LifeSci Capital KOL Series - Sarcopenia

KOL Series

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We recently attended a Key Opinion Leader event that focused on new clinical developments for Sarcopenia treatments. The event featured a presentation from Dr. Roger Fielding, a Professor of Nutrition, and Director and Senior Scientist of the Nutrition, Exercise Physiology and Sarcopenia (NEPS) Laboratory at Tufts University. The event also included a program update from Biophytis (Euronext Paris: ALBPS), on their lead candidate, *Sarconeos*, which is currently in Phase II development for Sarcopenic Obesity. A replay of the webcast is available here.

Analysts

Patrick Dolezal, M.S. (AC)
(212) 915-2579
pdolezal@lifescicapital.com

- **Sarcopenia is an Age Associated Loss in Muscle Mass and Function, and Represents a Substantial Unmet Need.** Sarcopenia has been defined in various ways, and Dr. Fielding noted that all operational definitions include an objective measure of muscle or lean mass, with muscle weakness or reduced physical functioning. The etiology of sarcopenia is multifactorial, as its development is influenced by an age-related decline in muscle use and production of anabolic hormones such as dehydroepiandrosterone (DHEA) and testosterone, as well changes in signaling at neuromuscular junctions. Genetic factors, dietary patterns, and the presence of other co-morbidities also contribute to the development of sarcopenia. According to Dr. Fielding, these factors contribute to an average muscle mass loss of 2% per year after the age of 50. As muscle mass decreases, there is a corresponding loss of muscle strength. Therefore, patients with sarcopenia frequently experience functional limitations and disability.

  There are currently no approved pharmacologic therapies for sarcopenia. The mainstays of treatment are physical activity and resistance exercise training, which have been shown to be the most effective interventions. Physicians may also recommend dietary changes, or vitamin D supplements. Many patients, particularly the elderly, may not be able to easily adopt changes in diet or physical activity. Thus, there is a need for an effective therapy that can slow muscle loss and functional decline.

- **Sarcopenia is Now Recognized by WHO and has an ICD-10 Code.** We note that increasing awareness and research on sarcopenia has resulted in its official recognition as a disease entity. In September 2016, an ICD-10 code was created for Age-related Sarcopenia, differentiating the disease from other causes of skeletal muscle loss. Internal Classification of Disease (ICD) codes are established by the World Health Organization (WHO) and serve as the diagnostic classification standard for all clinical and research purposes. They are used to monitor incidence and prevalence of disease, observe reimbursement and resource allocation trends and keep track of safety and quality guidelines. This official recognition may further increase physician interest in the disease and ultimately improve diagnosis.

- **The Importance of Skeletal Muscle is Undervalued.** Robust skeletal muscle is a central factor in whole body health and is essential for maintaining homeostasis. In addition to its fundamental role in mobility, skeletal muscle is also involved in oxygen consumption, whole body energy metabolism, and substrate turnover and storage. Furthermore, it is a potent secretory organ that synthesizes and releases compounds that have presumed effects on other tissues. Poor skeletal muscle performance is a critical component in many disease conditions including sarcopenia, orthopedic diseases, cachexia due to chronic diseases, and neuromuscular and degenerative muscle diseases. Moreover, poor mobility is associated with increased hospitalization rates, healthcare costs, and mortality. Therefore, preserving muscle mass and strength is important not only for the maintenance of functional ability and quality of life, but also for long-term survival.

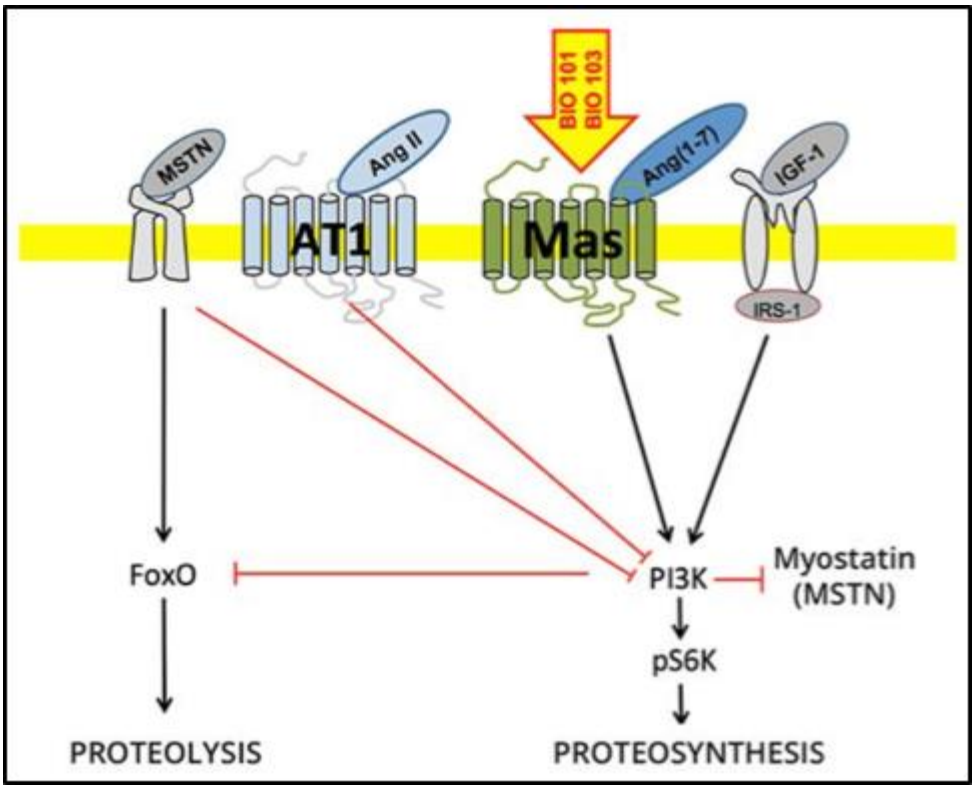
- **Growth of the Aging Population Will Likely Result in an Increased Prevalence of Sarcopenia.** As of 2015, an estimated 8.5% of the world's population, or 617 million people were aged 65 and older. By 2030, the number of people older than 65 years is expected to increase more than 60%, to approximately 1 billion people. Furthermore, the fastest growing segment of people older than 65 years old is the group that is 85 years or older. The KOL notes that with increasing life expectancy and the expansion of this segment of the population, an increase in people living with functional limitations, disability, and frailty is inevitable. He estimates that the current prevalence of sarcopenia is 0.5% to 13% across the general population, meaning as many as 39 million people in the US are affected by this condition. He also expects that the prevalence will likely increase as the elderly population grows, given the role advanced age plays in disease development. Due to the current prevalence of this disease, future population trends, and lack of approved treatments, sarcopenia represents a large market opportunity.

- **The Renin-Angiotensin System Plays a Role in Muscle Metabolism.** RAAS is a hormonal pathway that modulates a variety of physiological functions including sodium balance, cardiac outputs, arterial blood pressure, and muscle metabolism. This system is principally regulated by the peptide hormone angiotensin II (Ang II), which is produced by hydrolysis of angiotensin I by angiotensin-converting enzyme (ACE) in the lung and the vascular endothelium, and circulates throughout the body. Ang II is also thought to play a role in muscle metabolism, as it activates AT1R receptors and downstream signaling components that promote proteasome activity, one of the primary mechanisms of cellular protein degradation. Ang II also indirectly promotes the expression of myogenesis factors, including myostatin, glucocorticoids, IL-6, and TNF-a, which act to stimulate protein degradation and inhibit protein synthesis.

  Angiotensin1-7 (Ang1-7) is a second signaling peptide in the RAAS pathway that is thought to largely counteract the activities of Ang II. Ang 1-7 activates the G protein couple receptor (GPCR) MAS, which signals through the Akt/PI3 kinase pathway to stimulate protein synthesis and inhibit protein degradation. Data from preclinical models indicate that Ang 1-7 can prevent Ang II associated decreases in muscle mass and strength in part by inducing the expression of insulin growth factor-1 (IGF-1) and IGF-1 receptors in skeletal muscle cells. Biophytis's *Sarconeos*, binds the same GPCR as Ang 1-7, allowing it to activate the same signaling cascades that result in muscle anabolism.

- **Sarconeos has a Mechanism of Action that May Result in Increased Muscle Mass.** *Sarconeos* is an orally administered agonist of the MAS receptor that promotes protein synthesis and inhibits protein degradation in a similar way to similar to Ang 1-7. A detailed depiction of the mechanism of action is presented in **Figure 1**. *Sarconeos*-dependent activation of MAS induces Akt/PI3 kinase-mediated protein synthesis by stimulating the activity of the translational regular S6 kinase (S6K). Activation of the Akt/PI3 kinase pathway also leads to the inhibition of anti-myogenesis factor myostatin and its downstream effector FoxO. *Sarconeos*-dependent activation of MAS has the potential to slow the development of sarcopenia by increasing muscle cell diameter, stimulating protein synthesis, and S6K activity, and inhibiting myostatin production. The sum of the activity of *Sarconeos* is the promotion of muscle anabolism while counteracting the proteolytic effects of angiotensin II, which may lead to increases in muscle mass.

Figure 1. Sarconeos Signals Through the MAS Receptor

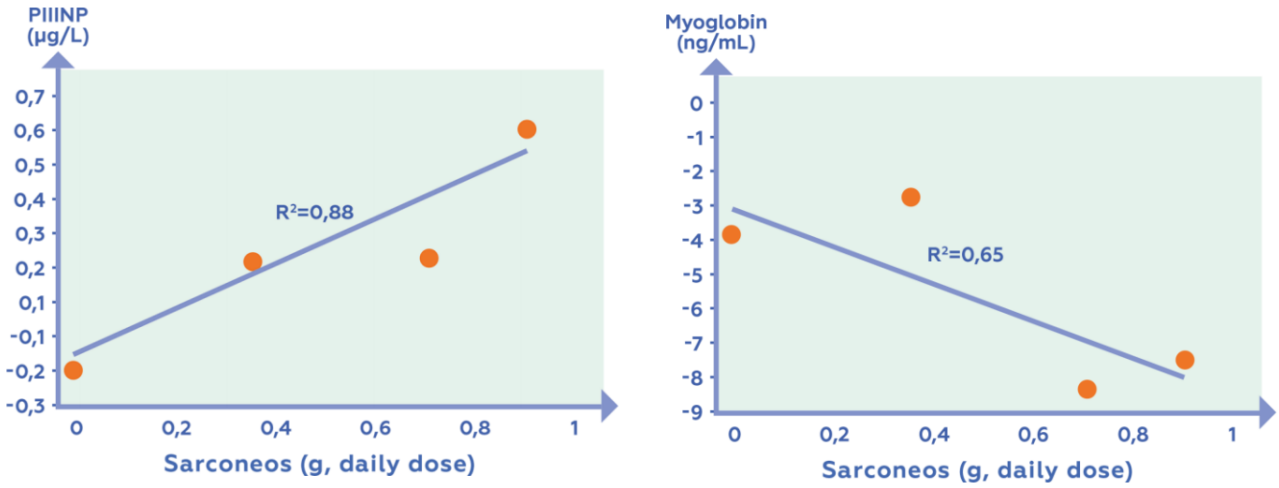


Source: Company Presentation

- **Phase I Trial-Safety and Pharmacokinetics.** Biophytis conducted the SARA-PK Phase I study evaluating the safety, tolerability and pharmacokinetic profile of oral *Sarconeos* in 54 healthy volunteers. The trial assessed both single ascending dose (SAD) and multiple ascending dose (MAD) administration. SAD administration was tested in 24 subjects of varying ages, while the MAD portion of the study enrolled 30 subjects over the age of 65. The SAD arm was a staggered design involving 3 cohorts of patients that received a 14-day course of oral *Sarconeos*. 2 cohorts of adults, aged 18 to 55, received escalating doses of 100 mg *Sarconeos* to 1400 mg *Sarconeos*, and 1 cohort of adults, aged 65 to 85, received 1400 mg *Sarconeos*. Participants in the MAD arm received a 14-day course of oral *Sarconeos* in escalating doses of 350 mg, 700 mg, then 900 mg, daily.

There were no reports of serious adverse events in either arm of the study, and an acceptable safety profile was observed in elder subjects. The pharmacokinetic profile of *Sarconeos* was also found to be favorable, as desired plasma concentrations of *Sarconeos* were maintained between oral administrations, and not influenced by patient age or food intake. Furthermore, the analysis of biomarkers confirmed the stimulation of muscular anabolism and the activation of the RAS system, which is presented in **Figure 2**. Data indicate dose-dependent increases in N-terminal Propeptide of Type III Collagen (PIIINP) and decreases in myoglobin, which serve as potential indicators of muscle anabolism and catabolism, respectively. Based on these findings, investigators were able to confirm drug safety and identify two doses to test in a Phase IIb trial.

Figure 2. Biomarker Data from Phase I Study for Sarconeos



Source: Company Presentation

- **Phase IIb Trial Design.** Biophytis is currently conducting SARA-OBS, an observational study of 300 sarcopenic patients being conducted to better characterize the sarcopenia patient population. The primary endpoint is performance during the 6-minute walk distance test (6MWD) or 400-meter walk test. The 6MWD test involves measuring the distance covered by a patient after walking for 6 minutes, whereas the 400-meter walk test is a measure of how long it takes a patient to walk 400 meters. During the 400-meter walk test, patients are expected to walk at their normal pace. It has been shown that patients who have a faster baseline gait speed have lower mortality. Thus, using the 400-meter walk test and allowing patients to walk with their normal gait speed, may provide more insight about mortality, than the 6MWD test. Dr. Fielding also noted that patients capable of walking a quarter mile have lower healthcare costs and hospitalization rates, further highlighting the important of walking metrics. Patients' mobility and muscular function will also be evaluated using assessments of grip strength, short physical performance battery (SPPB), muscle mass, fat mass, and plasmatic biomarkers. Patients in the observational study will be able to participate in the subsequent interventional study of *Sarconeos*, upon giving consent.

  SARA-INT is the interventional study to follow SARA-OBS, and will be a randomized, double-blind, placebo-controlled Phase IIb trial testing the safety and efficacy of *Sarconeos* in patients with sarcopenia. Approximately 333 participants will be randomized to receive a 6-month oral treatment course of twice-daily 175 mg *Sarconeos*, 350 mg *Sarconeos*, or placebo. The primary endpoint of this study will likely be either performance during a 6-minute walk test or 400-meter walk test. Secondary endpoints will likely include various evaluations of grip strength, SPPB, muscle mass, and fat mass. We also note that patients will wear an accelerometer device on their wrists that will collect data on mobility-related activity. Investigators are also interested in obtaining data that captures patients' perspective on the efficacy of the drug.

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We consider an investment in Biophytis to be a high-risk investment. Biophytis is currently in clinical-stage development and does not have any marketed or approved products. The Company has not entered Phase III clinical trials for any program. Failure to show convincing results in future pivotal clinical studies or failure to reach FDA or EMA approval could adversely affect Biophytis's stock price. Regulatory approval to market and sell a drug does not guarantee that the drug will penetrate the market, and sales may not meet expectations. As a clinical-stage company, Biophytis is not profitable and may need to seek additional financing from the public markets, which may result in dilution of existing shareholder value.

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