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REVIEW

Advancing treatment of spinal muscular atrophy through inhibition of the myostatin signaling pathway

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ABSTRACT

Introduction: In spinal muscular atrophy (SMA), irreversible loss of spinal motor neurons and progressive skeletal muscle atrophy cause continuous weakness and loss of motor function. Treatments that increase levels of survival motor neuron (SMN) protein in motor neurons have greatly improved prognoses for patients, but significant unmet needs remain. Myostatin is a protein secreted by skeletal muscle that acts as a negative regulator of muscle growth. Inhibition of the myostatin signaling pathway may improve motor function in SMA and other neuromuscular diseases.

Areas covered: This article reviews the role of muscle in SMA and the potential for treatments that inhibit the myostatin signaling pathway in neuromuscular diseases. Preclinical and clinical trial data are discussed for these muscle-targeted treatments in development for SMA.

Expert opinion: SMN-targeted disease-modifying treatments focus on motor neuron survival rather than muscle. Treated individuals nonetheless experience a range of persistent muscle weakness. Treatments that inhibit myostatin signaling represent a potential complementary pathway for direct muscle enhancement. In the evolving SMA treatment landscape, understanding how muscle-targeted treatment can be incorporated into clinical practice will facilitate individualized treatment decisions and identify outcomes that best encapsulate maintenance or improvement of motor function across the phenotypic spectrum of SMA.

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1. Background

1.1. Spinal muscular atrophy overview

Spinal muscular atrophy (SMA) is a rare and often severe neuromuscular disease in which irreversible loss of spinal and brainstem motor neurons leads to progressive skeletal muscle atrophy, muscle weakness, and progressive motor function decline [1–3]. In SMA, biallelic deletions or mutations of the *SMN1* gene lead to deficient survival motor neuron (SMN) protein production, the fundamental cause of motor neuron degeneration and subsequent muscle atrophy (Figure 1) [3]. Skeletal muscle from individuals with SMA is comprised of a mixture of denervated, atrophic, and nonfunctioning muscle fibers, and innervated functioning muscle fibers [4,5]. Muscle fiber architecture is disrupted, with groups of small, often rounded, atrophic fibers of types 1 and 2 intermingled with clustered, hypertrophic type 1 fibers, though fiber sizes may vary substantially within and between muscles, and between patients with SMA [5–8]. Progressive muscle atrophy and weakness lead to persistent functional deficits and continued loss of motor function over time [9–11].

SMA has historically been viewed primarily as a disease of motor neurons, in which muscle pathology is a downstream consequence of motor neuron degeneration [12–15]. In its more severe form, however, it is increasingly seen as a multisystem disorder, as SMN is ubiquitously expressed, particularly during gestational and neonatal development, and SMN depletion is associated with pulmonary, cardiac, vascular, metabolic, bone, and liver abnormalities [16–19]. In the severe infantile form, type 1 SMA, arrested development of muscle fibers has also been demonstrated [20]. In preclinical models, muscle-specific SMN deficiency has been demonstrated to cause muscle pathology independent of motor neuron degeneration [15,21,22]. Furthermore, findings from in vitro co-culture of human SMA muscle cells with rodent spinal cords, as well as muscle autopsy from an infant patient with SMA, suggest an intrinsic abnormality of SMA muscle that may precede and perhaps contribute to motor neuron degeneration [23,24]. These findings suggest the possibility that muscle-specific weakness also contributes to the motor function deficits of SMA [7,14,21,25].

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Article highlights

- Despite advances with treatments that increase production of survival motor neuron protein in motor neurons, most children and adults living with spinal muscular atrophy (SMA) experience persistent unmet needs due to weakness associated with muscle atrophy.
- Myostatin is a protein that acts to inhibit muscle growth. Under conditions in which myostatin signaling is blocked, muscle fiber hypertrophy and increased strength are observed.
- Remaining healthy muscle in SMA represents a potential target for treatments, such as inhibitors of the myostatin signaling pathway, to enhance muscle size and strength.
- There are three myostatin signaling pathway inhibitors that target muscle currently in clinical development for SMA: apitegromab and emugrobart are monoclonal antibodies that target latent/precursor forms of myostatin to prevent their cleavage into mature, active myostatin, and taldefgrobep alfa is a recombinant protein that binds mature myostatin and acts as a competitive antagonist of activin A and other ligands that bind the same receptor as myostatin.
- Apitegromab is the only of these muscle-targeted treatments to demonstrate statistically significant improvements in motor function in a placebo-controlled clinical trial for patients with SMA.
- Muscle-targeted treatments such as myostatin signaling pathway inhibitors may represent the next significant advance in the treatment of SMA.
- Key considerations for the inclusion of these treatments in a patient's care plan include patient age, age at symptom manifestation, developmental status, and level of functional ability.
- Additional clinical trial and real-world experience with these treatments will help determine their place in the SMA treatment landscape.

1.2. SMN-targeted treatment and unmet needs

The first three treatments approved for individuals with SMA were designed to restore SMN protein levels. Nusinersen and risdiplam are mRNA splicing modifiers that increase production of functional SMN from the *SMN2* gene, a less functional paralog of *SMN1*, and onasemnogene abeparvovec-xioi is a gene transfer therapy that inserts a functional cDNA copy of the *SMN1* gene [7,26]. These SMN-targeted treatments have provided profound and clinically meaningful improvements for individuals living with SMA by slowing disease progression, improving motor, respiratory, and feeding outcomes, and reducing mortality [2,25,27,28]. However, substantial unmet needs remain due to the weakness associated with denervation muscle fiber atrophy. Most patients who receive SMN-targeted treatments fail to achieve age-appropriate motor milestones [25–27,29]. This is largely commensurate with the magnitude of motor neuron degeneration before initiation of SMN-targeted treatment, whether because treatment was initiated only after symptomatic weakness led to diagnosis, or to prenatal neurodegeneration in those diagnosed at birth by newborn screening. Although the effect of SMN-targeted treatment can be dramatic, over time some individuals experience a decline in function, whether due to accumulating complications of muscle weakness, inadequate enhancement of SMN expression, other factors, or a combination of these. This can impact independence, activities of daily living, and quality of life [10,11,25]. Patients and caregivers have reported that mobility limitations and muscle weakness are the least improved symptoms with SMN-targeted treatments, with one survey finding persistent muscle weakness in 95% of pediatric and 100% of adult patients, despite the majority having received at least 2 years of continuous treatment with nusinersen or risdiplam [27].

Enhancing SMN protein levels cannot ameliorate neurodegeneration that occurred prenatally or prior to treatment initiation and does not directly address muscle atrophy [5,9,30]. Nusinersen, delivered intrathecally, cannot cross the blood–brain barrier in sufficient amounts to replace SMN in

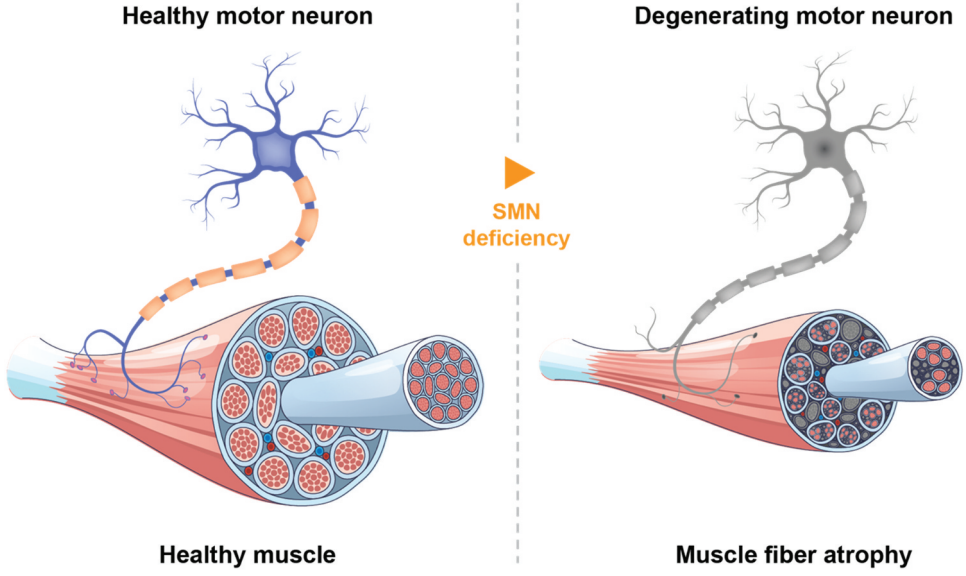

Figure 1. Illustration of motor neuron degeneration and muscle atrophy in SMA.

In SMA, SMN deficiency leads to degeneration of motor neurons, with consequent neurogenic muscle atrophy and weakness, and loss of motor function. There is also an element of developmental arrest noted in muscle biopsies from infants with severe type 1 SMA prior to the development of classic fiber type grouped atrophy. Disrupted muscle fiber architecture is characterized by groups of small, often rounded, atrophic fibers of types 1 and 2 intermingled with clustered, hypertrophic type 1 fibers. SMN-targeted treatments increase SMN protein levels in motor neurons. Remaining innervated, functional muscle fibers present a target for muscle-targeted treatments to improve muscle strength and motor function.

Abbreviations: SMA, spinal muscular atrophy; SMN, survival motor neuron.

muscle or other peripheral tissues [25]. Risdiplam and onasemnogene abeparvovec-xioi are administered systemically, but data on their biodistribution in muscle and other peripheral tissues of patients are limited [31,32]. Additionally, the non-integrating episome nature of the transduced gene in onasemnogene abeparvovec-xioi may lead to a loss of expression over a patient's lifetime; studies on the long-term durability of this therapy are ongoing [33,34]. An intrathecal formulation of onasemnogene abeparvovec (onasemnogene abeparvovec-brve) is also available as an approved treatment option in the US [35,36]; however, biodistribution and durability data beyond 12 months are limited [37,38]. Treatments that directly target muscle may provide an additional pathway to benefit motor function and address unmet needs in individuals receiving SMN-targeted treatment [2,9,25,26].

2. Role for inhibition of the myostatin signaling pathway in neuromuscular disease

2.1. *Myostatin regulates muscle mass*

Myostatin is a member of the transforming growth factor (TGF)-β superfamily of regulatory proteins that is secreted mainly by skeletal muscle, where it acts as a negative regulator of muscle growth [39–41]. Initially expressed as an inactive precursor polypeptide (promyostatin), myostatin is subsequently activated by two proteolytic cleavage steps (Figure 2) [41,42]. In the first step, proprotein convertases cleave promyostatin to form latent myostatin, a complex of the mature myostatin dimer and a prodomain that prevents receptor binding [41,42]. Metalloproteases subsequently cleave latent myostatin to release mature, active myostatin [42,43]. Binding of mature myostatin to its target skeletal muscle cell surface receptors, activin receptors IIA and IIB (ActRIIA and ActRIIB), restricts muscle cell growth through multiple intracellular mechanisms [41,42]. Postnatal expression of myostatin is predominantly restricted to skeletal muscle, highlighting its role in muscle growth and physiology [39].

Skeletal muscle consists of fascicles that are comprised of bundles of myofibers. Each myofiber represents an individual muscle cell, which contains sarcomeres – fundamental cellular units of actin and myostatin filaments that enable muscle contraction and relaxation [44]. Muscle satellite cells proliferate and differentiate into myoblasts, followed by fusion into myotubes and maturation into myofibers, via co-expression of the transcription factors Pax3 and Pax7 and myogenic-regulatory factors, including myogenic factor 5, Mrf4, myogenic differentiation (MyoD), and myogenin (MYOG) [45,46]. Myostatin-mediated loss of skeletal muscle is caused by reduced protein synthesis (inhibition of the Akt/mTOR

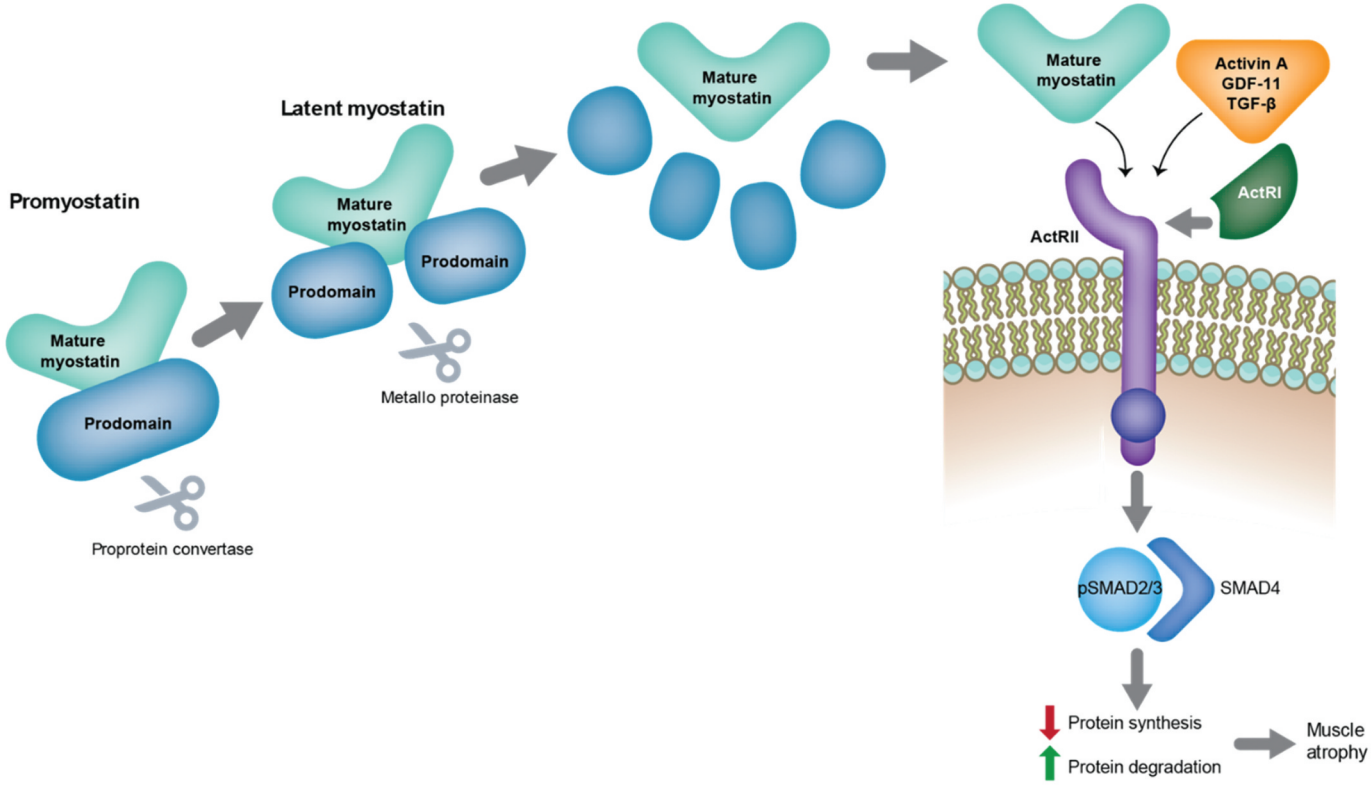

Figure 2. Myostatin activation and signaling mechanisms regulating muscle growth.

Myostatin is synthesized as a precursor polypeptide (promyostatin) composed of a mature, active myostatin dimer and a prodomain that prevents myostatin binding to its target receptors (ActRIIA and ActRIIB). Promyostatin is cleaved by proprotein convertases (e.g., furin protease) to form latent myostatin, an inactive complex of the mature myostatin dimer bound by two remaining prodomains. Latent myostatin is further cleaved by metalloproteinases of the bone morphogenic protein/tolloid family to release mature myostatin, allowing binding to ActRII. Binding of myostatin and other ligands in the TGF-β superfamily (activins, growth differentiation factors, TGF-β) to ActRII leads to the formation of a complex with ActRI and subsequent intracellular SMAD2/SMAD3 phosphorylation and homodimerization. The SMAD2/3 dimer binds SMAD4 and translocates to the nucleus. In muscle, activation of the SMAD2/3 signaling pathway leads to inhibition of protein synthesis and activation of protein degradation pathways, leading to muscle atrophy.

Abbreviations: ActR, activin receptor; GDF-11, growth differentiation factor 11; TGF-β, transforming growth factor-beta.

signaling pathway) and enhanced muscle catabolism (promotion of transcription of atrophy-related genes) [47,48]. In vitro, myostatin inhibits MyoD, MYOG, and Pax7 expression and myoblast differentiation [49–51], suggesting that inhibition of myostatin may increase satellite cell activation. However, in vivo studies suggest a far more limited role, with observed hypertrophy not requiring satellite cells [52,53]. Therefore, while myostatin inhibition drives significant muscle hypertrophy, its effects on myogenesis and satellite cells in vivo are likely limited.

Conditions in which myostatin signaling is blocked, lead to muscle fiber hypertrophy and increased strength. Multiple naturally occurring genetic myostatin-null animals, as well as experimental abrogation of myostatin signaling, manifest muscle hypertrophy without impacting survival or overall health [40,42,54,55]. A child with muscle hypertrophy, increased strength, and good health was found to have a spontaneous mutation impairing myostatin signaling [56]. These experiences have garnered substantial interest in myostatin signaling pathway inhibition as a potential muscle-targeted therapeutic strategy for SMA and other neuromuscular diseases [40,41,55].

2.2. Myostatin inhibition in neuromuscular diseases

Multiple strategies for inhibition of myostatin signaling have been developed and tested across a range of neuromuscular conditions. These include anti-mature myostatin neutralizing antibodies (for Becker [BMD], Duchenne [DMD], facioscapulohumeral [FSHD], and limb girdle muscular dystrophies); an anti-ActRII antibody (inclusion body myositis); ActRII ligand traps (DMD; FSHD); and an anti-mature myostatin adnectin (DMD) [54,57,58]. Despite the expectation that inhibition of myostatin signaling would improve motor function, outcomes from early clinical trials assessing efficacy and safety have generally been disappointing [41,57]. Contributing to the observed shortcomings of previous treatments designed to inhibit myostatin signaling may be nonselectivity. Approaches targeting mature myostatin may cause off-target effects related to the similarity between mature myostatin and growth differentiation factor 11 (GDF-11), another member of the TGF-β superfamily, which share 90% sequence identity within mature signaling domains [57,59]. Similarly, ligand traps, which are nonselective by design, may cause undesirable off-target effects due to effects on other ligands that share the ActRII receptor [60]. KER-065 is a modified ActRII ligand trap that binds myostatin, GDF-11, and activins A and B with reduced binding to bone morphogenic protein 9 (BMP9) to avoid vascular/bleeding events that have occurred with earlier ActRII ligand traps [58,61]. In a phase 1 clinical study, KER-065 was found to be safe and generally well tolerated in healthy participants, with dose-dependent increases in lean body mass and thigh muscle volume, though long-term safety in individuals with neuromuscular disorders remains unknown [61]. These findings support the advancement of KER-065 into a phase 2 trial in patients with DMD and its development for additional rare neuromuscular disorders [61].

In DMD and other muscular dystrophies, muscle atrophy and weakness result from primary effects of protein deficiencies or dysfunction in the muscle fibers themselves [62]. In contrast, muscle in SMA is composed of residual normal muscle fibers alongside denervated, atrophic fibers. The salutary effect of myostatin inhibition observed in normal muscle may thus be extended to the healthy, residually innervated fibers in the muscles of patients with SMA. These healthy innervated fibers are unencumbered by complexities of a primary muscle disease and are thus an attractive target for treatments that can enhance muscle size and strength [4,5,63].

Currently, 3 treatments designed to inhibit the myostatin signaling pathway are in clinical trials for SMA (Table 1) [64]. These treatments have been designed to overcome the drawbacks of previous inhibitors by either selectively targeting immature forms of myostatin or specifically blocking myostatin activation of ActRIIB receptors in muscle [42,65,66], thus minimizing the potential for off-target effects in both muscle and non-muscle tissues. By directly targeting skeletal muscle, these muscle-targeted treatments may help address the significant unmet need of progressive motor function loss and weakness that persists for patients receiving SMN-targeted treatments.

3. Inhibition of the myostatin signaling pathway in the treatment of SMA

3.1. Apitegromab

Apitegromab is a fully human monoclonal antibody that binds selectively and with high affinity to latent myostatin and promyostatin to inhibit cleavage and release of active, mature myostatin, and its binding to ActRII (Figure 3) [42,67]. The strategy of targeting the larger immature forms of myostatin enables greater specificity, as the myostatin prodomain shares a much lower sequence identity with the GDF-11 prodomain (52%) compared to that of the mature myostatin/GDF-11 sequences (90%) [59]. This selectivity sustains efficacy while decreasing potential safety concerns due to off-target activity [42,60,68]. An important mechanistic feature is that apitegromab-bound inactive latent myostatin is released into the circulation, thus providing a measurable intermediary of target engagement. In preclinical studies, apitegromab enhanced muscle mass and function in in vitro preparations, healthy mice, and mouse models of muscle atrophy [42]. In the SMNΔ7 mouse model of SMA, apitegromab was associated with increased muscle mass and function when coadministered with the SMN protein upregulator SMN-C1 compared with SMN-C1 administration alone [69]. Benefits of apitegromab were observed whether SMN-C1 began 1 or 24 days postnatally, suggesting therapeutic potential in SMA regardless of when SMN-targeted treatment is initiated.

In a phase 1 study of healthy adults, apitegromab demonstrated robust target engagement, as indicated by increased serum latent myostatin concentration, and a favorable safety and tolerability profile [70]. Subsequently, apitegromab was evaluated in the phase 2 (TOPAZ) and phase 3 (SAPPHIRE) clinical studies. TOPAZ (NCT03921528) was a parallel, active treatment study designed to assess the efficacy and safety of intravenous apitegromab in patients aged 2–21 years with Type 2 or 3 SMA

Table 1. Myostatin signaling pathway inhibitors for the treatment of SMA.

Treatment	Apitegromab [9,42,67,71,77,79,80]	Taldefgrobep alfa [66,82,83]	Emugrobart (GYM329) [65,85]
Manufacturer	Scholar Rock	Biohaven	Roche
Mechanism of action	Fully human monoclonal antibody that binds to promyostatin and latent myostatin with high selectivity, preventing release and activation of mature myostatin	Fully human adnectin that binds mature myostatin/GDF-11, prevents formation of the myostatin/ActRII complex, and inhibits activity of ActRII ligands	Humanized monoclonal antibody that binds to promyostatin and latent myostatin; 'sweeping' action reduces latent and mature myostatin in plasma
Key clinical trials	Phase 2 TOPAZ (NCT03921528) Phase 3 SAPPHIRE (NCT05156320) Long-term extension ONYX (NCT05626855)	Phase 3 RESILIENT (NCT05337553)	Phase 2/3 MANATEE (NCT05115110)
Patient enrollment and age range	TOPAZ: $N = 58$, aged 2–21 years SAPPHIRE: $N = 188$, aged ≥2 years ONYX: $N = 238$, aged ≥2 years	$N = 269$, aged 4–21 years	$N \approx 259$; Part 1: Cohorts A, B, D, aged 5–10 years; Cohort C, aged 2–4 years Part 2: aged 2–25 years
Primary endpoint	TOPAZ: Cohort 1: Change from baseline in RHS total score at week 52 Cohort 2,3: Change from baseline in HFMSE total score at week 52 SAPPHIRE: Change from baseline in HFMSE total score at week 52 ONYX: Long-term safety and tolerability	Change from baseline in MFM32 total score at week 48	Part 1: Safety, tolerability, efficacy, and PK/PD Part 2: Change from baseline in RHS total score at week 72
Concomitant treatment	TOPAZ: Current nusinersen SAPPHIRE: Current nusinersen or risdiplam	Current nusinersen or risdiplam and/or history of onasemnogene abeparvovec-xioi	Current risdiplam and/or history of onasemnogene abeparvovec-xioi
Delivery route	Intravenous infusion	Subcutaneous injection	Subcutaneous injection
Dosing frequency	Once every 4 weeks	Once weekly	Once every 4 weeks
Clinical trials status	TOPAZ: Completed February 28, 2024 SAPPHIRE: Completed December 18, 2024 ONYX: Active, not recruiting; estimated completion May 2029 OPAL: Active, recruiting	RESILIENT: Active, not recruiting; estimated completion January 2026	MANATEE: Active, not recruiting; estimated completion February 2029
Clinical trials outcomes	**TOPAZ**: Primary endpoint met. Cohort 1 mean RHS score change from baseline at 12 months of −0.4 (apitegromab 20 mg/kg alone) and −0.3 (apitegromab 20 mg/kg with nusinersen) points; Cohort 2 mean HFMSE score change from baseline at 12 months of 0.6 points; Cohort 3 mean HFMSE score change from baseline at 12 months of 5.3 (apitegromab 2 mg/kg with nusinersen) and 7.1 (apitegromab 20 mg/kg with nusinersen) points. **SAPPHIRE**: Primary endpoint met. Least squares mean difference in HFMSE change from baseline at 12 months of 1.8 points for apitegromab (combined doses) versus SMN-targeted treatment alone (least squares mean 0.6 vs − 1.2, respectively; $p = 0.0192$)	**RESILIENT**: Did not meet primary endpoint at interim analysis, though a significant difference was observed between taldefgrobep alfa and placebo on MFM32 at week 48 in the predefined population of patients with measurable free myostatin at baseline (least squares mean difference of 1.4 points in favor of taldefgrobep alfa; $p = 0.02$)	**MANATEE**: No results available

Abbreviations: ActRII, activin receptor type II; GDF-11, growth differentiation factor 11; HFMSE, Hammersmith Functional Motor Scale – Expanded; MFM32, 32-item Motor Function Measure; PD, pharmacodynamics; PK, pharmacokinetics; RHS, Revised Hammersmith Scale; SMA, spinal muscular atrophy; SMN, survival motor neuron.

[67,71]. Patients ($N = 58$) from study sites in the United States and Europe were divided into 2 open-label cohorts of patients aged 5–21 years with ambulatory Type 3 SMA who were receiving nusinersen or were treatment-naïve (cohort 1) and Type 2 SMA or nonambulatory Type 3 SMA receiving nusinersen (cohort 2), and 1 randomized, double-blind, low-high dose assignment cohort in patients aged ≥2 years with Type 2 SMA receiving nusinersen (cohort 3) [67]. Cohorts 1 and 2 were treated with apitegromab 20 mg/kg every 4 weeks, and cohort 3 was treated with apitegromab 2 mg/kg or 20 mg/kg every 4 weeks. The primary efficacy outcome for each cohort was change from baseline in motor function score on the Revised Hammersmith Scale (RHS; cohort 1) or Hammersmith Functional Motor Scale – Expanded (HFMSE; cohorts 2 and 3) at month 12. HFMSE was specifically designed as a valid, sensitive, and reliable assessment of motor function in SMA and is the gold standard assessment used in clinical trials, natural history studies, and often in clinical practice [72,73]. Patients receiving nusinersen had received approximately 9 doses (mean; mean treatment duration of 23.0 months) prior to enrollment [67].

At baseline, mean RHS scores for ambulatory patients (cohort 1) receiving apitegromab alone and apitegromab with nusinersen were 47.6 and 51.3 points, respectively (out of a possible 69) [67]. Mean RHS score changes from baseline at month 12 were −0.4 and −0.3 points, with 27.3% and 16.7% of patients achieving ≥3-point increase, respectively [67]. For patients in cohort 2, cohort 3 (2 mg/kg), and cohort 3 (20 mg/kg), baseline mean HFMSE scores were 22.7, 26.1, and 23.5 points (out of a possible 66), respectively [67]. At month 12, mean HFMSE changes from baseline were 0.6, 5.3, and 7.1 points. An HFMSE score increase of ≥3 points was achieved by 28.6% of patients in cohort 2 and 55.6% and 62.5% of patients in cohort 3 receiving apitegromab 2 mg/kg and 20 mg/kg, respectively. Apitegromab

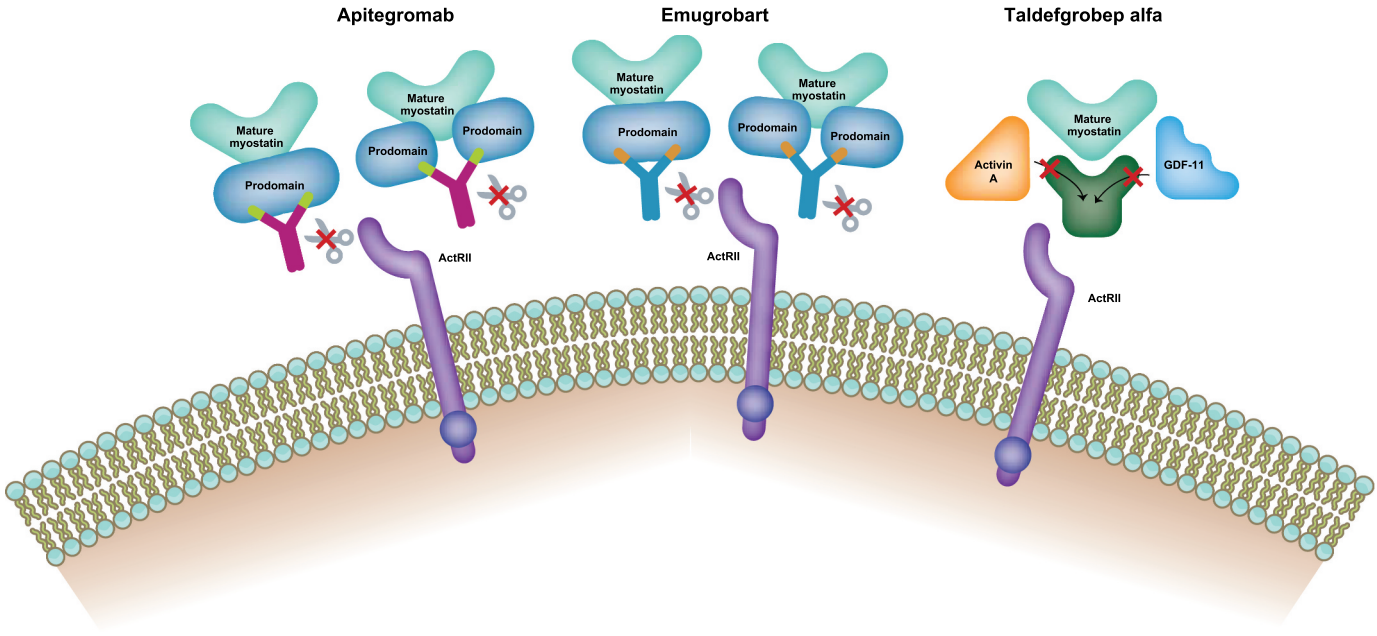

Figure 3. Myostatin signaling pathway inhibitors in development for SMA and other neuromuscular disorders.

Apitegromab is a human monoclonal antibody that binds promyostatin and latent myostatin to prevent release and activation of mature myostatin. Emugrobart is a human monoclonal antibody that binds promyostatin and latent myostatin to prevent release and activation of mature myostatin. Taldefgrobep alfa is a human adnectin fusion protein that binds mature myostatin and GDF-11 to prevent formation of the myostatin/activin receptor complex.

Abbreviations: ActR, activin receptor; GDF-11, growth differentiation factor 11; SMA, spinal muscular atrophy.

demonstrated a favorable safety profile at all doses, with incidence and severity of adverse events (AEs) consistent with the underlying SMA patient population and treatment with nusinersen.

Patients who completed TOPAZ could continue apitegromab treatment in 3 sequential 12-month extensions, during which all patients received apitegromab 20 mg/kg [74]. For nonambulatory patients (cohorts 2 and 3), who demonstrated notable motor improvements in the parent study, motor function outcomes showed sustained improvement across 48 months of treatment. Changes from baseline in HFMSE and Revised Upper Limb Module (RULM) scores were 5.3 and 3.6 points, respectively, after censoring data postsurgery for patients who underwent scoliosis surgery. No new safety findings were identified during the final extension period. In qualitative interviews performed after the first extension period (24 months of apitegromab treatment total), surveyed patients and caregivers ($N = 12$) reported decreased severity of SMA symptoms, particularly with respect to muscle weakness, fatigue, and balance issues, and no reported increases in severity of any symptom [75]. Patients achieved new motor skills, and both patients and caregivers reported decreased impact of SMA on daily activities, physical functioning, dependency, and social activities. Collectively, data from TOPAZ are consistent with findings that improvements in motor function in SMA are correlated with improvements in patients' levels of independence and both patients' and caregivers' health-related quality of life [76].

The phase 3 SAPPHIRE study (NCT05156320) was a randomized, double-blind study evaluating the efficacy and safety of intravenous apitegromab compared with placebo in nonambulatory patients aged 2–21 years with Type 2 or 3 SMA receiving nusinersen or risdiplam [9,77]. Patients aged 2–12 years were randomized (1:1:1) to receive apitegromab 10 mg/kg, apitegromab 20 mg/kg, or SMN-targeted treatment alone (placebo) every 4 weeks. Older patients aged 13–21 years were randomized (2:1) to receive apitegromab 20 mg/kg or placebo every 4 weeks. The primary efficacy outcome was change from baseline in HFMSE total score at 12 months in the population aged 2–12 years. SAPPHIRE enrolled 188 patients with a mean (min-max) age of 9 (2–21) years for the overall population; mean (min-max) age was 8 (2–12) for the population aged 2–12 years and 16 (13–21) for the population aged 13–21 years. At baseline, mean duration of nusinersen treatment in the overall study population (2–21 years) was 5 and 6 years in the groups receiving apitegromab and placebo, respectively, and mean duration of risdiplam treatment was 3 years in both groups. Mean baseline HFMSE total scores for the overall study population (2–21 years) were 24.7 and 27.0 for patients receiving apitegromab and placebo, respectively, far below the maximum possible score of 66, recapitulating the unmet need of patients with SMA receiving SMN-targeted treatment.

After the 12-month treatment period, the primary endpoint of the study was met, with a least squares mean difference in HFMSE change from baseline of 1.8 points for the combined apitegromab 10 mg/kg and 20 mg/kg doses versus placebo (least squares mean, apitegromab 0.6 and placebo −1.2; $p = 0.0192$) in patients aged 2–12 years [9,78]. Additionally, apitegromab treatment was associated with threefold higher odds of achieving ≥3-point increase in HFMSE score and numerically greater improvements in RULM scores and World Health Organization motor milestones than with placebo [9]. Across

the entire study population (aged 2–21 years), the least squares mean difference from baseline was also 1.8 points in favor of apitegromab versus placebo (least squares mean, 1.1 and −0.7, respectively; nominal $p = 0.0089$) [78]. SAPPHIRE confirmed the favorable safety profile of apitegromab observed in TOPAZ, as the incidence and severity of AEs were similar in the combined apitegromab and placebo groups and were generally consistent with underlying SMA and SMN-targeted treatment, and no new safety concerns were identified [9]. Pharmacokinetic assessment demonstrated dose-proportional exposure increases in patients receiving apitegromab, though concentrations of total latent myostatin with both doses were superimposable, indicating target saturation at 10 mg/kg. Consistent with this, efficacy and safety profiles were similar between the two doses evaluated. The similar efficacy, safety, and superimposable pharmacodynamic profiles observed with the two doses indicate that the benefit/risk profile is optimized with the 10 mg/kg dose [9].

Longer-term apitegromab efficacy and safety continue to be assessed in patients who completed TOPAZ or SAPPHIRE and enrolled in the ongoing ONYX extension study (NCT05626855) [79]. The ongoing OPAL study (NCT07047144) is designed to assess apitegromab pharmacokinetics/pharmacodynamics, efficacy, safety, and tolerability in patients aged <2 years who have delayed motor milestones for their age attributed to SMA or a Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders score of <55 [80]. OPAL is also expanding the patient population receiving apitegromab to include patients who have received onasemnogene abeparvovec-xioi. Data on safety and tolerability of apitegromab in patients ≥2 years of age and receiving SMN-targeted therapy, including onasemnogene abeparvovec-xioi, are additionally being collected as part of an ongoing apitegromab Expanded Access Program (EAP; NCT06877689) [81].

3.2. Taldefgrobep alfa

Taldefgrobep alfa is a fully human adnectin, an engineered recombinant protein that binds mature myostatin to inhibit myostatin/ActRII complex formation and subsequent downstream signaling. It also demonstrates binding affinity for GDF-11 and acts as a competitive inhibitor of ActRII ligands (myostatin, activin A, GDF-11; Figure 3) [66,82]. In two preclinical studies utilizing the SMNΔ7 mouse model of SMA, taldefgrobep alfa co-administered with SMN-C1 was associated with greater improvements in muscle size, type II muscle fiber size, body weight, and muscle function than SMN-upregulation alone [66].

In two phase 1 clinical studies, taldefgrobep alfa was found to be safe and well tolerated in healthy patients [66]. Dose-dependent increases in serum taldefgrobep alfa were observed, drug-myostatin complexes were detectable for weeks after dosing cessation, and across the range of doses administered, maximum reduction of free myostatin concentration was at least 90% [66]. In a subsequent phase 1/2 study in boys with ambulatory DMD, treatment with taldefgrobep alfa was associated with an increase in limb muscle cross-sectional area from baseline to week 24 of 5.45%, while those on placebo manifested a decrease in muscle cross-sectional area of 0.79%; a similar trend was observed at week 168 [66].

Following the conclusion of the phase 1/2 study, a phase 3 randomized, double-blind, placebo-controlled study (RESILIENT; NCT05337553) was initiated to assess safety and efficacy of taldefgrobep alfa administered subcutaneously once per week in patients with SMA [66,83]. RESILIENT enrolled a broad study population, including ambulatory and nonambulatory patients aged 4–21 years receiving nusinersen or risdiplam or who had received onasemnogene abeparvovec-xioi or any combination of SMN-targeted treatments [66]. Although motor function improvements were observed, the primary endpoint of Motor Function Measure-32 (MFM-32) scale change from baseline at week 48 was missed, though analyses of prespecified subgroups by race and ethnicity demonstrated clinically meaningful MFM-32 improvements at all timepoints [84]. Taldefgrobep alfa was well tolerated, with no treatment-related serious adverse events, and 97% of patients continued into the optional 48-week long-term extension [66,84].

3.3. Emugrobart (GYM329)

Emugrobart is a humanized monoclonal antibody that binds promyostatin and latent myostatin to prevent the release of mature, active myostatin (Figure 3) [65]. Emugrobart incorporates a 'sweeping function' by which the bound antibody/antigen complex is internalized by certain endothelial and immune cells and undergoes dissociation, after which the free myostatin is shuttled for degradation and the free antibody is recycled back to the cell surface for release into the extracellular space and reuse. In preclinical studies, emugrobart demonstrated enhanced muscle strength in mouse models of DMD, aging, and hindlimb suspension-induced atrophy, as well as increased muscle mass in cynomolgus monkeys [65].

Emugrobart is currently being assessed in the two-part phase 2/3 MANATEE study, a randomized, double-blind, placebo-controlled study in patients with SMA aged 2–25 years receiving emugrobart subcutaneously every 4 weeks and risdiplam (NCT05115110) [85]. Primary outcome measures for part 1 (ambulatory patients aged 2–10 years and nonambulatory patients aged 5–10 years) are safety, pharmacokinetics/pharmacodynamics, and change from baseline in thigh/calf muscle contractile area. For part 2 (ambulatory patients aged 2–25 years), the primary outcome measure is change from baseline in RHS total score. MANATEE enrollment is complete, and the study is ongoing. Emugrobart is additionally being assessed in MANOUEVRE (NCT05548556), a phase 2 study evaluating safety and thigh muscle contractile muscle volume in patients with FSHD [86]. MANOUEVRE enrollment is complete, and the study is ongoing.

4. Conclusion

With the arrival of SMN-targeting treatments, the trajectory for individuals with SMA was radically transformed; however, patients continue to experience significant unmet needs.

Targeting muscle via myostatin inhibition represents a unique and potentially impactful pathway to improve motor function outcomes in patients receiving SMN-targeted treatment. Three agents designed to improve muscle size and strength through inhibition of myostatin signaling have been investigated for patients living with SMA. Of these, apitegromab is the only one to demonstrate significant improvements in clinical trial primary endpoints (as of January 2026), warranting consideration of its role in the SMA treatment armamentarium. Additional long-term data and data from diverse patient subpopulations will help inform when, how, and for whom apitegromab and other myostatin pathway inhibitors may provide meaningful benefits.

5. Expert opinion

Muscle strength and motor function are consistently cited as unmet needs reported by individuals with SMA and their caregivers [27,87]. Achievement of new motor function was reported by 89% of adults with SMA as their greatest unmet need, and over half of children and approximately 80% of adults with SMA are nonambulatory [88]. Individuals receiving SMN-targeted treatments may still experience delays in achieving motor milestones and may never achieve levels of motor function equal to age-matched peers without SMA. In one study, over 95% of patients cited muscle weakness and over 40% cited fatigue as the least improved with ongoing SMN-targeted treatments [27]. Long-term clinical trial data demonstrate that, for some patients, early improvements in HFMSE scores with SMN-targeted treatments may plateau within the first 2–5 years of treatment and may slowly return to pretreatment levels [10,11]. Owing to the progressive nature of SMA, continued *SMN2*-enhancing treatment may delay, but not prevent, the eventual loss of motor function. Such attenuation of early motor function gains may be especially evident during periods of accelerated growth (e.g., puberty) or weight gain and with the evolution of scoliosis and joint contractures, which are common in nonambulatory 'sitters.'

In SMA, there is an opportunity to preserve and strengthen muscles that are partly or completely healthy. Atrophied muscles can be rescued to a degree with SMN-targeted treatment and may be further enhanced with a muscle-targeted treatment via myostatin inhibition. The development of agents to inhibit the myostatin signaling pathway represents a significant step forward in the SMA treatment landscape, and targeting neurons with SMN-targeted treatment and muscle via myostatin pathway inhibition represents a more comprehensive approach to treat patients.

Younger patient age and less severe disease at the initiation of SMN-targeted treatment are associated with better motor function outcomes [89]. Consensus for the use of SMN-targeted treatments in newly diagnosed patients, especially those with two *SMN2* copies, is that treatment should be initiated as early as possible to forestall motor neuron degeneration [89]. However, regardless of the timing of treatment initiation, patients may perceive suboptimal results with SMN-targeted treatment. In these cases, patients often switch to a different SMN-targeted treatment or add treatments to achieve greater motor function. In clinical trials, apitegromab demonstrated efficacy across a broad range of patient ages, SMA severity, and duration of SMN-targeted treatment. The SAPPHIRE trial represents the first placebo-controlled clinical trial demonstrating functional improvements with selective myostatin inhibition in any disease, and long-term data from TOPAZ demonstrate sustained motor function improvements with apitegromab over 48 months with a favorable safety/tolerability profile [74]. However, as TOPAZ was an open-label study with no internal control group, the trajectory of untreated patients with characteristics similar to those receiving apitegromab remains unknown.

Furthermore, infants with two *SMN2* copies treated early after diagnosis via newborn screening may still be delayed in achieving motor milestones, indicative of prenatal loss of motor neurons. Thus, outcomes with treatment may be greatest in infants, before a significant degree of muscle atrophy and replacement with fat and fibrotic tissue has occurred. Findings from the OPAL trial of apitegromab will provide important insight into the impact of muscle-targeted treatment in patients under 2 years old.

For patients diagnosed with SMA at a young age or via newborn screening, treatment goals focus on the acquisition of motor milestones. For adults, stabilization of motor function is a meaningful outcome, especially for those who have experienced some functional decline. The 48-month data on apitegromab from the TOPAZ study suggest promise for long-term safety and efficacy of muscle-targeted treatment, although patient access could be a limiting factor. The potential to offset the natural progression of SMA by 1–3 points on the HFMSE would represent an important benefit, as any HFMSE improvement is considered by caregivers as meaningful, and 75% of caregivers would consider participation in a clinical trial if there was a possibility of their child achieving only one additional ability as assessed by the HFMSE [90].

As with any SMA treatment, decision-making around initiation of muscle-targeted treatment must consider individual patient characteristics, treatment history, and potential treatment risks versus benefits. It is noteworthy that, in recent clinical trials, myostatin pathway inhibitors have demonstrated favorable safety and tolerability. For example, apitegromab and taldefgrobep alfa were well tolerated among patients receiving ongoing SMN-targeted treatment. In TOPAZ, ambulatory patients who were not receiving SMN-targeted treatment saw minimal changes in motor function with apitegromab monotherapy; however, the study enrolled a small number of these patients and additional data are needed to understand the efficacy of muscle-targeted treatment in patients not concurrently treated with SMN-targeted treatment [67]. In general, it appears reasonable that muscle-targeted treatment could be initiated concurrently with SMN-targeted treatment, particularly for patients with Type 2 SMA or who have progressive SMA symptoms. Intravenous administration may present a great burden for newborn or infant patients, though this could be reduced with subcutaneously administered formulations.

The development pipeline for muscle-targeted treatments for SMA includes other myostatin inhibitors

(e.g., emugrobart) and drugs targeting the neuromuscular junction [83,85,91]. While several of these agents have demonstrated motor function improvements, additional clinical trial data are needed to understand their potential role in the SMA treatment landscape and meeting the unmet needs of patients receiving SMN-targeted treatments.

Adolescents and adults represent the SMA patient population with the greatest unmet need, and risk losing abilities such as walking and/or activities of daily living. Adult patients often report limited benefits with nusinersen and risdiplam, and although gene therapy (onasemnogene abeparvovec-xioi) has not been available to them in the past, the recent approval of onasemnogene abeparvovec-brve represents a treatment opportunity that remains to be explored. Stabilization and maintenance of motor function are reasonable goals but may not be sufficient to meet patient expectations. For example, ambulatory patients' goal may be to maintain ambulation, whereas younger patients and their caregivers early in their treatment journey may have expectations of achieving new motor milestones not previously attained. In addition, many aspects of improvement are not captured by motor function scales, such as decreased fatigue/fatigability, stronger voice and cough, and decreased frequency of hospitalization. In a small subset of patients and caregivers from the TOPAZ trial, patients/caregivers perceived decreased severity of breathing, coughing/clearing secretions, and feeding/swallowing symptoms with 24 months of apitegromab treatment [75]. Additional clinical data are needed to understand the potential benefits of muscle-targeted treatment for bulbar function, respiration, fatigue, or activities of daily living.

Similarly, data are needed to understand both the mechanisms by which inhibition of myostatin signaling enhance muscle function and the potential for treatments that inhibit myostatin signaling to mitigate non-skeletal muscle pathology in SMA. Cardiac pathology and dysfunction are non-neuromuscular manifestations of severe SMA; in one study, congenital structural lesions were noted in 75% of infants with type 1 SMA and one *SMN2* copy [16,92]. In both mouse models and patients with SMA, cardiac alterations include decreased left ventricle mass that may reflect downstream effects of SMN deficiency and can occur independently of motor neuron or skeletal muscle pathology [93–95]. Myostatin is expressed in the heart to a lower extent than in the skeletal muscle, but preclinical data is conflicting on whether genetic loss of myostatin leads to cardiac hypertrophy [96–98]. Pharmacologic inhibition of myostatin is likely distinct from genetic null animals and prior preclinical studies have demonstrated no alterations in the heart with myostatin inhibition [99]. Importantly, there have been no reports of myocardial hypertrophy following myostatin inhibition in any published clinical trial data discussed in this review [9,66,67,70,82,100]. Moreover, extensive cardiac safety monitoring in the clinical trials for apitegromab (TOPAZ and SAPPHIRE) has demonstrated that inhibiting myostatin activation with the muscle-targeted treatment does not lead to meaningful changes in vital signs or cardiac safety parameters following several years of dosing.

For most adults, self-care and independence are key treatment goals, yet quality of life issues such as continuing to operate a motorized wheelchair or lifting a glass from a table, fall outside motor function scales. Although these benefits are measurable, and patient perception of benefit is essential, there is a challenge selecting which quality of life measure to apply. Across patient ages, fatigue is a frequently reported unmet need, yet it is difficult to objectively measure. Furthermore, changes in functional scale scores that might be considered clinically irrelevant may be perceived as significant by the patients themselves [101]. Development and adoption of patient-reported outcomes measures and methods to measure fatigue (eg, magneto-inertial sensors) are needed to fully assess patient perception of the benefits of muscle-targeted treatment.

Important considerations for the implementation of muscle-targeted treatment include patient age, developmental status, age at symptom manifestation, and level of functional ability prior to treatment initiation. Although data are needed, it is reasonable to predict that patients presenting with symptoms earlier in life and those with symptoms that persist despite SMN-targeted treatment may see the greatest benefits. Among older patients, for whom the benefits of SMN-targeted treatment alone may be more limited, muscle-targeted treatment may help sustain or improve endurance, though the capacity for muscle growth in older patients with SMA is an open question that warrants study. An additional consideration is how the patient's level of muscle strength may impact the effectiveness of myostatin signaling pathway inhibition. One might expect that the more muscle there is to preserve, the greater the potential benefit, though additional data are needed to confirm this. Identification of patient archetypes will inform decisions around muscle-targeted treatment, though more data are needed.

Regardless of individual characteristics, people living with SMA cannot afford to 'wait to fail' before initiating or adding treatments. There is an urgency to treat to mitigate additional neurodegeneration and muscle atrophy. Unfortunately, the high price of current SMN-targeted treatments has created accessibility concerns. The dual-modality approach of a muscle-targeted treatment and an SMN-targeted treatment regimen may potentially cause additional accessibility concerns.

Treatment compliance in the real world is not the same as in clinical trials; compliance to treatment with myostatin signaling pathway inhibitors will be closely tied to treatment burden and patients' perception of improvement. The majority of patients in the TOPAZ (84.5%) and SAPPHIRE (98%) trials of apitegromab and the RESILIENT trial of taldefgrobep alfa opted to continue treatment in their long-term extension studies [9,84,100], despite any potential hesitation that patients and caregivers may have had around monthly/weekly treatments, suggesting that treatment benefits, or perhaps just the fear of losing function, outweigh perceived treatment burden. Regardless, implementation of muscle-targeted treatment in clinical practice will require consideration of several operational considerations. For apitegromab treatment, engagement with an infusion center or home infusion service

for treatment delivery will incur travel and/or scheduling burden to patients and caregivers, as well as the need for additional clinical team resources to manage payer approvals, treatment orders, communication with patients and third-party infusion providers, and patient management. Formulations that can be administered subcutaneously would significantly reduce these challenges.

Despite these challenges, the persistent unmet needs of patients with SMA, particularly among adults and older adolescents, support the adoption of treatment with muscle-targeted treatments. With the continued demonstration of safety, added clinical benefit, and patient acceptance, these treatments will provide a valuable complement to SMN-targeted treatments for SMA. Effectively setting patient expectations will be critical to the acceptance of muscle-targeted treatment. In the SAPPHIRE trial, the difference in motor function outcomes between SMN-targeted treatment alone and apitegromab was driven largely by a decline among patients receiving SMN-targeted treatment alone; in contrast, patients receiving both SMN-targeted and muscle-targeted treatment had functional improvement. Thus, the concept of decline, even when on SMN-targeted treatment, must be explained and understood to provide context for the potential benefit of muscle-targeted treatment. Expectations can additionally be adjusted based on an increased understanding of responses to muscle-targeted treatment based on patient and SMA disease variables. To avoid overpromising results that have not been observed or are unknown, benefit expectations should be framed within threshold and ceiling responses to treatment observed in clinical trials in order to prevent frustration or treatment discontinuation if unrealistic expectations are not met. Given the heterogeneity of the SMA patient population, these thresholds or ceiling responses will likely be affected by patient age and, separately, functional status or severity of disease at baseline. Clear communication about eligibility for muscle-targeted treatment will be necessary, as it may not be appropriate for every patient, and regulatory approval may be limited to certain patient populations.

Patients and caregivers in the SMA community are well connected and may be interested in learning about and taking advantage of all available treatments. In the United States, approximately 29% of children and adults with SMA who have not participated in a clinical trial, have received 2 or more Food and Drug Administration-approved SMN-targeted treatments, and almost half of individuals receiving 1 approved treatment report interest in receiving an additional treatment [88]. Although there is preliminary evidence of a potential benefit of initiating nusinersen in infants and children with suboptimal clinical response to onasemnogene abeparvovec-xioi [102], clinical trials have not provided definitive evidence in favor of any combination of two SMN-targeted treatments. In the SAPPHIRE trial, significantly greater motor function outcomes were observed with apitegromab and SMN-targeted treatment over SMN-targeted treatment alone, providing rationale for a dual-modality approach that capitalizes on complementary motor neuron-targeted and muscle-targeted treatment. With the development of investigational therapies targeting the neuromuscular junction, there may someday be three potential mechanisms of action to leverage in the treatment of SMA. Additional data are needed to fully understand the long-term prospects for muscle-targeted treatment and relative benefits of different treatment combinations for different patient populations.

Given the expansion of treatment options for SMA, educating patients, caregivers, and their clinical teams on the development and clinical trial outcomes of muscle-targeted treatments is of ever-increasing importance. For patients and caregivers, websites of companies developing investigational muscle-targeted treatments provide clinical trial data and enrollment information [103–105], and advocacy groups serve as vital educational resources. In the United States, Cure SMA is a primary source of information through their website, live educational webinars, educational videos on social media, outreach programs, and their Annual SMA Conference [106]; SMA Europe plays an equivalent role as the primary patient advocacy group in Europe [107]. The Muscular Dystrophy Association (MDA) also offers patient and caregiver outreach programs [108]. For the members of a patient's clinical care team, information disseminated in presentations, posters, and manuscripts can be augmented via educational sessions at annual conferences such as the American Academy of Neurology Annual Meeting, the Cure SMA Annual SMA Research & Clinical Care Meeting, the Muscular Dystrophy Clinical & Scientific Conference, the Child Neurology Society Annual Meeting, and World Muscle Society Congress. Continued engagement of patients, caregivers, and clinical care providers is essential for educating on the critical role of muscle in SMA and the potential benefits of directly targeting muscle with treatments that inhibit the myostatin signaling pathway.

As the SMN treatment landscape evolves and adoption of newborn screening for SMA continues to increase worldwide, SMA treatment will undergo many significant changes. Just as the introduction of SMN-targeted treatments marked a sea change in the SMA treatment landscape, muscle-targeted treatment via myostatin signaling pathway inhibition may represent the next significant advance. Meanwhile, treatment options for SMA continue to evolve, new formulations of existing SMN-targeted treatments are in development (e.g., high-dose nusinersen) or have been approved (onasemnogene abeparvovec-brve), and new mechanisms of action are being explored (e.g., targeting the neuromuscular junction). Given this rapid evolution and remaining knowledge gaps regarding SMA treatments in various patient populations, continued research in both controlled clinical trial and real-world settings is needed to broaden our knowledge and optimize patient outcomes. To this end, for example, an ongoing EAP will provide additional insights into the real-world application and benefits of apitegromab in a broad population of children and adults living with SMA [109]. Greater knowledge and experience will make it possible to individualize treatment(s) based on patient characteristics. Treatment initiation will also continue to occur earlier in life, and increasingly presymptomatically, and a dual-modality approach that targets motor neurons and muscle will become the norm for an increasing number of patients. Biomarkers and wearable sensors will

allow for individualized follow-up, and nonpharmaceutical approaches, such as innovative rehabilitation and spine stimulation, will continue to be developed to advance patient outcomes. Moreover, improvements in patient-reported outcomes measures will allow for greater understanding and treatment of endurance, fatigue, and other unmet needs not currently addressed by functional motor scales.

The landscape of enhancing muscle function through inhibition of myostatin signaling continues to develop, with additional preclinical approaches being explored to identify new candidate mechanisms of myostatin inhibition. Short peptide inhibitors and self-inhibitory peptides have demonstrated promise in blocking myostatin–ActRII interactions, and in silico approaches may be used to model optimization of current myostatin inhibitors and enhancement of natural compounds, and to identify small molecules and other new compounds with the potential to inhibit myostatin activity [45,110,111].

Adoption of myostatin signaling pathway inhibitors that target muscle will be facilitated by additional data on long-term safety, off-target adverse events, treatment response, and durability of benefit (e.g., the ONYX and RESILIENT long-term extension trials) in different populations, such as younger patients (e.g., the OPAL trial of apitegromab) and adults with SMA (eg, the apitegromab EAP), and with heretofore untested dual therapy options (eg, emugrobart and risdiplam in MANATEE; apitegromab and onasemnogene abeparvovec-xioi in OPAL and the apitegromab EAP). Development will be further supported by understanding their effects on muscle mass and its relationship to benefits in strength, function, and endurance, as well as the creation of valid and reliable patient-reported outcome measures. Continued development of subcutaneous and other patient-friendly formulations will drive additional acceptance of muscle-targeted treatment for SMA.

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