularly in adults is highly desirable (Rouault et al., 2017, Cruz et al., 2018). However, given the more dramatic changes/gains seen in a younger population, we recognize that larger gains are also highly desired in the adult population.

Children, non-sitters (type 1b)	**Increased** <u>motility</u> of the <u>tongue</u>
	Increased <u>loudness</u> and <u>intelligibility</u> in voice
	Some <u>lateral neck movement</u>
Children, sitters and walkers	Trunk: **improved** <u>stamina</u>
	Improved <u>stamina</u> and **reduced** <u>fatigue</u>
	Increased Range of <u>movement (ROM)</u> of the neck
	Increased <u>forearm pronation / elbow flexors, upper limbs</u>
Adults, treated with nusinersen	**Improved** <u>voice strength</u> and <u>communication</u>
	Improved <u>articulation</u> and ability to speak on phone
	Improved ability to <u>chew</u> and <u>swallow</u>, expansion of dietary choice
	Improved <u>stamina</u> and **reduced** <u>fatigue</u>
	Improved <u>balance</u> and <u>confidence</u> in walking, <u>walking farther</u>
	Improved <u>trunk</u> <u>strength</u>, ability to <u>flex</u> and <u>straighten</u> back

Table 2. New features of SMA that have been observed/captured in treated children and adults with SMA (Day, Wolford et al., 2020, Elsheikh, Severyn et al., (2018).

Real-World Evidence on the Shifting Burden of SMA - Cure SMA Community Update Survey

According to preliminary results from the Cure SMA 2020 Community Update Survey, 37% of children with infantile onset SMA are able to sit independently, as reported by caregivers. *Over the last 3 years, we have witnessed a 20% increase in children with infantile-onset SMA, who have achieved the ability to sit* (Belter et al., 2020; [see **Figure 6**, below]). In 2019, 17% of SMA type II patients (N= 258 total patients) could stand with or without support. In the stander group, 82% were on drug, while in the non-stander group 70% were on drug (p<0.05).
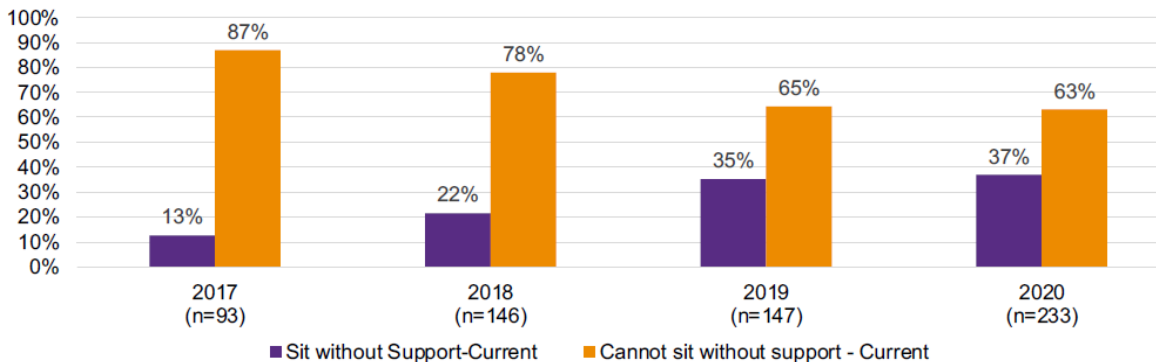

Figure 5. Percentage of infantile-onset (SMA type I) children who are able to sit without support

Gaps in Treatment (Symptoms not Addressed) - Cure SMA Community Update Survey

Patients who are administered a treatment or an experimental compound after symptom onset, continue to have significant unmet medical needs. To better capture the SMA experience, the Cure SMA 2019 & 2020 Community Update Survey, included the following question: *What are the most significant current unmet needs that you hope new therapies would address?* Possible answer choices were: 1)improve fatigue; 2)improve respiratory function; 3)improve swallowing; 4)gain muscle strength; 5)achieve new motor function; 6)improve communication through speech and/or technology; and 7)improving daily function.

Following is a list of significant symptoms/unmet medical needs that based on the responses to the above survey question, from adults and parents/caregivers of children and adults with SMA, across the spectrum, are currently not addressed by existing treatments. The treatment gaps below have been listed in order of importance to the patient's overall function or their assessment of clinical meaningfulness based on previous study findings (EL-PFDD for SMA, Rouault et al., 2017, Qian et al., 2015, Cure SMA Community Update Survey, 2019-2020). These are as follows,

A) Motor Function/ Muscle Strength
- Debilitating and progressive muscle weakness is a hallmark symptom of SMA. As such, any improvements in motor function and gains in muscle strength have been reported as clinically meaningful across the spectrum. You may refer to VOP for SMA (pp. 13,25, 54) for a more complete discussion on this. Results captured on the Cure SMA annual survey indicate the following,

- In 2019, *90.3%* of *adults and caregivers' survey respondents (N=566), completed this question, choosing gaining muscle strength as the most important unmet need among the SMA community with of respondents choosing this option* (see **Table 3**). Gaining muscle strength remained the most important unmet need regardless of whether someone had already been treated for SMA or not.

- In 2020, only affected adults were asked to respond to the above question. Of the 365 adult survey participants who completed this question, *95.6% of [adult] respondents identified gain muscle strength as the most important unmet need among the SMA community.* Gaining muscle strength *remained* the most important unmet need regardless of whether someone had received SMA treatment.

B) Musculoskeletal
- Scoliosis is a common complication of SMA, impacting roughly 68% of individuals with SMA types I or II (Fujak et al., 2013). Scoliosis management is achieved through surgical instrumentation and spine fusion. Based on the Cure SMA 2020 annual survey, *spinal complications, necessitating spinal surgery, continues to be a significant burden in patients with SMA type I/II.*
- In 2020, 68% of all Cure SMA community survey participants (N=1,061), reported having undergone scoliosis surgery; of these, 90% were diagnosed with SMA type II.

C) Respiratory
- Respiratory complications, including life-threatening respiratory symptoms (such as difficulty breathing, inability to clear secretions, lung infections and respiratory failure) affect most children with SMA types I and II and adults with advanced disease progression. Respiratory failure has traditionally been the number one cause of death in infants with SMA.

- Per the 2019 Cure SMA Community Update Survey, the most commonly used respiratory devices among those with SMA type I was a cough assist machine (71.2%), followed by bilevel positive airway pressure (BiPAP) machine (50.3%), then oxygen machine (23.7%) (Belter et al., 2019).

D) Gastrointestinal

- Per the 2019 Cure SMA Community Update Survey, the most common type of surgery among those with type **I was gastro surgery** (**79%**) (likely for G-Tube placement which has been a component of the recommended standard of care for SMA type I).

E) Speech/Swallow

- Depending on timing of first treatment dose, speech and/or swallowing difficulties, in SMA type I, may or may not be rescued (Darras et al., 2019, Finkel, 2017). Even when rescued, some children may regress and lose the ability to swallow/feed by mouth.

F) Communication Difficulties

- At the EL-PFDD polling section for those affected with SMA type I Communication difficulties was selected by 72% of all participating parents and caregivers of children with SMA type I when asked - "*Which of the following symptoms currently has the most significant impact on you/your loved one's life?* Select TOP 4- they selected ([VOP for SMA](#), pp.9, 35).

- In 2019, this remains a significant unmet need for 49% of those affected with SMA type I and close to 13% of those with SMA type II (Belter et al., 2019, Cure SMA Community Update survey).
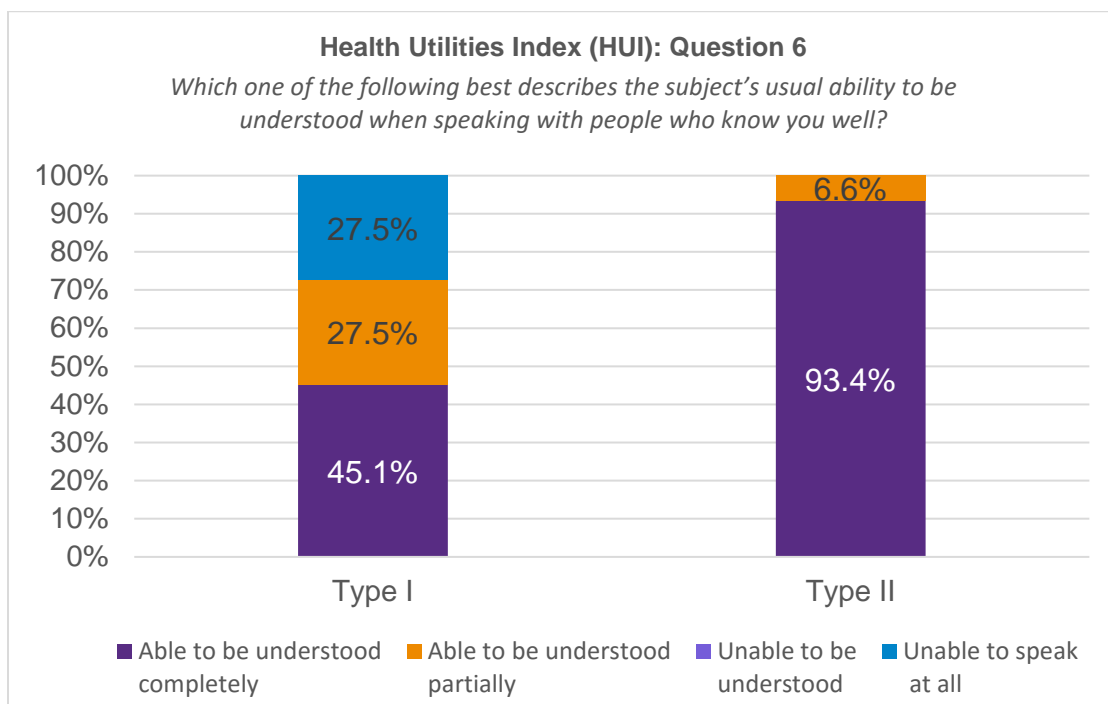

Health Utilities Index (HUI): Question 6
Which one of the following best describes the subject's usual ability to be understood when speaking with people who know you well?

Type I: Able to be understood completely 45.1%, Able to be understood partially 27.5%, Unable to speak at all 27.5%
Type II: Able to be understood completely 93.4%, Able to be understood partially 6.6%

Legend: ■ Able to be understood completely ■ Able to be understood partially ■ Unable to be understood ■ Unable to speak at all

Figure 6. Results from 2019 Community Update Survey on the HUI Q6 PROM

H) Fatigue

- The impact of fatigue on patients with SMA has been widely described and represents a significant to all affected, its mechanisms (systems involved, including defects in neuromuscular junction) are not well understood. Most patients with SMA report severe perceived fatigue and have physiological fatigue. This fatigue can impact their ability to participate in daily activities, physical therapy, and in community and school settings (Dunaway, et al., 2019; de Groot et al., 2013, Werlauff et al., 2014).

- In the 2019 Community Update Survey, **53%** of all participants, adults and caregivers alike, selected fatigue as *'the most significant, current unmet need.'*

- Fifty-seven percent (57%) of parents and caregivers of children and affected adults who participated in the EL-PFDD for SMA reported fatigue as one of the top 4 most significant symptoms affecting their lives and quality of life.

I) Activities of Daily Living in the Adult Population

- Cure SMA survey asked affected adults only: 'Of the activities you are currently able to do by yourself, which of these activities would be the most important for you to maintain or stabilize (Check one)' 1)Feed yourself; 2)Use the toilet by yourself; 3)Bathe yourself; 4)Dress yourself; 5)Brush or comb your hair; 6)Get in and out of bed by yourself 6)Turn over in bed by yourself; 7) Write with a pen; 8) Use a keyboard; 9)None of the above.

- *The majority of respondents, 41.8% (151/361), chose feed yourself. These results highlight the importance of independence in this population*. In fact, the loss of independence, particularly, in teens/young adults and adults with SMA is most feared (Rouault et al., 2017, Mazzella et al., 2020); and anything that increases endurance, and/or increases the affected individuals' independence, including stabilization of disease, is acutely meaningful (Qian et al., 2015, Rouault et al., 2017; Cruz et al., 2018 [VOP for SMA, p. 5], Osmanovic et al., 2020).

- *Three years after the SMA EL-PFDD was conducted, the symptoms that matter most to the adult population, remain virtually unchanged (Cruz et al., 2018, VOP for SMA [Appendix 3, Q.11, p.13, 40]).*

For a comprehensive summary of survey results detailing 'patients' and parents'/caregivers' expectations for treatment based on the 2019 Cure SMA Community Update Survey, see **Appendix C.**

Access to Treatment for Children and Adults in SMA in a Post-Treatment Era

As presented in data supplied in public disclosures by drug companies, sixty percent (60%) of all patients in the US remain untreated at this time. For SMA patients over 18 years old, this proportion increases to 70-80%. Cure SMA's internal data also shows a clear trend that fewer patients are on drug as age increases. In all there were 3,750 SMA patients on FDA approved drugs in the US on March 31, 2020, with approximately 3,230 on Spinraza and 520 on Zolgensma, both commercially and through other access channels. Importantly, *seventy-three percent (73%) of adults and caregivers who participated in the Cure SMA Community Update Survey chose 'achieving new motor function' as one of the most significant unmet needs that they hope a treatment will address*, whether they are currently being treated with a FDA approved therapy or not.

Conclusion

- The advent of new therapies and approaches to treat SMA has revolutionized the SMA landscape, and dramatically changed the natural history of SMA, most strikingly, through newborn screening (NBS) identification and when treated soon after symptom onset. Even so, there are still many unmet needs when addressing the complexities and burden of this multi-systemic disease.

- Specifically, *the most significant unmet need exists in the untreated child/adult, and then symptomatically treated patient,* including adults. For instance,
  - o From the ENDEAR-SHINE trial, after 3 years of treatment (end of 2018), we learned that, remarkably, 60% of type I babies treated before age 5.42 months (18/30) were able to sit versus

38% of type I's treated after 5.42 months of age (n=8/21) were able to sit. This leaves a significant portion who did not meet this milestone in this three-year time period. (Finkel et al., 2017).

- o A similar pattern is reflected through the Cure SMA survey results where 35% of type I's achieved the ability to sit.

- *Per the Cure SMA annual survey infants with type I SMA are being diagnosed at an average age of 9 months (*Belter et al., 2020). As we can see from the ENDEAR-SHINE study and RWD collected by Cure SMA, children with infantile-onset SMA have a relatively small window in which to be treated and obtain maximal long-term outcomes.

  - o Roughly 4% (4/39) of SMA type II children in the CHERISH-SHINE trial, under four years, were able to walk independently at study Day 960 (Darras et al., 2018).

  - o Similarly, as shown by the Walter et al., (2019), the Hagenacker et al., (2020), and Day et al., (2019) observational studies, long-standing SMA type II and non-ambulatory type III adults, see real but moderate changes. Patients with a milder disease phenotype benefit showed clinically meaningful improvements of > +3 points on the HFMSE and other outcomes (e.g., 6MWT, RULM, etc.), while more affected adults saw less.

- Given the rapidly evolving SMA phenotype, a suggested nomenclature for classifying SMA has been recommended and is being increasingly adapted. The new classification shifts from SMA type to highest function achieved – non-sitters, sitters/standers and walkers.

- Close monitoring of patients with systematic methods to capture this new 'natural' history in the treated patient (e.g., via clinician-entered registries, long-term trial data, PRO data, clinical research networks, etc.) will allow us to understand the new/ various disease trajectories and to develop long-term outcomes and endpoints.

- In terms of treatment access, 70% to 80% of individuals over the age of 18 years currently are <u>not</u> being treated.

- In summary, *people with SMA and their families have made clear that great unmet and urgent medical needs remain in the SMA community, particularly in older individuals with SMA types II and III*. These medical needs greatly impact their daily function and quality of life.

II. Exploring Novel and Clinically Meaningful Outcomes in the Adult SMA Population

In this section, we further explore the need for novel, more sensitive outcome measures for adults, including those currently being explored in a clinical setting.

Question 2

Part 1. How does the FDA view the *sensitivity of current outcome measures* for adults/older patients with SMA? Does FDA agree additional ones might be needed?

   a. **What are the current gaps in the utilized SMA tools, that makes them inadequate for adults?**
   b. **Are there additional endpoints that could provide early evidence of efficacy in the adult population?**

Part 2: In addition to the existing/validated outcomes in SMA, for Teens and Adults, which of the outcomes/clinical outcome assessments (COAs), we have proposed are of most interest to you in,

    c. **Assessing possible clinical benefit of an existing treatment including disease stabilization (i.e., improvements or stabilization in function, changes in how patients feel) and/or,**

    d. **Informing future drug assessment/development (improvements in function, changes in how patients feel)?**

Gaps in Existing Outcome Measures

Over the last decade, tremendous progress has been made in the development, testing and validation of various outcome measures, primarily in infants and young children with SMA. The wide array of motor function and development outcomes have comprehensively captured various aspects of disease, in children with SMA, including progression, functional ability and impact (burden) across SMA phenotypes, as known and defined in its natural history (Kaufmann, McDermott et al., 2012, Finkel, McDermott et al., 2014, Mercuri, Finkel et al., 2016, Montes, McDermott et al., 2018, Messina et al., 2019, Krosschell and Young, 2019).

In addition, new gaps in assessment have been identified given the changing phenotypes seen in treated SMA children, particularly those treated presymptomatically and via NBS. The commercial use of nusinersen has further shown that outcome measures such as the HFMSE or CHOP-INTEND do not capture all improvements or changes reported by caregivers and parents in some study participants with SMA. However, *the current outcome measures have limitations for the adult population. In particular, most have not been validated in an adult population and their primary focus is on gross and fine motor skills. Other important aspects of disease in the adult, for instance, bulbar function or fatigue, which significantly affect daily function, have not been fully assessed.*

Considerations for Selection of Outcome Measures

Outcome measures that relate to function in daily life, and not just muscle strength, have been shown to be more clinically relevant, meaningful, and essential to determine if change in strength can impact performance of an individual with SMA (Krosschell and Dunaway-Young et al., 2019; reviewed in Messina et al., 2019). *Functional scales have the advantage of capturing motor performance in a more comprehensive way while being able to be administered, reliably, to many individuals* (Mercuri et al., 2017).

Clinical trials to date have included individuals with SMA at varying levels of disease severity and progression. Finding the appropriate outcome measures that would be sensitive and reliable to quantify change across the disease spectrum (including those not previously studied in clinical trials), is desired.

Existing, Validated Outcome Measures in SMA

There are a set of 'core' outcome measures currently recommended for SMA (based on the World Health Organization (WHO) International Classification of Functioning (ICF) at the levels of body structure and function, activities, and participation (see **Figure 7**). Selection and use of outcome measures in a clinical setting may also be dependent on SMA type, current functional level (Non-Sitter, Sitter, Walker) and/or the patient's presenting symptoms, complaints and desired goals (**Figure 8**).
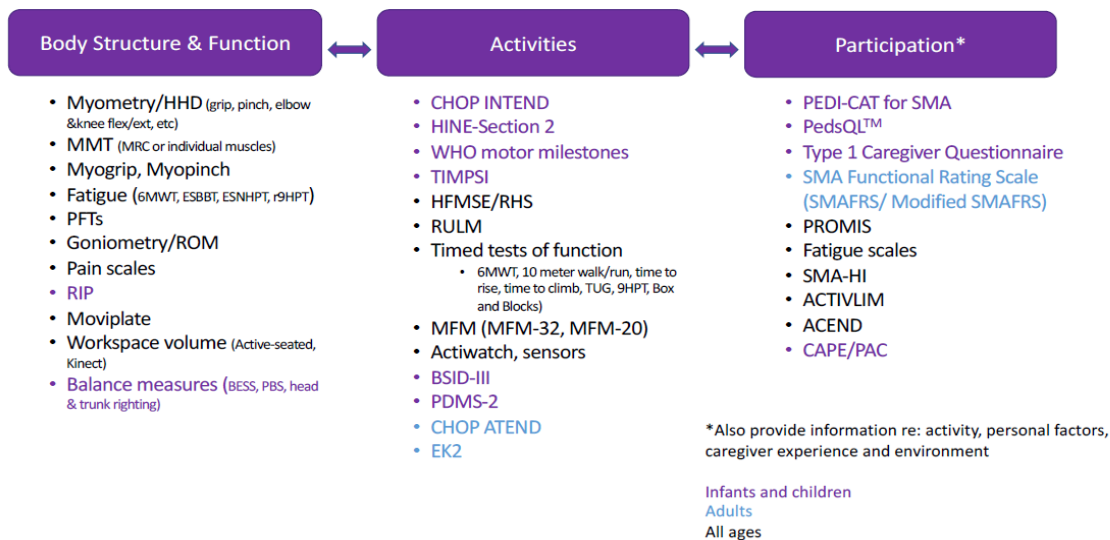
Figure 7. Commonly used SMA assessments across domains in the ICF framework (Cure SMA, Best Practices for Physical Therapists & Clinical Evaluators, Krosschell and Dunaway-Young et al., 2019*)*

Commonly Used Assessments across Domains of the WHO, International Classification of Functioning
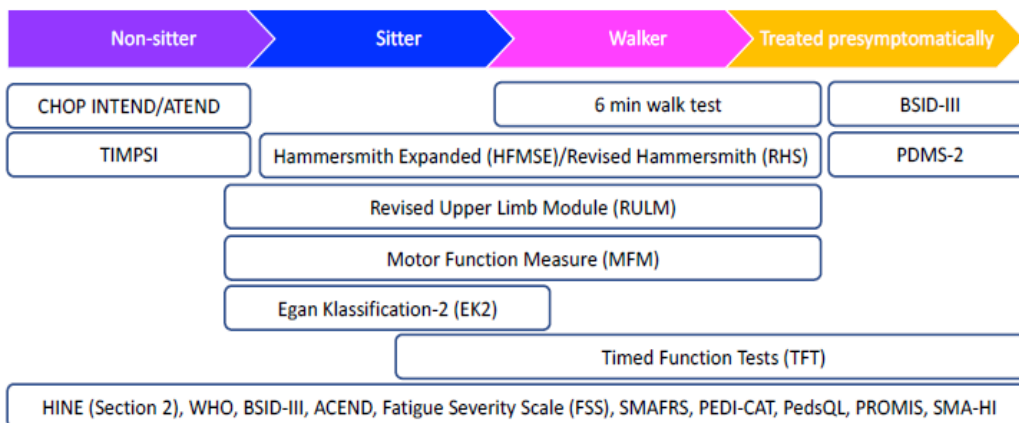

Figure 8. Commonly Used Assessments across functional domains (as classified by the WHO ICF).

The Need to Develop Novel, More Sensitive/Clinically Meaningful Outcomes in Adults

The understanding of treatment effects is tightly connected to having sensitive-enough outcomes to best capture the gains or improvements that have been observed using the existing outcomes. *The current data suggests that current outcomes, across all domains of the WHO International Classification of Functioning (CF), may not be sensitive enough to capture small and/or clinically meaningful changes in the more chronically affected adult population during their treatment journey.* Longer-term observational treatment studies that have included adults with SMA with long-standing functional disability and weakness (primarily type III) (Osmanovic et al., 2020, Walter et al., 2019, Hagenacker et al., 2020, Swoboda 2020, Veerapaniyan et al., 2020), highlight the urgent, collective, community need, to not only better define/understand the natural history of adults with SMA but also, to gain a better understanding of treatment effects and expectations for both, ambulatory and non-ambulatory adults, of various functional status. While these studies highlight outcomes demonstrating both stability and improvement over time, even changes that were deemed

statistically significant were not considered clinically meaningful across __all__ studies/cohorts, likely due to high levels of variability in response to treatment and small effect sizes (Walter et al., 2020, Swoboda et al., 2020,

> *Longer-term observational treatment studies in adults with SMA highlight the urgent community need, to better understand the suitability of existing outcomes to capture treatment effects and expectations in the weakest of patients with type I, II and III SMA.* While these studies highlight outcomes that show stability and improvement over time, *even changes that were deemed statistically significant were not considered clinically meaningful* across __all__ studies/cohorts.

Veerapaniyan et al., 2020). While the Hagenacker et al., (2020) study included a much larger and more heterogeneous cohort overall, which was inclusive of both stronger and weaker individuals, there was still a fair amount of variability in responsiveness amongst the cohort. Additionally, it is difficult to fully interpret their findings regarding one of the outcomes most applicable to the weaker group (the RULM) as the test is scored from 1-37, yet they report ranges up to 87 at baseline.

As such, *variability in findings across studies and within cohorts, as well as limited evidence for weaker and more involved adult cohorts (those with types I and II) substantiates the need for more robust, sensitive, and clinically meaningful outcomes for this population as a whole.* Efforts to develop such will be valued by those affected by the disease and their families, as well as by academicians/clinicians and industry partners.

Please refer to **Appendix D** for a summary table including a list of outcome measures in SMA by type, function, reliability, validity, functional relevance and clinical meaningfulness, among others. This summary table was developed based on the work from various SMA outcome workshops including ENMC Meeting in 2014, again EMA Meeting, 2016 (Montes et al., 2016). The latest table include the most the most up-to-literature (Krosschell and Dunaway-Young, 2019, Best Practices Toolkit).

Addressing Current Gaps in Outcome Measures Adults with SMA

Many in the SMA community – clinicians, clinical trialists, industry and non-profits, like Cure SMA, are working to address the aforementioned gaps/concerns in the treated/untreated SMA population. To address gaps in natural history in adults, for instance, the Pediatric Neuromuscular Clinical Research Network (PNCR) is conducting a longitudinal collection and assessment of a minimal data set in adults with SMA followed at PNCR sites (Columbia University, Nemours Children's, Children Hospital of Philadelphia, Boston Children's and Stanford University Medical Center). *The assessments being used to collect the progression and manifestation of SMA, include a comprehensive assessment of longitudinal motor function (gross and upper extremity), strength, pulmonary function, and patient reported outcomes* (Kaufmann, McDermott et al., 2012, Finkel, McDermott et al., 2014, Mercuri, Finkel et al., 2016, Montes, McDermott et al., 2018).

The PNCR will additionally continue to collect a minimal data set to report continued patterns of disease progression in infants, children, and adults with SMA. The existing minimal data set for all chronic adult SMA patients are categorized based on functional status and include a combination of strength, function and respiratory measures.

Outcome Measures	Non-ambulatory, Unable to sit independently	Non-ambulatory, Able to sit	Ambulatory
	• Pinch • CHOP ATEND • PFTs • SMAFRS	• RULM • CHOP ATEND • HFMSE • PFTs • SMAFRS	• 6MWT • TUG • HFMSE • PFTs • SMAFRS

Figure 9. Validated, exploratory outcomes currently being used with adults of various functions (Day, Wolford et al., 2018)

Patient-Reported Outcomes/Health-related Quality of Life Measures

SMA researchers have been diligently working to capture other aspects of disease burden /symptoms that matter most to patients and caregivers affected by SMA via patient reported outcome measures, PROs (reviewed by Messina et al., 2020, Heatwole, 2019). These include but are not limited to SMA-HI, health-related quality of life measure (HRQOL), such as the WPAI, HUI, Spinal Muscular Atrophy Independence Scale (SMAIS), etc. *However, to date, very few QoL measures have been specifically developed for SMA.*

To date, there are no published data on SMA specific PROMS, although validation of the SMA-HI publication is under review (Heatwole et al., 2020). Additionally, a few adult neurologist/clinicians in the field have started to look at speech, swallow, jaw stuff, voice projection, etc. as well- pretty relevant to function.

Additionally, *it is important that we continue to explore and better understand correlations between existing HRQoL measures, Patient Reported Outcomes (PROs), and functional scales – particularly in the most severely affected population. Furthermore, we must better understand how increases or improvements in motor function measures (specific scores) relate to function and clinically meaningful changes* (Pera, Mazzone et al., 2017). That is, what does a change on a given scale (e.g., HFMSE or CHOP ATEND) mean in terms of how it may improve the quality of life of an adult with SMA? And, given the heterogeneity across the spectrum, do these outcomes effecting and consistently capture meaningful change for this population? We may also need new outcomes to enable us to capture new changes in phenotype, that have been observed/captured in treated patients through clinical observation (see **Table 2**).

Exploratory Outcome Measures Adults with SMA

The need for novel outcomes in an adult and chronically treated population that reflect clinically meaningful changes in function/improvements in quality of life is essential. These proposed or exploratory outcomes, currently being captured through clinical or observational studies must meet some of the following key criteria, There are currently a number of validated, exploratory outcome measures that are currently being used in clinic, with adults of various functional abilities, to assess the effects on treatments in adults (Bakri, Day, Zaidman, 2020).

Aspects of disease that must be evaluated / Target audience	Function – ADLs/Clinical Meaningfulness	Exploratory Outcomes (As assessed by)
Endurance -All types/ functions	• Can do schoolwork longer; sit-up longer; • Interact with friends after school /work; • Play a longer time with children (for adults); • Socialize after school/work	• 6MWT in ambulatory type III adults; • TUG
Fatigue - all types/ functions	• As reviewed in the previous section fatigue continues to be a burdensome aspect of the SMA patient experience that is not well understood or well captured via the existing HRQL and ADL measures (PROMs/Surveys) here explored.	• NEW HRQoL Measure/ Novel Outcome possibly needed • ADLs • 6MWT – Ambulatory Adults • UE Fatigue Test
Voice projection, diction, pronunciation	• Improved communication; • Improved social and personal interactions	Possible, App-based voice recordings/analytics
Bulbar function -non-sitters; sitters	• Can chew and swallow with more ease/less difficulty • Increased chewing strength/ can chew longer without tiring	• Swallow studies? • Novel outcome possibly needed • Jaw ROM
Muscle Strength/Function (includes finger strength finger movement)	• For the weakest of patients/non-sitters • Assess improvements in fine motor function; particularly in non-sitters	• SMA Functional Rating Scale (SMAFRS); • Electrophysiological studies; SMUP, MUNE • Novel Outcomes possibly needed • CHOP ATEND
Mental Health – Anxiety, Depression, etc.	• Mental Health inventories (levels of depression and anxiety often reported)	• HRQL – Depression and Anxiety Instruments
Respiratory Measures – all types	• Ability to breathe (with or without support) • Intercostal muscle strength	• Spirometry – FVC, MIP, PFTs • Hours on BiPAP
Impact of disease symptoms on functioning in patients' daily lives	• QOL /Independence/Schooling/ Socialization	• SMA-HI • SMAIS • Activlim • PROMIS
Tongue motility (type I's)	• Novel outcomes	

Table 3. Proposed or exploratory outcomes, currently being captured through clinic or observational studies must meet some of the following key criteria

Conclusion

As we move forward in addressing the evolving need of our community, particularly in adults, we need to consider novel and even more sensitive outcomes to capture small yet clinically meaningful changes in the most severely affected adults. Ultimately, such outcomes should capture change across all levels of the ICF, capture change for all adults with SMA and demonstrate robustness.

• Continued understanding of the effect of treatment and clinical meaningfulness of existing and exploratory outcomes in adults with SMA remains an utmost priority for our community.

- Outcome measures also play an essential role in assessing the clinical effectiveness of approved treatments and facilitating insurance approvals. As such, exploring additional option for outcomes for the chronically treated (ambulatory and non-ambulatory) adult population, to ascertain improvements/clinically meaningful outcomes is essential to ensuring continued access to treatment in the adult SMA population.

III. Neurofilaments as Biomarkers for SMA

Question 3.

Part 1. What is FDA's thinking regarding the potential utility of neurofilament as a pharmacodynamic biomarker likely to predict clinical benefit during the drug development process?

Part 2. When thinking about the qualification of the pharmacodynamic biomarker, does the agency see the need to establish threshold values or is change from baseline or over time an acceptable measure for assessing drug effect? If so, do we need determine a % Delta

a. In the view of the FDA, what control data is needed in terms of healthy and SMA patient data and what kind of correlation to other outcome measures (i.e. motor scales, CMAP, MUNE) should be considered?

Neurofilaments (NF) are cytoplasmic proteins abundantly expressed in axons that have been recognized as promising diagnostic, prognostic, and monitoring biomarkers in a range of neurological disorders associated with axon loss (74-76). These intermediate filaments are uniquely expressed in neurons, and when released into extracellular fluid upon perikaryal or axonal degeneration, can be detected in cerebrospinal fluid (CSF) and blood. NFs comprise three proteins differentiated by molecular weight, light (NF-L), medium, and heavy (NF-H). Initial discovery studies focused on modulation of *SMN2* splicing in children with SMA identified NFs as potential biomarkers of disease progression and therapeutic response (77-78).

Data from infants treated with Nusinersen in the pre-symptomatic phase of disease in the NURTURE trial showed that plasma pNF-H levels declined rapidly following the loading phase of nusinersen and then stabilized (79). NURTURE (NCT02386553) enrolled infants ≤6 weeks of age at first
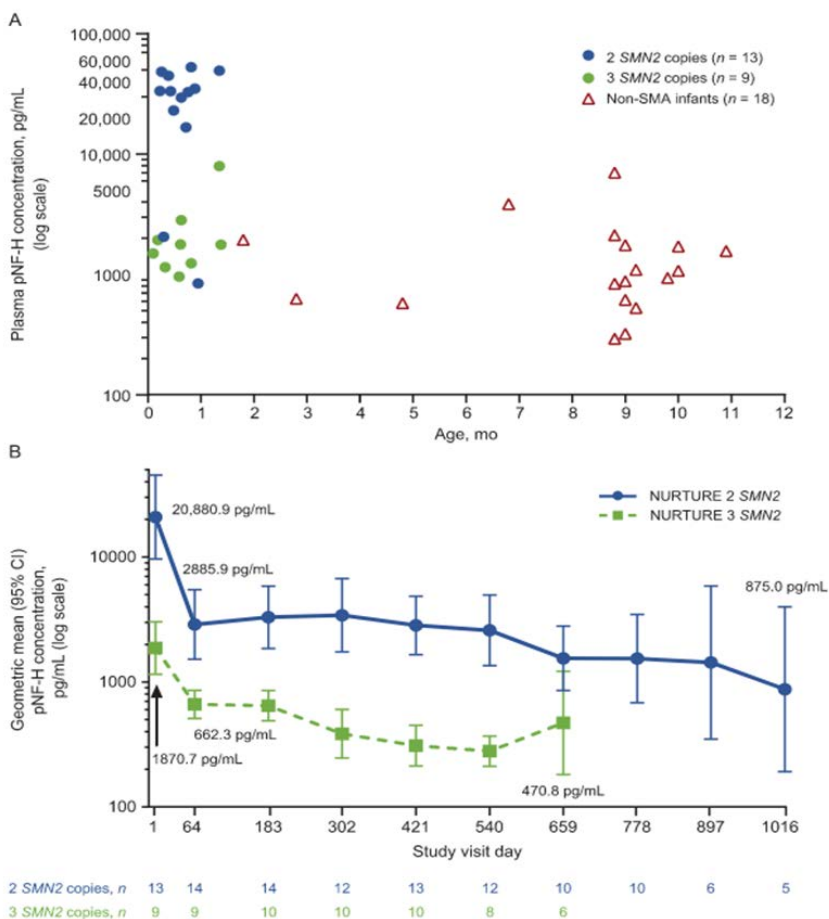
Figure 10. (A) Plasma pNF-H levels at baseline in NURTURE infants and infants <1 year of age without SMA, (B) plasma pNF-H levels in NURTURE infants by study visit.* pNF-H levels were evaluated using a pNF-H ELLA from ProteinSimple. Baseline pNF-H values in NURTURE infants were obtained on Study Visit Day 1, either prior to nusinersen administration or four h post-dose.

*Timepoints with n≥5 included.

dose and considered to most likely to develop SMA type 1 or type II based upon *SMN2* gene copy number. Baseline pNF-H levels were higher in most presymptomatic infants with SMA compared with non-SMA infants and were significantly higher in most SMA infants with two *SMN2* copies compared to those with three *SMN2* copies. (plasma P = 0.0050; CSF P = 0.0020) (**Figure 10**). A similar pattern of decline followed by stabilization was also seen in CSF pNF-H levels. Correlations to identify the strongest predictors of motor function were calculated. Baseline pNF-H level was the strongest predictor of HINE-2 total motor milestone score at Day 302 (rs= −0.53; P=0.0120; n=22) and age of achievement of WHO walking along (rs=0.55; P=0.0147; n=19). Plasma pNF-H levels at Day 64 were
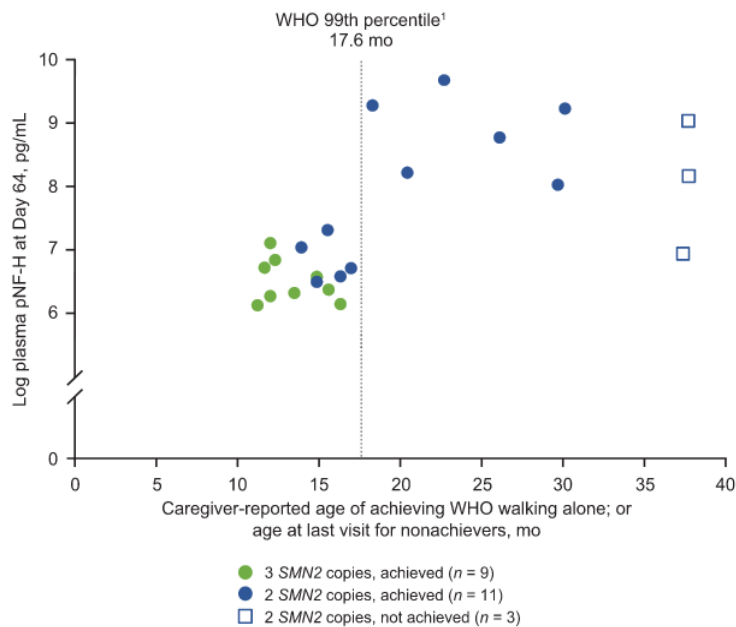

Figure 11. Plasma pNF-H levels at Day 64 and achievement of WHO motor milestone of walking alone.[1] WHO 99th percentile for age of achievement for development of healthy children.

the best predictor of future motor function achievement in the overall population. Plasma pNF-H levels at Day 64 were significantly correlated with the total HINE-2 motor milestone score at Day 302 (rs=−0.67; P=0.0005; n=23) and with achievement of the WHO motor milestone walking alone (rs=0.64; P=0.0025; n=20). Lower plasma pNF-H levels at day 64 were associated with earlier achievement of walking alone (**Figure 11**). In participants with 2 *SMN2* copies, Day 64 weight for age (rs=0.72; P=0.0027; n=15) and Day 64 CMAP amplitude (rs=0.66; P=0.0098; n=14) were correlated with total HINE-2 motor milestone achievement at Day 302, and similar results were observed for age at achievement of WHO walking alone. Plasma pNF-H levels at Day 302 were evaluated in relationship to those from individuals without SMA and to motor milestone achievement and other outcomes. Plasma samples were analyzed from 18 non-SMA individuals who ranged in age from 0.15 to 0.91 years. These individuals had plasma pNF-H levels ranging from 293 to 7033 pg/mL (Q1, 616pg/mL; Q3, 1753pg/mL). NURTURE Day 302 was selected for this analysis based on the age range of non- SMA individuals. Twenty-two NURTURE participants had a recorded measurement for Day 302 plasma pNF-H level, 13 of whom (3 with 2 *SMN2* copies; 10 with 3 *SMN2* copies) had a result below Q3 (≤1753 pg/mL) for non-SMA individuals <1 year of age. Among these 22 NURTURE participants, all children who initiated ventilation support (n=4), met the protocol definition of clinically manifested SMA at Day 700 (n=6), and/or had delayed or no achievement of sitting or walking alone (per WHO 99th percentile window) had a Day 302 plasma pNF-H level above the Q3 (>1753pg/mL) for non-SMA individuals <1 year of age.

In March 2019, a study investigating changes in NF levels in response to Nusinersen in the ENDEAR trial was published (78). ENDEAR (NCT02193074) was a phase III, randomized, double-blind, sham procedure–controlled study that assessed the efficacy and safety of nusinersen in participants with infantile-onset SMA (aged<6 months at symptom onset, with 2 *SMN2* copies, and considered most likely to develop SMA type I). Plasma pNF-H concentration declined over time in both the nusinersen and sham control groups (**Figure 12**). In the nusinersen-treated arm, the pNF-H concentration declined more rapidly and to a greater magnitude before stabilizing at a level below the sham control arm at any point of the study. In contrast, participants in the sham control arm experienced a steady and gradual decline in pNF-H concentration over the study duration. At the end of the dosing period, pNF-H levels were 90.1% reduced in nusinersen-treated participants and 60.3%

reduced in the sham control group (compared with pretreatment levels). Similar trends were seen in the CHERISH trial which enrolled children aged 2-12 years with later-onset SMA. pNF-H levels declined over time in the nusinersen and sham-control groups. However, decline was continual in the sham-control group compared to a greater initial decline with nusinersen treatment followed by stabilization (80).

In a recently published exploratory study on a small cohort of SMA type 3 patients, preliminary findings on the effects of Nusinersen administration on motor function over the short-term and changes over time in the CSF concentration of both pNf-H and Nf-L were reported (81). A total of 12 patients diagnosed with SMA type 3 were enrolled in the study. The age of first treatment ranged from a minimum of nine to a maximum of 74 years, with nine patients (75%) >18 years old. The minimum disease duration at the start of treatment was 7.5 years, while the maximum duration was 32 years. pNf-H and Nf-L levels at baseline in the CFS of SMA type 3 patients were comparable to those observed in controls (n = 9, age: 29.0 [22.0-54.5] year-old) and were far below the average values described in patients affected by either SMA type 1 (6.874 ng/mL and >10 000 pg/mL, respectively) or amyotrophic lateral sclerosis (5.270 ng/mL and 2961 pg/mL11). No significant correlation was observed between pNf-H and either age at treatment or duration of the disease.

Figure 12. (A) Mean plasma pNF-H concentration (pg/mL) over time during the ENDEAR trial, and (B) percentage change from baseline in pNF-H concentration (pg/mL) over time (nusinersen offset left for the purposes of graphic display). The results presented are statistical means and do not imply that the assay is capable of the sensitivity or precision necessary to generate results>3 significant figures. pNF-H=phosphorylated neurofilament heavy chain; SE=standard error

However, a positive correlation was found between Nf-L and age at treatment (r = 0.59, P = .046) along with a marginally significant correlation between Nf-L and duration of the disease (r = 0.55, P = .066). Interestingly, the comparison between the values of both neurofilament types before and after 6 months of treatment start showed a slight but significant decrease (pNfH: median of differences −0.0236 ng/mL, P = .016—NfL: mean of differences −70.0 ± 97.7 pg/mL, P = .031) (**Figure 11**). However, no significant correlation was observed between the pre-post–difference in HFMSE scores and the change of either pNf-H or Nf-L over time (**Figure 13**) (79). Limitations of this study include the small number of patients and the relatively short duration of follow-up. However, overall, this study suggests that both pNf-H and Nf-L are reduced by Nusinersen administration in a significant proportion of SMA type 3 patients as early as six months after the first treatment. In a recently published study, serum and cerebrospinal fluid (CSF) samples of 11 patients with adult SMA type 3 were prospectively collected and analyzed during loading with nusinersen. No significant pathological alterations in levels of NF-H were detected in the CSF or blood samples under baseline conditions or during loading with nusinersen leaving the authors to conclude that the slow progression rate of SMA type 3 may not lead to detectable elevation of levels of common markers of axonal degradation (82). Another study looked at biomarker assessments of CF to access effects of Nusinersen on axonal damage in adult SMA patients. NFs as a marker of neuroaxonal damage were below the measurable range in all patients (n=19) at baseline prior to therapy. This contrasts with pediatric SMA patients, where strongly elevated pNf-H levels were observed prior to therapy, which decreased with progression and age with and without therapy. Interestingly, pNf-H became
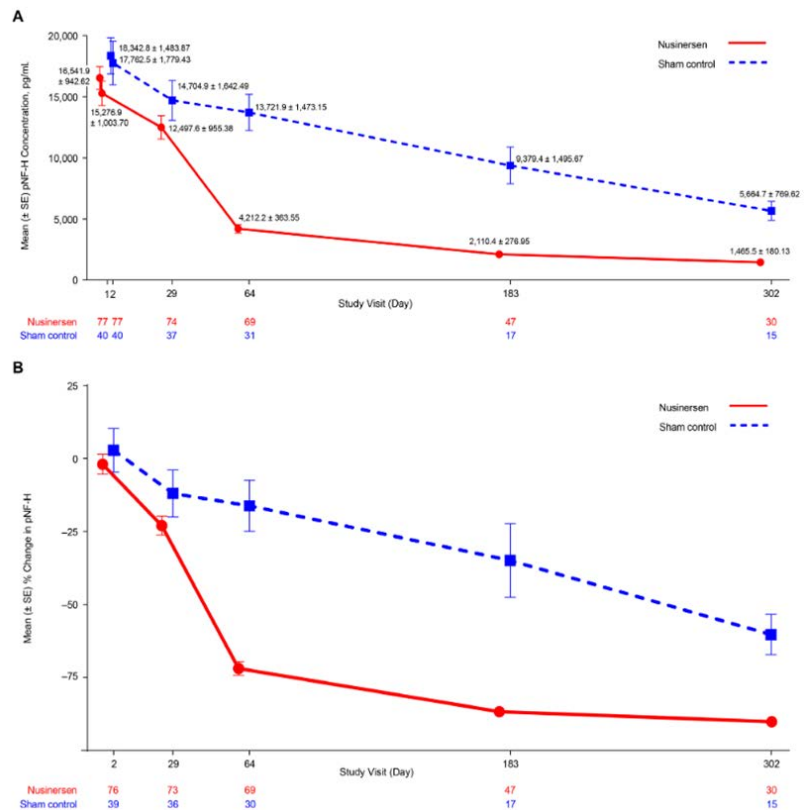
detectable in four patients following treatment, with one patient showing levels compatible with degenerative motor neuron disease. This patient also presented with improvements in motor function. This observation raises doubt if the level of neurofilaments could serve as a prognostic or confirmative marker in terms of treatment response in adult patients with SMA (83). This is supported by another study showing concluding that in adolescent and adult SMA type 2 and 3 patients, neurodegeneration is not reflected by increased Nf-L levels and short-term therapeutic effects cannot be observed (84,85).

Recent data presented at the 2020 Cure SMA Clinical Care and Research Meeting (June 2020) investigated the association between pNF levels and the achievement of the motor milestone of sitting in nusinersen-treated individuals with infantile-onset SMA who participated in the ENDEAR trail and transitioned to the SHINE extension study (NCT02594124)(86). Among participants in ENDEAR who developed the ability to sit within ENDEAR or SHINE, both the plasmas and CSF log pNF-H level at baseline was statistically significantly associated with achieving sitting earlier (p=0.0128) after controlling for baseline age and CHOP INTEND score (**Figure 14**). Furthermore, plasma log pNF-H level at Day 64 was statistically significantly associated with achieving sitting earlier (p=0.0121) after controlling for baseline age and CHOP INTEND score. The data presented show a possible role of pNF-H as a predictive biomarker able to predict future motor function.
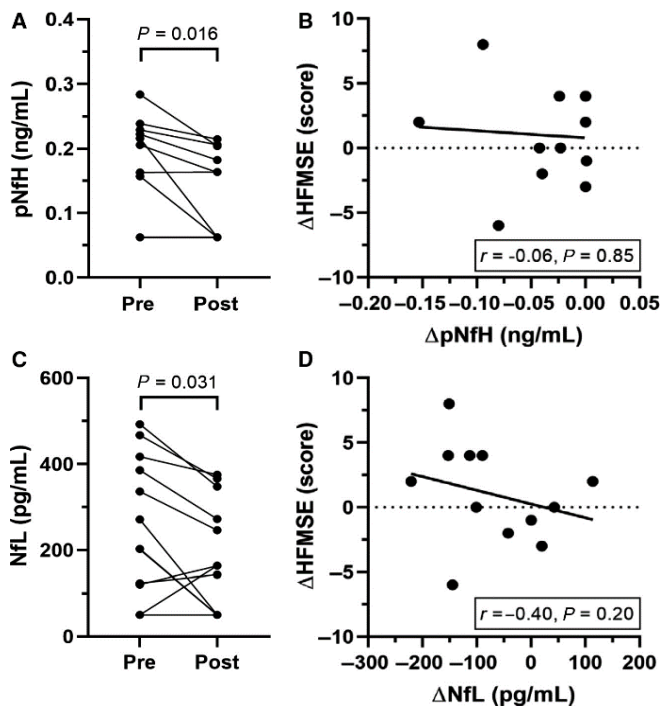

Figure 13. CSF concentrations of pNf-H and Nf-L at baseline and after treatment with Nusinersen. Individual CSF pNF-H levels (A) and Nf-L levels (C) of SMA type 3 patients at baseline (Pre) and after five injections (Post) of Nusinersen (6-month follow-up) (n = 12); four patients had undetectable pNf-H levels both at baseline and during follow-up, while two patients displayed a similar baseline value of Nf-L (201.1 and 202.7 pg/mL) that became undetectable in both cases at the end of the follow-up. Correlation between the change in pNfH (B) or NfL (D) values and variations in HFMSE scores over time (n = 12); two patients displayed identical differences in HFMSE scores (4 points) and differences in pNf-H levels (0 ng/mL)

Across these various studies and others, plasma pNF-H levels differentiated SMA individuals from non-SMA controls and treatment initiation with nusinersen was associated with rapid decline followed by stabilization of pNF-H. In untreated patients, pNF-H has been shown to decline with advanced aging. This may be due to reductions in numbers of motor neurons or disease activity. Further investigation is needed to determine if decline seen in aging treated populations is due to physiological aging or is indicative of treatment response. While the studies highlighted here focus on pNF-H, NfL levels have also been evaluated in clinical trials investigating branaplam, a small molecule RNA splicing modulator (87). Preliminary findings show an inverse correlation between NfL levels and motor function scores in participants with Type I SMA. It is currently unclear if NF-H or NF-L is more sensitive in detecting disease onset or response to treatment.
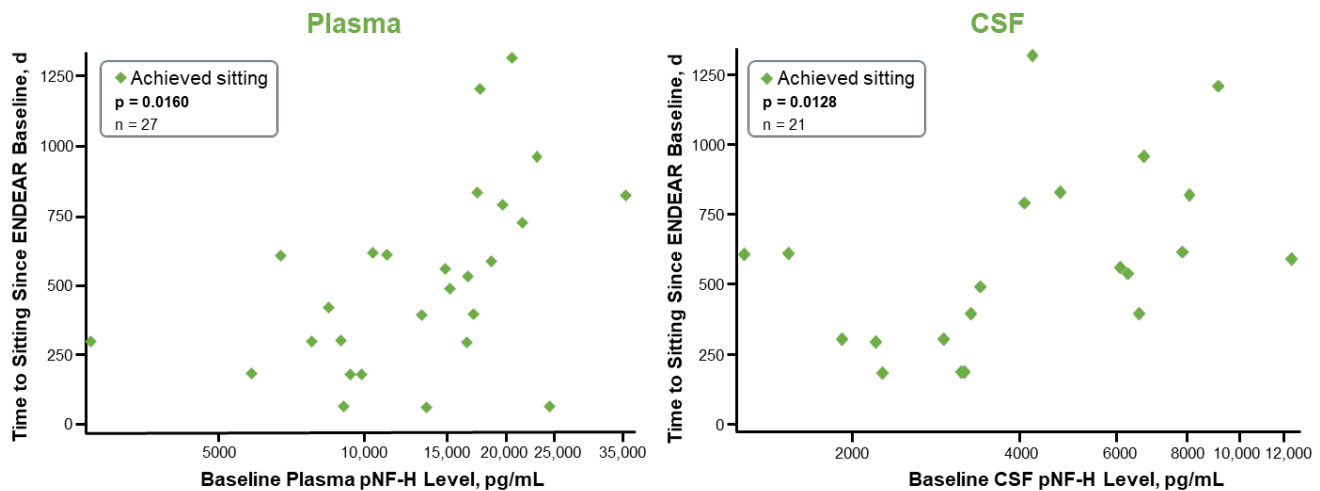
Figure 14. Among participants in ENDEAR who developed the ability to sit within ENDEAR or SHINE, the plasma and CSF log pNF-H level at baseline was statistically significantly associated with achieving sitting earlier (p=0.0160) after controlling for baseline age and CHOP INTEND score.

The rapid decline of highly elevated pNF-H levels following initiation of nusinersen in participants who later demonstrated clinical stabilization or improvement compared to sham-control-treated participants suggest that pNF-H levels may be a pharmacodynamic biomarker for nusinersen and likely, other SMN-dependent therapeutics. To further the qualification of NF as a biomarker, it must be determined if there is a need to establish threshold values or if change from baseline over time is an acceptable measure for assessing drug effect as there is large intrapersonal variation of NF levels in healthy controls. Additionally, the need for control data from healthy subjects and its correlation to other outcome measures likely should be considered. Analysis of pre- and post-treatment plasma and CSF pNF-H and NF-L levels across SMA populations and evaluation of correlations with efficacy outcomes will lend more robustness to the use of NF as a potential biomarker for SMA and lend insight as to the utility of NF to predict clinical benefit during drug development.

IV. Clinical Trials Involving Combination of Therapies for SMA

Question 4.

Does the FDA have advice on how to optimize clinical protocols to test the use of combinations of therapies in SMA?

   a. **In FDA's view, what is an acceptable control in trials? Can published data about treatment effect of an approved SMN-upregulating therapy be used as "historical control" if received according to package insert during combination treatment trial(s)?**
   * **If so, what is the best manner to control/normalize for age of patient at administration of an SMN-upregulating therapy?**
   * **Is there potential to group them into cohorts (i.e., patients initiating an SMN upregulating therapy at <6 months of age, with 2 copies of *SMN2*)?**
   b. **What would the FDA consider as a suitable outcome measure to detect small changes/maintenance of function over time that might be predicted with the use of a second drug or in the case that the patients have topped out scales with a ceiling effect on scales such as the CHOP Intend?**

Recent breakthroughs have led to FDA approval of two new SMN-upregulating therapies, Spinraza® and Zolgensma®, that have provided the SMA community with new options for treatment. However, given the many variables involved with SMA -- including the varying age of onset and severity of symptoms/impact on activities of daily living – these therapies may not be appropriate or effective for all patients, and the type of administration and related safety issues can place significant burdens on patients and their families (88).

As real-world experience with these new treatments increases, we are learning more about how they work and in which disease-setting and situations the treatments are most effective (as well as where there are still important gaps in available treatments). For example, therapeutic intervention with the currently approved therapeutics is more effective when it occurs in the earliest stages of disease (including before symptoms are evident). This leaves a significant area of unmet need among patients with more advanced disease, who may need therapies directed towards non-SMN targets in addition to SMN-upregulating therapeutics for maximal therapeutic effect (**Figure 15** and **Table 4**).

As has been documented by the landmark Cure SMA Voice of the Patient Report and survey activities, SMA patients have an array of serious unmet medical needs that must be addressed by treatment approaches. Furthermore, there is a critical need for clinical trial design to accommodate the background use of these new SMN upregulating therapeutics which are now considered standard-of-care.
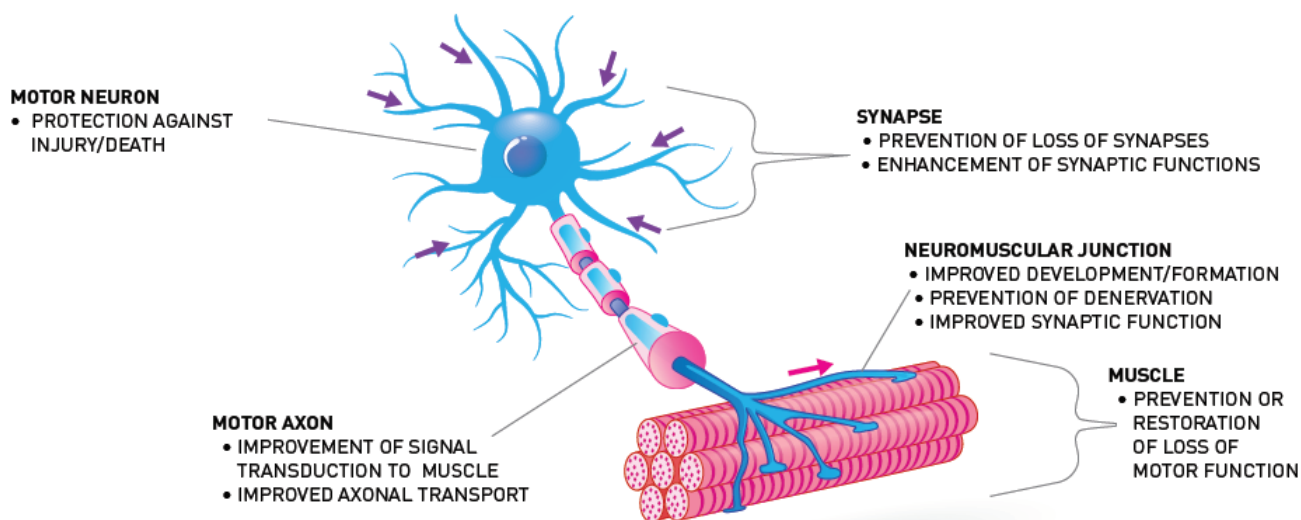

Figure 15. Potential points of therapeutic intervention being investigated as therapeutic targets for SMA.

For the purpose of this briefing and the subsequent meeting, we define "combination therapy" to mean: "Two or more therapeutic agents (generally drugs or biologics) -- working through the same or different mechanisms of action -- that are used concurrently. In the case of clinical trials, this refers to patient use of an FDA-approved SMN-upregulating therapeutic administered according to its label and the administration of the investigation new drug in clinical trials.

Currently, there is a phase 2 trial studying the effect of an investigational drug in patients on an approved SMN-upregulating therapy. In addition, many nonclinical studies investigating drug combinations have been performed. Furthermore, real world data from patients receiving multiple drugs is also of relevance and demonstrates the desire amongst the patient community to use multiple therapy modalities to address their unmet needs.

When thinking about proper design of other trials involving enrollment of patients using an FDA-approved therapeutic with an investigational drug candidate safety, many factors must be carefully considered. These factors include, but are not limited to- acceptable controls, along with consideration as to if treatment effect

of an approved SMN-regulating therapy may be used as a "historical control" if received according to label during a combination treatment trial should be determined.

The manner in which to control and normalize variables such as patient age at drug administration and *SMN2* copy number must also be considered. Furthermore, the consideration of suitable outcome measures to detect small changes and/or maintenance of function over time that might be predicted with use of a second drug or in cases of patients who have reached maximal function on other scales is needed. These and other consideration are paramount when considering effective trial design.

severity time point of intervention	peripheral pathology		
	SMA-type I	SMA-type II	SMA-type III
pre-symptomatic	central SMN-restoration	central SMN-restoration	central SMN-restoration
	peripheral SMN-restoration	peripheral SMN-restoration	peripheral SMN-restoration
	SMN-independent regeneration	SMN-independent regeneration	SMN-independent regeneration
onset	central SMN-restoration	central SMN-restoration	central SMN-restoration
	peripheral SMN-restoration	peripheral SMN-restoration	peripheral SMN-restoration
	SMN-independent regeneration	SMN-independent regeneration	SMN-independent regeneration
symptomatic	central SMN-restoration	central SMN-restoration	central SMN-restoration
	peripheral SMN-restoration	peripheral SMN-restoration	peripheral SMN-restoration
	SMN-independent regeneration	SMN-independent regeneration	SMN-independent regeneration

(Left axis label: SMN-irreversibility)

Table 4. Severity and time point of intervention determines treatment strategy. Central SMN-restoration in the CNS is needed in all patients (black), since SMN reduction commonly effects motor neurons. According to the hypothesis of SMN organ-specific thresholds, more severely affected patients with a strong SMN reduction may be more susceptible for peripheral organ defects. While this makes a peripheral SMN-restoration important in SMA type I patients (black), this is less important for SMA type II patients (dark gray) and possibly neglectable for milder affected patients (light gray). Moreover, later disease stages show pathological changes which cannot be reversed by SMN-restoration only—they are SMN-irreversible. As a consequence, SMN-independent strategies are needed which allow reversal of symptoms or regeneration. While pre-symptomatically treated patients may not depend on such strategies (light gray), this may be more important for patients which are treated at disease onset (dark gray), and critical for symptomatically treated patients (black). In summary, different patient cohorts with different needs for treatments can be defined. It is likely that a single compound may not address central and peripheral SMN-restoration at the same time. Moreover, a combinatorial treatment regimen should include regenerative SMN-independent drugs (adapted from Hensel N, Kubinski S, Claus P, The Need for SMN-Independent Treatments of Spinal Muscular Atrophy (SMA) to Complement SMN-Enhancing Drugs. Front Neurol. 2020; 11: 45.PMID: 32117013)

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