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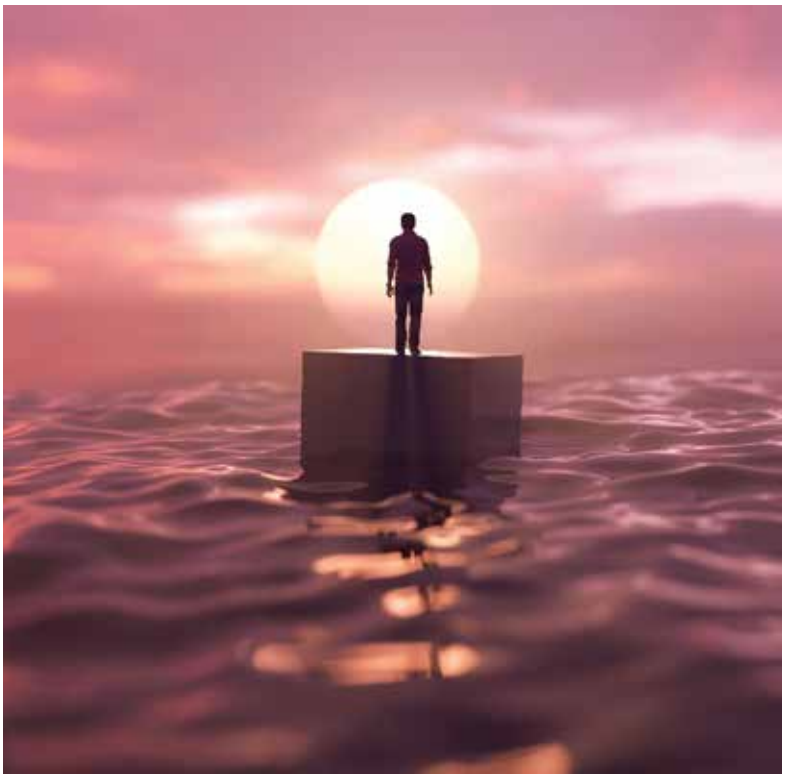

The introductions of Spinraza and Zolgensma in SMA offer new insights into how to address neurodegenerative diseases. But more real-world evidence is needed.

BY ALESSIA DEGLINCERTI, FRANK BOROWSKY AND MARK RATNER

With the approval of two disease modifying agents, some patients with SMA are becoming healthier and their medical needs are shifting.

A new natural course of the disease is emerging, with a larger population of individuals having stabilized disease. But the extent of residual issues is not yet known – a picture that will only come into focus over time.

So what? This evolution is influencing the clinical development and implementation of new treatments, leading to greater opportunity for franchises that include supportive therapies. SMA could become a blueprint for development and market access for other neurological diseases.

The landmark FDA approval of Novartis AG's Zolgensma (onasemnogene abeparvovec-xioi) in May 2019 shook the biopharma world in several ways including its price ($2.1m per dose) and as important, the very small data set on which the FDA primarily based its decision – an ongoing open-label single arm trial of 21 infantile-onset patients with spinal muscular atrophy (SMA) under two years old. Biogen Inc.'s Spinraza (nusinersen) had already been approved in SMA in December 2016.

As disease-modifying therapies, these compounds are a rarity in the field of neuromuscular diseases of genetic origin. They are also at the core of a fascinating, ongoing real-world case study in how the natural course of a disease can change rapidly. How companies' SMA drug development and market access strategies evolve, both in terms of new disease-modifying agents and supportive therapies that address residual symptoms, could become a blueprint for other neuromuscular diseases like Duchenne's Muscular Dystrophy (DMD) or Huntington's Disease.

Changing The Natural Course Of SMA

SMA is a genetic disease caused by an absence of or defect in the SMN1 gene, which encodes the survival motor neuron (SMN) protein. A back-up gene, SMN2, also produces SMN, although at lower levels (approximately 10-20% of what SMN1 makes) due to alternative splicing. Zolgensma is an adeno-associated virus vector-based gene therapy that delivers a fully functional copy of human SMN gene into the target motor neuron cells. Spinraza and also Roche's risdiplam, a small molecule in late-stage clinical trials licensed from PTC Therapeutics Inc., modulate splicing of SMN2 so that it produces levels of full-length SMN protein similar to that of SMN1.

Exhibit 1

Disease-Modifying Therapies Are Favorably Shifting The Natural Course of SMA

	TYPE 1	TYPE 2	TYPE 3	TYPE 4
Symptoms	Severe muscle weakness; does not achieve milestones, including sitting Trouble breathing, coughing and swallowing	Delays in achieving milestones; some can sit up without assistance whereas others need support General weakness, difficulty coughing, joint contractures	Can stand and walk but develops increasingly limited mobility Difficulty running, climbing steps, or rising from a chair	Similar symptoms to type 3 (progressive muscle weakness), but with later onset
Prognosis	Onset between 0 and 6 months with a lifespan of 2 years Mortality often associated with pulmonary complications	Onset between 6 and 18 months Life expectancy is ~30 years old, with mortality often due to respiratory impairment	Onset between 2 and 17 years old Normal or near-normal life span but ~50% become wheelchair dependent	Onset during adulthood –typically after 20 years old Normal life span

SOURCE: Bionest Partners

SMA falls into four categories based on a combination of age and severity (see *Exhibit 1*). The hope is that disease-modifying therapies can lessen the severity of the disease: type 1s may become more like type 2s, and similarly up the chain to 3s and 4s.

Before Spinraza, and now Zolgensma, infants with SMA were often unable to move by the time they were six months old, needing ventilation and by the time they were two, a feeding tube. They often did not live past two years old – or with rigorous intervention, maybe to five years old. "Now, we have kids that are walking sometimes, and certainly not ending up on ventilators, who are speaking and able to feed themselves," said David Rind, chief medical officer of the the Institute for Clinical and Economic Review (ICER), whose amended *Final Evidence Report* from May 2019 found that Zolgensma can be reasonably considered cost-effective even at its $2.1m price. "That's an enormous change."

What happened with Zolgensma was also unusual, Rind said – to have Phase I trial results results so dramatic that it was obvious the drug worked. The only other treatments Rind could recall having that level of dramatic effect were protease inhibitors in HIV (the triple therapy) and, to some extent, Novartis's Gleevec (imatinib) in chronic myelogenous leukemia. "We don't have many events like that in medicine where suddenly a treatment comes along and the degree of change is so large that it's obvious, even with a small number of patients, that it is something patients should be getting," he said.

"We are inevitably seeing a dramatic change in the time course of new cases of the disease," added John Day, director of the neuromuscular disorders program at the Stanford Neuroscience Health Center. But for prevalent cases already in existence, it is more of a leveling out of the disease course so that individuals with SMA are no longer progressing.

"These are amazingly effective treatments but they can't significantly reverse profound disability," Day said. "We are increasing life span but in a sense increasing the morbidity associated with the disease because very few of these children will be actually physically normal or typical." After treatment, already-symptomatic patients will have some residual degree of motor neuron loss and attendant weakness and fatigue. The earliest onset features are proximal weakness in the lower extremities. "That will continue to be a fairly common element, depending on the age and stage of development," he said. The degree of change will also depend on the level of severity of the disease and the degree to which the patient had been affected before starting treatment.

The Future Treatment Journey

In the discussions leading to the ICER report, there was back-and-forth between Biogen and Novartis over which therapy was getting to all the necessary places to alter production of SMN, as the drugs target different loci in the body. The question points to unknowns around how these drugs will change the natural course of the disease: over what period of time are the effects sustainable, and for which patients? (With Gleevec, for example, its effects ultimately proved not to be as durable as originally hoped.) "We don't really know what the long term looks like for these kids with either therapy," Rind said.

New morbidities may also emerge, although presently there is no concrete evidence of this. That is because even with a static disease process, as a child matures, the growth in body weight, height and bone length increase the strain on muscles. "As you get taller there may very well be a functional decline even though there is no ongoing disease process," Day said, not unlike a post-polio syndrome.

"The challenge we and others will face

in this field is what is the new natural history of the disease," offered Scott Jordan, senior vice president, new product planning and commercial development, at Cytokinetics Inc. "With these new SMN-directed therapies, I think we are looking at a change from an approach of characterizing patients based on their genotype to one centered based on their phenotype," he said, perhaps measured by meeting milestones over time instead of looking at the number of functional copies of SMN2, age of disease onset, or assessments based on the ability to sit without support, stand or walk.

"It remains to be seen what the new disease is," added C. Frank Bennett, senior vice president, research, at Ionis Pharmaceuticals Inc., which discovered Spinraza and licensed the asset to Biogen as part of the companies' broad strategic partnership around the use of antisense oligonucleotides to treat neurological diseases.

The ability to upregulate SMN production to stop disease progression, and delineating this new natural course of disease, opens the door for development of novel supportive treatments, today focused on therapies that address the decline in muscle function that SMA causes. Targeting muscle function is "a very appropriate approach now that we believe the underlying disease process is under control," Day said. He is also optimistic there might be ways to increase energy utilization through addressing the metabolic side of muscle function, although that work is still early. These strategies are aimed at improving the health, function and longevity of the depleted pool of motor neurons in patients with SMA, as even with disease stabilization, that pool of motor neurons remains reduced. Muscle regeneration could also address the deficit, but again, research in this area is early-stage.

Cytokinetics has been developing reldesemtiv, a next-generation skeletal muscle compound, in SMA in partnership with Astellas Pharma Inc. It is intended to slow the rate of calcium release from the regulatory troponin complex of fast skeletal muscle fibers to improve muscle function and physical performance. In 2018, Cytokinetics announced results from a Phase II study of the compound in SMA that showed increases in the Six Minute Walk as well as a measure of respiratory muscle strength, but failed to demonstrate differences as compared with placebo across several other assessments commonly used in SMA. "We are evaluating the best way to move forward with reldesemtiv," Jordan said.

According to Day, if reldesemtiv increases muscle efficiency or force production by 20% or 25%, it could be a very valuable addition to any of the SMN upregulating treatments. Increasing the efficiency of muscle force production means it would take less effort and energy utilization to generate the required force, which should improve stamina.

Cytokinetics's approach is based on modulating the biology of muscle contraction. Alternatively, several companies are developing myostatin inhibitors, which could allow muscle to generate more force per action potential, allowing individuals to do more work without having to increase neuronal activity, which is depleted in SMA.

The most advanced myostatin inhibitor is SRK-015 from Scholar Rock Holding Corp. Myostatin is a preferential regulator of fast twitch muscle fibers (type II muscle, which fatigues easily following exertion). In SMA, there is a prominent atrophy and deficit in fast twitch fiber mass and function. "In our view, the logical hypothesis is that in SMA there is prominent atrophy of fast twitch fibers and so the idea is to block myostatin to address the motor deficit," said Yung Chyung, Scholar Rock's CMO.

Myostatin inhibitors may work best in individuals with growth capable muscle, like younger people in SMA. Notably, in SMA the skeletal muscle does not appear to have any intrinsic structural defects, at least in later onset SMA. "That's important because we think if you build fiber mass in an impaired muscle, it is not clear it will translate into meaningful motor functional gains," Chyung said.

Scholar Rock's Phase II trial of SRK-015 is focused on patients with type 2 and 3 disease. Most will have already been receiving Spinraza. "It is our belief that a muscle-directed therapy would complement any SMN directed therapy irrespective of the way they achieved restoration of SMN," Chyung said, whether through gene therapy or a small molecule or antisense drug.

Taken together, the availability of disease-modifying agents with different mechanisms that target different cell populations, the expectation of residual disease for patients already showing symptoms and the promise of muscle-directed supportive therapy suggest that sequencing of treatments and establishing the benefit of combination therapies for different sub-populations will be important future considerations. "One drug for one patient is probably not the wave of the future," said Susan Begelman, vice president, rare disease and neuroscience medical unit, US medical affairs at the Genentech Inc. unit of Roche.

Roche plans to submit risdiplam for approval before the end of the year: On November 11, it announced that the compound met its primary endpoint – change from baseline in an assessment of motor function at year one versus placebo – in a pivotal Phase II/III study. An oral formulation that could be administered on an outpatient basis, it is being tested in pivotal studies enrolling a broad range of SMA patients from presymptomatic up to the age of six. Roche also has an ongoing study looking at individuals on previous treatments, which include the approved disease modifiers and also olesoxime, a neuroprotectant via the acquisition of Trophos SA, on which Roche stopped development in June 2018.

"The way we think about our entry with risdiplam is that there are still quite a few patients who do not have any treatment options or access to any treatment options," Begelman said. An oral drug could be advantageous for older patients. It also could help Roche compete with Spinraza, which is an intrathecal therapy and can be challenging to administer in individuals with scoliosis or spine fusion resulting from SMA.

Similarly, Biogen is testing more convenient dosing schedules for Spinraza: delivering higher doses administered less frequently could be a benefit for older patients. It also has access to a small molecule program aimed at modulating SMN splicing via a 2019 discovery collaboration with Skyhawk Therapeutics Inc.

Understanding which patients should get which treatments and when they

should receive them is critical. Assuring that the best subpopulation is enrolled to be better able to demonstrate benefit will also be a priority. Real-world evidence (RWE) will show longitudinally how patients change over time. But in SMA, those data are limited. That's a challenge, Jordan said, when it comes to doing clinical trials. "What are the appropriate endpoints for ambulatory patients and non-ambulatory patients when we don't know the natural history," he posed, in particular if patients have been treated with the new SMN-directed therapies. "That will complicate clinical trial design."

Assessing outcomes becomes complicated when layering in a therapy where you don't know when a patient is stabilized according to a short-term endpoint measure like the Six Minute Walk, especially as children grow. "The questions are: When does a patient become stable following treatment with these new SMN-directed therapies? And what is the new natural history of the disease?" Jordan said.

Engaging with patients, advocates, regulators and health technology assessment groups can help to direct clinical trial strategy and study design given this evolving natural history – identifying the best outcomes measures important to patients regardless of the natural history, then conducting a study that allows you to look at a patient and make sure you are seeing the benefit associated with a supportive therapy rather than another therapy they may be on or have been treated with historically.

Market Access Considerations

Optimizing clinical design will help determine the range of access to patient populations for both disease-modifying and supportive treatments. Establishing the duration of response of a disease-modifying treatment and the benefit of sustained treatment will also help define the extent of access to certain SMA populations. Eventually, guidelines will emerge.

It is likely that a large number of SMA patients are untreated today. Those with less severe forms of the disease may not have enrolled in clinical trials or may go undiagnosed for some time because of a delayed manifestation. "SMA is not top of mind for a local treating physician, as opposed to say type 1 babies who immediately start to have problems," Begelman said.

Disease stabilization should lead to an increase in the number of people living with what becomes a chronic disorder, who will have to deal with the consequences of adjusting to and managing their various symptoms. Increased awareness could mean more older individuals living with milder forms of SMA will seek (or return to) treatment. Conversely, in some cases, older adults given a clinical diagnosis of SMA without genetic testing are now getting tested and found not to have SMA, Day said.

Indeed, assessing SMA in adults without a genetic diagnosis can be tricky. In studies done at key medical schools evaluating the effect of Spinraza in adults, patients reported a perceived benefit in stamina and more ability to do things, said Bennett, but the clinical measures being used did not capture those. "The challenge is to develop new metrics for adult patients," he said.

It is unclear whether the evolution in SMA care will signal a move away from Centers of Excellence into secondary and tertiary medical practices as the disease stabilizes. "We are a little bit anxious about that," Day said: Especially for the newly diagnosed patients, the concern is that they will likely still need other services such as physical therapy, pulmonology, respiratory therapy or occupational therapy, because of some degree of physical disability. "We want to make sure those are being addressed and attended to, and consequently we are working hard to coordinate with the local providers and pediatricians, at least for the pediatric side of the equation, to make sure all of the chronic care needs are being attended to."

Newborn screening for SMA is gradually spreading throughout the US, with the promise that all newborns will have it in a few years. So, access for presymptomatic and infantile-onset SMA patients is virtually assured. Reimbursement is also a given for these patients. ICER found both Spinraza and Zolgensma clinically effective, and in the case of Zolgensma, cost-effective as well. (The group thought Spinraza was overpriced: "It's very hard for a drug that costs as much as Spinraza year after year to be cost effective," Rind said.)

Still, the high price of these drugs has prompted discussion of new payment models, especially with scant RWE. In the case of Zolgensma, payers have embraced an outcomes-based model, but have shown little interest in the installment plan model proffered at the time of approval.

"In many cases, ICER feels outcomes-based contracts don't accomplish very much," Rind said. "If you have a PCSK9 inhibitor, for example, and you say if somebody has a myocardial infarction or a stroke within the given timeframe, we'll give back money, it's basically like a discount," based on the likelihood the event will occur, he explained. "You might as well just give that discount to people." However, with a $2.1 million one-shot therapy where you are basing the value of that price on the expectation of sustained benefit over decades, an outcomes-based contract potentially makes more sense, he said. "If you've paid with the expectation of long-term benefit and over time it's shown that's not true, you've way overpaid."

The thornier question is what to do when new therapies come along. To date, no studies have been done using two SMN splicing modifiers, leaving open questions of the overall value to a patient of combining them, and how that would be looked at by a payer in terms of cost. "That is one of the challenges today," Begelman said.

If a new disease-modifying drug like risdiplam comes along that's intended to be used in place of or on top of another one, it would have to be used before loss of function occurs, Rind suggested. For add-ons like muscle-directed therapies, in principle there is no reason why they could not be started in tandem with a disease-modifying treatment. But payers may require proof of disease stabilization first.

Building a Neurodegenerative Disease Franchise

Three large biopharmas – Novartis, Biogen and Roche – are aiming to establish disease-modifying SMA franchises (*see Exhibit 2*). Biogen and Roche are also developing therapies to address muscle

Exhibit 2
Overview Of The SMA Pipeline

COMPANY	PRODUCT/PROGRAM	STATUS
Biogen	Spinraza (IV infusion SMN2 upregulator)	Approved 2016
Novartis (AveXix)	Zolgensma (SMN gene therapy)	Approved 2019
Roche/Chugai/PTC Therapeutics	Risdiplam (oral SMN2 upregulator)	Phase III, filing expected 2019
Scholar Rock	SRK-015 (myostatin inhibitor monoclonal antibody)	Phase II
Astellas/Cytokinetics	Reldesemtiv (oral fast skeletal troponin activator)	Phase II
Catalyst/Jazz Pharmaceuticals	Firdapse (oral potassium channel blocker)	Phase II
Novartis	Branaplam (oral SMN2 upregulator)	Phase I/II
Biogen/AliveGen	BIIB110 (Activin receptor IIA/B antagonist protein)	Phase I

SOURCE: Biomedtracker

atrophy, suggesting a portfolio strategy. Roche is planning a Phase III study of the anti-myostatin adnectin candidate RG6206 (BMS-986089) in a different indication, DMD, while Biogen has licensed recombinant proteins from AliveGen USA Inc. that inhibit myostatin by interfering with the activin receptor.

To compete, companies developing novel SMA drug candidates must address the key questions around how to design efficient trials to optimize treatment timing and effect and whether alternative routes of administration offer advantages.

In the hundreds of ultra-rare neurodegenerative diseases, being able to show a large effect size in a small patient population is a necessity. With Spinraza, for example, after 20 patients, Ionis knew the drug was working. "We are counting on a large effect size to make our strategy work for rare diseases where it is difficult to find homogeneous patients for clinical trials," Bennett said. And to be able to demonstrate efficacy in a relatively short amount of time, as was also the case with Spinraza.

The evolution of SMA treatment could become the blueprint for developing disease-modifying and supportive therapies in other neuromuscular and neurodegenerative diseases and in the case of the latter, potentially applying them across indications. Fatigue, for example, is common across many disorders including multiple sclerosis, Alzheimer's Disease, and DMD. A myostatin inhibitor or reldesemtiv might have a beneficial effect in several.

The fact that Spinraza and Zolgensma are significant revenue-generating drugs with obtainable reimbursement also provides a benchmark for future clinical and cost-effectiveness assessments in other diseases, and with Spinraza, shows that companies should also have a broad-based plan for evidence development – an even more important consideration in other neuromuscular diseases, with multi-factorial causes and symptomology compared to SMA.

Had the Spinraza data been only pretty good rather than great, Biogen's research plan for it, where they did multiple randomized trials looking at different groups, might have been a saving grace. "I think it should be a model for looking at diseases and new treatments for diseases," Rind said. Contrast that with the studies of Sarepta Therapeutics Inc.'s Exondys51 (eteplirsen) in DMD, another neuromuscular disease in children. ICER panned that drug in a recent review of DMD drugs. "I can't tell from the data we have now if Exondys51 works or doesn't work," Rind said. "They didn't do a trial that looked like what Biogen did. If Sarepta had done what Biogen did, we would certainly know by now whether it is helping patients."

The nature of SMA made it a good starting point for drug development, which the Neurogenetics Branch of the National Institute of Neurological Disorders and Stroke recognized in the 1990s when it identified SMA as an appropriate target to develop novel treatments because of the disease's almost idealized clinical features. SMA affects motor neurons but not a lot else. It does not alter cerebral function: as opposed to most infants with weakness, children with SMA are alert and awake and fully interactive – they have a fairly isolated muscle weakness due to the motor neuron loss. Plus, it is a recessive disorder with a back-up gene that makes the identical same protein, providing two ideal targets to try to correct genetically.

Technologies altering genes have matured and companies now have multiple gene-targeting platforms to choose from. "I think the thought all along was SMA would allow us to move this methodology into other neurodegenerative and neuromuscular diseases," said Day.

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