VIOLA ADVISORY

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1Q19 Sangamo Therapeutics (SGMO) Summary: BUY @ PT $17.00

TABLE 1: SGMO – Key Valuation Metrics

Mkt. Cap.			Mkt. Price 7/11/19	P/S	YTD	Viola Advisory Rating	Viola Advisory PT	Upside Potential 52-Week High	Upside Potential PT
1.36B	SGMO	Sangamo Therapeutics	11.26	16.2	-2.9%	Buy	17.00	71%	51%

Source: Yahoo Finance and YCharts.com

Summary: **Sangamo's lead experimental drug SB-525 indicated for hemophilia A was granted RMAT (regenerative medicine advanced therapy) designation by the FDA which could enable it for accelerated approval and reduce the lead time required to bring its gene therapy to market. The company is currently in third place behind BioMarin and Spark Therapeutics. However, recent data presented shows SB-525 to be as efficacious as BioMarin's gene therapy and safer than Spark's lead drug candidate.**

Sangamo's partner, Pfizer, will now be responsible for the upcoming pivotal study and they have a resident expert on accelerated approvals sitting on the board – ex-FDA commissioner Scott Gottlieb, who recently joined the company. If Pfizer and Sangamo can produce a relatively clean safety profile with a consistent and effective level on response rates and no bleeds, then they could overcome their late start in the hemophilia A market.

I. Sangamo's SB-525 Target Indication – Hemophilia A

Hemophilia is a rare bleeding disorder in which the blood does not clot normally. Hemophilia is a monogenic disease (a disease that is caused by a genetic defect in a single gene). Individuals with hemophilia experience bleeding episodes after injuries and spontaneous bleeding episodes that often lead to joint disease such as arthritis.

Hemophilia is caused by mutations in genes that encode protein factors which help the blood clot and stop bleeding when blood vessels are injured. There are two types of hemophilia – hemophilia A and hemophilia B. Hemophilia A (hem A) is the most prevalent form of the disease and is caused by a defect in the factor 8 gene. On the other hand, hemophilia B (hem B) is caused by a defect in the factor 9 gene. The most frequent forms of hemophilia affect males.

According to the Centers for Disease Control and Prevention (CDC), an estimated 400,000 people worldwide live with hemophilia with the disease affecting 1 in 5,000 male births. Each year, about 400 babies are born with hemophilia A. There is an estimated 20,000 people with hemophilia in the U.S. Around 16,000 of them have hem A while around 4,000 have hem B.

Currently, hem A patients rely on regular injections of synthetic factor 8 to improve clotting. Those therapies cost about $270,000 a year. Hem A remains an incurable disease, putting the lifetime cost of treatment well into the millions of dollars. An approved gene therapy would substantially change the treatment paradigm.

But much depends on what price manufacturers decide to charge and how much payers are willing to reimburse providers for those treatments.

II. Hemophilia A Competitive Landscape

A. The 3 Front-runners: BioMarin, Spark and Sangamo/Pfizer

Hemophilia has become one of the most competitive spaces in the emerging field of gene therapy. BioMarin Pharmaceutical is the front-runner to market. The company plans on submitting its hem A gene therapy, valrox (valoctocogene roxaparvovec), to U.S. and European regulators sometime in 4Q19, which could bring an approval decision as early as mid-2020.

Spark Therapeutics is the second runner-up with its gene therapy SPK-8011 undergoing phase 1/2 clinical trial. The company is expected to provide further updates of the phase 1/2 study in mid-2019. In addition, Spark announced a Phase 3 run-in study on 4Q18 with the aim of collecting data on 5-10 clinical trial patients who were administered SPK-8011 with a prophylactic steroid. The company hopes to win approval in 2020 or later.

Sangamo's hem A experimental gene therapy SB-525, which the company is co-developing with Pfizer, is in phase 1/2 clinical development with 10 patients enrolled. SB-525 is designed to deliver a copy of the factor 8 gene to a patient's liver cells enabling them to produce the blood clotting protein at the root of hem A. If effective, the gene therapy will raise factor 8 levels, freeing patients from the burden of managing the disease and the symptoms it causes.

Sangamo recently posted impressive efficacy data on SB-525 that was competitive to valrox and much better than Spark's SPK-8011. The data showed a fast response among 4 patients receiving the highest dose of SB-525. Results of the clinical trial were encouraging in that the FDA granted SB-525 an RMAT designation – regenerative medicine advanced therapy status – that could possibly earn it an accelerated FDA approval.

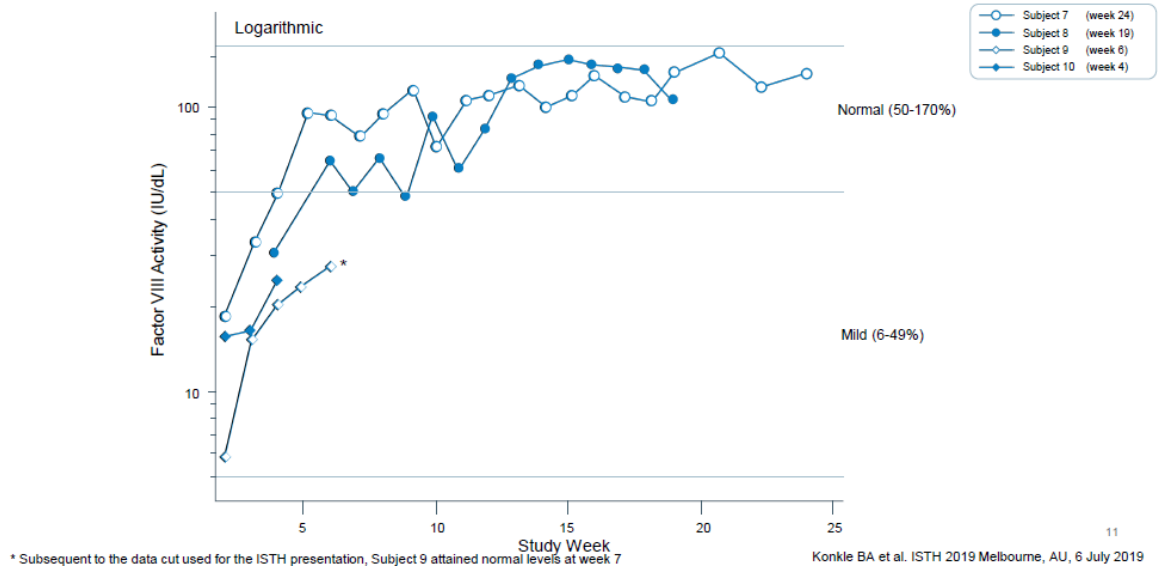
B. Submission for Approval – Timing is Everything

Being first to market is critical for gaining and keeping market share. So far, BioMarin seems to be first on track to secure an approval for the first gene therapy to treat hem A based on the results of its Phase 3 study. Management at BioMarin stated that securing a full approval would help in establishing a barrier to entry for others who are looking to get accelerated approval. A full FDA approval may require other drug developers to do a larger and longer study in order to get their drugs on the market.

However, both Sangamo and Pfizer are optimistic that they could also gain an accelerated approval which would substantially cut down the lead time of both BioMarin and Spark. Patients in the highest dose cohort of SB-525 saw a quick response on the levels of factor 8, the clotting blood protein factor that is missing in hem A patients. Two patients (subjects #7 and #8) treated with the highest dose reached normal levels by week 5 of the study and continued to stay within the normal range as determined by chromogenic assay (see Figure 1).

Two other patients (subjects #9 and #10) on the highest dose cohort also showed a rapid rise in factor 8 levels although only subject #9 has reached the normal range so far.

FIGURE 1: SB-525 Factor 8 activity at highest dose: 3x10[13] vg/kg using Chromogenic Assay



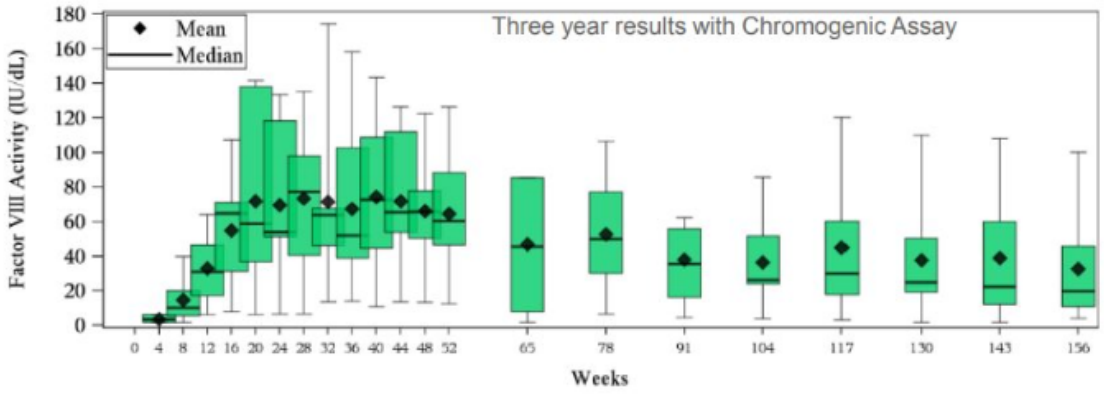
Source: ISTH presentation, July 6, 2019

C. Why SGMO could still catch up to BioMarin and Spark

Based on the current data, SB-525 looks at least as good as valrox, although the usual caveats about cross-trial comparisons apply, and the results should also be treated with caution given the small number of patients treated so far.

In Biomarin's Phase 2 trial, the chromogenic assay found factor 8 levels around 60% of normal at 25 weeks in patients treated with the high dose of valrox, 6x1013 vg/kg (see Figure 2). However, there are questions regarding the long-term durability of valrox. BioMarin reported last May that factor 8 levels in high-dose patients decreased by more than half from peak levels of around 60% of normal (week 25) to a median of 20% of normal in three years.

FIGURE 2: Valrox Factor 8 activity at highest dose: 6x10[13] vg/kg using Chromogenic Assay



Source: BioMarin presentation, May 28, 2019

There is some market concern that if valrox's factor 8 levels continue to decrease at the same rate, it may end up below 5% of normal in 5 years. This could raise some payer concerns on reimbursement, since 5% is the minimum level for clinical benefit. Although valrox could still be approved, it does not look like the once-and-done gene therapy that the market was hoping for based on earlier data.

Meanwhile, Spark Therapeutics' SPK-8011 is moving forward with a dose ($2x10^{12}$ vg/kg) that is much lower than BioMarin and Sangamo. Moreover, SPK-8011 also has safety problems – 2 of the 7 patients who received the high dose saw the patient's immune system turn against SPK-8011 and reduce factor 8 levels. This caused Spark to apply prophylactic steroid treatments before the onset of any immunologic response.

Moreover, unlike BioMarin and Sangamo, Spark's SPK-8011 factor 8 levels were not able to reach the normal threshold of 50%. Two patients infused with the lowest dose achieved mean factor 8 levels of 10% and 16% after 12 weeks. Two patients infused with the middle dose achieved 13% after 14 weeks and the other patient achieved 9% after 19 weeks. The highest dose increased average factor 8 levels to 30% of normal.

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