Neurocrine Biosciences Presented Baseline Data from the CAHtalyst™ Program in CAH and Study Data for Modified-Release Hydrocortisone in Primary Adrenal Insufficiency and CAH at ECE 2024

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- CAHtalyst™ Phase 3 Baseline Characteristics Highlight Limitations of Current CAH Treatment Paradigm in Children, Adolescents and Adults
- Phase 2 Study for Modified-Release Hydrocortisone in Adults with Adrenal Insufficiency Demonstrated Participants Achieved Physiological Morning Cortisol Levels after 4 Weeks
- Phase 3 Extension Study Data for Modified-Release Hydrocortisone in Adults with CAH Demonstrated Reduction in Median Daily Hydrocortisone Dose and an Increase in Responders at Levels ≤ 25 mg/day

SAN DIEGO, May 14, 2024 /PRNewswire/ -- Neurocrine Biosciences, Inc. (Nasdaq: NBIX) and Diurnal Ltd., a Neurocrine Biosciences company, presented baseline data from the CAHtalyst™ Phase 3 studies of crinecerfont in adult and pediatric patients with congenital adrenal hyperplasia (CAH), and modified-release hydrocortisone (Chronocort®) data for a Phase 2 clinical study (CHAMPAIN) in participants with primary adrenal insufficiency and in a Phase 3 extension study in CAH. These data, along with several additional posters were presented at the European Congress of Endocrinology 2024 meeting in Stockholm.

CAHtalyst Phase 3 Pediatric and Adult Studies— Baseline Characteristics
Baseline characteristics of the subjects who enrolled in the CAHtalyst Pediatric Phase 3 study were presented (Poster# P225). The study enrolled 103 subjects 4 to 17 years of age with a medically confirmed diagnosis of CAH due to 21-hydroxylase deficiency, with 52% male, mean age 12 years old, and majority in Tanner stages 3-5. There was evidence indicating inadequate adrenal androgen control in many of these patients despite supraphysiologic glucocorticoid dosing. At baseline, more than a third of the participants reported comorbidities of advanced bone age, early puberty, and obesity. Hirsutism (excessive hair growth, 12%) and irregular menses (12%) were reported in females, and testicular adrenal rest tumors were identified in more than a third of males.

Baseline characteristics of 182 adults with CAH enrolled in the CAHtalyst Adult Phase 3 study were also presented (Poster# P423). Despite supraphysiologic GC dosing, levels of adrenocorticotropic hormone, 17-hydroxyprogesterone and androstenedione (A4) were elevated at baseline, with levels of testosterone (females) and A4/testosterone (males) also elevated. Common comorbidities included anxiety, osteopenia, depression, hypertension and hyperlipidemia. Overall, close to half of participants were overweight. Forty-seven percent of females reported a history of hirsutism (excessive hair growth) and acne (23%), and testicular adrenal rest tumors were identified in 66% of male participants.

"At baseline, many participants in the CAHtalyst Pediatric study showed clinical evidence of elevated glucocorticoid doses and adrenal androgen excess. Many exhibited obesity, advanced bone age, and early puberty, all of which can negatively impact development in childhood and adolescence," said Eiry W. Roberts, M.D., Chief Medical Officer at Neurocrine Biosciences. "Baseline characteristics in the CAHtalyst Phase 3 study in adults saw this trend continue. Despite being in their 30s, many of the CAHtalyst Adult study participants have been diagnosed with disorders that are more common in people twice their age, including osteopenia, hypertension and hyperlipidemia. In both studies, adrenal androgen and other steroid markers were elevated at baseline despite supraphysiologic doses of glucocorticoids, demonstrating the need for novel glucocorticoid-independent approaches to reducing adrenal androgens and supraphysiologic glucocorticoid dosing in CAH patients at all ages."

In 2023, Neurocrine Biosciences announced top-line data from the CAHtalyst Pediatric and CAHtalyst Adult Phase 3 clinical studies evaluating the efficacy, safety, and tolerability of crinecerfont in adult and pediatric patients with CAH due to 21-hydroxylase deficiency. Data from both studies supported two New Drug Application submissions to the U.S. Food and Drug Administration in April 2024.

Phase 2 Data of Modified-Release Hydrocortisone (Chronocort®) in Primary Adrenal Insufficiency
The Phase 2 data of modified-release hydrocortisone (MRHC) in adults with primary adrenal insufficiency (CHAMPAIN study) demonstrated that participants receiving MRHC achieved a physiological morning cortisol level after four weeks of treatment (Abstract #4275, RC3.4). In the study, twice daily MRHC developed by Diurnal was compared with once-daily Plenadren (modified-release hydrocortisone) in patients aged ≥ 18 years with confirmed primary adrenal insufficiency (defined as morning pre-dose cortisol <50 nmol/L).

Of the 49 evaluable participants in the CHAMPAIN Phase 2 study with primary adrenal insufficiency, 45 achieved a physiological morning cortisol level after four weeks on MRHC compared to 2 participants after four weeks on Plenadren ($P < 0.0001$). The mean (standard deviation) waking cortisol was 422.85 (203.50) versus 36.98 (113.87) nmol/L, respectively.

"Treatment with modified-release hydrocortisone resulted in a greater proportion of patients with a physiological morning cortisol level than treatment with Plenadren in patients with primary adrenal insufficiency," said Eiry W. Roberts, M.D., Chief Medical Officer at Neurocrine Biosciences. "Further analyses will test the hypothesis that waking with physiological cortisol levels improves fatigue and quality of life in these patients."

Phase 3 Extension Study of Modified-Release Hydrocortisone (Chronocort®) in Congenital Adrenal Hyperplasia
MRHC also demonstrated potential value in improving control of CAH compared to current glucocorticoid treatment (Abstract #4271, RC3.1). In a 48-month Phase 3 extension study, MRHC-treated participants showed a reduction in the median daily hydrocortisone dose from 30mg to 20mg. Participants were considered responders when their 9:00 a.m. 17-hydroxyprogesterone level was ≤ 36 nmol/L or their androstenedione level was ≤7 nmol/L while receiving MRHC ≤ 25 mg/day.

"The number of participants achieving responder status increased after four years in the MRHC Phase 3 extension study in patients with CAH. MRHC demonstrated improved control of CAH, with an ability to closely replicate cortisol diurnal rhythm when compared to current glucocorticoid treatment," Dr. Roberts added.

Neurocrine Biosciences abstracts presented at ECE 2024 included:

- Baseline Characteristics of Children and Adolescents with Classic Congenital Adrenal Hyperplasia Enrolled in CAHtalyst Pediatric, a Phase 3 Study of Crinecerfont, a Corticotropin-Releasing Factor Type 1 Receptor Antagonist (Poster #P225)
- Baseline Characteristics of Adults with Classic Congenital Adrenal Hyperplasia Enrolled in CAHtalyst Adult, a Phase 3 Study of Crinecerfont, a Corticotropin-Releasing Factor Type 1 Receptor Antagonist (Poster #P423)
- 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 (Abstract #4275, Rapid Communication #RC3.4)
- Biochemical Control with Dose Reduction in Chronic Glucocorticoid Therapy over 4 Years: A Phase III Extension Study of Chronocort (Efmody®) in the Treatment of Congenital Adrenal Hyperplasia (CAH) (Abstract #4271, Rapid Communication #RC3.1)
- 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 #P215)
- Morning Cortisol Levels in Patients with Established Primary Adrenal Insufficiency (Poster #P13)

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 (21-OHD). 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 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 adrenocorticotropic hormone 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 treatment portions of both studies are ongoing.

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

About Primary Adrenal Insufficiency
Primary adrenal insufficiency is a chronic endocrine condition that occurs when the body does not make enough of certain adrenal hormones, including cortisol and often aldosterone. Glucocorticoids such as hydrocortisone are used to replace the missing cortisol, but typical dosing regimens do not match the natural diurnal rhythm of the body's cortisol production.

About Modified-Release Hydrocortisone (MRHC)
Diurnal Ltd. developed modified-release hydrocortisone, a preparation of hydrocortisone that has been specifically designed to replicate the natural circadian rhythm of cortisol, when given in a twice-a-day "toothbrush" regimen, (administered last thing at night before sleep and first thing in the morning on waking). In 2021, modified-release hydrocortisone (EFMODY®) received marketing authorization for the treatment of congenital adrenal hyperplasia from the Medicines and Healthcare products Regulatory Agency (MHRA) in Great Britain (England, Wales, and Scotland) and from the European Commission in the European Union. Neurocrine Biosciences acquired Diurnal Group plc. in November 2022. A new drug application for the modified-release hydrocortisone formulation has not been submitted to the U.S. Food and Drug Administration.

About MRHC Phase 2 Study in Adrenal Insufficiency (CHAMPAIN)
The CHAMPAIN Phase 2 clinical study compared the efficacy, safety and tolerability of twice daily DNL0200 (Chronocort), a modified-release hydrocortisone, with once daily Plenadren, a combination of immediate- and delayed-release hydrocortisone (authorized for use in the European

Union), over a treatment period of up to 2 months in participants ≥18 years of age and diagnosed with primary adrenal insufficiency.

About the Phase 3 Extension Study for MRHC in CAH (DIUR-006)

The DIUR-006 Phase 3 open-label extension study assessed the long-term efficacy, safety and tolerability of twice-daily DNL0200 (Chronocort®), a modified-release hydrocortisone in adults with CAH. The study was performed to build on the results of feeder studies DIUR-003 (Phase 2 in adults with CAH) and DIUR-005 (EU Phase 3 Registrational Open-Label Study of Chronocort compared to standard of care in adults with CAH), to evaluate the long-term safety of Chronocort and also its long-term efficacy in improving control of serum androgen levels (using 17-OHP and A4 as biomarkers).

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 certain of our products. Among the factors that could cause actual results to differ materially from those indicated in the forward-looking statements include: risks that regulatory submissions for our products and/or product candidates may not occur or be submitted in a timely manner, or accepted for filing; our products and/or product candidates may not obtain regulatory approvals; or that the U.S. Food and Drug Administration or regulatory authorities outside the U.S. may make adverse decisions regarding our products and/or product candidates; our products and/or product candidates will not be found to be safe and/or effective or may not prove to be beneficial to patients; that development activities for our products and/or product candidates may not be completed on time or at all; that 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 our products and our product candidates, 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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