Spruce Biosciences Presented Phase 2 POWER Study Results of Tildacerfont for the Treatment of Polycystic Ovary Syndrome at ENDO 2024

June 3, 2024

Significant Reduction in Dehydroepiandrosterone Sulfate (*DHEAS) Versus Placebo Observed in Women with Elevated DHEAS Levels at Baseline*

Increase in Serum Sex Hormone Binding Globulin (SHBG) Versus Placebo Observed

Tildacerfont was Well-Tolerated with No Safety Signals

SOUTH SAN FRANCISCO, Calif.--(BUSINESS WIRE)--Jun. 3, 2024-- Spruce Biosciences, Inc. (Nasdaq: SPRB), a late-stage biopharmaceutical company focused on developing and commercializing novel therapies for endocrine disorders with significant unmet medical need, presented results from its Phase 2 POWER study of tildacerfont, a second-generation CRF_1 receptor antagonist, for the treatment of polycystic ovary syndrome (PCOS) at the 2024 Annual Meeting of the Endocrine Society (ENDO 2024).

“There is a significant unmet medical need for new PCOS treatments as there are currently no FDA-approved therapies, and the standard of care only addresses symptoms,” said Lubna Pal, MBBS, FACOG, M.S., Director, Program for Polycystic Ovary Syndrome, Yale Reproductive Endocrinology, Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine. “The results of this study are exciting; by demonstrating the ability of tildacerfont to reduce DHEAS, it is plausible that a myriad of health risks that are consequent to chronic hyperandrogenism could be harnessed with this approach.”

Will Charlton, M.D., M.A.S., Chief Medical Officer, Spruce Biosciences, commented, “We are grateful to our partners, study investigators, and patients who contributed to the POWER study, which brings us one step closer to more effective treatments for PCOS, a highly prevalent condition with significant unmet medical need. Further studies of tildacerfont for the treatment of PCOS are warranted, and we continue to evaluate strategic collaboration opportunities to advance this potentially disease-modifying treatment option forward.”

Phase 2 POWER Study Results

The POWER study enrolled 27 women with a confirmed diagnosis of PCOS. Participant demographics and baseline hormone levels are detailed in Table 1 below.

Table 1. Summary of Demographics and Baseline Hormones; Intent to Treat Analysis Population

Key Variables Mean (SD)	Tildacerfont (n = 17)	Placebo (n = 10)	Total (n = 27)
Age	28.4 (5.6)	29.3 (5.5)	28.7 (5.4)
Age at PCOS Diagnosis	22.6 (6.3)	21.6 (6.0)	22.3 (6.1)
BMI (kg/m^2)	32.1 (5.8)	32.4 (12.5)	32.2 (8.6)
DHEAS (µg/dL)	351.3 (90.5)	387.8 (107.2)	364.8 (96.7)
17-OHP (ng/dL)	83.2 (86.3)	62.1 (54.1)	75.4 (75.5)
ACTH (pg/mL)	23.9 (11.9)	22.3 (12.0)	23.3 (11.7)
A4 (ng/dL)	185.2 (75.2)	130.0 (66.0)	166.8 (75.6)
T (ng/dL)	61.0 (22.0)	61.1 (27.0)	61.0 (23.4)
Screening DHEAS > ULN, N (%) Yes No	 12 (70.6%) 5 (29.4%)	 7 (70.6%) 3 (29.4%)	 19 (70.4%) 8 (29.6%)

In women with elevated baseline DHEAS, a significant reduction in DHEAS versus placebo was observed (p = 0.020).

*Table 2. Change from Baseline in DHEAS (*µg/dL*) at Week 12; Modified Intent to Treat Analysis; Baseline DHEAS > Upper Limit of Normal (ULN)*

	Tildacerfont (n = 12) [1]	Placebo (n = 7) [1]
n	11[2]	5[3]
Mixed Model of Repeated Measures		
Least Squares (LS) Geometric Mean Ratio (% Change from Baseline)	0.876 (-12.4%)	1.057 (5.7%)
95% Confidence Interval (CI) of Geometric Mean Ratio	0.802, 0.955	0.931, 1.200
95% CI of Percent Change from Baseline	-19.8%, -4.5%	-6.9%, 20.0%
Difference LS Mean Ratio [tildacerfont/placebo]	0.828	N/A
95% CI of Difference LS Mean Ratio	0.709, 0.967	N/A

p-value	0.020	N/A

1. Eight subjects (five in the tildacerfont arm and three in the placebo arm) did not meet inclusion criteria #3 requiring DHEAS to be greater than the ULN and were excluded from the analyses.
2. One subject was excluded from the analyses due to no post-baseline DHEAS assessment.
3. Two subjects were excluded from the analyses due to concomitant glucocorticoid (GC) use, which confounded assessment of adrenal steroid reduction.

In study participants, a significant increase in SHBG versus placebo was observed (p = 0.012).

Table 3. Change from Baseline in SHBG (nmol/L) at Week 12; Modified Intent to Treat Analysis

	Tildacerfont (n = 17)	**Placebo (n = 10)**
n	16[1]	9[1]
Mixed Model of Repeated Measures		
LS Geometric Mean Ratio (% Change from Baseline)	1.329 (32.9%)	0.919 (-8.1%)
95% CI of Geometric Mean Ratio	1.124, 1.571	0.735, 1.148
95% CI of Percent Change from Baseline	12.4%, 57.1%	-26.5%, 14.8%
Difference LS Mean Ratio [tildacerfont/placebo]	1.446	N/A
95% CI of Difference LS Mean Ratio	1.093, 1.913	N/A
p-value	0.012	N/A

1. Two subjects (one in the tildacerfont arm and one in placebo arm) did not have a week 12 SHBG assessment completed.

The Phase 2 study was not powered to test for statistical significance on the primary endpoint. However, the lowering of DHEAS, an adrenal androgen precursor, observed with 12-week exposure, suggests that tildacerfont may be of therapeutic benefit for some women with PCOS. Additionally, the observed increase in SHBG may potentially result in lower levels of free, bioactive sex hormones such as testosterone.

Tildacerfont was well-tolerated with no safety signals observed. The majority of adverse events were mild to moderate. No serious adverse reactions were reported.

About POWER Study

The POWER study was a Phase 2 proof-of-concept, randomized, placebo-controlled dose escalation study which evaluated the safety and efficacy of tildacerfont titrated to 200 mg QD compared to placebo at 12 weeks of treatment in 27 female subjects with polycystic ovary syndrome (PCOS) and adrenal androgens as measured by dehydroepiandrosterone sulfate (DHEAS) levels at baseline. The primary endpoint of this clinical trial was the absolute change from baseline in DHEAS. Additional secondary endpoints included safety and tolerability, the proportion of subjects who achieve a 30% or greater reduction in DHEAS and change from baseline in hormonal biomarkers.

About Tildacerfont

Tildacerfont is a potent and highly selective, non-steroidal, oral antagonist of the CRF_1 receptor, which is the receptor for corticotropin-releasing factor (CRF), a hormone that is secreted by the hypothalamus. The CRF_1 receptor is abundantly expressed in the pituitary gland where it is the primary regulator of the hypothalamic–pituitary-adrenal (HPA) axis. By blocking the CRF_1 receptor, tildacerfont has the potential to reduce the production of adrenocorticotropic hormone (ACTH) in the pituitary gland and limit the amount of androgens produced downstream from the adrenal gland. Adrenal androgen excess in PCOS appears to result from an elevation of, or hypersensitivity to, ACTH. Tildacerfont may provide a therapeutic option to treat the underlying cause of disease through reductions of ACTH, which may improve clinical symptoms of PCOS, such as hair growth, acne, irregular periods and infertility. No drug-related serious adverse events have been reported related to tildacerfont treatment in completed studies.

About Polycystic Ovary Syndrome (PCOS)

Polycystic ovary syndrome, or PCOS, is a hormonal disorder common among females of reproductive age affecting nearly five million females in the United States and approximately 115 million females worldwide. PCOS is characterized by elevated levels of androgens, cysts in the ovaries and irregular periods. Females with PCOS present with additional symptoms, including hirsutism, alopecia, acne, infertility, weight gain, fatigue, depression and mood changes. The underlying causes of PCOS are unknown. However, excess insulin secretion and low-grade inflammation, which stimulate the polycystic ovaries, have been linked to androgen excess. The source of this androgen excess may be ovarian, adrenal, both adrenal and ovarian, or from other sources. Adrenal androgen excess in PCOS may occur independently of ovarian androgen excess, suggesting it may represent an intrinsic and possible primary source of abnormal synthesis of androgens. Adrenal androgen excess in PCOS does not result from enzymatic deficiencies, but rather from an altered adrenal responsivity to ACTH.

About Spruce Biosciences

Spruce Biosciences is a late-stage biopharmaceutical company focused on developing and commercializing novel therapies for endocrine disorders with significant unmet medical need. Spruce is developing tildacerfont, a second-generation CRF_1 receptor antagonist, for patients suffering from classic congenital adrenal hyperplasia (CAH) and polycystic ovary syndrome (PCOS). To learn more, visit www.sprucebio.com and follow us on X @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 design, results, conduct, progress and timing of Spruce's clinical trials; the potential of tildacerfont to reduce DHEAS for the treatment of PCOS; the potential of tildacerfont to increase SHBG and lower free bioactive sex hormones; and Spruce's product candidate, strategy and regulatory matters. 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 "potential", "suggest" 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 geopolitical and macroeconomic events, 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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