Spruce Biosciences Provides Clinical Program Updates and Outlook for 2022

January 24, 2022

Topline Data from CAHmelia-203 and CAHmelia-204 Anticipated in 2H 2023 and 2H 2024, Respectively

Strategic Reprioritization Extends Anticipated Cash Runway by 6 Months into Q2 2024

CAHmelia Program in Adult Classic CAH to Significantly Expand Sites Globally, Planned Increase of Up to 50 New Sites

Company Implementing Protocol Amendments to Enhance Design of and Accelerate Patient Recruitment in CAHmelia-203 and CAHmelia-204 Trials

SAN FRANCISCO--(BUSINESS WIRE)--Jan. 24, 2022-- Spruce Biosciences, Inc. (Nasdaq: SPRB), a late-stage biopharmaceutical company focused on developing and commercializing novel therapies for rare endocrine disorders with significant unmet medical need, today provided an update on its clinical programs, upcoming milestones and strategic priorities for enhancing the design of and accelerating patient recruitment into the CAHmelia studies, which are evaluating tildacerfont for the treatment of adult classic congenital adrenal hyperplasia (CAH).

“Following a comprehensive assessment of the CAHmelia program, we’ve identified opportunities to accelerate patient recruitment and enhance the designs of the studies evaluating the potential of tildacerfont as a treatment for adult patients with classic CAH,” said Javier Szwarcberg, M.D., MPH, Chief Executive Officer of Spruce Biosciences. “By increasing the number of global trial sites and effecting protocol amendments, we will be well-positioned to meet our revised topline data milestones. In addition, we have reprioritized activities which has enabled us to extend our anticipated cash runway by approximately 6 months, taking us into Q2 2024. We look forward to building momentum in 2022 with this new focus, wherein we execute on our strategic business and clinical objectives.”

Anticipated Milestones

- Completion of enrollment from the Phase 2 proof of concept clinical trial in polycystic ovary syndrome (PCOS) by the end of 2022 and topline results by the first half of 2023
- Topline results from CAHmelia-203 in adult classic CAH patients with poor disease control by the second half of 2023
- Topline results from CAHmelia-204 in adult classic CAH patients with good disease control by the second half of 2024

Tildacerfont Program Updates

Late-Stage CAHmelia Program in Adult Classic CAH

- **Study Site Global Expansion for CAHmelia Program to Increase Enrollment:** To increase patient enrollment in Spruce’s CAHmelia-203 and CAHmelia-204 studies, the company plans to significantly expand the number of study sites by up to 50 new sites, for a total of up to 130 sites worldwide. This includes adding sites to currently selected regions in the United States, Australia, Canada, Germany, Denmark, Spain, Italy, Netherlands, Poland, Sweden, and the United Kingdom. Further, the company plans to expand the study and identify sites within new countries. The additional sites are anticipated to expand recruitment capabilities to accelerate enrollment.

- **Protocol Amendments to Enhance Recruitment in CAHmelia-204:** Following the completion of a full assessment of the study protocol for the CAHmelia-204 study, Spruce is implementing two key protocol changes: amending the androstenedione (A4) inclusion criteria and eliminating the glucocorticoid conversion requirement.
    - Amending A4 Inclusion Criterion: Spruce is amending the A4 inclusion criterion for the study from ≤1.5X to ≤2.5X the upper limit of normal (ULN). The amended A4 criterion will provide adult patients with slightly elevated A4 levels and baseline glucocorticoid regimen of ≥30 mg/d hydrocortisone equivalent (HCe) the opportunity to enter the study and reduce glucocorticoid usage according to a study protocol pre-defined algorithm. Based on current screening to date, the amended criterion is anticipated to increase enrollment into CAHmelia-204.
    - Elimination of Glucocorticoid Conversion Requirement: Under the revised protocol, patients enrolling in the study will be allowed to continue their existing glucocorticoid regimen while receiving study drug. Previously, patients in the study were required to convert their existing glucocorticoid regimen to sponsor-provided glucocorticoids as outlined in the study protocol, a requirement that led to declining interest in the study. To accommodate this protocol amendment, the company will implement a robust accounting system to track glucocorticoid use and compliance for study participants.

- **Protocol Amendments to Enhance Designs of CAHmelia-203 and CAHmelia-204:** Following the completion of a full assessment of the CAHmelia-203 and CAHmelia-204 study protocols, Spruce is amending the primary endpoint in CAHmelia-204 and adjusting the A4 and adrenocorticotropic hormone (ACTH) inclusion criteria in CAHmelia-203.
    - Amending Primary Endpoint of CAHmelia-204 to a Responder Analysis: Spruce is amending the primary endpoint of CAHmelia-204 assessed at Week 24 from an absolute change in HCe to a responder analysis evaluating the

proportion of patients with ≥5 mg/d HCe dose reduction while maintaining an A4 level within normal limits. A 5 mg/d HCe reduction while maintaining androgen control is considered a clinically important outcome and reflects a measure of individual clinical benefit for each study subject. Change in HCe will become a key secondary endpoint under the revised protocol.

- Amending A4 and ACTH Inclusion Criteria in CAHmelia-203: Spruce is increasing the A4 inclusion criterion to >2.5X the ULN and is removing the ACTH inclusion criterion as the A4 level inclusion criterion alone provides sufficient evidence of excessive adrenal stimulation by ACTH.

- **Implementation of Optional Pre-Screening Protocol:** Spruce will be implementing an optional pre-screening protocol to enable prompt determination of key inclusion criteria under the revised CAHmelia-203 and CAHmelia-204 study protocols. The pre-screening protocol streamlines screening activities for both CAHmelia-203 and CAHmelia-204 into a single protocol and is anticipated to increase overall screening and allow for more efficient assessment of eligibility by study sites into either CAHmelia-203 or CAHmelia-204.

Pediatric Classic CAH Program

- **Phase 2 Clinical Trial in Pediatric Classic CAH Now Initiated:** Spruce is investigating tildacerfont for the treatment of classic CAH in children and recently initiated a Phase 2 clinical trial. There is a significant medical need to bring androgen-lowering and glucocorticoid-sparing therapies to pediatric classic CAH patients to reduce the risk of premature puberty and the adverse effects of glucocorticoids, including stunted growth resulting in short stature as adults. The Phase 2 open-label clinical trial will utilize a sequential 3 cohort design to evaluate the safety, pharmacokinetics, and exploratory pharmacodynamics of tildacerfont in children 6 to 17 years of age with classic CAH.
- **Pediatric Investigational Plan (PIP) for Tildacerfont Adopted by European Medicines Agency (EMA):** The Pediatric Committee (PDCO) of the EMA adopted a positive opinion on its agreement with the proposed PIP of tildacerfont for the treatment of CAH. The PIP opinion from PDCO endorsed the clinical program to evaluate the safety, tolerability and efficacy of tildacerfont for the treatment of CAH in patients from one year of age to less than 18 years of age. PDCO also granted a waiver for the treatment of CAH in patients less than one year of age. The adoption of the PIP paves the way for the initiation of a Phase 3 registrational program in pediatric classic CAH following a successful completion of the current Phase 2 clinical trial.

Polycystic Ovary Syndrome (PCOS) Program

- **Phase 2 Proof of Concept Clinical Study in PCOS Now Initiated:** Spruce recently initiated a randomized, placebo-controlled, dose escalation study which will evaluate the safety and efficacy of tildacerfont titrated to 200 mg once daily compared to placebo at 12 weeks in subjects with PCOS and elevated adrenal androgens as measured by dehydroepiandrosterone sulfate (DHEAS) levels at baseline. PCOS is a hormonal disorder common among females of reproductive age characterized by hirsutism, irregular periods, and ovarian cysts. Adrenal androgen overproduction is thought to contribute to the clinical manifestations of PCOS in some patients. By reducing ACTH-stimulated adrenal androgen production, tildacerfont has the potential to treat the clinical sequelae of PCOS.

Financial Update

The company estimates that its cash, cash equivalents, and investments were $121.4 million as of December 31, 2021. This amount is unaudited and preliminary and is subject to completion of financial closing procedures.

Strategic prioritization of activities has resulted in projected program cost reductions and deferrals of expenditures that are aligned with updated program timelines. Spruce has extended its expected cash runway by approximately 6 months, from Q4 2023 into Q2 2024.

About Spruce Biosciences

Spruce Biosciences is a late-stage biopharmaceutical company focused on developing and commercializing novel therapies for rare endocrine disorders with significant unmet medical need. Spruce is initially developing its wholly-owned product candidate, tildacerfont, as the potential first non-steroidal therapy for patients suffering from classic congenital adrenal hyperplasia (CAH). Classic CAH is a serious and life-threatening disease with no known novel therapies approved in approximately 50 years. Spruce is also developing tildacerfont for women suffering from a rare form of polycystic ovary syndrome (PCOS) with primary adrenal androgen excess. To learn more, visit www.sprucebiosciences.com and follow us on Twitter @Spruce_Bio, LinkedIn, Facebook and YouTube.

Forward-Looking Statements

Statements contained in this press release regarding matters that are not historical facts are “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995. Such forward-looking statements include statements regarding, among other things, the results, conduct, progress and timing of Spruce’s clinical trials, including the impact of the strategies to enhance the design of and accelerate patient recruitment into the CAHmelia studies, the fulfillment of Spruce’s strategic business objectives, the advancement of Spruce’s drug development pipeline, and Spruce’s expectations regarding its extended cash runway. Because such statements are subject to risks and uncertainties, actual results may differ materially from those expressed or implied by such forward-looking statements. Words such as “plans”, “will”, “believe”, “potential” and similar expressions are intended to identify forward-looking statements. These forward-looking statements are based upon Spruce’s current expectations and involve assumptions that may never materialize or may prove to be incorrect. Actual results could differ materially from those

anticipated in such forward-looking statements as a result of various risks and uncertainties, which include, without limitation, risks and uncertainties associated with Spruce's business in general, the impact of the COVID-19 pandemic, and the other risks described in Spruce's filings with the U.S. Securities and Exchange Commission. All forward-looking statements contained in this press release speak only as of the date on which they were made and are based on management's assumptions and estimates as of such date. Spruce undertakes no obligation to update such statements to reflect events that occur or circumstances that exist after the date on which they were made, except as required by law.

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