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J.P. Morgan Notebook Day 4: Novartis CEO Weighs In On AI, Sangamo's Next Steps And More

by Joseph Haas

Additional highlights from the J.P. Morgan Healthcare Conference, including Takeda's partnering outlook, Sage's guidance on Zulresso sales, Frequency's next steps for its hearing loss drug and Revance's preparations to take on the aesthetics market.

Sangamo Hopes To Demonstrate Reliability In Hemophilia A In Coming Months

Sangamo Therapeutics Inc. may be months away from demonstrating that its gene therapy for hemophilia A – SB-525, partnered with *Pfizer Inc.* – offers best-in-class sustainability of its therapeutic effect, which is crucial because competitor *BioMarin Pharmaceutical Inc.* is positioned to get to market first with a gene therapy for the disease.

The potential of showing "reliability" represents Sangamo's best chance to overcome BioMarin's expected first-to-market advantage, CEO Sandy Macrae said at the J.P. Morgan Healthcare Conference on 16 January. The exec has previously explained that an optimal gene therapy for hemophilia A – replacing regular treatment with Factor VIII – must be "safe, reliable and predictable." (Also see "*Hemophilia A Gene Therapy Race Intensifies With Updated Sangamo/Pfizer Data*" - Scrip, 2 Apr, 2019.)

In San Francisco, Macrae said Sangamo has shown that SB-525 is safe and predictable in updated results from its Alta trial, but demonstrating reliability will only come from longer-term data expected in the next three to six months. BioMarin's Phase III program for valoctocogene roxaparvovec (valrox)

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showed some patients' Factor VIII levels eventually dipped below 50%, the bar for a diagnosis of hemophilia. (Also see "*Hemophilia A Gene Therapy: BioMarin In Lead, Sangamo 'Prays' For Superior Results*" - Scrip, 22 Nov, 2019.) An FDA action date for valrox is expected in August, and the product also is under review by the European Medicines Agency.

"We're waiting to see that we're reliable because that's the debate that everyone's having," Macrae said on 16 January. "Everyone's seen the results of our friends at BioMarin and wonders about the reliability of that medicine."

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A Muted J.P. Morgan, But The Focus Is Execution – And That's Good News

If a gene therapy for hemophilia A does not permanently correct the patient's Factor VIII level, retreatment presents a challenge because first-generation candidates produce an immune response in the patient that results in neutralizing antibodies to a subsequent dose. BioMarin is working on a next-generation adeno-associated virus (AAV) vector version of valrox that could enable re-treatment.

Macrae added that the Alta study has shown a peak effect within six to 10 weeks and that patients in the highest-dose cohort have had no bleeding episodes. Sangamo has transferred the SB-525 program to Pfizer under their 2017 partnership, with the pharma enrolling a Phase III lead-in trial. 201720222 Pfizer plans to launch a pivotal study of SB-525 later this year. SB-525 and *Roche*/*Spark Therapeutics Inc.*'s Phase III SPK-8011 are thought to be a year or more behind BioMarin in reaching market.

Sangamo now can realize $300m between the completion of the investigational new drug (IND) application transfer to Pfizer and the first commercial patient for SB-525, Macrae said, after which it can earn sales royalties ranging from the low teens up to 20%. "One can imagine this having a substantial effect on the finances of Sangamo and it really will pay for our research in years to come."

Macrae said Sangamo's vision is to move beyond gene therapy. "Eventually, we will become more and more a cell therapy company. And then, ultimately, we will do gene and genome editing. And this range of modalities that we have at our fingertips allows us a range of medicines," the

CEO noted.

Novartis Leaves Financial Forecasting to AI

While artificial intelligence (AI) and machine learning still suffers an image problem in the biopharma sector because of excessive hype, it is nevertheless becoming a part of day-to-day business in the industry. It was a recurrent theme at J.P. Morgan this year, with leaders citing its use from drug discovery to clinical trials recruitment to salesforce productivity.

Novartis AG CEO Vas Narasimhan has made his company an early adopter of AI and data science technology, and says he believes rapid uptake can give it an edge over competitors.

Speaking at a spin-off summit of CEOs and R&D leaders hosted by health care venture capital firm Medicxi on 14 January, Narasimhan said Novartis has tried to adopt the technology broadly across the company, and at scale and speed.

"Digital data science technologies can fundamentally give you an edge in decision making in your operations," said Narasimhan.

He said that so far the biggest impact has been leveraging the technologies in Novartis' core operations, with chief digital officer Bertrand Bodson appointed in 2017 to lead 12 digital lighthouse projects to embed the technology across the business.

"To give you a concrete example, in 2020 our entire financial forecasts were generated by data science and AI," Narasimhan said. "We have AI generated predictions of every single product in every market, as well as optimization algorithms on how to optimize our investment and spending."

He added that commercial and other teams naturally engage in conversations about future product expectations, but that taking the forecasting responsibility allows them to focus on other aspects of the business.

However, it is clear that AI is no panacea.

Speaking on a second panel at the event, alongside other big pharma R&D leaders, *Bristol-Myers Squibb Co.*'s new president of research and early development Rupert Vessey agreed that AI was now "pervasive" in many R&D functions.

He couldn't resist making a tongue-in-cheek but nonetheless serious warning note on Novartis' forecasting application, however. He repeated the well known "garbage in, garbage out" observation that analytics technology can't perform well if the original data fed into it is flawed.

“Actually I’m really worried about the prediction of market valuation that Vas brought up. Because every single market valuation I have ever seen was wrong…and if they’re putting the same data into the AI, it is just going to be wrong all over again!”

Takeda's Appetite For Partnering Is Big

Takeda Pharmaceutical Co. Ltd. R&D President Andrew Plump said the company will be actively partnering in 2020. "We won't do major acquisitions. We don't have the capital or the interest or the need, but the model that we put in place, the R&D partnership model will continue as long as I'm here," he said in an interview at J.P. Morgan.

Takeda closed the $62bn acquisition of Shire a year ago and has largely completed the integration. (Also see "*Takeda's Weber: ‘Everything Relies On Our Ability To Deliver Innovative Medicines’* " - Scrip, 7 Jan, 2019.) The company highlighted the combined pipeline at an R&D Day in November, with a therapeutic focus in four areas: oncology, rare disease, gastroenterology and neuroscience. (Also see "*Takeda: 12 NMEs Poised To Launch In Five Years, And Deliver $10 Bn In Peak Sales*" - Scrip, 19 Nov, 2019.)

At J.P. Morgan, Plump said the company has earmarked the same level of spending for business development in 2020 as it did in 2019. While a lot of the company's recent activity has focused on oncology, he said the therapeutic area with the biggest gap right now is rare disease.

In January, Takeda signed a small deal with *Silence Therapeutics PLC* to use the company's gene-silencing platform to generate siRNA molecules against an undisclosed target. (Also see "*Silence Signs Takeda Deal And Sets Sights On US*" - Scrip, 7 Jan, 2020.) Another interesting deal last year linked the company with MD Anderson Cancer Center to develop cord blood-derived CAR-directed NK cell therapies. In December, Takeda signed a bigger deal with *Turnstone Biologics Inc.* in which it agreed to pay $120m in upfront cash, equity and near-term milestones to collaborate on the development of multiple products using its vaccinia virus platform in cancer.

"We will clearly still look in oncology, but we actually have a nice portfolio of opportunities there," Plump said. "My guess is that we will be a little bit more active in the rare space, maybe neuroscience as well."

Sage Expects To See Zulresso Growth In Second-Half 2020

Sage Therapeutics Inc. prepared investors for a slow ramp-up in sales for its postpartum depression (PPD) drug Zulresso (brexanolone) after the product’s launch in mid-2019, and that will continue through the first half of 2020, Sage chief business officer Mike Cloonan told *Scrip* in an interview at the J.P. Morgan Healthcare Conference. (Also see "*Sage's Zulresso Launch Is Off, But Not Running* " - Scrip, 6 Aug, 2019.)

The company continues to work with hospitals to help them get certified under the Risk

Evaluation and Mitigation Strategy (REMS) for Zulresso, which requires continuous monitoring of patients admitted for the drug's 60-hour infusion due to the risk of sedation and sudden loss of consciousness. Once certified and a treatment protocol is established, hospitals must negotiate reimbursement for the cost of the drug and the associated care.

"We're making a lot of progress with the 140 sites that are REMS-certified; 11 were treating at the end of Q3, so there's that gap between 140 and 11, because they have to work through those steps," Cloonan said.

Sage is working with hospitals and health care providers to create a sense of urgency and to share best practices from sites that have completed the certification and reimbursement processes to make more treatment sites available.

"What we've said is modest [sales] growth over the first half of the year while we build this foundation and then we expect a significant increase in revenue in the second half of the year while we have more sites set up and as we have the access for moms," Cloonan said.

Payers have recognized the efficacy and the need for Zulresso as well with favorable reimbursement policies for 75% of covered lives in the US, including commercial health plans and Medicaid.

"The payers recognize the unmet need; they're willing to cover Zulresso and we'll continue to work through that 25% that hasn't been established yet," Cloonan said.

Everything that Sage has learned from the Zulresso launch will benefit its second drug, SAGE-217, which is seen as a much larger opportunity as it's an oral drug in development for both PPD and major depressive disorder (MDD). The drug has generated positive Phase III results in PPD and mixed results in MDD, but the company will meet with the US Food and Drug Administration in the first quarter to discuss a path forward for SAGE-217 in MDD. (Also see "*Sage Still Sees Approval Path After Depression Drug Fails In Phase III Trial*" - Scrip, 5 Dec, 2019.)

"The market that '217 is going to launch into in postpartum depression is going to be different than the one that Zulresso launched into because of Zulresso. It's going to pave the way in many ways for '217," Cloonan said.

Frequency Aims For Clear Signal In Hearing Loss Trial

Frequency Therapeutics raised $84m in its initial public offering in October 2019 based on its lead candidate for hearing loss, and the company is hoping that a Phase IIa trial reading out at the end of 2020 will help establish the potential of its technology.

The firm is working on small molecule candidates that can reactivate progenitor cells – providing

a potentially far simpler and lower-cost way of regenerating cells within the body compared to cell or gene therapy platforms.

Its lead candidate, FX-322, will initially target a US market of around 30 million patients with sensorineural hearing loss (SNHL), the most common form of hearing loss, but could move on to a much larger global market.

SNHL is the most common form of hearing loss and results from damage to the hair cells in the inner ear or problems with the nerve pathways that convert sound waves from the inner ear to the brain. FX-322 is designed to treat the underlying cause of SNHL by regenerating these hair cells through activation of progenitor cells already present in the cochlea.

CEO David Lucchino told the J.P. Morgan audience that progenitor cells are "underutilized assets that Mother Nature put in your body but [until now] there has been no way to turn them back on."

FX-322 has shown benefit in a Phase I/II study already, with more data on the way later this year.

Frequency has a deal with Astellas on ex-US rights to the drug, involving an $80m upfront payment, further milestone payments and double-digit royalties.

The company is planning an IND for its next candidate in the second half of 2021, a drug aimed at bringing about remyelination of nerve cells in multiple sclerosis.

Revance Readies For Daxi Launch With Dermal Filler Deal

Revance Therapeutics Inc. has responded to concerns that it might have a tough time selling its neuromodulator daxi (daxibotulinumtoxinA or RT002) to dermatologists and plastic surgeons without being able to offer a bundle of medical aesthetics products with discount pricing for the individual offerings – a strategy that has helped *Allergan PLC* boost sales for its blockbuster aesthetic Botox (onabotulinumtoxinA) – by bringing in a dermal filler line.

Revance announced on 10 January that it entered into an agreement with Teoxane SA to sell its Resilient Hyaluronic Acid (RHA) line of dermal fillers in the US and *Scrip* spoke with Revance CEO Mark Foley during the J.P. Morgan Healthcare Conference – where he presented on 16 January – about the strategic importance of the deal for daxi.

The company submitted its biologic license application (BLA) to the US Food and Drug Administration for daxi in the treatment of moderate-to-severe frown lines in November and it anticipates approval in the fourth quarter of this year – and it is hoping for a label in late 2020 that allows for treatment as infrequently as every six months, versus Botox's quarterly injections. (Also see "*Another Botox Competitor: Revance Prepares Longer-Lasting RT002 For BLA Submission*"

- Scrip, 22 Feb, 2019.)

“Other more recent product launches suggest that overall in medical aesthetics physicians are open to trying new things,” Foley said. “Having said that, when we looked at what other products to add to the bag, a filler was the most logical.”

Teoxane’s dermal filler line is approved in Europe and the US; Revance is hiring its sales team in anticipation of a second quarter launch in the US. In Europe, Teoxane has sold more than 10m syringes. The agreement is a 10-year exclusive US distribution deal with the ability for Revance to extend the agreement for two more years.

“When daxi comes out, we will be established with user relationships,” Foley said. “We feel very fortunate on the timing. It significantly strengthens our position in the marketplace.”

As for the company’s other partnership – a deal with *Mylan NV* for the development and commercialization of a Botox biosimilar – the big generics maker needed more time to decide whether to opt in to that opportunity because of its pending merger with Pfizer’s Upjohn business into a new company called *Viatris GMBH*. (Also see "*Mylan Gets Until April 2020 To Decide On Biosimilar Botox Collaboration With Revance*" - Generics Bulletin, 4 Sep, 2019.)

“They came to us and said that because of the Upjohn relationship [they] need more time. They gave us another $5m to extend the relationship,” Foley said. He noted that if Mylan has to walk away from the Botox biosimilar agreement, Revance is confident that another deal can be negotiated with one of the other companies that previously was interested in such a partnership. (Also see "*Mylan Set To Develop Biosimilar Botox In Deal With Revance*" - Scrip, 28 Feb, 2018.)

[Editor's Note: This article was updated to note that Teoxane has sold 10m syringes of its RHA line of dermal fillers in Europe, not 1m.]