Neurocrine Biosciences Presented CAHtalyst™ Phase 3 Pediatric and Adult Studies, CAHtalog™ Registry and Disease- and Glucocorticoid-Related Comorbidities Data in CAH at ENDO 2024

June 3, 2024

SAN DIEGO, June 3, 2024 /PRNewswire/ -- Neurocrine Biosciences, Inc. (Nasdaq: NBIX) and Diurnal Ltd., a Neurocrine Biosciences company, presented information from its neuroendocrinology pipeline at the Endocrine Society Annual Meeting, ENDO 2024, including primary data just published in *The New England Journal of Medicine* from its CAHtalyst™ Phase 3 registrational studies of crinecerfont in pediatric and adult patients with congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency. In addition, Neurocrine Biosciences presented CAHtalog™ Registry data regarding the negative impact of high glucocorticoid (GC) doses and natural history in pediatric and adult CAH patients, as well as disease- and GC-related comorbidities data in CAH patients.

"We were thrilled to share our just published primary CAHtalyst Phase 3 data with ENDO 2024 attendees this past weekend," said Eiry W. Roberts, M.D., Chief Medical Officer at Neurocrine Biosciences. "Crinecerfont offers the potential of a long-awaited new treatment paradigm for endocrinologists in managing CAH. Our CAHtalyst Phase 3 data demonstrate the potential of crinecerfont to reduce elevated androgen levels and lower supraphysiologic glucocorticoid doses while maintaining androgen control in CAH patients of four years and older."

CAHtalyst™ Phase 3 Pediatric and Adult Data
In an oral presentation on June 1, Richard Auchus, M.D., Principal Investigator, Professor of Pharmacology and Internal Medicine, Division of Metabolism, Endocrinology, and Diabetes at the University of Michigan, presented CAHtalyst Phase 3 Adult data demonstrating that the study met its primary and important key secondary endpoints, with 63% of crinecerfont-treated participants achieving reduction in GC dosing to physiologic range (≤ 11mg/m^2/day) while maintaining androstenedione control at Week 24 as compared with just 18% with placebo control participants. The data were published in an online edition of *The New England Journal of Medicine* and will appear in a future print issue of the journal.

In a poster presentation on June 2, Kyriakie Sarafoglou, M.D., Professor, Department of Pediatrics and Department of Experimental and Clinical Pharmacology, Divisions of Endocrinology and Genetics & Metabolism, at the University of Minnesota, presented CAHtalyst Phase 3 Pediatric data demonstrating that the study met its primary and key secondary endpoints and was well tolerated, showing 29.9% of crinecerfont participants achieved a reduction in GC dosing to a physiologic range (≤11mg/m^2/day) at Week 28 while maintaining androgen control versus 0% of placebo participants (Poster #SUN-441). The data were published in an online edition of *The New England Journal of Medicine* and will appear in a future print issue of the journal.

CAHtalog™ Registry—Negative Impacts of Supraphysiologic Dosing in Patients with CAH
A real-world study explored the effects of high GC doses in pediatric and adult patients enrolled in the CAHtalog registry, highlighting the fluctuations in GC dose and androstenedione over time and the relationship between higher GC dose and negative clinical outcomes in patients with CAH (Poster #SUN-685). The findings included:

- Among 44 pediatric patients, 12 (27.3%) received a high GC dose (>15 mg/m^2/day), that was associated with:
  - Premature adiposity rebound starting at ~2 years of age (usual age is ~6 years)
  - Early growth acceleration attributed to advanced bone age, followed by blunted pubertal growth
- In 69 patients (45 pediatric, 34 adult and 10 in both groups) with available comorbidity-related data, hypertensive diseases and metabolic complications were significantly more prevalent with high versus low GC doses
  - In pediatric patients, short stature was more common with high versus low GC dose
- In 40 patients (27 pediatric, 14 adult and 1 in both groups) with ≥ 3 matched GC-androstenedione records, 92% had ≥ 1 transition in health state over the median 7-year observation period
  - Higher GC dose with androstenedione < upper limit of normal (ULN) was the most common health state observed at the first recorded datapoint (48%), with only 3% maintaining that health state throughout the observation period
  - Although 22% of patients presented with lower GC and androstenedione <ULN at the start of the observation period, none sustained this health state throughout the observation period; all patients (100%) had a higher GC dose and/or loss of androstenedione control at some point in their health state patient journey
  - Limitations included absence of temporal context, variation in observational period and number of records per patient and blood draw timing

"Higher rates of overweight/obesity, hypertensive and metabolic comorbidities related to high glucocorticoid dosing and androgen excess were seen across all age groups in this study," said Oksana Lekarev, D.O., Associate Professor of Clinical Pediatrics, Co-Medical Director of the Weill Cornell

Medicine Comprehensive Care Center for Congenital Adrenal Hyperplasia and an Associate Attending Pediatrician at New York-Presbyterian/Weill Cornell Medical Center and member of the CAHtalog Scientific Advisory Board. "The variability in control of adrenal androgens throughout the observation period underscores the difficulty in reaching a steady state in adrenal control and highlights the challenges that physicians face in managing CAH over a patient's lifetime."

CAHtalog^{TM} Registry—Natural History of CAH

The results of a longitudinal study were presented using medical records from the CAHtalog registry and provided insight into the natural history of classic CAH, including the height and weight trends that carry across pediatric and adult patient groups (Poster# SUN-417). Data were analyzed from 42 pediatric patients (55% female) and 32 adult patients (72% female) enrolled in the registry. Median duration of observation was 9 years in pediatric patients and 13 years in adults. The findings included:

- Pediatric patients had early growth acceleration followed by blunted pubertal growth. This trend was more pronounced in females, with mean height-for-age generally exceeding the 90th percentile at ages 4–10 years but dropping below 50th percentile at ages 13–17 years.
- Mean bone age-to-chronological age ratios were highest in females aged 5 years and males aged 7 years.
- The mean body mass index (BMI)-for-age consistently exceeded the 85th percentile (i.e., overweight or obese) in males aged ≥ 5 years and females aged ≥ 6 years.
- Across adult age groups in both sexes, median BMI met the threshold for overweight (≥ 25 kg/m^2) or obesity (≥30 kg/m^2).
    - 83% of female patients (all ages) and 100% of male patients had a BMI ≥ 25 kg/m^2
    - 74% of female patients and 33% of males had a BMI ≥ 30 kg/m^2
- Obesity, hypertension, fatigue, acne, and hyperlipidemia were common, particularly among adults. Among adults, the comorbidity of obesity (68%) was more prevalent than in the general population (42%).

Analyses of these real-world data highlight the limitations of current conventional GC therapies, which usually require supraphysiologic doses to manage adrenal androgen excess. High rates of comorbidities related to GC treatment and androgen excess indicate the challenges with current GC treatments in maintaining androgen control without causing adverse effects.

"CAHtalog Registry data reveals a persistent abnormal growth pattern in children, characterized by accelerated growth in early childhood and deceleration in adolescence, along with early obesity that was sustained into adulthood," said Perrin C. White, M.D., Chief, Division of Pediatric Endocrinology at the University of Texas Southwestern Medical Center, and a member of the CAHtalog Scientific Advisory Board. "These patterns along with high frequencies of comorbidities, including hypertension, fatigue, acne, hyperlipidemia, and insomnia and sleep disturbances, demonstrate the need for optimized disease management in patients living with CAH."

Claims-Based Cohort Analysis—Disease- and GC-Related Comorbidities in CAH

A retrospective cohort study was conducted analyzing insurance claims from 2020-2022 within the Merative MarketScan commercial and Medicaid databases (Poster #SUN-437). The frequency of comorbidities related to adrenal androgen excess and/or supraphysiologic GC dosing was captured using International Classification of Diseases, 10th Revision (ICD-10) codes. Matching between the CAH and general population (GenPop) cohorts was based on age, sex, payer type, region and enrollment duration with a 1:5 ratio (CAH:GenPop). Compared with GenPop, CAH patients had significantly greater rates of multiple chronic conditions related to both excess adrenal androgens and supraphysiologic GC doses, including short stature, anxiety disorders, and diabetes.

- Top significant comorbidities in adults with CAH versus GenPop:
    - Anxiety disorders—34% versus 26%
    - Fatigue—27% versus 18%
    - Depression—26% versus 19%
    - Obesity—23% versus 13%
    - Hirsutism/excess hair (female only)—11% vs 1%
- Top significant comorbidities in pediatric patients with CAH versus GenPop
    - Obesity—14% versus 5%
    - Fatigue—13% versus 6%
    - Anxiety disorders—12% versus 8%
    - Hirsutism/excess hair (female only)—11% versus 1%
    - Acne—10% versus 6%

"These data show a statistically higher clinical burden of CAH compared with a matched control, with patients of all ages suffering comorbidities that result from high adrenal androgens, such as short stature and hirsutism, and from supraphysiologic GC dosing, such as cardiovascular disease, metabolic disorders, and bone loss," Dr. Roberts said. "The data show that many of these comorbidities are chronic, with cardiovascular disease and the associated risk factors such as obesity and hypertension increasing in prevalence as patients age. This amplifies the clinical burden and demonstrates the significant need for a new treatment approach."

Neurocrine Biosciences posters presented at ENDO 2024 included:

- **(OR20-05):** CAHtalyst: Results from the Randomized, Double-Blind, Placebo-Controlled Period of a Phase 3 Trial of Crinecerfont, a Corticotropin-Releasing Factor Type 1 Receptor (CRF_1) Antagonist, in Adults with Classic Congenital Adrenal Hyperplasia
- **(Poster #SUN-441):** CAHtalyst: Results from the Randomized, Double-Blind, Placebo-Controlled Period of a Phase 3 Trial of Crinecerfont, a Corticotropin-Releasing Factor Type 1 Receptor (CRF_1) Antagonist, in Children and Adolescents with

Classic Congenital Adrenal Hyperplasia

- **(Poster #SUN-685):** Negative Impacts of Supraphysiologic Glucocorticoid Dosing in Patients with Classic Congenital Adrenal Hyperplasia: An Analysis of Data from the CAHtalog™ Registry
- **(Poster #SAT-437):** Disease- and Glucocorticoid-related Comorbidities in Classic Congenital Adrenal Hyperplasia: A Claims-Based Retrospective Cohort Analysis
- **(Poster #SUN-417):** Natural History of Classic Congenital Adrenal Hyperplasia: Results from Pediatric and Adult Patients in the CAHtalog Registry
- **(Poster #MON-676, RF36-01):** CHAMPAIN Study: Initial Results from a Phase II Study of Efficacy, Safety and Tolerability of Modified-Release Hydrocortisones: Chronocort® (Efmody®) versus Plenadren, in Primary Adrenal Insufficiency
- **(Poster #SAT-427):** Incidence of Adrenal Crisis in Congenital Adrenal Hyperplasia (CAH) Patients During a Prospective Monitored Long-Term Study of Modified-Release Hydrocortisone (MRHC) Capsules, (Efmody)
- **(Poster #SAT-412):** Morning Cortisol Levels in Patients with Established Primary Adrenal Insufficiency

About Congenital Adrenal Hyperplasia
Congenital adrenal hyperplasia (CAH) is a rare genetic condition that results in an enzyme deficiency that alters the production of adrenal hormones which are essential for life. Approximately 95% of CAH cases are caused by a mutation that leads to deficiency of the enzyme 21-hydroxylase. Severe deficiency of this enzyme leads to an inability of the adrenal glands to produce cortisol and, in approximately 75% of cases, aldosterone. If left untreated, CAH can result in salt wasting, dehydration, and even death.

Glucocorticoids (GCs) are currently used not only to correct the endogenous cortisol deficiency, but doses used are higher than cortisol replacement needed (supraphysiologic) to lower the levels of adrenocorticotropic hormone (ACTH) and adrenal androgens. However, glucocorticoid treatment at supraphysiologic doses has been associated with serious and significant complications of steroid excess, including metabolic issues such as weight gain and diabetes, cardiovascular disease, and osteoporosis. Additionally, long-term treatment with supraphysiologic GC doses may have psychological and cognitive impact, such as changes in mood and memory. Adrenal androgen excess has been associated with abnormal bone growth and development in pediatric patients, female health problems such as acne, excess hair growth and menstrual irregularities, testicular rest tumors in males, and fertility issues in both sexes.
To learn more about CAH, click here.

About Crinecerfont and the CAHtalyst™ Studies
Crinecerfont is an investigational, oral, selective corticotropin-releasing factor type 1 receptor (CRF_1) antagonist being developed to reduce and control excess adrenocorticotropic hormone (ACTH) and adrenal androgens through a glucocorticoid-independent mechanism for the treatment of congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency. Antagonism of CRF_1 receptors in the pituitary has been shown to decrease ACTH levels, which in turn decreases the production of adrenal androgens and potentially the symptoms associated with CAH. Our data demonstrate that lowering adrenal androgen levels enables lower, more physiologic dosing of glucocorticoids and thus could potentially reduce the complications associated with exposure to greater than normal glucocorticoid doses in patients with CAH.

The CAHtalyst™ Pediatric and Adult Phase 3 global registrational studies are designed to evaluate the safety, efficacy, and tolerability of crinecerfont in children and adolescents, and adults respectively, with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. The primary portions of the CAHtalyst Phase 3 studies have completed and enrollment is closed, while the open-label extension treatment portions of both studies are ongoing. Data from the CAHtalyst Pediatric and CAHtalyst Adult Phase 3 studies supported two New Drug Application submissions to the U.S. Food and Drug Administration in April 2024.

To learn more about crinecerfont and the CAHtalyst studies, click here.

About the CAHtalog ™ Registry
In 2021, the CARES Foundation, Neurocrine Biosciences and PicnicHealth partnered to establish the CAHtalog (**C**ongenital **A**drenal **H**yperplasia: Patien**t** and Clinic**al** **O**utcomes in Real-World Practice Setting**s**) Registry. The CAHtalog Registry is a U.S. based CAH patient registry, or collection of clinical patient data, for patients with CAH due to 21-hydroxylase deficiency. The database was developed to support patient-centered clinical research to enhance the scientific community's foundational knowledge about CAH, and ultimately help patients who live with the condition. For more information about the CAHtalog Registry, please visit CAHtalog.com.

About Neurocrine Biosciences, Inc.
Neurocrine Biosciences is a leading neuroscience-focused, biopharmaceutical company with a simple purpose: to relieve suffering for people with great needs, but few options. We are dedicated to discovering and developing life-changing treatments for patients with under-addressed neurological, neuroendocrine and neuropsychiatric disorders. The company's diverse portfolio includes FDA-approved treatments for tardive dyskinesia, chorea associated with Huntington's disease, endometriosis* and uterine fibroids*, as well as a robust pipeline including multiple compounds in mid- to late-phase clinical development across our core therapeutic areas. For three decades, we have applied our unique insight into neuroscience and the interconnections between brain and body systems to treat complex conditions. We relentlessly pursue medicines to ease the burden of debilitating diseases and disorders, because you deserve brave science. For more information, visit neurocrine.com, and follow the company on LinkedIn, X (formerly Twitter), and Facebook.
(*_in collaboration with AbbVie_)

Forward-Looking Statements
In addition to historical facts, this press release contains forward-looking statements that involve a number of risks and uncertainties. These statements include, but are not limited to, statements regarding the potential benefits to be derived from crinecerfont. Among the factors that could cause actual results to differ materially from those indicated in the forward-looking statements include: the crinecerfont NDAs may not be accepted for filing by the FDA or may not obtain regulatory approval or such approval may be delayed; additional regulatory submissions may not occur or be

submitted in a timely manner; the FDA may make adverse decisions regarding crinecerfont; crinecerfont may not be found to be safe and/or effective or may not prove to be beneficial to patients; development activities for crinecerfont may not be completed on time or at all; clinical development activities may be delayed for regulatory or other reasons, may not be successful or replicate previous and/or interim clinical trial results, or may not be predictive of real-world results or of results in subsequent clinical trials; competitive products and technological changes that may limit demand for our products; uncertainties relating to patent protection and intellectual property rights of third parties; our dependence on third parties for development and manufacturing activities related to crinecerfont, and our ability to manage these third parties; our future financial and operating performance; risks and uncertainties associated with the commercialization of our products; and other risks described in the Company's periodic reports filed with the Securities and Exchange Commission, including without limitation the Company's quarterly report on Form 10-Q for the quarter ended March 31, 2024. Neurocrine Biosciences disclaims any obligation to update the statements contained in this press release after the date hereof.

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