First Take

Biophytis SA (BPTS)

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Price: $4.22; Market Cap (M): $63; *2/2/2022 Close*

Rating: Buy; Price Target: $15.00

Joseph Pantginis, Ph.D. - (646-975-6968) / jpantginis@hcwresearch.com
Emanuela Branchetti, Ph.D. - (646-975-6950) / ebranchetti@hcwresearch.com

Sarconeos Brings Hope to Severe COVID-19 Patients in Brazil; Regulatory Approval to Start Treating

Brazilian regulators approve the use sarconeos in a group of severe, ventilated COVID-19 patients. This morning, Biophytis announced that the Brazilian Health Regulatory Agency (ANVISA) has approved the company's Expanded Access Program (EAP) request for sarconeos, the company's MAS receptor activator, to treat severe COVID-19 patients under mechanical ventilation. ANVISA's EAP approval requires that: 1) the product targets patients with a serious debilitating and/or life-threatening disease; 2) there is no registered therapeutic alternative in the country; and 3) the authorization to use the product is under the responsibility of the prescribing physician. Brazil currently has the second-highest number of COVID-19-related deaths and is third-highest in the number of COVID-19 cases, with an increasing number of ICU admissions. A maximum of 80 hospitalized patients, mechanically ventilated in the intensive care units of Brazilian hospitals, are expected to be treated with sarconeos for up to 28 days with the objective to prevent further deterioration and death. Treating these critically ill patients, complements the COVA Phase 2/3 trial that is currently evaluating sarconeos in the U.S., Europe and Latin America in non-intubated hospitalized COVID-19 patients with severe respiratory complications. Based on this first approval and following the completion of the COVA study, which is expected during 1H22, Biophytis plans to extend the EAP submission to other countries. We believe that the Brazilian EAP approval of sarconeos can provide important safety and efficacy data, and potentially bring sarconeos closer to commercialization.

Patient recruitment for COVA clinical trial restarts in U.S. centers. Recently, Biophytis announced that after a short pause while interim analysis of Sarconeos global COVA clinical trial for COVID-19 was undertaken, patient recruitment re-opened in U.S. centers. In September, the independent data monitoring committee (DMC) indicated that the study had no futility, demonstrated a favorable safety profile and a promising zone of efficacy, and recommended the unmodified continuation of the trial. Now, the FDA has confirmed that following the DMC recommendation, patient enrollment can restart in the U.S. To date, COVA Phase 2/3 study has enrolled 216 patients hospitalized with severe pneumonia from COVID-19 infection in 35 centers in the U.S., Brazil, France, and Belgium. The company expects 5 out of 15 targeted clinical centers to start recruiting patients in Brazil and in the U.S. soon, granting COVA clinical trial a network of around 50 centers enrolling between 310 and 465 patients. The trial aims to confirm the promising efficacy reported in the interim analysis and validate Sarconeos as a therapeutic solution for patients hospitalized with severe respiratory manifestations, without pharmacological treatment options. Biophytis expect to complete patient recruitment and report final results during 1Q22. Emergency Use Authorization (EUA) in the U.S. and Conditional Marketing Authorization (CMA) in Europe for Sarconeos in the treatment of COVID-19 is expected by 2Q22. Additional information on the COVA clinical trial, Sarconeos and Biophytis can be found in our recent initiation: *Phytochemical Approach for Conditions With Unmet Need; Initiating at Buy and $15 PT*.

Taking the path(way) less traveled; Sarconeos as a COVID-19 treatment option. Even with the development of vaccines against COVID-19, there remain breakthrough cases and millions still remain unvaccinated. With incomplete vaccination coverage, therapeutics continue to play a key role. With many anti-inflammatory and anti-viral treatments currently in development, Sarconeos has the potential to be a first-in-class treatment option targeting RAS, which is known to be dysregulated upon SARS-CoV-2 infection and induce respiratory failure. Though 80% of COVID-19 cases are mild, 20% are severe/critical with a high propensity for respiratory infections, the latter of which is the target population of Sarconeos. The competitive landscape of COVID-19 treatments targeting RAS system is still limited, and Biophytis thus far has had two interim analyses with positive feedback from an independent data monitoring committee (DMC), which recommended the COVA Phase 2/3 studies proceed unmodified. The company is currently scaling up manufacturing activities with a targeted commercialization timeline in 2022.

Sarconeos (BIO101) likely a pipeline in a drug. Using a proprietary platform, the company focuses on targeting pathways that slow the degenerative processes associated with aging and improving functional outcomes in patients. The company's lead asset, Sarconeos (BIO101) is purified from the plant *Stemmacantha carthamoides*, cultivated in China and used for medicinal purposes in traditional Chinese medicine. Sarconeos (BIO101) targets the MAS receptor of the Renin Angiotensin System (RAS), a complex hormonal signaling pathway implicated in several physiological processes, including blood pressure, inflammation and fibrosis. This mechanism of action allows it to be leveraged across a growing range of indications. The furthest along in clinical development is the company's COVID-19 program, COVA, aimed at treating severe respiratory failure in COVID-19 patients. Sarconeos is also being developed for sarcopenia and Duchenne Muscular Dystrophy (DMD). Sarcopenia is a disorder involving skeletal muscle degeneration, weakness and movement impairment occurring in elderly individuals, has no current approved therapy and afflicts over 17M people in just the U.S. and Europe. DMD is a rare, genetic neuromuscular disease in male children with no cure and limited treatment options. We believe the shares should be attractive to investors based on: (1) potential commercialization of Sarconeos for COVID-19 on the horizon; (2) upcoming clinical milestones across multiple programs; and (3) an expanding portfolio in several indications continues, which could further value of the shares over the long term.

Sarconeos well-positioned to advance in clinical development for sarcopenia. Sarcopenia is an age-associated syndrome characterized by loss of muscle mass and function. With an aging patient population and no currently approved medication or widely accepted standard of care for the disease, there remains are large market potential for Sarconeos. Sarconeos activates key signaling pathways involved in maintaining skeletal muscle strength and mobility (AKT and AMPK) through the activation of the RAS receptor, MAS. In clinical studies to date, Sarconeos has shown a favorable safety and efficacy profile. Topline phase 2 data from the SARA-INT trial have shown that at the highest dose (350 mg bid), Sarconeos treatment led to a clinically meaningful improvement of 0.1 m/s in the 400-meter walk test, the primary endpoint of the study. The company is preparing to start a Phase 3 pivotal program with Sarconeos at the highest dose in 2022. By reaching this milestone, Sarconeos stands to be the only drug candidate in Phase 3 currently being tested for sarcopenia. We believe Biophytis would likely partner Sarconeos for pivotal development.

Sarconeos expands its reach to DMD where poor skeletal muscle performance is a hallmark of disease. DMD develops as a result of the genetic deficiency of dystrophin, rendering muscles unable to repair themselves following mechanical stress which is normal when they contract. As a consequence, patients with DMD progressively lose skeletal, cardiac and in many cases, respiratory functions. Currently, there is no known cure for DMD and treatment options are limited to corticosteroids and precision medicine approaches which target only ~20% of DMD patients that harbor particular genetic mutations. Specific intracellular signaling pathways implicated in both anabolism (Akt/mTOR) and regeneration (MAPK), among others, contribute substantially to the degenerative process in DMD. Of note, both of these pathways feed through the MAS receptor. Emerging studies also implicate systemic mitochondrial defects as a cause of muscle atrophy. Preclinical studies have successfully demonstrated that Sarconeos activates signaling pathways impaired in DMD and increases skeletal muscle performance with improved mitochondrial respiration and anabolism. Biophytis was granted IND approval in December 2019 to initiate a Phase 1/2 clinical proof of concept trial (MYODA-INT) of an oral pediatric formulation of Sarconeos with a primary endpoint of respiratory function. We believe Sarconeos in DMD presents a significant commercial opportunity as there is a clear, well-defined target market of patients with a high unmet need. As the safety profile of Sarconeos has already been established in two other indications, we anticipate a relatively straightforward path for clinical development. Further, and importantly, we believe that Sarconeos has the potential to be complimentary to both approved approaches and the heralded gene therapy approaches currently under development.

Seeing is believing; Macuneos (BIO201) has blockbuster potential in dry-AMD. The company's second lead molecule Macuneos (BIO201), is designed to treat dry age-related macular degeneration (AMD). Dry AMD accounts for over 85% of AMD cases, and remains largely untreated, affecting nearly 30M people in the US and Europe. As with sarcopenia, dry-AMD is likely to increase in prevalence given the aging demographics of the populations in developed countries. The combination of demographics, growing prevalence and lack of approved therapies to date, creates a market in dry-AMD primed for an innovative, blockbuster drug. Macuneos acts by preventing the photo-oxidative and inflammatory stresses induced by the accumulation of N-retinylidene-N-retinylethanolamine (A2E) in retinal pigment epithelial (RPE) cells, which are responsible for the retinal degeneration observed in AMD. While still several years away from market entry, pre-clinical proof-of-concept data in animal models have shown that Macuneos preserves

retinal function and the number of photoreceptors in the eye. Biophytis plans to initiate a Phase 1 clinical trial (MACA-PK) to assess Macuneos safety and PK/PD in healthy volunteers in 2Q21, followed by a Phase 2a/b interventional study (MACA-INT) in patients with geographic atrophy (GA) in one eye and intermediate-stage AMD in the fellow eye. Following MACA-PK in early 2022, Biophytis also plans to explore clinical development of Macuneos for Stargardt disease, the most common form of inherited macular degeneration that typically develops in childhood.

Valuation and risks to price target achievement. We reiterate our Buy rating and $15 price target. Our valuation is based on our clinical net present value (NPV) model, which allows us to flex multiple assumptions affecting a drug's potential commercial profile. We currently value only Sarconeos and its two lead indications, sarcopenia and COVID-19; at this point we are not including Macuneos in our valuation to be conservative, though it has the potential to be a significant contributor to the valuation based on the lack of approved therapies for dry-AMD. Regarding Sarconeos, the two indications referenced contribute approximately 50% each to our valuation. For COVID-19, the revenue opportunity is much closer for the company where we project a 2022 launch and $525 million in peak sales in the U.S. What this does not take into account is: (1) the underlying risk of the need for COVID-19 therapies waning, though we believe the endemic properties of the virus should keep a baseline market for drugs; and (2) the potential recurring revenue opportunity for Sarconeos should any governments look to stockpile the asset and either increase the order over time, or re-up orders based on shelf life of the asset. With respect to sarcopenia, the addressable population is quite large, and therefore we believe that our projections are conservative. The biggest risk, in our belief, is what the regulatory path could look like regarding primary clinical endpoints as this indication continues to be relatively amorphous as to how a first-to-market drug might make it. To this end, we are projecting a 2026 launch off of a 55% chance of success and $1.2 billion in peak sales in the U.S. Moving forward, we believe upside potential to our valuation exists based on: (1) attaining higher market penetration than anticipated; (2) adding additional assets and indications to our valuation, such as Macuneos based on development stage and clinical data; and (3) augmenting projected chances of success based on clinical progress. Factors that could impede reaching our price target include failed or inconclusive clinical trials, the inability of the company to secure adequate funding to progress its products through the development pathway or the occurrence of dilutive capital raises, and lack of commercial success.

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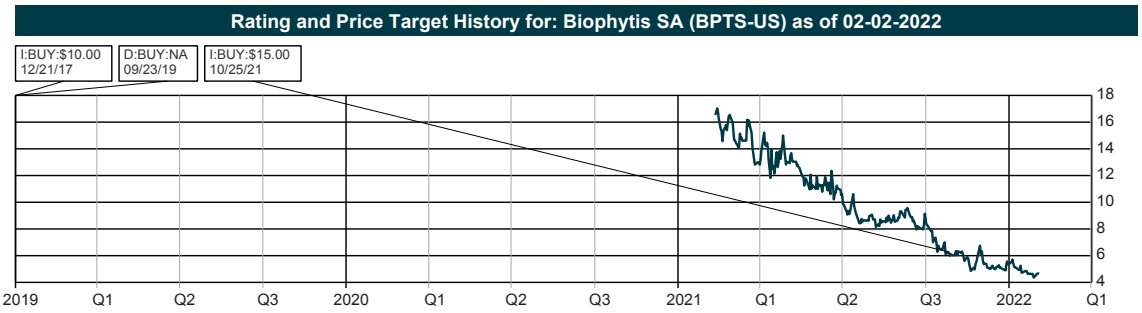

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			IB Service/Past 12 Months	
Ratings	Count	Percent	Count	Percent
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Neutral	41	6.45%	12	29.27%
Sell	1	0.16%	0	0.00%
Under Review	8	1.26%	2	25.00%

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