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Advances and Limitations for the Treatment of Spinal Muscular Atrophy

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Abstract

Spinal Muscular Atrophy (5q-SMA;SMA) is a genetic neuromuscular condition affecting spinal motor neurons. SMA is caused by a defect in both copies of the SMN1 gene that produces Survival Motor Neuron (SMN) protein. The highly homologous SMN2 gene primarily expresses an unstable, rapidly degraded isoform of SMN protein. Diminished levels of SMN protein cause anterior horn cell degeneration, progressive motor neuron loss, skeletal muscle atrophy and weakness. Severe cases result in limited mobility and ventilatory insufficiency and, when untreated, are the leading genetic causes of death in young children. Recently, three therapeutics that increase SMN protein levels in patients with SMA have been approved. These therapies include Spinraza, Zolgensma, and Evrysdi. While these therapeutic approaches have a clinically significant impact by providing incremental improvements in motor function and developmental milestones, as well as preventing the worsening of symptoms in SMA, they are not curative. For many patients, there remains a significant disease burden. A potential therapy under development for SMA targets myostatin, a negative regulator of muscle mass and strength. Myostatin inhibition in animal models increases muscle mass and function. Apitegromab is an investigational, fully human, monoclonal antibody that specifically binds to proforms of myostatin, which include promyostatin and latent myostatin, thereby inhibiting myostatin activation. A recently completed phase 2 trials demonstrated the potential clinical benefit of apitegromab by increasing or stabilizing motor function in patients with Type 2 and Type 3 SMA.

Keywords: Spinal muscular atrophy; Survival motor neuron-1 gene; Survival motor neuron; Nusinersen; Onasemnogene abeparvovec xioi; Risdiplam; Myostatin;apitegromab;SRK-015

Introduction

Spinal Muscular Atrophy (SMA) is a rare, genetic neuromuscular condition causing progressive muscle wasting (atrophy) and weakness leading to loss of movement. SMA is often cited as the leading genetic cause of death in young children [1,2]. The exact prevalence of SMA in the United States is not known with certainty and varies by type [3] (Table 1).

An overall prevalence of SMA between one and two per 100,000 people has been suggested [4] with a frequency of 1/11,000 births [5]. Prevalence of SMA in the U.S. and European Union is estimated to be 30,000-35,000 cases [6]. With an overall incidence estimated to be approximately 1/6000 to 1/10,000 births [4, 7-9].

Table 1: Spinal muscular atrophy prevalence.

Type	Birth Prevalence	Overall Prevalence
1	8.5/100,000	8,526
2	9.4/100,000	9,429
3	10.3/100,000	10,333

Homozygous deletion of the survival motor neuron-1 [SMN1] gene on chromosome 5q is responsible for the autosomal recessive disorder in more than 95% of cases [10]. 5q-SMA [hereafter referred to simply as “SMA”] phenotypes vary widely

in severity, but all are associated with some degree of muscle weakness [8]. Marked SMN deficiency results in spinal motor neuron degeneration that may affect upper and lower extremity strength, head and neck movement, crawling and walking abilities, breathing and swallowing [1]. Due to the preserved inverted duplication of chromosome 5q13.2, there are two nearly identical SMN genes (SMN1 and SMN2) [11]. SMN1 expresses full length Survival Motor Neuron [SMN] protein while the highly homologous SMN2 gene expresses a small amount of full length SMN, but due to a splicing difference primarily expresses a shortened, unstable, and rapidly degraded isoform of the SMN protein [10] (Figure 1).

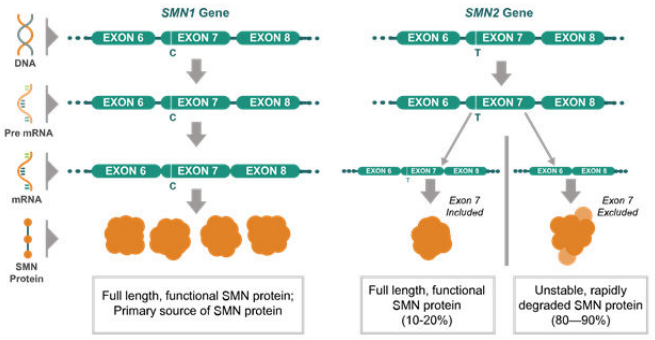

Figure 1: Normal SMN protein expression.

Survival motor neuron gene 1 (SMN1) encodes full length SMN protein needed to ensure survival of motor neurons and normal muscle growth and function (left). The nearly identical SMN2 gene differs by only two nucleotides, a C T base change inside exon 7 that affects gene splicing and leads to exon 7 skipping in the majority of SMN2 mRNA (messenger ribonucleic acids). SMN2 mRNA transcripts with exon 7 included provide a supplementary source of normal SMN protein; SMN2 mRNA lacking exon 7 encodes truncated, rapidly degraded SMN protein (right) [73,74].

The net effect of SMN1 defects is diminished levels of full length, stable SMN protein. Complete absence of SMN is embryonically lethal, while diminished SMN in individuals fully reliant on SMN2 expression causes anterior horn cells to degenerate, ultimately resulting in motor neuron loss and subsequent skeletal muscle atrophy and weakness [12]. (Figure 2) Although the SMN2 gene can express small amounts of the full-length SMN transcript, the number of SMN2 copies, which varies among affected individuals, affects disease severity, with more copies correlated with milder disease [13].

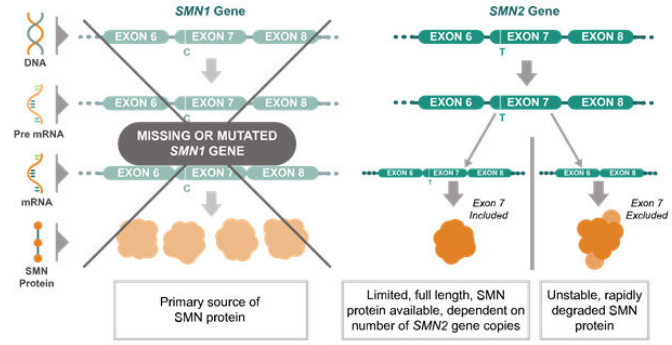

Figure 2: SMN protein expression in patients with spinal muscular atrophy.

In patients with SMA, there is a homozygous deletion or loss function of the SMN1 gene, eliminating the body's main source of SMN protein (left). The functional protein made by the SMN2 gene is identical to that produced by the SMN1 gene but is produced in insufficient quantity to support normal motor neuron functioning, muscle growth, and development (right); however, patients with SMN may have up to eight copies of the SMN2 gene, all of which can produce limited quantities of SMN protein. Patients with more SMN2 gene copies generally have less severe SMA [73,75,76].

Proximal muscles are more highly denervated and atrophic compared to distal musculature in SMA [14]. Depending on the number of SMN2 gene copies, symptoms can range from profound neonatal weakness with respiratory failure, often leading to death before the age of 2 years, to mild proximal lower extremity weakness in adulthood. These have been historically classified as Types 0 to 4 (Table 2) however, SMA classifications are changing due to the presymptomatic use of SMN restoration therapies in patients increasingly being diagnosed by newborn genetic testing.

Table 2: Historical spinal muscular atrophy subtypes.

Type	Onset	Symptoms	Milestones
0	Prenatal	Respiratory failure at birth	
1	0-6 months	Severe deficits in motor function. Difficulties in breathing, coughing, and swallowing, fasciculations of the tongue	No sitting
2	<18 months	Severe deficits in motor function. Delay in motor development, weakness, difficulties in coughing, joint contractures, scoliosis	Sitting, no walking

3	>18 months	Variable degree of weakness, joint contractures, scoliosis, loss of ambulation	Independent walking
4	30 years	Variable, but milder weakness	Independent walking

Historically, untreated patients with Type 1 SMA had a 50% survival probability at 8-10 months of age and 8% survival at 20 months of age [3]. For patients with Type 2 SMA, the 1-year survival probability is 100%, decreasing to 82% at 10 years [3]. Overall survival of these patients is improving in the United States due to improved standards of care, and the recently implemented newborn screening efforts [15]. That increasingly allows treatment of presymptomatic or oligosymptomatic patients [16].

Since the introduction of new drug treatments for SMA, the observed disease trajectories differ significantly from the known natural history of the disease. The new phenotypes now also cross the traditional subtypes of SMA (Table 2). For example, patients exhibiting symptoms at 6 months of age or younger [traditionally, SMA type 1] might achieve independent sitting (historically, SMA type 2 by definition) if treatment is initiated early. It is now more appropriate to rely on a combination of age and functional status at start of drug treatment, age of symptom onset or number of SMN 2 copies, rather than the traditional subtypes to define a clinical phenotype of SMA [17]. Despite these achievements, significant disability persists among patients treated after developing signs of SMA, including limited mobility, ventilator insufficiency and difficulty swallowing [18].

With the availability of disease-modifying therapies, it is important to define the new disease trajectories in order to better interpret patient response to treatment and remaining deficits. Opportunities to maintain motor function throughout a patient's lifetime as well as impacting fatigue, endurance, and patient-reported outcomes, have the potential to positively influence quality of life, shifting patient outcomes from survival to thriving [19].

SMA newborn screening programs

Treatment is more successful if patients are treated presymptomatically, suggesting newborn screening is highly beneficial for this patient population [20, 21]. SMA was added to the U.S. Federal Recommended Uniform Screening Panel [RUSP] for newborn screening in 2018 [22]. The RUSP is a list of disorders that the Secretary of the Department of Health and Human Services recommends for states to screen as part of their state universal newborn screening programs. Disorders on the RUSP are chosen based on evidence that support the potential net benefit of screening, the ability of states to screen for the disorder, and the availability of effective treatments. It is recommended that every newborn be screened for all disorders on the RUSP. As of August 2021, 38 states in the U.S. routinely screen newborns for SMA, testing 85% of all infants born in the country [23].

Screening is conducted using DNA extracted from dried blood spots with a multiplex real-time quantitative polymerase chain reaction assay targeting SMN 1 exon 7 which can be differentiated from SMN 2 exon 7 and is homozygously deleted in 95% of SMA patients [24]. SMA screening methods have high (100%) positive predictive value, and no false positives have been found when screening for deletions of exon 7 on both alleles [25].

Newborn screening is expected to increase the likelihood that pediatricians and family practice physicians will encounter patients with SMA. The U.S.-based Cure SMA organization has produced a booklet titled "What You Need to Know about an SMA Diagnosis. A Guide for Healthcare Providers." This free guide is intended to provide healthcare providers with background information about SMA, available treatments, the importance of quickly initiating treatment, and referral options to SMA experts and centers of excellence in the U.S [26].

The European Alliance for Newborn Screening in Spinal Muscular Atrophy is striving for newborn screening programs in all European countries by 2025 [27]. Additional information is available from the organization, SMA Europe [28].

Approved therapies for treating SMA

As SMN is expressed throughout the body, SMA can involve peripheral tissues in addition to motor neurons [29]. Management of SMA patients requires a multidisciplinary approach that includes, but is not limited to pulmonary, nutritional and orthopedic care [30], in combination with disease-modifying treatments. Three therapies that address the SMN-deficiency of SMA, referred to as SMN upregulators or SMN correctors, are FDA-approved and have recently received marketing approval in the European Union.

SPINRAZA (nusinersen) injection, for intrathecal use

Nusinersen modulates the splicing of SMN 2 pre-messenger RNA [mRNA] and was approved in the U.S. in 2016 and the E.U. in 2017. The approvals are for treatment of SMA patients of all ages with 5q SMA based on the results of two phase 3 clinical trials. Nusinersen is an intrathecally administered antisense oligonucleotide that corrects SMN 2 exon 7 splicing to increase the proportion of full-length transcripts, leading to higher levels of functional SMN protein [31] (Figure 3).

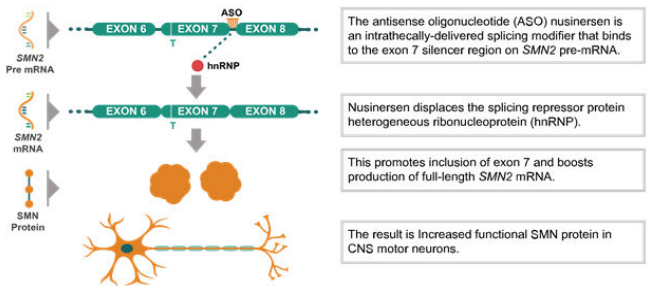

Figure 3: Nusinersen mechanism of action.

The antisense oligonucleotide (ASO) nusinersen is an intrathecally-delivered splicing modifier that binds to the exon 7 silencer region on SMN 2 pre-mRNA (Pre mRNA). By displacing the splicing repressor protein hnRNP, nusinersen promotes inclusion of exon 7 and boosts production of full-length SMN 2 mRNA. Functional SMN protein in central nervous system motor neurons is increased (32,73,74,77).

Subjects in a randomized, double-blind, sham procedure-controlled study in symptomatic infants ≤ 7 months of age (N=121) who were genetically confirmed to have SMA and had symptom-onset before 6 months of age were randomized to receive intrathecal 12 mg nusinersen or a sham injection loading doses followed by active treatment or sham maintenance doses every 4 months [32]. A planned interim efficacy analysis included subjects who died, withdrew, or completed at least 183 days of treatment and who received nusinersen [n=52] and sham-control [n=30]. Responders were defined as subjects achieving improvement in more categories of motor milestones than worsening according to Section 2 of the Hammersmith Infant Neurologic Exam (HINE). The HINE evaluates seven different areas of motor milestone development, with a maximum score between 2-4 points for each developmental motor milestone. A total maximum HINE score is 26. A treatment responder is defined as any subject with at least a 2-point increase in ability to kick or at least 1-point increase in the motor milestones of head control, rolling, sitting, crawling, standing, or walking [29].

Among the eligible subjects (n=82), a significantly greater percentage in the nusinersen group [41%] were responders compared to the sham control group (0%) in the interim diagnosis. Among subjects in the final analysis [n=81], the primary endpoint was time to death or permanent ventilation. A 47% reduction in the risk of death or permanent ventilation in the nusinersen group (p=0.005) and a 63% reduction in the risk of death among nusinersen-treated subjects (p=0.004) was found. Median time to death or permanent ventilation was 22.6 weeks in the sham-control group and was not reached in the nusinersen group [32]. The most common adverse reactions were lower respiratory infection and constipation, occurring in ≥ 20% of treated subjects and at least 5% more frequently in treated than in control subjects, but were attributable primarily to the underlying disease than to the treatment. The serious adverse event of atelectasis was more frequent in nusinersen-treated subjects than in control subjects (18% *vs.*10%), but was again attributed to the underlying disease rather than the experimental treatment [32].

A second randomized, double-blind, sham-controlled study enrolled symptomatic children with later-onset SMA with symptom-onset after 6 months of age (N=126) [32]. Subjects were randomized to receive intrathecal 12 mg nusinersen or sham injections as a loading regimen followed by maintenance doses every 4 months. The primary endpoint was the change from baseline Hammersmith Functional Motor Scale - Expanded [HFMSE] scores after 15 months. The HFMSE evaluates motor function in patients with limited ambulation. It is comprised of 33 scored activities that give objective information on motor ability and clinical progression, such as the ability to sit unassisted, stand, or walk. Each item is scored from 0-2, with a maximum total score of 66. Higher scores indicate better motor function.

Among nusinersen-treated subjects, the mean change in baseline total HFMSE scores was 3.9, versus -1.0 in the sham-treated group (p=0.0000001). The proportion of subjects who achieved a ≥ 3-point improvement in baseline total HFMSE scores was 56.8% in the nusinersen group (p=0.00064) versus 26.3% in the sham-control group. A 3-point increase in HFMSE scores represents improvements in two or three motor skills. The most common adverse reactions that occurred in ≥ 20% of treated patients and occurred at least 5% more frequently than in control patients were pyrexia, headache, vomiting, and back pain, consistent with the underlying disease process of SMA and effects of lumbar puncture [32].

ZOLGENSMA (onasemnogene abeparvovec-xioi) Suspension for intravenous infusion. Onasemnogene abeparvovec-xioi is an intravenously administered adeno-associated virus vector-based gene replacement therapy approved in the U.S. in 2019 for the treatment of pediatric patients who are <2 years old with bi-allelic mutations in the SMN 1 gene [33]. It was also approved for use in the E.U. in 2020. Onasemnogene abeparvovec-xioi gene therapy is designed to deliver a copy of the gene encoding human SMN protein to motor neurons in patients with SMA [34] (Figure 4).

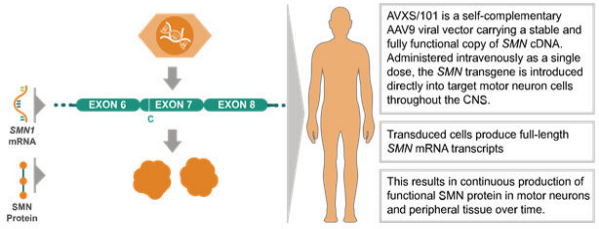

Figure 4: Onasemnogene abeparvovec-xioi mechanism of action.

Adeno Associated Virus 9 (AAV 9) delivers a fully functional copy of SMN complement deoxyribonucleic acid (cDNA). Administered intravenously as a single-dose, the SMN transgene passes the blood-brain barrier and is introduced directly into target motor neuron cells throughout the CNS. Transduced cells produce full-length SMN mRNA transcripts, which enable continuous production of SMN protein in motor neurons and peripheral tissue over time [33,73,74,78-80].

An open-label, single-arm, ascending-dose clinical trial assessed the safety and efficacy of onasemnogene abeparvovec-xioi in subjects <2 years old with genetically confirmed bi-allelic SMN 1 gene deletions, two copies of the SMN 2 gene, and absence of the c.859G>C modification in exon 7 of the SMN 2 gene and SMA symptom-onset before 6 months of age. Onasemnogene abeparvovec-xioi was administered as a single intravenous infusion to low-dose [n=3] and high-dose groups (n=12). After 24 months, one subject in the low-dose cohort required permanent ventilation while all subjects in the high-

dose group were living without need of permanent ventilation. None of the subjects in the low-dose group were able to sit without support, stand or walk. In the high-dose group, nine subjects (75.0%) could sit without support for ≥ 30 seconds, and two (16.7%) could stand and walk without assistance.

The most frequent adverse events with an incidence >5 observed in four open-label studies of 44 subjects receiving IV infusion, were elevated aminotransferases exceeding the upper limit of normal (27.3%)and vomiting (6.8%) [33].

A phase 3 open-label, single-arm, single-dose trial enrolled symptomatic subjects <6-month-old (n=22) with SMA due to biallelic SMN 1 mutations (deletion or point mutations) and one or two copies of SMN 2 [30]. Subjects received a single 30-60 min IV infusion of onasemnogene abeparvovec-xioi (1.1 × 1014 vg/kg). Subjects were then assessed once weekly for 4 weeks, and then monthly until age 18 months or early termination.

Coprimary efficacy outcomes were independent sitting for ≥ 30 seconds (Bayley-III item 26) at 18 months of age and freedom from permanent ventilation at age 14 months. By the data cutoff, 13 of the 19 subjects continuing in the trial reached 14 months of age without permanent ventilation, one of the study's coprimary efficacy endpoints.

In addition to survival, assessment of the other coprimary efficacy endpoint found that 10 of the 21 subjects (47.6%) achieved the ability to sit without support for ≥ 30 seconds between 9.2 and 16.9 months of age (mean age was 12.1 months). Based on the natural history of the disease, subjects who met the study entry criteria would not be expected to attain the ability to sit without support, and only approximately 25% of these subjects would be expected to survive [i.e., being alive without permanent ventilation] beyond 14 months of age. In addition, 16 of the 19 subjects had not required daily Non-Invasive Ventilation [NIV].

Serious adverse events were reported in 10 [45%] of subjects, most commonly being consequences of the underlying disease including some form of respiratory tract infection. Seven subjects [32%] had transient transaminase elevation despite the required use of 1 mg/kg prednisolone daily, and two of these subjects [9%] developed severe elevation of transaminases that required adjustment in the prednisolone dose, but all signs of hepatic toxicity responded to steroids without need for other treatment.

Two subjects [9%] developed low platelet counts (≤ 75,000 / µL) that were not associated with clinical sequelae and resolved spontaneously [30].

EVRYSDI [risdiplam] for oral solution

Risdiplam (RG 7916/R O7034067) is an orally administered, centrally and peripherally distributed small molecule that modulates SMN 2 pre-mRNA splicing to increase SMN protein levels [Figure 5] [35]. It was approved for use in the U.S. in 2020 [35] and subsequently in the E.U. [36].

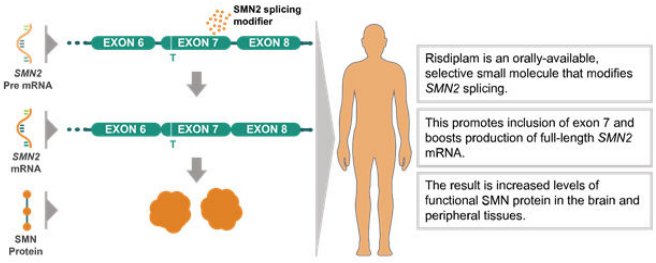

Figure 5: Risdiplam mechanism of action.

Risdiplam is an orally available, selective small molecule that modifies SMN 2 pre-mRNA (Pre mRNA) splicing. Risdiplam increases exon 7 inclusions in SMN 2 mRNA transcripts and production of full-length SMN protein in the brain. This leads to increased production of functional SMN protein in the brain as well as throughout peripheral tissues [35, 81][83].

An open-label study assessed the efficacy, safety, pharmacokinetics, and pharmacodynamics of risdiplam in subjects with Type 1 SMA and symptom-onset between 28 days and 3 months of age (n=21) [35]. Subjects were randomized to a high-dose group [n=17] and had their dose adjusted to 0.2 mg/kg/day before 12 months of treatment while the low-dose group [n=4] did not. Efficacy endpoints were the ability to sit without support for ≥ 5 seconds (Item 22 of the Bayley Scales of Infant and Toddler Development, 3rd Edition [BSID-III] gross motor scale) and survival without permanent ventilation. Among subjects in the high-dose group, seven [41%] could sit independently for ≥ 5 seconds after 12 months of treatment and 19 (90%) were alive without permanent ventilation and reached ≥ 15 months of age. After ≥ 23 months of treatment, 17 subjects (81%) were alive without permanent ventilation and reached an age of ≥ 28 months. The most frequent adverse reactions reported in >10% of these subjects were upper respiratory tract infections including nasopharyngitis, rhinitis, respiratory tract infections, pneumonia, and also constipation and vomiting [32].

The primary endpoint of a second randomized, double-blind, placebo-controlled study for Type 2 and 3 subjects aged 2-25 was the change in baseline Motor Function Measure 32 [MFM32] score after 12 months [35]. A key secondary endpoint was the proportion of subjects with a ≥ 3-point change in baseline MFM32 total score (maximum score 100) where a score of >3 is considered clinically significant [37]. The MFM32 measures fine and gross motor function abilities that relate to daily functions from standing and walking to the use of hands and fingers.

Another key secondary endpoint was the Revised Upper Limb Module (RULM), a tool used to assess upper limb motor performance of SMA subjects that can capture progressive muscle weakness across the spectrum of the disease. Thresholds of improvement identified in previous studies as clinically meaningful are ≥ 2-point changes on the RULM (maximum score 37) [38]. Nonambulatory subjects [N=180] with Type 2 (71%) or Type 3 (29%) SMA were enrolled and randomized to receive risdiplam (n=120) or placebo [n=60].

The change in mean baseline total MFM 32 score after 12 months was 1.36 in the risdiplam group versus -0.19 in the placebo group (p=0.0156) and the proportion of subjects with a mean change from baseline MFM 32 total score of ≥ 3 was 38.3% in the risdiplam group versus 23.7% in the placebo group (p=0.0469). The change in mean baseline RULM total score was 1.61 in the risdiplam group versus 0.02 in the placebo group (p=0.0469). Thresholds of improvement identified in previous studies as clinically meaningful are ≥ 2-point changes on the RULM [38].

The most common adverse reactions reported in at least 10% of subjects treated with risdiplam and with incidence greater than placebo-treated subjects were fever, diarrhea, and rash. Additional adverse reactions reported in >5% of subjects and with an incidence >5% greater than placebo subjects were mouth and aphthous ulcers, arthralgia and urinary tract infection [35].

These treatments address the genetic cause of the disease and have shown remarkable advances in SMA. In spite of these significant achievements, there remain unmet medical needs for this patient population.

Limitations and unmet needs

Despite the strides made with transformative SMN-dependent therapies, uncertainties regarding treatment response and long-term outcomes for patients with SMA remain. The currently approved treatments offer a clinically meaningful therapeutic advance in patients with SMA; however, unmet need remains for several reasons, some of which will be described below.

Earlier treatment often leads to better outcomes

Recent research has demonstrated that abnormalities of motor axon development begin prenatally in infantile onset SMA patients and that these defects are associated with rapid postnatal degeneration of motor neurons [39]. These results suggest that minimizing treatment delay is essential to maximize therapeutic efficacy in patients. Indeed, it has been shown, through numerous clinical trials and real-world evidence, that early treatment of SMA leads to better outcomes for patients [40]. For example, in NURTURE, subjects treated presymptomatically showed greater improvements in motor milestone scores in comparison to the treatment of symptomatic subjects with infantile onset SMA in the ENDEAR study [41]. Among subjects with later onset SMA in the CHERISH clinical trial, those treated later in their disease course with nusinersen often show more modest improvements or a stabilization in motor function compared to those treated earlier. This presents an issue for older children and adults living with SMA who represent two-thirds of the overall SMA population [40]. That may not have been treated early in their disease course due to lack of availability of treatments, clinical parameter restrictions, or age restrictions in drug labels. More specifically, the intrathecal route of administration required for nusinersen is particularly challenging for patients with contractures, scoliosis and spinal fusion, whereas risdiplam and onasemnogene abeparvovec-xioi are currently limited to certain age population [42].

Even for the patients treated early, questions remain whether sufficient SMN protein levels are achieved uniformly in all motor neurons to halt neurodegeneration, and whether the motor neuron dysfunction is fully reversible. For example, interim results from the ongoing NURTURE trial of nusinersen in presymptomatic subjects with SMA showed that even with early intervention, not all infants achieved age-appropriate milestones such as walking independently. In addition, due to the degree of motor neuron loss and dysfunction at the time therapy is initiated, treated patients are vulnerable to progressive functional loss accompanying body and skeletal growth [43,44].

Questions also remain about durability of effect and the safety and efficacy of repeated gene therapy administration. This is being investigated among patients with advanced disease with SMN upregulator combinations. Therapeutics that are independent of SMN upregulation may help improve outcomes for treated patients that have not achieved maximum benefit [43,44].

SMN upregulation outside the CNS and SMN-independent mechanisms

Although SMA is typically thought of as a disease of motor neurons, recent work has shown that SMN may play an important role in tissues outside of the CNS; this suggests that SMN upregulation may also be required in peripheral tissues, particularly in muscle. Because nusinersen does not sufficiently cross the blood–brain barrier, the drug must be delivered intrathecally, limiting its exposure to the CNS [42]. Similarly, though delivered systemically, it is not yet clear how well onasemnogene-abeparvovec-xioi transduces different cell types; further, because the virus does not integrate into a cell's genome, it can be lost from replicating cells. Studies that follow patients for longer periods of time will help determine if patient outcomes are improved by systemic as opposed to restricted CNS restoration of SMN.

The pathophysiology of SMA extends beyond motor neuron function to include primary and secondary effects on muscle, pulmonary function and other organs. The recently approved treatments for SMA, used singly or potentially in combination, may now fully restore SMN in all tissues and cell types, but there will still be unmet needs for most SMA patients in the magnitude of motor function improvement and the need to further restore muscle function. SMN-independent strategies may address these additional features of the disease and further improve motor function and general health [45,46]. Although SMN upregulators do improve motor function, patients with SMA are not reaching the top end of motor function scores, and would ideally benefit from a two-pronged approach: treatments that optimize SMN restoration, and treatments that augment motor function by SMN-independent approaches [14,30].

For example, among children with Type 2 SMA in the CHERISH study, data showed a clinically meaningful improvement in HFMSE scores after nusinersen therapy. With a total possible HFMSE score of 66, their mean HFMSE scores increased from the low 20s at screening, to mid- or high 20^{s} after 1-2 years of treatment [47,48]. The relatively modest increase in mean HFMSE score in children with later onset SMA could be due to

the fact that some of the more difficult items on the HFMSE (i.e., squatting, jumping, stair climbing) are simply harder to achieve regardless of SMA type. Although the level of motor function improvement was deemed clinically meaningful, the low final outcome score highlights the need for additional enhancements to maximize motor function.Patients with SMA experience limitations in mobility, daily activities associated with the progressive deterioration in motor function, alongside emotional challenges including depression, anxiety, fatigue, social isolation, and a lack of effective interventions to address these aspects of quality of life (QoL)[19].

SMA also has a substantial and multidimensional burden on affected adults. While advances in supportive care and the new transformative treatments are rapidly reshaping the therapeutic environment, understanding the natural history, care pathways, and patient-reported outcomes associated with SMA in adulthood are critical to advancing research and clinical care.

In studies including patient-reported outcomes to date, subjective well-being has not improved [49]. It has not been possible to identify a single treatment associated with statistically higher QoL; however, parents showed a trend toward belief that their children with SMA have a greater QoL with current treatments compared to supportive care [49].

SMA remains a debilitating genetic disorder for many patients, despite the revolutionary effects of SMN up-regulators to slow or stop motor neuron degeneration; there are still unmet needs that demonstrate the importance of exploring SMN-independent mechanisms, specifically muscle-directed treatments, which can be used in combination with the recently approved treatments. Combining SMN restoration with SMN-independent treatment may address the varying degrees of muscle weakness, fatigue and immobility affecting SMA patients after receiving SMN up-regulating treatment.

Myostatin as a potential therapeutic target

Myostatin is a member of the transforming growth factor beta [TGF-β] superfamily of growth factors and is expressed primarily in skeletal muscle cells where it inhibits muscle growth [50] (Figure 6). Since myostatin is a negative regulator of muscle mass, vertebrates lacking the myostatin gene are healthy but display increased muscle mass and strength [51]. In contrast, high levels of circulating myostatin are associated with muscle wasting in patients with cancer, HIV infection and other illnesses [52].

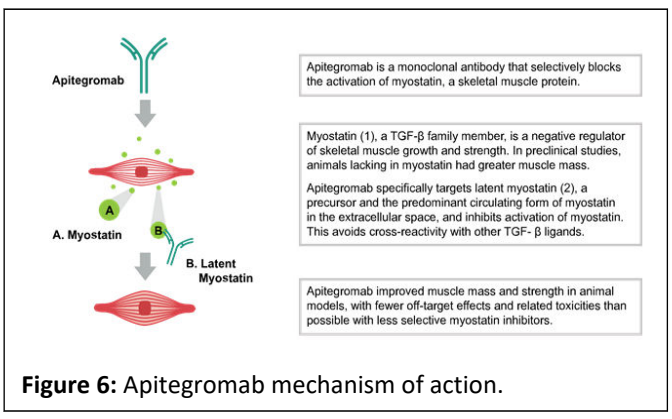

Figure 6: Apitegromab mechanism of action.

Apitegromab is a monoclonal antibody that selectively blocks the precursor, or inactive form of myostatin, to block its activation in the skeletal muscle. Myostatin (1), a transforming growth factor ß protein (TGF-ß) family member skeletal muscle protein, is a negative regulator of skeletal muscle growth. In preclinical studies, animals lacking in myostatin have greater muscle mass and strength. Apitegromab specifically targets the upstream latent form of myostatin (2), which avoids cross-reactivity with other TGF-ß ligands and inhibits activation of myostatin. Apitegromab improved muscle mass and strength in animal models, with fewer off-target effects and related toxicities than possible with less selective myostatin inhibitors [63,84].

Numerous preclinical and clinical studies have demonstrated the potential role of myostatin in muscle atrophy [53]. Generating interest in myostatin as a promising therapeutic target for patients with muscle-wasting conditions, including SMA [54]. Many previous anti-myostatin drug candidates prevent the active, mature myostatin from binding to its receptors. In multiple preclinical models of muscle atrophy, including SMA, myostatin inhibition is effective at maintaining muscle mass and function [55-61].

One limitation with previous myostatin inhibitors that block mature myostatin from binding to its receptors is their lack of selectivity. There is a high degree of homology between the active, mature myostatin and other active, mature TGF- super family members, such as Activin A and GDF-11 which all signal through the same receptor type IIB (ActRIIB) receptor. Molecules targeting either the myostatin growth factor or the receptor often inhibit the activity of multiple growth factors, resulting in unwanted effects, such as telangiectasias and epistaxis [62].

One method by which selective targeting can be achieved is by targeting the myostatin prodomains in the precursor forms (preforms) of myostatin which include promyostatin and latent myostatin. The divergent nature of various growth factor prodomains allow for development of an antibody specific for the prodomains of myostatin, resulting in selective inhibition of myostatin activity.

Activation of myostatin requires two distinct proteolysis events to generate the mature active growth factor [63]. The first cleavage step of promyostatin is carried out by a proprotein convertase to produce the latent complex. Activation and release of the active, mature myostatin growth factor is accomplished after cleavage by an additional protease from the BMP/tolloid family [64].

Apitegromab, a selective inhibitor of myostatin activation

The divergent nature of the various growth factor prodomains permitted development of a specific antibody for the myostatin prodomains, resulting in a more specific anti-myostatin effect. Scholar Rock is developing apitegromab as a potential treatment for patients with SMA.

Apitegromab is an antibody that specifically recognizes the proforms of myostatin, promyostatin and latent myostatin, without recognizing the mature, active growth factor [63]. It was

developed to uniquely target the latent form of myostatin, specifically inhibiting myostatin activation in muscle, rather than the traditional approach of blocking activated myostatin or the ActRIIB receptor. By targeting the latent form of myostatin, apitegromab does not inhibit the activity of other closely related members of the TGFβ superfamily. Inadvertently influencing other members of the TGFβ superfamily may lead to undesirable side effects or treatment interruption or withdrawal, leading to limited effective dosing [62][Figure 7].

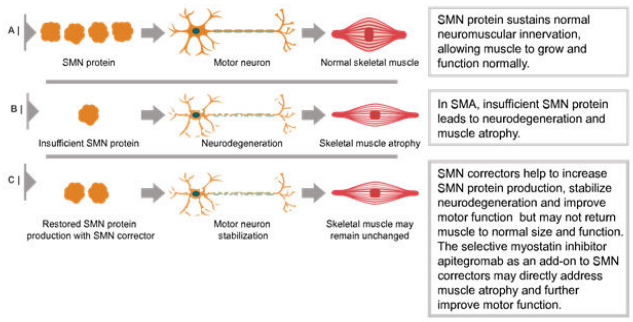

Figure 7: Mechanism of action of apitegromab as an Add-on to SMN correctors.

- SMN protein promotes normal motor neuron function, which in turn provides the signals that activate and sustain muscle tissue.
- In SMA, insufficient SMN protein leads to degeneration of motor neurons and subsequent skeletal muscle atrophy.
- SMN correctors help to increase SMN protein production, stabilize neurodegeneration, and improve or maintain motor function, but may not return muscle to its normal size and function. (73,75, 84,85). The selective myostatin inhibitor apitegromab as an add-on to SMN correctors may directly address muscle atrophy and further restore motor function.

Preclinical studies

The effects of inhibiting myostatin activation have been demonstrated in multiple animal models. Administration of a murine equivalent of the apitegromab parental molecule (muSRK-015P) to healthy mice for 4 weeks significantly increased muscle mass/strength and functional muscle performance [63]. In addition, a single 20 mg/kg dose of apitegromab completely prevented dexamethasone-induced muscle atrophy in mice [63]. Apitegromab administration for 8 weeks also increased muscle mass/strength in healthy cynomolgus monkeys, *via* the increase of the weight of gastrocnemius and biceps brachii muscles up to 25% [65].

Pharmacokinetic studies showed maximum apitegromab serum concentrations were achieved 1-hour postdose in adult rats and monkeys with relative dose-proportional accumulation of apitegromab at doses of 10 to 100 mg/kg. Apitegromab displayed a similar pharmacokinetic profile across animal species [66].

As apitegromab prevents the activation of mature myostatin in mice, pharmacodynamic studies showed dose-dependent accumulation of latent myostatin in the serum following repeated weekly IV administration of apitegromab at doses of 10 to 300 mg/kg in rats [66].

Administration of eight weekly doses of apitegromab to cynomolgus monkeys also resulted in a dose-dependent [but not dose-proportional] response in accumulated latent myostatin.

These apitegromab-induced increases in serum latent myostatin that are observed in animals, healthy volunteers and patients with SMA (see below), are considered indicative of target [latent myostatin] engagement with apitegromab and complex formation of latent myostatin with apitegromab in the muscle that is ultimately reaching systemic circulation and measured in the serum [67].

Phase 1 clinical study

A phase 1 clinical trial in healthy, adult subjects was undertaken to assess the safety and tolerability of single and multiple IV doses of apitegromab. Secondary objectives were to assess the pharmacokinetics and immunogenicity of apitegromab, as well as to assess exploratory measures, such as the assessment of apitegromab pharmacodynamics [68].

During Part A, subjects received single, ascending doses of apitegromab ranging from 1 to 30 mg/kg as a 120-minute intravenous [IV] infusion. During Part B, subjects were administered multiple; ascending doses of apitegromab 10, 20, or 30 mg/kg biweekly on Days 0, 14, and 28 as a 120-minute IV infusion.

Serum latent myostatin displayed dose-dependent pharmacodynamics. Both single and multiple doses of apitegromab resulted in dose-dependent and sustained increases in serum latent myostatin, indicating robust target engagement.

The mean pharmacokinetic parameters after single IV infusions of apitegromab are summarized in Table 3 [68]. Serum apitegromab concentrations increased dose-proportionally and maximum plasma concentrations were observed within 8 hours following the end of infusion.

Apitegromab demonstrated linear, dose-proportional pharmacokinetics. Mean Cmax values ranged from 25 µg/mL in the 1 mg/kg dose group to 744 µg/mL in the 30 mg/kg dose group. Apitegromab concentrations remained detectable for 112 days after infusion in all dose groups.

Table 3: Mean pharmacokinetic parameters after single IV infusions of apitegromab.

Dose (mg/kg)	Cmax (µg/mL)	Tmax (hr)	AUC(0-last) (hr*µg/mL)	AUC(0-inf) (hr*µg/mL)	CL (mL/hr)	Vz (L)	t1/2 (hr)
1	25	6.0	11647	12748	6.05	6.8	786
3	83	4.7	33097	35037	7.69	6.9	624
10	278	3.4	105973	126053	7.29	5.4	543
20	555	4.7	216171	227308	7.10	5.7	588
30	744	5.3	347298	367866	6.60	5.9	623

Cmax, maximum plasma concentration; Tmax, time to peak plasma concentration; AUC, area under the curve; CL, clearance; Vz, volume of distribution; t1/2, serum half-life.

Safety signals observed for apitegromab were consistent with the underlying population and background therapy. The only adverse event occurring in more than one subject was headache [n=3] and there were no clinically significant abnormalities or changes in vital signs, laboratory parameters, cardiac telemetry results, ECG results, or physical examinations. Immunogenicity, as evaluated by antidrug antibody testing, was negative for all subjects. The pharmacokinetic data support the potential for infrequent dosing. The results from this clinical trial and the preclinical studies supported further development and investigation of apitegromab in a phase 2 trial.

Phase 2 TOPAZ clinical trial

A recently completed phase 2 proof-of-concept clinical trials assessed the use of apitegromab for treating later-onset Type 2 and Type 3 SMA in pediatric and adult subjects, 2 to 21 years of age, with and without concomitant nusinersen therapy [69]. The primary objectives were to evaluate safety and tolerability of apitegromab and efficacy by assessing changes in motor function outcome measures. Secondary objectives were to determine the time to therapeutic effect between low [2 mg/kg] and high-dose [20 mg/kg] apitegromab and assess the immunogenicity of apitegromab.

The overall study design is summarized in Table 4. Subjects received apitegromab every 4 weeks via IV infusion during the 52-week treatment period. Subjects were randomized into three groups:

- Nonambulatory subjects ≥ 2 years old treated with concomitant nusinersen initiated prior to age 5 years were randomized in a double-blind manner to receive apitegromab 2 mg/kg or 20 mg/kg
- Nonambulatory subjects 5 to 21 years old with concomitant nusinersen initiated after age 5 years received apitegromab 20 mg/kg.
- Ambulatory subjects 5 to 21 years old with or without concomitant nusinersen

Table 4: TOPAZ Trial – study design.

	Ambulatory	Nonambulatory	Nonambulatory
Design	N=23; age 5-21 years Open-label, single-arm 20 mg/kg SRK-015 IV Q4W 12-month treatment period	N=15; age 5-21 years Open-label, single-arm 20 mg/kg SRK-015 IV Q4W 12-month treatment period	N=20; age ≥ 2 years Double-blind, randomized (1:1) to 2 mg/kg or 20 mg/kg SRK-015 IV Q4W 12-month treatment period
Patients	Ambulatory Type 3 SMA Concomitant therapy with approved SMN upregulator (n=12) or monotherapy (n=11) RHS Scores ≤ 63	Type 2 or nonambulatory Type 3 SMA Concomitant therapy with approved SMN upregulator HFMSE Scores ≥ 10	Type 2 SMA Initiated treatment with approved SMN upregulator before age 5 years HFMSE Scores ≥ 10
Primary Objectives	Safety Mean change from baseline in RHS	Safety Mean change from baseline in HFMSE	Safety Mean change from baseline in HFMSE

RHS, Revised Hammersmith Scale; HFMSE, Hammersmith Functional Motor Scale Expanded

The nonambulatory subjects ≥ 2 years old randomized to high-dose apitegromab with nusinersen (n=10) achieved improvements in baseline HFMSE scores by ≥ 3-points (n=5, 63%), and ≥ 6 points (n=5, 63%). Subjects receiving low-dose apitegromab (n=10) achieved improvements in baseline HFMSE scores by ≥ 3-points (n=5, 56%).

Nonambulatory subjects 5 to 21 years old [n=14] achieved improvements in baseline (HFMSE) scores by ≥ 3-points (n=4, 29%). The ambulatory subjects 5 to 21 years old (n=23) achieved

improvements in baseline Revised Hammersmith Scale scores by ≥ 3-points (n=5, 22%) [62]. It should also be noted that any increase or stabilization of HFMSE score is a distinct and evident improvement over comparable natural history cohorts that have demonstrated progressive decreases in score over similar time frames [70,71]. Among individuals with SMA type 2 or 3 and their caregivers, slowing of disease progression and stabilization of disease course were considered clinically meaningful [70,71].

A 3-point change in the HFMSE represents a clinically meaningful change involving two or three skills. A 6-point improvement reflects achievements in three to six skills; for example, rising from the floor, squatting, jumping, and using the stairs [37,72].

The doses explored in TOPAZ showed dose-dependent and dose-proportional increases in apitegromab exposure, with the high dose achieving approximately 10-fold increases in serum concentrations of apitegromab compared to the low dose [67]. Both doses explored in TOPAZ, showed high target engagement, as measured by latent myostatin (>100-fold increase from baseline) [69]. The higher 20 mg/kg dose offered relatively higher magnitude of target engagement. Scalable increases in HFMSE were seen following both high and low doses incremental with background chronic maintenance dosing with nusinersen. The 20 mg/kg dose increases in HFMSE were greater at all timepoints. Both the magnitude of target engagement and the magnitude of efficacy increased with increasing dose.

Incidence and severity of adverse events were consistent with the underlying patient population and background therapy. There was no evidence of immunogenicity. The most frequently reported treatment-emergent adverse events were headache, pyrexia, upper respiratory tract infection, cough, and nasopharyngitis [62].

Conclusion

Recent approaches to treating SMA have been highly effective in increasing SMN protein production by either modifying SMN2 gene splicing [nusinersen and risdiplam], or SMN gene replacement therapy [onasemnogene abeparvovec-xioi], slowing or stopping the progression of the disease and still, unmet needs remain that include achieving age-appropriate milestones and treating the effects of SMA on peripheral tissues [73-80].

The recent introduction of newborn screening programs is identifying patients with SMA earlier, enabling early treatment referrals to SMA experts, who could recommend presymptomatic treatment; however, despite improvements in motor function with SMN-dependent treatments, there remain limitations of the current SMN-upregulating treatments that may contribute to unmet patient needs, including motor deficiencies.

The monoclonal antibody apitegromab, which blocks the activation of the negative regulator of muscle growth, myostatin, is in clinical development being explored to address unmet needs in SMA. This potential treatment may represent a unique, SMN-independent approach, more specifically, a muscle-targeted therapeutic option for patients that still experience motor function deficits despite SMN protein-increasing therapy. Apitegromab, in conjunction with an SMN upregulator may further enhance motor function. A phase 3 apitegromab clinical trial for SMA is planned [81-85].

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