Company Report: Selecta Biosciences; SELB

March 28, 2017

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AMP Biotech Research

Company: Selecta Biosciences; NASDAQ: SELB

Financials

Market Cap: $255M
Cash: ~$85M (as of 4Q16)
Burn: $16.8M/Q (as of 4Q16)

Near-term Binary Events:

- Updated Phase 2 data of SEL-212 in chronic, refractory gout due June 2017

Investment Thesis: In the last few months, Selecta share price has fallen to all-time lows. Following the release of preliminary data on SEL-212 in refractory gout, the price has rebounded, but still only to IPO levels. We see this as a good entry point prior to additional data to be presented in June. Currently we believe the market undervalues the broad potential of SVP-rapamycin in indications treated with injectable biologics. This discrepancy seems mostly driven by the lack of clinical data supporting efficacy and the remaining questions on dosing. However, we believe the design of their current Ph2 trial will identify the appropriate dose combination to achieve efficacy and tolerability and will provide confidence for future studies.

Background and context

Selecta Biosciences is a small cap biotech company developing synthetic nanoparticles engineered to manipulate the immune system. Their platform utilizes the FDA-approved polymer poly(lactic-co-glycolic acid) (PLGA) to create uniform nanoparticles that target antigen presenting cells (APCs) and deliver cargo. Depending on the cargo contents, it has the potential to either augment or mitigate an immune response to a specific antigen. With around $85M in cash as of last quarter, plus expected milestone payments, management believes they have operational runway through 1H18. Their next expected catalyst is likely to come from updated data from their current Ph2 trial where an additional high dose and longer-term treatment with SEL-212 will be evaluated.

Lead Program

SEL-212 (Pegciticase (PEGylated recombinant uricase) + SVP-rapamycin) is currently being evaluated in a Phase 2 study of patients with tophaceous gout.

Initial Indication

Gout is a common form of inflammatory arthritis and is caused by elevated levels of uric acid in blood (hyperuricemia). The accumulation of blood uric acid results in deposits that cause severe inflammation. Accumulation and deposits occur when serum uric acid exceeds physiologic saturation (~6.8mg/dL). Hyperuricemia most often results from underexcretion by the kidneys. Gout typically presents as episodic flares between periods of time without symptoms, although it can become chronic. In chronic conditions, gout can lead to the formation of tophi, or the physical accumulation of large uric acid crystals near joints.

Standard of care and competitive landscape

The basic treatment goal for patients with gout is to achieve serum uric acid levels <6mg/dL. Sustaining levels below this threshold results in the eventual dissolution of uric acid crystal deposits. Current first-line therapy is xanthine oxidase inhibitors (XOIs) that

effectively reduce uric acid production. However, since most (>90%) hyperuricemia results from reduced kidney excretion, this approach is not always effective. Furthermore, many patients are contraindicated due to their existing medications. When XOIs are either ineffective or contraindicated, uricosuric agents are used. These are a logical pharmacologic approach as they work to increase uric acid excretion by the kidneys. However, increasing uric acid excretion can result in the formation of kidney stones, which has significantly hindered their uptake and overall clinical use.

Recombinant uricase therapy: sound rationale but significant limitations

Uric acid crystals can be broken down by the enzyme uricase. As such, a recombinant therapy could be used to treat gout. The FDA approved the first recombinant uricase enzyme for treatment of chronic gout in 2010. This therapy (KRYSTEXXA) is a PEGylated version of the uricase enzyme and is administered via an I.V. infusion. As expected, administration of this enzyme leads to rapid reductions in serum uric acid levels. However, its efficacy is short-lived and comes with a black box warning on its label due to severe infusion reactions. Data from their clinical trials indicated that 6.5% of patients had anaphylaxis compared to 0% with placebo. Total infusion reactions were reported in 26% and 41% of patients taking KRYSTEXXA every 2 and 4 weeks, respectively. Perhaps for these reasons, its uptake in the market has been dismal. KRYSTEXXA ownership has now changed several times and most recently landed in the hands of Horizon Pharmaceuticals (NASDAQ: HZNP). Even with adverse reactions that are severe and relatively common, Horizon is optimistic and projects peak sales to hit ~$250M. In our view, if SEL-212 can truly prevent the formation of ADAs and infusion reactions, it has the potential to displace KRYSTEXXA and take full command of the severe gout market. Furthermore, given the potential for significant improvements in tolerability, SEL-212 could penetrate a larger market share and well exceed these sales projections.

Market Opportunity

Gout affects an estimated 8.3M people in the U.S. However, around 3M of these cases go either untreated or undiagnosed. Of those that are diagnosed and treated, most are not deemed serious enough to require recombinant uricase therapy. According to most estimates, around 10% of treated patients (~500K) are severe enough to see a Rheumatologist. Of these, around 30% present with tophi, putting the total addressable market in the U.S. at ~150K.

Synthetic Vaccine Particles (SVPs)

Science and rationale behind SVPs

SELB's proprietary platform is called Synthetic Vaccine Particles, or SVPs. These particles are made up of the biodegradable polymer PLGA and are loaded with rapamycin to dampen the immune response to a co-administered antigen. Their goal is to use these particles in parallel with biologic therapeutics to prevent the unintended formation of anti-drug antibodies (ADAs) and allergic hypersensitivity disorders.

Rapamycin, which inhibits mTOR signaling, has been known to potently induce a tolerogenic immune response. This effect, mediated through dendritic cells (DCs), leads to regulatory T cell differentiation, expansion, and immune tolerance. However, systemic exposure of rapamycin results in several unwanted side effects limiting its overall therapeutic utility. SVP-rapamycin was designed to overcome this and specifically deliver rapamycin to DCs and other antigen presenting cells (APCs). Nanoparticles are an ideal choice for accomplishing this as APCs are naturally tuned to phagocytose nano-sized particles like viruses.

Phase 1 data

Selecta's SVPs have been evaluated in many preclinical animal models of disease. We plan to focus on their available human data and encourage our readers to see

their publications for details regarding their preclinical work. Their initial Ph1a study was designed to determine the dose range for their recombinant uricase enzyme (pegsiticase) and to establish the formation of ADAs following injection. They then used this dose (0.4mg/kg) in their Ph1b study where they evaluated the effect pegsiticase alone or in combination with a single ascending dose of SVP-rapamycin on serum uric acid levels, and ADAs over a 30-day period.

As the data shows, there was a dose-dependent reduction in serum uric acid levels that inversely correlated with the levels of anti-uricase antibodies (not shown, but find it here). For their Ph2 design, they will include two doses of pegsiticase (0.4 and 0.2mg/kg) with and without three doses of SVP-rapamycin (0.05, 0.08, and 0.10mg/kg) administered monthly over 3 months followed by 2 months with pegsiticase only. Given that their Ph2 included multiple doses and the promising data from Ph1, we predicted a high chance at least some of the combinations would come back achieving a balance of efficacy and tolerability (see Seeking Alpha article here). According to the preliminary data announced during their Q4 earnings call, this is looking to be the case. The preliminary results include those from the low and mid-dose cohorts with varying durations of treatment. As of the time for the Q4 call, the majority of the mid-dose cohort had received three infusions and throughout that time achieved durable uric acid management. While this doesn't definitively mean ADAs were being managed, given the association between the two, it is suggestive. Moreover, management indicated that they had not seen any SAEs or infusion reactions in this cohort. If this is maintained for the full duration of treatment, we see this as an important area for clinical differentiation from KRYSTEXXA where infusion reactions are common.

Commercial Considerations

Initially, it was planned that antigen or protein be simultaneously delivered as cargo within the SVP. However, this approach has significant commercial limitations that would have required optimization for each companion biologic tested. Management recognized this and subsequently established proof of concept using a more universal approach where SVP is co-administered with the biologic rather than administered together inside the SVP. Beyond establishing success as an adjunct therapy, the findings in this *Nat. Nanotechnology* paper also demonstrated that the SVP-rapamycin could match the route of delivery for the specific biologic. Together, these data alleviate some of the commercialization concerns for the SVP platform and better position the technology for broad companion use with biologic therapies.

Pipeline and Partnerships

The remaining pipeline is still in its early stages of development but shows promise for a number of indications. Recently, they presented preclinical data demonstrating an effective isotype switch (IgE to IgG) with the potential to prevent IgE-driven peanut allergies and subsequent anaphylaxis. They have also made progress with their preclinical program in Pompe Disease, demonstrating co-administration of SVP-rapamycin with alglucosidase alpha results in significant increases in glycogen clearance and mitigates the development of ADAs. The details of these data have not been fully discussed, but the press releases allude to their efficacy and plans for continued development. We also believe the partnership with Spark Therapeutics (NASDAQ: ONCE) represents an excellent opportunity to further validate their platform without bearing the full cost burden. This partnership makes a lot of sense for both parties as Spark is in need of an approach to mitigate ADAs and Selecta needs to grow their pipeline. Under this partnership, Selecta is entitled to receive an initial cash payment of $10M plus Spark will purchase $5M in common stock. Within one year, Spark will make an additional payment of $5M in cash and purchase $10M in common stock. Finally, Selecta will also be eligible for up to $430M in milestones for each target, and tiered royalties in the mid single to low double digits.

Risks:
-This is an early technology with the inherent development risks
-Partnership with Sanofi was terminated, raising questions about this technology in allergic conditions
-Sales of refractory gout therapeutics has been difficult (but perhaps because of immunogenicity)
-Relative difficulty of manufacturing SVPs consistently and to scale is unknown

Summary
Overall, Selecta Biosciences is developing a platform technology that has tremendous upside potential should it show efficacy in these early clinical trials. We are optimistic for SEL-212 in refractory gout and believe their pipeline, although early, has depth and potential to treat a number of unmet needs.

For more information see: http://selectabio.com/

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