VIOLA ADVISORY

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1Q19 Sarepta Therapeutics (SRPT) Summary: BUY @ PT $170.00

TABLE 1: SRPT – Key Valuation Metrics

Mkt. Cap			Mkt. Price 6/14/19	Fwd. P/E	YTD	Viola Advisory Rating	Viola Advisory PT	Upside Potential 52-Week High	Upside Potential PT
8.93B	SRPT	Sarepta Therapeutics	119.57	(111.0)	11.2%	BUY	170.00	48%	42%

Source: Yahoo Finance and YCharts.com

Summary: **We believe Sarepta Therapeutics' SRP-9001 gene therapy will be the market leading gene therapy treatment for Duchenne Muscular Dystrophy (DMD) – a rare disease that mostly affects boys with a high unmet clinical need. The DMD market is becoming increasingly crowded but Sarepta has the most advanced treatment in the clinical trial development phase. Furthermore, its most recent Phase 1/2 data readout has produced strong results encouraging the company to begin a larger Phase 2 confirmation trial this year. Sarepta is also expecting FDA approval for its latest non-gene therapy DMD drug (an exon-53 skipping therapy called Golodirsen) expected to be approved in August 2019. This will bring the total number of treatments that serve DMD patients to 3 drugs – with Sarepta holding 2 of the 3 drugs – Eteplirsen (Exondys 51) and Golodirsen. This firmly solidifies Sarepta's position as the market leader in the DMD space.**

I. Sarepta's Target Indication – Duchenne Muscular Dystrophy (DMD)

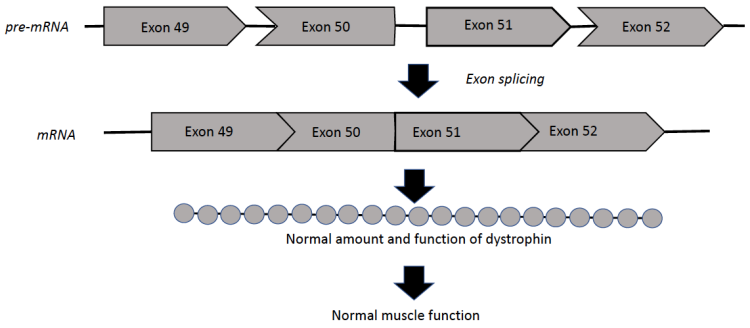
Duchenne muscular dystrophy (DMD) is a genetic disorder characterized by progressive muscle degeneration and weakness. DMD is caused by an absence of dystrophin, a protein that helps keep muscle cells intact. Symptom onset is in early childhood, usually between ages 3 and 5. The disease primarily affects boys, but in rare cases it can affect girls. It is the most common pediatric muscular dystrophy with a prevalence of one in 3,500 to 5,000 live male births, or about 400 to 600 boys per year in the US.

DMD is caused by any of more than 2,000 mutations in the dystrophin gene that result in loss of expression of the dystrophin protein. Muscle weakness can begin as early as age 3, first affecting the muscles of the hips, pelvic area, thighs and shoulders, and later the skeletal (voluntary) muscles in the arms, legs and trunk. By the early teens, the heart and respiratory muscles also are affected.

Many patients (70%) have single- or multi-exon deletions or duplications that are amenable to detection via genetic testing. The absence or lack of functional dystrophin results in muscle degradation and scarring, leading to progressive skeletal weakness, wasting, and cardiomyopathy. Levels of dystrophin in patients with DMD are generally less than 3% of normal. Severity of disease appears to vary with mutation, resulting in a heterogeneous population with differing rates of progression.

II. How Sarepta's Gene Therapy, SRP-9001, works to cure Patients with DMD

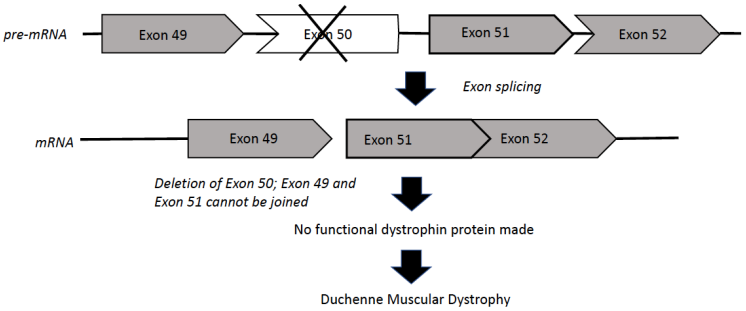
FIGURE 1: Normal Synthesis of Dystrophin Protein



As part of ribonucleic acid (RNA) synthesis, exons are connected to generate messenger RNA (mRNA) that encodes dystrophin (see Figure 1).

In patients with DMD, mutations in the exons (regions that code for the dystrophin protein) of the DMD gene cause misalignments in the transcription reading frame that lead to nonfunctional or absent dystrophin (see Figure 2).

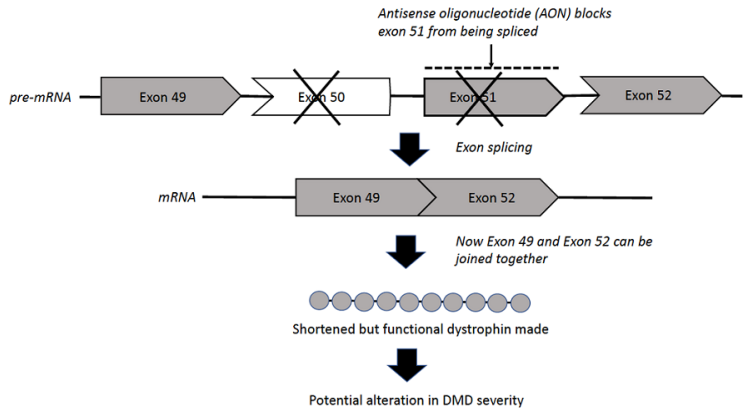
FIGURE 2: Exon Deletion causing lack of Dystrophin production in DMD



Mutations in a single exon can disrupt all downstream synthesis of protein if the reading frame is disrupted (so-called "out-of-frame deletion"), leading to non-functional (and generally markedly shortened) protein being produced. The absence of functional dystrophin leads to inflammation and degeneration of muscle.

Exon-skipping therapies are anti-sense oligonucleotides that target dystrophin pre-messenger RNA (mRNA) and induce skipping of the mutated exons, converting the mutation into an in-frame mutation, and allowing downstream exons to be transcribed. The remaining exons form a shortened mRNA that encodes a shortened but partially functional dystrophin protein (Figure 3).

FIGURE 3: Exon-Skipping Therapy leads to a shortened but functional Dystrophin production



Animal models and observational data suggest that restoration of small amounts of dystrophin (between 2-4% of normal) may be beneficial in slowing progression of the disease, though clinical correlation has yet to be established.

Source: Duchenne Muscular Dystrophy: Draft Evidence Report, Institute for Clinical and Economic Review, May 22, 2019

III. Reasons for our Bullish Sentiment

1. Latest SRP-9001 Data Readout showed robust results

On October 3, 2018, Sarepta released a nine-month data on four boys with Duchenne muscular dystrophy (DMD) enrolled in Study-101 testing SRPT's microdystrophin gene therapy SRP-9001. Results of the study were robust, showing marked improvements in the boys' functional performance, unprecedented biomarker results and a good, clean safety profile with no signs of adverse effects.

SRP-9001 uses an adeno-associated virus, or AAV, to deliver microdystrophin, a shorter version of the dystrophin gene that contains enough information to produce and restore the function of dystrophin. The therapy was developed by researchers at Nationwide Children's Hospital in Ohio and licensed by Sarepta. SRP-9001 delivers the microdystrophin gene exclusively to the muscle tissue – in particular, the heart muscle. Rescuing heart muscle function is vital since DMD patients frequently die of heart disease.

A. Clinical Study-101 Design

- Clinical Study-101 (NCT03375164) enrolled four boys with DMD, ages 4 to 7, with blood levels of creatine kinase (CK), a marker of muscle inflammation, at the beginning of the trial (baseline) between 20,000 and 35,000 U/L (upper limit).
- Each was given a single dose of SRP-9001 administered into the bloodstream. To prevent their immune system from targeting and destroying the therapy, they also received corticosteroids. A high dose was given through the first 30 days, followed by their standard-of-care corticosteroid dose.
- The study's primary goal was safety, but several secondary endpoints focused on changes in muscle function, including the 100-meter timed test, time to rise, four-stair climb test, as well as the North Star Ambulatory Assessment (NSAA).
- NSAA is a 17-item rating scale used to measure motor abilities – such as the ability to rise from the floor, to get from lying to a sitting position and from sitting to standing – in ambulant patients. Scoring ranges from zero (patients unable to perform any of these activities) to 34, when all are achieved.

B. Summary of Clinical Study-101 Results

- Analysis of muscle biopsies done at 90 days post-gene therapy injection showed a widespread localization of dystrophin at the sarcolemma (muscle membrane).
- Researchers quantified the amount (called intensity) of microdystrophin at the muscle membrane and reported a 96% increase compared to baseline or pre-treatment.
- Researchers also detected 81.2% of microdystrophin-positive muscle fibers across the four patients at 90 days post-treatment.
- Another technique, called Western blot, was used to quantify the total amount of microdystrophin protein. After adjusting for fat and fibrosis, a 95.8% increase in microdystrophin was seen compared to study start. An increase of 74.3% was still seen when not adjusting the results.
- The microdystrophin gene was present at 3.3 copies per cell. Biopsy data taken together was very consistent in terms of the number of copies and the amount of dystrophin present. Researchers saw a high level of widespread microdystrophin expression 90 days post-biopsy.

- Almost nine months (270 days) after treatment, NSAA scores showed a significant improvement in motor abilities.
- NSAA data from patients one, two and four, ages 4 to 5, showed that the score increased by eight points in about nine months. Natural history data on 4- to 5-year-olds with DMD shows that steroid treatment leads to an improvement of two points in the NSAA score.
- Patient number three, 6 years old at the trial's beginning, had the highest baseline NSAA score – 26 – and still showed an improvement of two points at nine months. This small improvement is important, as natural history data from 6- and 7-year-olds show an actual decline by four points over the course of a year.
- Pooled data from all patients showed a mean improvement of 6.5 points from baseline (study start) in the NSAA score. The results indicate that the patients can do six activities independently that other untreated DMD boys cannot do.
- Findings across every additional functional measure – time to rise, four-stair climb test, and the 100-meter timed test – also showed an improvement from baseline until day 270 across all four patients.
- According to the new data, the time to rise improved by 0.8 seconds, time in four-stair climb test improved by 1.2 seconds, and the 100-meter test by 7.95 seconds.
- The inflammation biomarker CK showed an overall decreasing trend over time. Although there was some variability, which researchers linked to a break in protocol guidance – namely, patients engaging in these activities before CK was measured (activity can induce a spike in biomarker levels), the data shows an overall trend toward decreased levels of CK, which researchers deemed encouraging.
- While CK levels in DMD boys ages 4 to 7 was between 20,000 to 40,000 U/L, this range was only detected at the study's start. In later measurements, the values were always declining. Most importantly, when looking at the improving NSAA scores in relation to lowering CK levels during the nearly nine-month period, there was a clear consistent improvement.
- Researchers saw that the decrease in CK was linked with steroid use, a finding seen in other studies.
- No immune responses against microdystrophin were seen throughout the trial.
- Safety signals remained positive, with patients continuing to do well and free of evidence of adverse side effects.
- Three patients had elevated gamma-glutamyl transferase (GGT), a marker of liver damage, but these levels returned to normal within a week after increasing the dose of steroids.
- The study will follow these patients for a total of three years. No further biopsies are scheduled for intermediate time points.

Sarepta plans no further updates in these first patients, with the focus now shifting to a Phase 2 placebo-controlled trial.

Study-102 (NCT03769116) will be enrolling 24 boys with DMD, ages from 4 to 7 years old and will randomize participants to gene therapy or placebo. The trial's main outcome is to continue to assess the therapy's safety and changes in microdystrophin protein expression after 12 weeks. Around 13 patients have already been enrolled.

Sarepta is also planning a multi-center trial before the end of 2019 to test a commercial supply of the microdystrophin therapy. The trial will take place in at least 10 clinical sites in the US and potentially in sites outside the US.

2. Sarepta is the current market leader in the DMD space

Along with sickle cell disease and beta-thalassemia, muscular dystrophies have become an attractive target for companies working in gene therapy. DMD, especially, is the focus of several companies' research – with Sarepta, Pfizer and Solid Biosciences considered the most advanced (see Figure 4). Vertex Pharmaceuticals new entry into the space using CRISPR/Cas9 gene editing also adds a new platform to the mix.

FIGURE 4: Competitor Pipeline for Select DMD Projects

Project	Company	Mechanism	2024e Sales ($M)
Filed			
Golodirsen	Sarepta Therapeutics	Exon 53 binding oligonucleotide (RNAi)	331
Phase 3			
Casimersen	Sarepta Therapeutics	Exon 45 binding oligonucleotide	250
Suvodirsen	Wave Life Sciences	Exon 51 binding oligonucleotide	235
Phase 2			
SRP-9001	Sarepta Therapeutics	Microdystrophin gene therapy	1,820
SGT-001	Solid Biosciences	Microdystrophin gene therapy	577
GALGT2	Sarepta Therapeutics	GALGT2 gene therapy	3
Phase 1			
PF-06939926	Pfizer (ex-Bamboo)	Microdystrophin gene therapy	-

Source: "Vertex's Second Transformation: Duchenne Time," VantageDaily June 7, 2019

Current treatment options for DMD remain limited with Sarepta holding the most recent FDA approval (in late 2016) for its controversial drug Exondys 51 (eteplirsen). Experimental drugs from Sarepta, Pfizer and Solid Bioscience propose a genetic fix for the mutated dystrophin gene behind the disease. By delivering a functional copy of the gene to muscle tissue – an approach known as gene transfer – the companies aim to spur production of the needed dystrophin protein that is missing in DMD patients.

Solid Bioscience's initial Phase 1/2 data readout (on February 7, 2019) for its SGT-001 gene therapy was disappointing. The results showed that at low doses, SGT-001 may lack the potential to be an effective treatment for DMD compared to current products on the market. Muscle biopsy results showed low levels of microdystrophin protein expression – below the 5% level in Western blot assay and around 10% in muscle fibers via immunofluorescence. This is in stark contrast to Sarepta's results which showed microdystrophin levels at 74%, as measured by Western blot and 96% using a method from Nationwide Children's Hospital.

These cross-trial comparisons should be interpreted with caution, as both Solid and Sarepta are likely using different assays to measure microdystrophin expression. Moreover, the dosing levels are different with Solid starting its SGT-001 dosing at a lower level of $5x10^{13}$vg/kg compared to Sarepta's SRP-9001 dosing at the higher level of $2x10^{14}$vg/kg.

Solid Biosciences' management has said that it plans to continue to move forward with its dose escalation strategy in the near-term.

Pfizer also has a DMD gene therapy candidate, PF-06939926, originally developed by Bamboo Therapeutics, in a Phase 1 trial. Data readout is expected to be around June 2019.

Disclosure Information

Analyst Certification

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