Spinal Muscular Atrophy

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Summary: Spinal muscular atrophy (SMA) is a potentially devastating and lethal neuromuscular disease frequently manifesting in infancy and childhood. The discovery of the underlying mutation in the survival of motor neurons 1 (*SMN1*) gene has accelerated preclinical research, leading to treatment targets and transgenic mouse models, but there is still no effective treatment. The clinical severity is inversely related to the copy number of *SMN2*, a modifying gene producing some full-length *SMN* transcript. Drugs shown to increase *SMN2* function in vitro, therefore, have the potential to benefit patients with SMA. Because several drugs are now on the horizon of clinical investigation, we review recent clinical trials for SMA and discuss the challenges and opportunities associated with SMA drug development. Although an orphan disease, SMA is well-positioned for successful trials given that it has a common genetic etiology in most cases, that it can be readily diagnosed, that preclinical research in vitro and in transgenic animals has identified candidate compounds, and that trial networks have been established. **Key Words:** Spinal muscular atrophy, clinical trials.

INTRODUCTION

Spinal muscular atrophy (SMA) is an autosomal recessive disorder characterized by weakness due to degeneration of anterior horn cells. Hoffmann[1] and Werdnig[2] first independently described this disorder in the 1890s, and the genetic defect was localized to 5q11.2~q13.3 a century later. Since the identification of the survival motor neuron gene (*SMN*), there have been many advances in the understanding and treatment of this disorder.[3,4] The diagnosis is now easily made by genetic testing, a deletion or point mutation in the *SMN1* gene (telomeric copy) is found in most patients with SMA, and the clinical severity is in part determined by the copy number of the *SMN2* gene (centromeric copy). The *SMN2* mRNA lacks exon 7, resulting in a truncated and less stable protein, with an estimated 10% to 50% of the protein produced being full length. This contributes to the rescue effect of *SMN2*, in that *SMN2* copy number is inversely related to disease severity across the broad phenotypic spectrum of SMA.[5] Increasing *SMN2*-derived full-length protein is one important focus of therapeutic development.

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Historically, the clinical classification of SMA is based on age at onset and motor function impairment.[6] In SMA type 1, onset is before 6 months of age, and patients never achieve the ability to sit. SMA type 2 is defined by onset between 6 and 18 months, with patients not reaching the motor milestone of standing. Patients with SMA type 3, by definition, have disease onset after 18 months and gain the ability to walk. SMA type 4 describes patients with adult onset SMA who reach the ability to walk. Children with SMA type 2 and type 3 survive to adulthood. Historically, children with SMA type 1 were predicted to die before their second birthday, but in recent years, with more proactive clinical care, survival has significantly improved.[7] Because all SMA types are part of one spectrum and have a single underlying etiology, the patient selection for clinical trials is independent of the historical classification, and is determined by the intervention characteristics and the choice of endpoints.

The pathogenesis of SMA is incompletely understood. SMN is expressed in all tissues, but almost exclusively affects lower motor neurons.[8] SMN protein is localized in nucleus and cytoplasm. Nuclear SMN is largely associated with so-called Gems (or Gemins), cell structures thought to have a role in mRNA metabolism.[9,10] SMN is also believed to play a role in spliceosome assembly and to function as a specificity factor preventing potentially

deleterious nonspecific RNA binding.[11] Cytosolic SMN is found in axons,[12] growth cones,[13] and also postsynaptically at the neuromuscular junction in certain model systems[14] and within the Z-bands of striated muscle,[15] suggesting that the pathogenesis does not exclusively involve the motor neuron cell body. This yields multiple potential treatment targets, in addition to the pharmacological gene therapy opportunity provided by the presence of *SMN2*, potentially a druggable modifying gene. Several treatments have already been studied in early-phase clinical trials, and as a result, there has been remarkable progress in SMA trial network infrastructure and endpoint development. SMA is therefore well positioned for clinical drug development, because a common genetic cause can be easily diagnosed, because trials infrastructure and endpoints have been developed, and because there are multiple targets and encouraging preclinical results.

CURRENT TREATMENT

The mainstay of treatment in SMA is supportive care, with emphasis on a multidisciplinary approach. Variability in clinical care among centers can affect the clinical course of the disease, and so creates a challenge for determining the true efficacy of future therapeutic trials. To address variability in current practice, an international coordinating committee for spinal muscular atrophy (the ICC) developed a consensus statement document on care issues.[16]

When a child is diagnosed with SMA, we offer information on the disease, develop a multidisciplinary intervention plan, and discuss clinical trial opportunities. Genetic counseling with regards to sibling recurrence risk, carrier testing, and reproductive planning is provided. If neonatal screening for SMA were available, this would theoretically afford opportunities for presymptomatic treatment trials; however, neonatal screening for SMA is unlikely to become reality in the near future. Although we believe that earlier supportive care might prolong survival and reduce morbidity in these children, neonatal screening remains controversial.

Pulmonary complications are the main cause of morbidity and mortality in SMA types 1 and 2. They primarily result from respiratory muscle weakness that prevents the normal expansion and clearance of the lungs, leading to a restrictive defect. Ineffective cough leads to poor clearance of airway secretions, with resulting atelectasis and collapse. Secretion mobilization with chest physiotherapy and postural drainage along with mechanically assisted cough devices (mechanical insufflation–exsufflation) are commonly used and helpful. These children are also at risk of nocturnal hypoventilation, which can be diagnosed and treated with nocturnal noninvasive ventilation with bilevel positive pressure (NIV). In children with SMA type 1, the early use of NIV is believed to improve chest wall and lung development.[17] NIV support is also used during the day if daytime hypoventilation and respiratory fatigue are present.[18] Tracheostomy for chronic ventilation remains an individualized option in more severely affected patients. Immunization and infection prophylaxis recommendations to prevent upper respiratory tract infections address respiratory syncytial virus (palivizumab; Synagis, MedImmune, Gaithersburg, MD), *Streptococcus pneumoniae* (pneumococcal polyvalent vaccine; Pneumovax, Merck, Whitehouse Station, NJ), and influenza immunization strategies.

Gastrointestinal problems are relatively common in SMA types 1 and 2, with constipation, delayed gastric emptying, and gastroesophageal reflux. The last of these can be a cause of morbidity and mortality with aspiration pneumonia, especially in children with SMA type 1 and 2. Medical management includes acid neutralizers, inhibitors of acid secretion, or promotility agents. In children at high risk of aspiration, a gastrostomy tube insertion, often along with Nissen fundoplication, is the preferred definitive treatment. Maintaining an ideal weight is important in these children. SMA type 1 children with increased work of breathing have higher energy expenditure and are at risk of undernutrition, with further loss of lean body mass and function. Children with SMA type 2 are at risk of overnutrition with decreased energy expenditure, and excessive weight can decrease their functional status.

Weakness and reduced mobility place these children at risk for contractures, scoliosis, and reduced function and independence. With weakness of the paraspinal muscles, scoliosis is slowly progressive in these children and must be monitored periodically. The incidence of kyphoscoliosis increases with age and with loss of ambulation. In children who are no longer ambulatory, weight bearing and standing are encouraged through the use of standers. Positional curve controls, such as wheelchair modifications with back support and bracing with spinal orthotics, can improve function and comfort with better positioning. Because they cannot prevent progression of the curvature, surgical correction is often needed to maintain function and respiratory reserve.

Regular physical and occupational therapy are encouraged, such as stretching, nonfatiguing active range of motion exercise, and especially aquatherapy. Recent technological advances have created opportunities to improve function and quality of life for people living with SMA. Children as young as 18 months old can be evaluated for power mobility.[19,20] In children with limited hand function, adaptive devices are available for power mobility control. Home modifications should be made for safe accessibility and optimal independence. Innovative communication devices are available to patients who cannot use speech effectively.[21] Gravity-neutral orthoses can improve arm function and facilitate computer ac-

cess.[22] Children who reach the age to drive can follow adaptive driver's education, and vehicles can be adapted to fit their needs. With proactive medical care and rehabilitation, many SMA patients can enjoy full and productive lives and often have a normal life expectancy.

CLINICAL TRIALS

Several mechanisms have been targeted in SMA drug trials: neuroprotective drugs to rescue anterior horn cells,[23] creatine to improve energy metabolism,[24] and albuterol for its anabolic properties and possible effect on SMN2.[25,26] Gene therapy has shown some benefit in murine SMA, but has not been tested in human SMA.[27] More recently, therapeutic efforts have been dominated by drugs targeting an increase of SMN2 function, as SMN2 copy number is inversely correlated with phenotypic severity in SMA patients and transgenic SMA mice.[28,29] Therefore, drugs thought to increase full-length SMN (e.g., exon splicing modulators or histone deacetylase inhibitors), are expected to mitigate the deleterious effects of SMN haploinsufficiency. Drugs increasing SMN2 function *in vitro* include compounds currently approved by the U.S. Food and Drug Administration (FDA) for use in other indications (e.g., valproate,[30] hydroxyurea,[31] and the butyrates[32]). The use of high-throughput screening techniques has accelerated this area of preclinical drug discovery.[33]

The advances in preclinical research have resulted in several clinical trials for SMA and in the formation of several clinical trials networks, including AmSMART (American Spinal Muscular Atrophy Randomized Trials, at http://acsresearch.swmed.edu/amsmart/), Project Cure SMA (http://www.fsma.org/Research/Clinical/ProjectCureSMA/), the Pediatric Neuromuscular Clinical Research Network (http://www.urmc.edu/sma/), a collaborative group of selected European countries and Israel (EuroSMART: European Spinal Muscular Atrophy Randomized Trial I and II, http://www.enmc.org/workshop/?id=73&mid=54), and an Italian clinical trials network.

In addition to those already under investigation in human trials, several novel drug candidates are approaching clinical testing.

Completed trials

- Two placebo-controlled trials of gabapentin were negative.[34,35]
- Riluzole, a neuroprotective agent with modest benefit in amyotrophic lateral sclerosis (ALS), has shown possible benefit in seven SMA type 1 patients, but a subsequent open-label study of 44 subjects had insufficient enrollment.[23]
- An open-label study of albuterol showed modest benefits in strength in 13 SMA type 2 and 3 patients treated over 6 months.[25]
- Thyrotropin-releasing hormone in a controlled pilot study of six SMA patients treated for 5 weeks resulted in significant improvements in muscle strength.[36]
- Phenylbutyrate has shown promise in an open-label pilot study,[37] but a placebo-controlled trial of intermittent treatment over 13 weeks yielded negative results.[38,39]
- A European trial of acetyl-L-carnitine and a U.S. trial of creatine, both negative, were placebo-controlled and designed to show motor benefit.[40]
- Hydroxyurea treatment for 8 weeks has shown slight benefit in muscle strength scores.[41] Two randomized placebo controlled pilot trials of hydroxyurea in SMA type 1 and SMA type 2/3 have completed recruitment in the United States (see NCT00084006 and NCT00083746 at http://www.clinicaltrials.gov).
- Valproic acid (VPA) resulted in increased SMN mRNA and protein levels increased after treatment in 7 of 10 carriers and 7 of 20 patients, but remained unchanged or decreased in 13 patients.[42] In a second open-label pilot study in the United States, 7 SMA type 3/4 patients aged 17 to 45 years treated with VPA for 8 months on average showed improvement in muscle strength and function.[43] Another open-label pilot study in 42 patients with SMA types 1, 2, and 3 of ages 2 to 31 years was recently completed in the United States (NCT00374075 at http://www.clinicaltrials.gov). A multicenter, randomized, placebo-controlled Phase II trial of VPA in combination with carnitine in SMA patients over 2 years of age was recently completed in the United States (NCT00227266 at http://www.clinicaltrials.gov) and is pending analysis.

Ongoing trials

- In the United States, an open-label pilot study of phenylbutyrate in presymptomatic SMA type 1 and 2 patients is open to recruitment (NCT00528268 at http://www.clinicaltrials.gov). A Phase I/IIa study initiated by the U.S. National Institute of Neurological Disorders and Stroke to identify the maximum tolerated dose and to evaluate for biological activity is ongoing in the United States (NCT00439218 and NCT00439569 at http://www.clinicaltrials.gov).
- A placebo-controlled, randomized trial of VPA in SMA type 3 patients is currently recruiting in the United States (NCT00481013 at http://www.clinicaltrials.gov).

Table 1. *Clinical Trials in Spinal Muscular Atrophy*

Drug	Study Site	Design	Cohort	Comments
HU	Taiwan	OL	SMA type 1 & 2	Functional benefit
HU	Taiwan	PCR	SMA type 2 & 3	Recruiting
HU	USA	PCR	SMA type 2 & 3	Recently completed, pending analysis
HU	USA	PCR	SMA type 1	Recruitment completed
VPA and carnitine	USA	PCR	SMA type 2 & 3	Recently completed, pending analysis
VPA	USA	OL	SMA type 1,2 & 3	Recently completed
VPA	Germany	OL	SMA type 1,2, & 3 and carriers	Increased mRNA & protein in some
VPA	USA	OL	SMA type 3 & 4	Improved strength & function
VPA	USA	PCR	SMA type 3	Recruiting
SPB	Italy	OL	SMA type 2	Increased mRNA
SPB	USA	OL	SMA type 1 & 2 presymptomatic	Recruiting
SPB	Italy	PCR	SMA type 2	Negative
SPB	USA	OL	SMA type 1	Recruiting
SPB	USA	OL	SMA type 2 & 3	Recruiting
Riluzole	USA	PCR	SMA type 1	Safe, may increase survival
Riluzole	USA	OL	SMA type 1	Poor enrollment
Gabapentin	USA	PCR	SMA type 2 & 3	Negative
Gabapentin	Italy	PCR	SMA type 2 & 3	Negative
Albuterol	UK	OL	SMA type 2 & 3	Modest benefit in strength
TRH	USA	PCR	SMA type 2 & 3	Improved strength
Acetyl-L-carnitine	Europe	PCR	SMA type 1 & 2	Negative
Creatine	USA	PCR	SMA type 2 & 3	Negative

HU = hydroxyurea; OL = open-label [trial]; PCR = placebo-controlled randomized [trial]; SMA = spinal muscular atrophy; SMN = survival motor neuron [gene]; SPB = sodium phenylbutyrate; TRH = thyrotropine-releasing hormone; VPA = valproic acid.

- A Phase II/III placebo-controlled, randomized trial of hydroxyurea is recruiting patients with SMA type 2 and 3 in Taiwan (NCT00485511 at http://www.clinicaltrials.gov).

For an overview of completed and active trials, see Table 1.

CHALLENGES IN FINDING NEW TREATMENTS

Phenotypic heterogeneity: one genetic etiology leads to a broad clinical spectrum

SMA has a broad spectrum of age of onset and clinical disease severity, such that no single trial design or outcome fits all. For studies in young children with SMA type 1, functional outcome measures are largely not developmentally appropriate or feasible. Therefore, time-to-event approaches have been suggested: for example, the time to requiring ventilatory support for more than 16 hours daily.[40,44,45] In addition to the paucity of suitable outcomes measure, trials in SMA type 1 infants are challenging, because recruitment and retention are affected by the often severe and frequent concurrent illnesses in this population. On the other hand, SMA type 1 patients are probably most in need of treatment, given the grave prognosis without intervention. SMA type 1 patients have been studied in dedicated trials, and several studies have chosen to combine SMA type 2 and 3 subjects in one trial. For SMA type 2 or 3 patients, motor function measures or muscle strength measures have been suggested as outcomes.[46,47]

The need to tailor a trial in its design and outcomes to a subgroup within the total SMA population has to be balanced against the feasibility of timely recruitment. In other words, if the trial is designed for too small a fraction of the SMA population, recruitment may not be feasible within a reasonable time frame.

Natural history of SMA: presymptomatic motor neuron loss and early progression are followed by a period of relative stability

The natural history of SMA poses challenges as most of the disease progression occurs early on in the course, and is followed by a relatively stable phase. This implies that potential SMA clinical trial participants are likely in a stable phase of their disease course so that trials have to aim at improving the disease. This is different from the concept underlying many trials in neurodegenerative disease, in which the goal is to slow disease progression. Aiming at improvement builds on the expectation that suboptimally functioning neurons can be brought to increase their function resulting in clinical benefit (e.g., through reinnervation). Although this may appear quite optimistic, it is the only feasible strategy.

Another conceptual challenge is the fact that the loss of functional motor neurons probably occurs in a silent,

acute phase of the disease, prior to symptom onset. As in many other diseases, theoretically neuroprotective strategies would be most effective if trials were initiated presymptomatically. In reality, however, this will not be feasible until there is universal newborn screening, the infrastructure needed to expedite enrollment of affected newborns into clinical trials, and the ethical and regulatory approvals of treating presymptomatic infants.

Outcome measures are imperfect

Successful clinical trials for SMA require outcome measures that are feasible, reliable, sensitive to change, economical, and clinically meaningful.[33,40,45] Motor function measures, pulmonary measures, muscle strength testing, and quality of life measures have been studied as outcomes in SMA and were found to be reliable.[46–50] Muscle strength measures and motor function measures are correlated in SMA.[49] Motor function testing is considered more easily feasible in young children, however, and more inherently clinically meaningful.[46,50] Given the relatively stable disease course of SMA, only a trial with an effective drug would allow investigators to estimate the sensitivity of these outcomes.

There is no validated biomarker to assess preliminary drug activity

When testing new treatments in SMA patients, researchers are currently evaluating for clinical benefit, even in early Phase II trials. This typically requires a relatively large sample size and long observation periods. For efficient early-phase drug development, biomarkers can accelerate drug discovery. If a biomarker is associated with a clinical outcome and can provide an early read-out after a relatively short treatment period, then the preliminary efficacy of a new drug can be studied more efficiently. Biomarkers can have the potential advantages of decreasing the sample size required in early Phase II trials, of being more easily measured than clinical outcomes, and of increasing the measured dynamic range of a disease process.[51,52]

SMA mouse models have not been validated

There are several transgenic mouse models for SMA, some closely mimicking the human genotype. A homozygous deletion of the murine survival motor neuron (*Smn*) gene is embryonically lethal. Inserting the human *SMN2* gene ($Smn^{-/-}$; $hSMN2^{+/+}$) rescues the earliest lethality and results in a severe mouse phenotype that resembles severe human SMA.[53] Incorporating the *SMN2* cDNA lacking exon 7 into this SMA model ($Smn^{-/-}$; $hSMN2^{+/+}$; $hSMN2delta7^{+/+}$) has been shown to extend survival from 5.2 days[53] to 13.3 days.[54] Another mouse model has been generated through deletion of the murine *Smn* gene directed to neurons.[55] Given that no effective treatment has been identified in human trials to date, it is too soon to judge how predictive the results of the mouse trials will be. Finally, mouse trials are often performed under conditions that vary between laboratories. Recent efforts to conduct standardized medium-throughput mouse trials in one laboratory under controlled conditions can in part overcome this limitation.[56,57]

SMA is an orphan disease

Although SMA is a relatively common orphan disease, its overall prevalence likely requires geographically large, and probably international, clinical trial collaborations for Phase II and certainly for Phase III studies. This poses challenges in dealing with multiple languages, cultures, and ethical and regulatory approval bodies, as well as in dealing with large groups of investigators, coordinators, and evaluators distributed over a wide geographic area. Nonetheless, the technological advances in electronic communication and Web-based data management systems can render large, international trials more efficient.

A further implication of SMA being considered a rare disease is that some pharmaceutical companies are not attracted to orphan indications. As a result, industry often enters the field long after patient groups and academic investigators have taken the lead in clinical development activities. Incentives provided by the U.S. Orphan Drug Act of 1983 (http://www.fda.gov/orphan/oda.htm) have had some effect on industry involvement, although there is room for more innovation in this area.

Recruitment has been slow

Some recent SMA clinical trials in North America have experienced difficulties recruiting patients.[40,58] Given that there is no effective treatment for SMA to date, and given even conservative prevalence estimates,[6,59] there should be a sufficient number of potential study participants even if only a small proportion of patients enrolled. This experience has helped investigators in recognizing factors that may have contributed to recruiting difficulties, including 1) lack of perceived drug promise (e.g., creatine), 2) lack of information or education on clinical trials in the physician and patient community, 3) geographic or other barriers to trial access, or 4) trial characteristics as such (e.g., the number of participating sites, inclusion criteria, the number and length of visits, or the nature of study procedures). Investigators are now better positioned in planning for adequate recruitment. Also, any treatment trial studying a novel intervention would be expected to attract participants more easily.

Open-label trials have yielded positive results that remain unconfirmed in controlled trials

The SMA trials to date illustrate a problem inherent to all clinical trials with outcomes that are subject to bias. Most SMA trials to date have been open-label designs, and many of these uncontrolled studies have suggested a

treatment benefit. However, when a positive, open-label study was followed by a larger placebo-controlled trial, the controlled trial yielded negative results.[37,38]

Two arguments are often made in favor of open-label trials. First, the presence of a placebo group is said to hinder recruitment. However, there are several examples of controlled trials or no-treatment studies that have completed enrollment.[38,40,60] Second, the argument is sometimes made that it is unethical to offer SMA patients placebo. However, clinical trials are conducted because one does not know if the new drug is beneficial or harmful. Controlled trials are an efficient way to find the answer, and they have a built-in safety monitoring plan. Recent examples in adult motor neuron disease have shown that new drugs may not only lack benefit, but can be associated with outcomes worse than placebo.[61,62]

NEW TREATMENT APPROACHES, NOW AND IN THE FUTURE

Increased efficiency through patient–researcher collaboration, increased resources, and innovative design and outcomes

Several examples in the recent history of drug development show that new treatments can be found when sufficient resources are devoted to the effort and when clinical trials are embraced by the patient community. This can result in a high proportion of the affected population enrolled in clinical trials and can accelerate the completion of trials. Human immunodeficiency virus (HIV) and pediatric leukemia, both once considered untreatable, now have several treatment choices available to patients and carry a much improved prognosis.[63–66] To replicate a similar success in SMA, patients and their advocacy groups can help by embracing clinical trials and by encouraging SMA families to participate. Trials with rapid recruitment avoid confounders such as a time effect, and can accelerate the overall rate of SMA drug development.

Education of referring physicians and patients on the importance of clinical trials in SMA can accelerate the discovery of an effective treatment. Successful clinical trials require adequate resources. The collaboration between patient advocacy groups and researchers in raising awareness and funding for trials in neuromuscular disease is important in obtaining the resources needed for successful SMA clinical trials. The SMA community is setting the stage for success through investigator meetings and ongoing collaborations (e.g. the International Coordinating Committee for SMA).

Innovative trial designs can help overcome some of the challenges in conducting trials in a relatively rare disease. In ALS for example, an innovative Phase II design was conducted with 185 participants, about one-fourth of the number of participants that would have been needed in a conventional trial design.[67]

Innovative outcome measures are another approach to increasing recruitment and retention. Outcome data that can be collected over the phone, via Internet, or in the patient's home rather than at a clinical trial site has the potential of increasing patient participation by reducing the burden of travel to the clinical site. A multicenter ALS trial, for example, that established the reliability of using a functional scale over the phone has had timely recruitment and unprecedented high retention.[68]

Gene therapy and stem cell approaches

In addition to drug treatments discussed above, gene therapy approaches have been considered for SMA—although these will require much preclinical work before evaluation in patients is possible. A nonprimate equine infectious anemia virus was pseudotyped with a rabies virus-derived glycoprotein conferring retrograde axonal transport to this vector. Multiple injections of a lentivirus vector expressing human SMN in various muscles of SMA transgenic mice restored SMN to motor neurons, reduced motor neuron death, and increased the life expectancy by an average of 3 and 5 days (20% and 38%), compared with controls.[27]

Stem cell approaches offer promise as a cellular replacement strategy in the treatment of SMA. Stem cells have the ability to develop into many different cell types, including motor neurons, but several obstacles must be overcome before they can be considered for human treatment.

First, researchers have to be able to generate large quantities of pure and differentiated human motor neuron populations from stem cells.[69] Second, partially differentiated cells must populate the nervous system after transplantation and persist there. Third, the cells have to be able to extend axons and create synapses. Finally, and most important, all of this must result in meaningful functional recovery.

There are promising data showing that stem cell-derived motor neurons can grow axons and form neuromuscular junctions in preclinical experiments.[70–72] Also, stem cell transplants have resulted in axonal growth and recovery form paralysis in rat models.[73,74] In addition to the scientific issues, however, there are several regulatory concerns that need to be addressed before stem cell therapies become a part of human trials. In summary, stem cell–based treatments are promising, but unlikely to be evaluated in SMA patients in the near or intermediate future. Far greater hope is placed in the use of differentiated stem cells in as research tools in drug discovery.

CONCLUSIONS

SMA is a promising indication for drug development. This often severely physically disabling disease affecting people with normal cognition and potentially normal life expectancy constitutes a major unmet medical need, in

that there is no cure. SMA can be easily diagnosed through genetic testing, because the SMN-linked spinal muscular atrophies account for the majority of cases. There has been dramatic preclinical progress in the last two decades with the discovery of the gene and of a druggable modifying gene that provides one of several promising targets for treatment. SMA is a relatively common orphan disease. Investigators and patient groups are increasingly well organized, nationally and internationally, and are setting the stage for clinical trials (e.g., the ICC and Treat NMD). Several investigator groups are poised to conduct clinical trials. Suitable outcomes have been developed,[47,50] and the FDA has already reviewed trials for this indication. These advances raise the hope that we will find an effective treatment for SMA.

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