CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218808Orig1s000, 218820Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	IND #132849
Request Receipt Date	11 October 2023
Product	Crinecerfont (NBI-74788)
Indication	Treatment of classic congenital adrenal hyperplasia
Drug Class/Mechanism of Action	Corticotropin releasing factor type 1 receptor antagonist
Sponsor	Neurocrine Biosciences, Inc
ODE/Division	OND/OCHEN/Division of General Endocrinology
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	10 December 2023

Note: This document must be uploaded into CDER's electronic document archival system as a ***clinical review: REV-CLINICAL-24 (Breakthrough Therapy Designation Determination) even if the review is attached to the MPC meeting minutes and*** *will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):** treatment of classic congenital adrenal hyperplasia in adults patients and children aged ≥ 4 years

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

3. **Was the BTDR submitted to a PIND?** ☐YES ☒NO
   If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

4. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 4a is checked "No," please provide the rationale in a brief paragraph below and send the completed BTDDRT to Miranda Raggio for review so that the BTDR can be denied without MPC review. Once reviewed and cleared by Miranda this BTDR will be removed from the MPC calendar, and you can skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

   b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?
      ☒ YES, the BTDR is adequate and sufficiently complete to permit a substantive review

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

☐ Undetermined
☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g., only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g., multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:

If 4b is checked "No", BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTD Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

6. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

7. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

The Sponsor is developing crinecerfont, a selective corticotropin releasing factor-1 (CRF_1) receptor antagonist, for treatment of classic congenital adrenal hyperplasia (CAH) caused by 21-hydroxylase deficiency. Deficiency of 21-hydroxylase results in glucocorticoid (cortisol) and mineralocorticoid (aldosterone) deficiencies. Feedback to the pituitary gland results in excess adrenocorticotrophic hormone (ACTH) production in patients with CAH. Excess ACTH stimulates the adrenal cortex to produce excess androgen. Androstenedione and 17-hydroxyprogesterone (17-OHP) levels are measured clinically as biomarkers of excess adrenal androgen production in CAH. Approved

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

therapies for CAH, which are considered the standard of care (SOC), consist of glucocorticoid (e.g., hydrocortisone) and mineralocorticoid (fludrocortisone) replacement, and salt supplementation (in infants).

Supraphysiologic doses of glucocorticoid are often necessary to suppress the high ACTH levels and control adrenal androgen production in patients with CAH, creating the clinical management challenge of balancing disease control (by normalizing adrenal androgen levels) with avoiding iatrogenic Cushing's syndrome due to excess glucocorticoid exposure. The Sponsor hypothesizes that by reducing pituitary ACTH production via CRF_1 antagonism, crinecerfont helps to 1) better control adrenal androgen levels and 2) reduce the total daily glucocorticoid dose required to manage the disease clinically. By reducing total daily glucocorticoid requirements, adjuvant treatment with crinecerfont should ultimately minimize the adverse health consequences of long-term exposure to supraphysiologic glucocorticoid doses, which include adverse effects on metabolism, the cardiovascular system, bone health, and growth (in children). Thus, compared to SOC therapies, adjuvant treatment with crinecerfont has the potential to improve both the efficacy (via improved control of adrenal androgen levels) and safety (via reduction in adverse glucocorticoid effects) of disease management in patients with CAH.

The Agency has previously granted crinecerfont orphan (15 March 2019) and fast track (15 June 2021) designations.

8. Information related to endpoints used in the available clinical data:

a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

The Sponsor considers reduction in glucocorticoid dose requirements while maintaining control of adrenal androgen levels, and in particular reduction to physiologic glucocorticoid doses (which avoids the adverse health consequences of supraphysiologic GC exposure), to be clinically meaningful endpoints supporting the BTDR. *Of note, DGE has previously agreed with the Sponsor that reduction in glucocorticoid dose requirements to physiologic levels is considered a clinically meaningful endpoint in patients with CAH.*

Specifically, the Sponsor considers the following endpoints from the adult phase 3 (CAH3003) and pediatric phase 3 (CAH2006) studies as supporting the BTDR:

- Study CAH3003 (primary endpoint): percent change from baseline in glucocorticoid daily dose at week 24, while week 24 androstenedione is ≤120% of baseline value or ≤ upper limit of normal for age and sex.
- Study CAH2006 (key secondary endpoint): percent change from baseline in glucocorticoid daily dose (in hydrocortisone equivalents adjusted for body surface area) at week 28, while week 28 androstenedione is ≤120% of baseline value or ≤ upper limit of normal according to sex and either age (for Tanner stage 1) or pubertal status (for Tanner stages 2-5).
- Study CAH3003 (key secondary endpoint): percent of subjects achieving reduction to a physiologic glucocorticoid dose (≤ 11 mg/m^2/day hydrocortisone equivalent) at week 24, while maintaining androstenedione control.
- Study CAH2006 (secondary endpoint): percent of subjects achieving reduction to a physiologic glucocorticoid dose (≤ 11 mg/m^2/day hydrocortisone equivalent) at week 28, while maintaining androstenedione control.

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

- *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*

- *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*

- *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit*.

The Division has previously agreed that reduction in glucocorticoid daily dose while maintaining control of androstenedione levels, as well as proportion of subjects achieving physiologic glucocorticoid daily doses (≤ 11 mg/m^2/day hydrocortisone equivalent) while maintaining androstenedione control, are clinically meaningful endpoints for patients with CAH. This is in consideration of the well-known negative health consequences (including those on bone, metabolism, and growth, among others) of chronic exposure to supraphysiologic glucocorticoid levels. Maintaining a balance between excess androgen levels and avoiding iatrogenic Cushing's syndrome due to high dose glucocorticoid is considered the biggest challenge in the clinical management of CAH.

In their NDA package, the Sponsor will be asked to provide supportive evidence that long-term reduction in daily glucocorticoid dose requirements achieved with the addition of crinecerfont therapy is associated with clinically meaningful health benefits in patients with CAH. Such evidence may come from improvements in one or more secondary endpoints from the phase 3 trials, such as growth parameters in children or metabolic measures in adult and/or pediatric patients, and/or from published literature supporting the beneficial effects of avoiding chronic exposure to supraphysiologic glucocorticoid doses in patients with CAH, who require lifelong glucocorticoid replacement.

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

None. The Division has previously communicated to the Sponsor that reduction in adrenal androgen levels (androstenedione and/or 17-OHP) alone are not considered clinically meaningful endpoints for patients with CAH because these endpoints are biomarkers of disease control. Phase 2 trials showed marked reductions in both androstenedione and 17-OHP levels with the addition of crinecerfont in patients with CAH while maintaining glucocorticoid doses. Phase 3 trials showed reduction of androstenedione and 17-OHP levels with the addition of crinecerfont, allowing patients to reduce their total daily glucocorticoid dose, in many cases to physiologic levels.

9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*

- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

Standard of care for the treatment of classic CAH in children includes glucocorticoid (hydrocortisone) and mineralocorticoid (fludrocortisone) therapy. The addition of sodium chloride supplementation is recommended in newborns and infants. Treatment for adults consists of glucocorticoid therapy, with the addition of mineralocorticoid therapy when clinically indicated. Hydrocortisone tablets were approved in 1952 and no formal clinical trials were conducted to support its approval for the CAH indication. (b) (4)

Table 1: FDA-Approved Therapies for Congenital Adrenal Hyperplasia

Drug Class	Approved Therapies
Glucocorticoid	• Hydrocortisone tablets (Cortef, NDA #008697) • Prednisone tablets (ANDAs) • Prednisone delayed-release tablets (Rayos, NDA #008697) • Methylprednisolone tablets (Medrol, NDA #011153) • Prednisolone sodium phosphate oral solution (NDA #019157) • Prednisolone sodium phosphate orally disintegrating tablets (OraPred-ODT, NDA #021959) • Dexamethasone oral tablets (ANDAs)
Mineralocorticoid (approved "as partial replacement therapy for primary adrenocortical insufficiency" and "treatment of salt-losing adrenogenital syndrome")	• Fludrocortisone acetate (ANDAs)

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation.[3]

None.

11. Information related to the preliminary clinical evidence:

a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design,[4] trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

Table 2: Clinical Trials Supporting BTDR for Crinecerfont

Trial NBI-74788-CAH3003	Trial NBI-74788-CAH2006
TRIAL DESIGN	
• Phase 3, 24-week, multi-center, randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of crinecerfont in adult female and male participants with classic CAH caused by 21-hydroxylase deficiency, followed by open-label treatment. • Participants were randomized 2:1 to crinecerfont 100 mg oral capsule twice daily vs. placebo. • Glucocorticoid dose was titrated to a goal of 8-10 mg/m^2/day to achieve adequate control of androstenedione levels (i.e., ≤120% of baseline or ≤ upper limit of normal for age and sex).	• Phase 3, 28-week, multi-center, randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of crinecerfont in pediatric subjects aged 2-17 years with classic CAH caused by 21-hydroxylase deficiency, followed by open-label treatment. • Participants were randomization 2:1 to crinecerfont or placebo. The dose was weight-based: o 10 to <20 kg - 25 mg BID via oral solution o 20 to <55 kg - 50 mg BID via oral solution o ≥55 kg - 100 mg BID via oral capsules • Glucocorticoid dose was titrated to a goal of 8-10 mg/m^2/day, while controlling androstenedione levels.
INCLUSION & EXCLUSION CRITERIA	
• Adult subjects	• Pediatric subjects aged 2 to 17 years

[3]Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.
[4] Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

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- CAH due to 21-hydroxylase deficiency
- On a glucocorticoid dose of >13 mg/m^2/day in hydrocortisone equivalents, stable for ≥1 month
- Subjects with suppressed 17-hydroxyprogesterone and androstenedione were excluded, but no cutoff for inclusion (treatment goal is to target these in ULN to slightly above normal limits).

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- Body weight >10 kg
- CAH due to 21-hydroxylase deficiency
- On a glucocorticoid dose of >12 mg/m^2/day in hydrocortisone equivalents, stable for ≥1 month
- Androstenedione level greater than the midpoint of reference range
- 17-hydroxyprogesterone level >2x ULN

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<tr><td colspan="2">SUBJECT DISPOSITION</td></tr>
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- 182 subjects randomized and 181 subjects received at least 1 dose of study treatment
- 174 completed week 24, all continued to open-label

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- 103 subjects randomized and 102 received at least 1 dose of study treatment
- 97 subjects completed week 28, all continued to open-label

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	Crinecerfont	**Placebo**
Randomized	122	60
Received treatment	122	59
Completed week 24 and continued to open-label	117	57

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	Crinecerfont	**Placebo**
Randomized	69	34
Received treatment	69	33
Completed week 28 and continued to open-label	66	31

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Exposure to Crinecerfont	
≥0 weeks	179
≥24 weeks	136
≥48 weeks	41

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Exposure to Crinecerfont	
≥0 weeks	100
≥24 weeks	64
≥52 weeks	21

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<tr><td colspan="2">EFFICACY RESULTS</td></tr>
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Primary Endpoint:
Percent change from baseline in glucocorticoid daily dose at Week 24, while Week 24 androstenedione is ≤120% of baseline or ≤ upper limit of normal for age and sex.

LS Mean (SEM)
Crinecerfont = -27.3 (2.4)
Placebo = -10.3 (3.2)

LS Mean difference [CI]
Crinecerfont – Placebo = -17 [-23.8, -10.2]
p-value = <0.0001

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Key Secondary Endpoint:
Percent change from baseline in glucocorticoid daily dose (in hydrocortisone equivalents adjusted for body surface area) at Week 28, while Week 28 androstenedione is ≤120% of baseline value or ≤ upper limit of normal according to sex and either age (for Tanner stage 1) or pubertal status (for Tanner stages 2-5).

LS Mean (SEM)
Crinecerfont = -17.97 (1.8)
Placebo = 5.57 (2.7)

LS Mean difference [CI]
Crinecerfont – Placebo = -23.5 [-29.9, -17.2]
p-value = <0.0001

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Key Secondary Endpoint:
Percent of subjects achieving reduction to a physiologic glucocorticoid dose (≤ 11 mg/m^2/day hydrocortisone equivalent) at Week 24, while maintaining androstenedione control (≤120% of baseline or ≤ upper limit of normal for age and sex).

Crinecerfont = 74/118 (62.7%)
Placebo = 10/57 (17.5%)
Crinecerfont – Placebo = 45.2%

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Secondary Endpoint:
Percent of subjects achieving reduction to a physiologic glucocorticoid dose (≤ 11 mg/m^2/day hydrocortisone equivalent) at Week 28, while maintaining androstenedione control (≤120% of baseline value or ≤ upper limit of normal according to sex and either age [for Tanner stage 1] or pubertal status [for Tanner stages 2-5]).

Crinecerfont = 20/67 (29.9%)
Placebo = 0/31 (none)

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p-value <0.0001	p-value <0.0001
Key Secondary Endpoint: Serum androstenedione, change baseline to Week 4 LS Mean (SEM) Crinecerfont = -299.14 (37.82) ng/dL Placebo = 45.6 (51) ng/dL LS Mean difference [CI] Crinecerfont – Placebo = -344.7 [-457, -232] ng/dL p-value = <0.0001	**Primary Endpoint:** Serum androstenedione, change baseline to Week 4 LS Mean (SEM) Crinecerfont = -96.7 (39.4) ng/dL Placebo = 70.9 (56.2) ng/dL LS Mean difference [CI] Crinecerfont – Placebo = -267.6 [-403.3, -131.9] ng/dL p-value = 0.0002
Secondary Endpoint: Serum 17-OHP, change baseline to Week 4 Results not provided.	**Key Secondary Endpoint:** Serum 17-OHP, change baseline to Week 4 LS Mean (SEM) Crinecerfont = -5864.7 (572) ng/dL Placebo = 556.3 (818) ng/dL LS Mean difference [CI] Crinecerfont – Placebo = -6421 [-8388, -4454] ng/dL p-value = <0.0001
Other Key Secondary Endpoints: HOMA-IR change, baseline to Week 24 Weight % change, from baseline at Week 24 Total fat mass change, baseline to Week 24 None achieved statistical significance	**Other Secondary Endpoints:** Body mass index SDS change, baseline to Week 28 Mean 24-hr salivary 17-OHP change, baseline to Week 28 Study drug acceptability and palatability at Week 4 Bone age/chronologic age ratio change, baseline to Week 28 Predicted adult height SDS change, baseline to Week 52 Results not provided.
Other Secondary Endpoints: Blood pressure Glucose tolerance (subjects without diabetes) Waist circumference Menstrual irregularity Testicular adrenal rest tumor size and characteristics Results not provided.	

SAFETY RESULTS

	Crinecerfont	**Placebo**		**Crinecerfont**	**Placebo**
Any TEAE	101 (82.8%)	48 (81.4%)	Any TEAE	58 (84.1%)	27 (81.8%)
Any SAE	4 (3.3%)	0	Any SAE	1 (1.4%)	4 (12.1%)
TEAE leading to treatment discontinuation	4 (3.3%)	0	TEAE leading to treatment discontinuation	2 (2.9%)	0

Deaths	0	0	Deaths	0	0
TEAEs more frequent in crinecerfont (delta risk ≥2%) Fatigue (25% vs. 15%) Coronavirus infection (14% vs. 9%) Dizziness (8% vs. 3%) Arthralgia (7% vs. none) Back pain (6% vs. 3%)			TEAEs more frequent in crinecerfont (delta risk ≥2%) Headache (25% vs. 6%) URI (12% vs. none) Influenza (9% vs. 6%) Abdominal pain (7% vs. none) Fatigue (7% vs. none) Nasal congestion (7% vs. 3%) Pharyngitis streptococcal (6% vs. none) Viral infection (6% vs. 3%)		

b. Include any additional relevant information. Consider the following in your response:

- *Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.*

  In adults with CAH (trial CAH3003), the percent change (SEM) from baseline in glucocorticoid daily dose at Week 24, while Week 24 androstenedione level was controlled, was -27.3% (2.4) for the crinecerfont group and -10.3% (3.2) for the placebo group, with a mean difference of -17% (95% CI: -23.8, -10.2; p<0.0001). In children with CAH (trial CAH2006), the percent change from baseline in glucocorticoid daily dose (in hydrocortisone equivalents adjusted for body surface area) at Week 28, while Week 28 serum androstenedione level was controlled, was -17.97% (1.8) for the crinecerfont group and +5.57% (2.7) for the placebo group, with a mean difference of -23.5% (95% CI: -29.9, -17.2; p<0.0001) (**Table 2**).

  In addition, in adults with CAH, 74/118 (62.7%) subjects in the crinecerfont arm and 10/57 (17.5%) in the placebo arm (difference of 45.2%, p<0.0001) achieved physiologic glucocorticoid daily doses (≤11 mg/m^2/day) at Week 24, while androstenedione levels were controlled. In pediatric patients with CAH, 20/67 (29.9%) subjects in the crinecerfont arm compared to 0/31 (none) in placebo arm achieved a reduction in glucocorticoid daily dose to physiologic levels (≤11 mg/m^2/day) at Week 28, while androstenedione levels were controlled (p<0001, **Table 2**). Reduction to physiologic glucocorticoid dosing should help to reduce or prevent the well-established negative consequences of supraphysiologic glucocorticoid dosing on metabolism, cardiovascular and bone health, and growth (in children), among others.

  In conclusion, data from two placebo-controlled trials (one adult and one pediatric) demonstrate that crinecerfont, when used as an adjuvant to standard of care glucocorticoid replacement therapy, has the potential to provide a substantial improvement in safety and efficacy over currently available therapies. Patients treated with crinecerfont were able to achieve statistically significant reductions in total daily glucocorticoid dose requirements compared to placebo, in many cases to physiologic doses. By allowing patients to maintain disease control (as evidenced by adrenal androgen levels) with lower glucocorticoid doses, crinecerfont has the potential to reduce or even prevent the adverse health effects associated with chronic exposure to supraphysiologic glucocorticoids. Crinecerfont has the potential to substantially improve the safety and efficacy of overall CAH disease management when compared to standard of care therapy alone.

- *Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.*

  The Sponsor provided literature references supporting the known negative consequences of long-term supraphysiologic glucocorticoid dose exposure on growth (in children), bone health, metabolic and cardiovascular risk, and cognitive function. In a National Institutes of Health registry study, 139 pediatric patients with classic CAH had an average glucocorticoid dose of 15 mg/m^2/day hydrocortisone equivalents, and 20% had a predicted adult height standard deviation score that was –2.0 or less.[1] The same registry showed that 37% of the 44 adult patients with classic CAH (mean hydrocortisone equivalent dose of approximately 17 mg/m^2/day) had low bone mineral density.[1] Multiple studies show that patients with CAH taking supraphysiologic doses of glucocorticoid have a high prevalence of obesity, diabetes, hyperlipidemia, and hypertension.[2] In a cohort of 203 adults with CAH, 41% had a body mass index (BMI) in the obese range (≥30 kg/m^2), and 37% were overweight.[3] A study in children with CAH found that, compared to age- and sex-matched controls, children with CAH had impairments in visual memory and cortical executive function, and that higher cumulative hydrocortisone dose correlated with worse visual memory.[4]

- *Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.*

  Crinecerfont was overall well tolerated in both adult and pediatric patients with CAH (see **Table 2** above). The low-risk safety profile of crinecerfont provided reassurance to the Division that this drug could be readily added to standard of care regimens and in fact, has the potential to improve the overall safety of CAH disease management by reducing glucocorticoid dose requirements, as discussed above.

  In the phase 3 trials, the proportion of subjects who experienced at least one treatment emergent adverse event (TEAE) was similar between the treatment and placebo arms in both the adult (82.8% crinecerfont and 81.4% placebo) and pediatric (84.1% crinecerfont and 81.8% placebo) cohorts. Serious adverse events (SAEs) were observed in 4 (3.3%) subjects in the crinecerfont arm in the adult study and included acute adrenocortical insufficiency, acute cholecystitis, cellulitis and groin abscess, and presyncope. No subjects in the placebo arm experienced any SAEs. In the pediatric study, SAEs were observed in 1 (1.4%) subject in the crinecerfont arm (pyrexia), compared to 4 (12.1%) subjects in the placebo arm. No pediatric subjects exposed to crinecerfont experienced an event of acute adrenal insufficiency.

  TEAEs resulting in treatment discontinuation were observed in the crinecerfont arm in 4 (3.3%) subjects in the adult study and 2 (2.9%) in the pediatric study compared to none in the placebo arm of either study. TEAEs that occurred more frequently (delta risk >2%) in the crinecerfont group included fatigue (24.6% vs. 15.3% in adults, 7.2% vs. none in the pediatric study), and headache (24.6% vs. 6.1%) in the pediatric study.

12. Division's recommendation and rationale (pre-MPC review):

☒ GRANT:

Provide brief summary of rationale for granting:

Preliminary clinical evidence from two well-controlled phase 3 trials suggests that crinecerfont may provide a substantial safety advantage over currently available standard of care regimens in overall disease management in patients with CAH. Specifically, when added to standard of care glucocorticoid therapy, crinecerfont reduced total daily glucocorticoid dose requirements, and in many cases, allowed reduction from supraphysiologic to physiologic glucocorticoid doses. It is well established that long-term exposure to supraphysiologic doses of glucocorticoids has adverse health effects on

metabolism, cardiovascular function, bone density, and growth (in children). Thus, if crinecerfont substantially reduces glucocorticoid dose requirements while maintaining control of adrenal androgen levels, these negative health consequences may be reduced or prevented.

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

☐ DENY:

Provide brief summary of rationale for denial:

13. Division's next steps and sponsor's plan for future development:

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

Not applicable given that the sponsor is currently in phase 3 of development, with plans to submit an NDA in 2024 for the treatment of CAH in adult and pediatric patients ages 4 years and older.

b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

14. List references, if any:

1. Finkielstain GP, Kim MS, Sinaii N, et al. Clinical characteristics of a cohort of 244 patients with congenital adrenal hyperplasia. *J Clin Endocrinol Metab*. 2012 Dec;97(12):4429-38.
2. Reisch N. Review of Health Problems in Adult Patients with Classic Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency. *Exp Clin Endocrinol Diabetes*. 2019 Feb;127(2-03):171-177.
3. Arlt W, Willis DS, Wild SH, et al.; United Kingdom Congenital Adrenal Hyperplasia Adult Study Executive (CaHASE). Health status of adults with congenital adrenal hyperplasia: a cohort study of 203 patients. *J Clin Endocrinol Metab*. 2010 Nov;95(11):5110-21.
4. Amr NH, Baioumi AY, Serour MN, et al. Cognitive functions in children with congenital adrenal hyperplasia. *Arch Endocrinol Metab*. 2019 Mar-Apr;63(2):113-120.
5. Speiser PW, Arlt W, Auchus RJ, et al. Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2018 Nov 1;103(11):4043-4088. Erratum in: *J Clin Endocrinol Metab*. 2019 Jan 1;104(1):39-40.

15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

16. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KAREN S VOGT
12/19/2023 01:09:13 PM

SHANNON D SULLIVAN
12/19/2023 05:22:11 PM

THERESA E KEHOE
12/20/2023 08:15:58 AM

December 08, 2023

The original version of the meeting minutes didn't include the sponsors responses to the FDA preliminary comments.

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

IND 132849

MEETING MINUTES

Neurocrine Biosciences, Inc.
Attention: Kristine Kim
Executive Director, Regulatory Affairs
12780 El Camino Real
San Diego, CA 92130

Dear Kristine Kim:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for crinecerfont (NBI-74788).

We also refer to the video conference between representatives of your firm and the FDA on November 15, 2023. The purpose of the meeting was to discuss the proposed NDA contents, statistical analyses, and timeline for submission of an NDA for crinecerfont for the treatment of congenital adrenal hyperplasia (CAH) in patients 4 years of age and older.

A copy of the official minutes of the video conference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Dana Smith, Regulatory Project Manager at 240-402-9906.

Sincerely,

{See appended electronic signature page}

Shannon Sullivan, MD, PhD.
Clinical Team Lead
Division of General Endocrinology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	November 15, 2023 3:00 PM-4:00 PM EST
Meeting Location:	Videoconference
Application Number:	IND 132849
Product Name:	crinecerfont (NBI-74788)
Indication:	treatment of congenital adrenal hyperplasia in patients 4 years of age and older
Sponsor Name:	Neurocrine Biosciences, Inc.
Regulatory Pathway:	505(b)(1) of the Federal Food, Drug, and Cosmetic Act
Meeting Chair:	Shannon Sullivan, M.D., Ph.D, Clinical Team Lead
Meeting Recorder:	Dana Smith, B.S., Regulatory Project Manager

FDA ATTENDEES

Office of New Drugs (OND), Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN)

Hylton V. Joffe, M.D., MMSc, Director
Lisa B. Yanoff, M.D., Deputy Director

OND, OCHEN, Division of General Endocrinology

Theresa Kehoe, M.D., Division Director
Naomi Lowy, M.D., Deputy Division Director
Marina Zemskova, M.D., Deputy Director for Safety
Shannon Sullivan, M.D., PhD, Clinical Team Lead
Shivangi Vachhani, M.D., Clinical Reviewer
Karen Vogt M.D., Clinical Reviewer

OND, Office of Regulatory Operations, Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Elisabeth Hanan, M.S., Chief, Project Management Staff
Dana Smith, B.S., Regulatory Project Manager

OND, OCHEN, Division of Pharmacology/Toxicology for Cardiology, Hematology, Endocrinology and Nephrology
David Carlson, Ph.D., Nonclinical Supervisor
Daniel Minck, Ph.D., Nonclinical Team Lead
Mekonnen Lemma Dechassa, Ph.D., Nonclinical Reviewer

Office of Translational Sciences (OTS), Office of Clinical Pharmacology
Li Li, Ph.D., Clinical Pharmacology Team Lead
Justin Earp, Ph.D., Clinical Pharmacology/Pharmacometrics Team Lead
Tian Zhou, Ph.D., Clinical Pharmacology Reviewer
Jiajun Liu, PharmD., MSc, Pharmacometrics Reviewer

OTS, Office of Biostatistics
Feng Li, Ph.D., Statistical Team Lead
Kyunghee Song, Ph.D. Statistical Reviewer

SPONSOR ATTENDEES

Name	Title
Eiry Roberts, MD	Chief Medical Officer
Ingrid Delaet, PhD	Chief Regulatory Officer
Darshna Patel	Vice President, Regulatory Affairs
Arline Nakanishi, MS	Vice President, Biometrics
Julia Sturgeon, MS	Principal Biostatistician
Mayra Nunez	Sr. Manager, Statistical Programming
Jean L. Chan, MD	Vice President, Clinical Development - Endocrinology
Vivian Lin, MD	Executive Director, Clinical Development - Endocrinology
Bob Farber, PhD	Vice President, Clinical Development
Gordon Loewen, PhD	Vice President, Preclinical Development
Nagdeep Giri, PhD	Sr. Scientific Director, Clinical Pharmacology
Kristine Kim, MS	Executive Director, Regulatory Affairs
Amy Le, MS	Sr. Specialist, Regulatory Affairs

1.0 BACKGROUND

Crinecerfont (NBI-74788) is a corticotropin releasing factor-1 (CRF1) receptor

antagonist being developed as a treatment for classic congenital adrenal hyperplasia (CAH). The investigational new drug (IND) application for crinecerfont was submitted to the Food and Drug Administration (FDA) on December 23, 2016.

Orphan drug designation was granted to crinecerfont on March 15, 2019, for the treatment of classic CAH.

The Sponsor requested a type B end-of-phase 2 meeting on January 6, 2020, to discuss the plan for a pivotal phase 3 study in adults with classic CAH. A teleconference meeting was conducted on March 17, 2020. The meeting minutes were issued on May 27, 2020.

The Sponsor requested Fast Track designation on April 29, 2021. Fast Track designation was granted on June 15, 2021, for the treatment of classic CAH.

The Sponsor requested a type C written responses only meeting on June 4, 2021, to obtain guidance (b) (4) for the ongoing adult pivotal Study NBI-74788-CAH3003 (Study CAH3003)[1] (b) (4) (b) (4) The Division disagreed with the (b) (4) Written responses were issued on August 3, 2021.

The Sponsor requested a type C meeting on July 12, 2022, to obtain guidance on the content and planned analyses specified in the study NBI-74788-CAH3003 Statistical Analysis Plan (SAP) and the proposal for the data package from clinical studies conducted by the previous sponsor (Sanofi SA), including data acquired with low bioavailability formulations in a future NDA submission. Written responses were issued on September 20, 2022.

The Sponsor requested a type C meeting on December 7, 2022, to discuss the content and planned analyses specified in the study NBI-74788-CAH2006[2] SAP. Written responses were issued on February 14, 2023.

The Sponsor requested a type D meeting on May 15, 2023, for which written responses only were granted. The background package was included with the meeting request and included the Sponsor's rationale for their proposed supplementary analyses for study NBI-74788-CAH3003, which were intended to inform the potential impact of androstenedione (A4) variability on the primary and key secondary endpoints, and

[1] Entitled, "A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Crinecerfont (NBI-74788) in Adult Subjects with Classic Congenital Adrenal Hyperplasia, Followed by Open-Label Treatment"
[2] Entitled, "A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety And Efficacy of Crinecerfont (NBI-74788) in Pediatric Subjects with Classic Congenital Adrenal Hyperplasia, Followed by Open-Label Treatment"

information to support discussion of whether the tipping point analysis had been sufficiently addressed in the SAP. Written responses were issued on June 21, 2023.

The Sponsor requested a type C meeting on July 21, 2023, [redacted] (b) (4) Written responses were issued on October 3, 2023.

The Sponsor requested this type B pre-NDA meeting on September 15, 2023, to discuss the proposed crinecerfont NDA contents, statistical analyses, and timeline for NDA submission. The Sponsor plans to seek approval of crinecerfont for the treatment of classic CAH based on the results of studies CAH3003 and CAH2006 and will submit separate NDAs for a proposed soft gelatin capsule (pre-assigned NDA No. 218808) and oral solution formulation (pre-assigned NDA No. 218820). The Sponsor requested a separate CMC-only pre-NDA meeting and written responses were issued in response to that request on November 14, 2023.

The meeting objectives are to discuss (1) the proposed nonclinical and clinical packages for the planned crinecerfont NDA submission, (2) the organization and content of Modules 2.7.3 Summary of Clinical Efficacy (SCE) and 2.7.4 Summary of Clinical Safety (SCS) for the NDA submission, (3) the proposed plan for the assessment of abuse liability, (4) the proposed population pharmacokinetics (PopPK) and exposure response analyses, (5) the available safety database at the time of the planned NDA submission, (6) the content and organization of the Day 120 update, and (7) the proposed content and format of the crinecerfont NDA constituting a fileable marketing application.

The Sponsor submitted their briefing package for this meeting on October 16, 2023.

FDA sent Preliminary Comments to Neurocrine Biosciences, Inc., on November 13, 2023.

2.0 QUESTIONS AND RESPONSES

The Sponsor's questions are repeated below in regular font, followed by FDA's responses in **bold**, Sponsor's responses (*italicized*), and the meeting discussion (***bolded/italicized***).

FDA General Comments:

1. **Your proposed indication is [redacted] (b) (4) The final indication of a drug is ultimately an NDA review issue; however, crinecerfont is given as an adjuvant medication along with standard of care (SOC) glucocorticoid replacement therapy to reduce total daily glucocorticoid (GC) dose requirements. Hence, the final indication will need to reflect the specific effects of the drug and its specific purpose for use.**

Sponsor Response for General Comment 1: *The Sponsor acknowledges the FDA's comment and will propose labeling accordingly in the NDA.*

Discussion for General Comment 1: ***No discussion occurred.***

2. **We note in your briefing package that you propose to submit two NDAs for crinecerfont as follows: 1) pre-assigned NDA 218808 (crinecerfont soft gelatin capsules) as a Type 1 New Molecular Entity, and 2) pre-assigned NDA 218820 (crinecerfont oral solution) as a Type 3 new dosage form. However, if both of your planned NDAs for crinecerfont are under FDA review concurrently, both NDAs will be tentatively classified as Type 1 New Molecular Entity products and will be subject to "the Program" under PDUFA VII. Refer to Section 3.0 below, Discussion of the Content of a Complete Application, for additional information about "the Program." FDA tentatively assigns NDA classification codes by the filing date for new applications and reassesses the code at the time of approval.**

   Sponsor Response for General Comment 2: *The Sponsor acknowledges the FDA's feedback that both NDAs will be tentatively classified as Type 1 New Molecular Entity products and will be subject to "the Program" under PDUFA VII.*

   The Sponsor seeks to clarify crosslinking between eCTDs and refers FDA to the Sponsor response to Question 10.

   Discussion for General Comment 2: ***No discussion occurred.***

2.1. Development Program Presentation in NDA

Question 1: Does the FDA agree that the completed nonclinical program for crinecerfont, including safety pharmacology, absorption, distribution, metabolism, excretion (ADME), and toxicity studies, are sufficient to support an NDA submission?

FDA Response to Question 1:
We agree that the completed nonclinical program for crinecerfont submitted to date and described in the meeting briefing document appears sufficient to support an NDA submission. All nonclinical study reports supporting your planned NDA should be completed and included in the NDA at the time of submission, including carcinogenicity and pre- and postnatal development (PPND) study reports which have not yet been submitted to IND 132849. Cross-references, with active hyperlinks to study reports submitted to IND 132849, will be helpful for the NDA review but the NDA should be materially complete with all data and study reports at the time of submission.

Please consider the following general guidelines when preparing your

submission:

a. Final study reports of the nonclinical studies are required at the time of NDA submission. Draft reports would not be acceptable.

b. Histopathology data should include individual animal reports as well as tabulated data that include incidence and severity scores.

c. Include a Table that specifies the drug batches used in nonclinical and clinical studies, including links to impurity profiles.

Sponsor Response for Question 1: *The Sponsor acknowledges the FDA's feedback; no additional discussion is needed.*

Discussion for Question 1: ***No discussion occurred.***

Question 2*:* Does the FDA agree that crinecerfont is not considered a drug with a potential for abuse based on crinecerfont's site of action at pituitary corticotrophs (ie, outside the blood-brain barrier), low brain penetration, and absence of behavioral signs in animals or adverse events (AEs) suggestive of psychoactive effects in clinical studies, and that formal nonclinical and clinical abuse potential studies are not needed for the crinecerfont NDA submission?

FDA Response to Question 2:
We agree the studies submitted and reviewed under IND 132849 have not identified findings consistent with abuse potential and have not resulted in a recommendation for additional dedicated nonclinical or clinical abuse potential studies to date. Your discussion in the briefing materials, including your plans outlined in Appendix 1 to submit an overview of abuse potential in the NDA, seems reasonable. The potential for abuse will be reviewed in the NDA in consultation with the Agency's controlled substances staff.

Sponsor Response for Question 2: *The Sponsor acknowledges the FDA's feedback; no additional discussion is needed.*

Discussion for Question 2: ***No discussion occurred.***

Question 3: Does FDA agree that the clinical pharmacology plan, including PopPK and exposure-response analysis plans, is adequate to support an NDA submission?

FDA Response to Question 3:
The completed clinical pharmacology studies appear adequate to support an NDA submission. Given the weak drug-drug interaction (DDI) potential identified with the strong CYP3A inhibitor ketoconazole (approximately 40%

increase in AUC), it is possible that other significant metabolism pathways may be involved. Provide a detailed metabolism profile of crinecerfont, including the contributions of individual metabolism pathways and their corresponding enzymes. Discuss if other enzyme pathways (e.g., CYP2B6) could lead to DDI concerns. We recommend that you address the effect of a weak or moderate inducer of CYP3A4 on the PK of crinecerfont (e.g., conduct clinical DDI studies) to support the dosing of crinecerfont when taken with these drugs.

We also have the following comments on PopPK and exposure- response analysis for your consideration:

1. **Given that weight reduction is possible in adults, and weight and height gain are expected in pediatric subjects during the treatment period, consider incorporating longitudinal covariate data, when applicable, (instead of only baseline assessments) during the covariate screening process for the development of the population PK model.**

2. **Address the following:**

   a. **For the efficacy endpoints, clarify how the individual exposure metrics for exposure-efficacy analysis will be derived. As an example, daily average metrics (i.e., AUC, C_{max}) are generated up to 6 months.**

   b. **For your safety endpoints, clarify whether you will use time averaged exposures up to time of AE (i.e., daily average AUC up to time to safety event) to evaluate exposure-safety relationships. Additionally, consider the assessment of exposure metrics during a time window prior to the AE of interest (i.e., individual time average exposure X weeks prior).**

   c. **To better reflect drug exposures in clinical studies, clarify how dose interruptions will be considered in evaluating the exposure metrics.**

3. **Submit the pharmacometric data and models as per Agency recommendations.[3]**

Sponsor Response for Question 3: *The Sponsor acknowledges the FDA's feedback. A detailed discussion of the metabolism profile of crinecerfont including the contributions of different drug-metabolizing enzyme systems and the potential for those systems to contribute to DDI will be provided in the NDA.*

[3] https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/model-data-format

Regarding the potential for weak or moderate CYP3A4 inducers to affect crinecerfont PK, the Sponsor plans (b) (4) [redacted]

Additionally, the Sponsor provides specific responses to FDA comments 3.1, 3.2a, b, and c, and 3.3:

Sponsor Response to 3.1: *The Sponsor acknowledges the feedback and will discuss the potential impact of changes in the body weight and height during the treatment period on crinecerfont exposure in the NDA.*

Sponsor Response to 3.2a, 2b and 2c:

a. *Individual exposure metrics will be derived from the final population PK model, incorporating PK data from the pediatric and adult efficacy trials. Steady state PK exposure metrics (i.e., Cmin, Cmax, AUC) will be evaluated for a relationship with the relevant efficacy endpoints. The Sponsor will describe the exposure metrics considered for the exposure-response analysis and their derivation methodology in the NDA. Justification for the selection and, when feasible, an assessment of the impact of the selections, will be provided in the NDA.*

b. *As described in the briefing book, crinecerfont was well tolerated during the Phase 3 studies and the incidence of TEAEs in the studies was low. The Sponsor is currently reviewing the safety data to determine the approach for exposure-response analysis, if any, for safety endpoints and will take the FDA's recommendation into consideration.*

c. *The Sponsor will incorporate dosing records into the development of the population PK model. An evaluation of the potential impact of dose interruptions on the interpretation of the exposure-response results will be included in the NDA.*

Sponsor Response to 3.3: *The Sponsor acknowledges the FDA's feedback and will provide pharmacometrics data and models per FDA recommendations.*

Discussion for Question 3:

Based on the Sponsor's follow-up comments to FDA's response to this question, the Agency asked the Sponsor to further clarify (b) (4) [redacted]

(b) (4)

The Sponsor stated that they will provide the methodology and justifications for these assessments in the NDA package.

Question 4: Does the FDA agree that the results from CAH3003 and CAH2006 provide substantial evidence of efficacy and can be the basis for submission of an NDA for crinecerfont for the treatment of CAH for adult and pediatric patients?

FDA Response to Question 4:

Your proposal to submit data from two adequate and well-controlled phase 3 trials (Trials CAH3003[4] and CAH2006[5]) to support substantial evidence of the effectiveness of your product to treat CAH seems reasonable.

Based on a review of the data included in the meeting package, we can provide the following recommendations regarding your presentation of the efficacy results in your NDA:

1. **We acknowledge that we have indicated that long-term reduction in daily glucocorticoid dose requirements, and particularly to physiologic levels, is considered a clinically meaningful endpoint in patients with CAH. It will be important in your NDA package to provide supportive evidence that long- term reduction in daily glucocorticoid dose requirements achieved with the addition of crinecerfont therapy results in clinically meaningful health benefits in patients with CAH. Such evidence may come from improvements in one or more secondary endpoints from your phase 3 trials, such as growth parameters in children or metabolic measures in adult and/or pediatric patients, and/or from published literature supporting the beneficial effects of avoiding chronic exposure to supraphysiologic glucocorticoid doses, particularly in patients with CAH, who require lifelong glucocorticoid replacement.**

2. **The proportion of subjects receiving crinecerfont who achieved physiologic glucocorticoid daily doses compared to placebo differed substantially between adult and pediatric patients in the two phase 3 trials (treatment difference compared to placebo of 44% in adult patients versus 29% in pediatric patients, respectively). In your NDA package, include**

[4] A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Crinecerfont (NBI-74788) in Adult Subjects with Classic Congenital Adrenal Hyperplasia, Followed by Open-Label Treatment.
[5] A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety And Efficacy of Crinecerfont (NBI-74788) in Pediatric Subjects with Classic Congenital Adrenal Hyperplasia, Followed by Open-Label Treatment.

adequate justification for this finding (e.g., increased hormonal variability due to growth and development in pediatric subjects, differences in clinical practice guidelines for treatment of adult vs pediatric patients with CAH) to provide support for use of change in androstenedione level at Week 4, along with change in total daily GC dose at Week 28 and other secondary outcome measures, as substantial evidence of the effectiveness of your duct to result in a clinically meaningful benefit in pediatric patients with CAH.

3. **For the subgroup of subjects who achieved physiologic GC doses while on crinecerfont, and separately for subjects who did not achieve physiologic GC doses, include analyses of the magnitude of dose reduction for all subjects. This should include the difference (absolute and percent changes) in total daily GC dose from baseline required to either achieve or not achieve physiologic GC doses in all trial subjects.**

Sponsor Response for Question 4: *The Sponsor acknowledges the FDA's feedback and will address these recommendations in the NDA submissions; no additional discussion is needed.*

Discussion for Question 4: ***FDA reiterated that it will be crucial for the Sponsor to provide adequate justification that the daily glucocorticoid dose reduction observed in the clinical trials with the addition of crinecerfont therapy results in clinically meaningful benefits in patients with CAH.***

Question 5: Does the FDA agree that efficacy results from CAH3003 and CAH2006 can be presented separately for each study in the Module 2.7.3 SCE and that no content will be submitted in the Integrated Summary of Efficacy (ISE)?

FDA Response to Question 5:
Yes, we agree that efficacy results from CAH3003 and CAH2006 can be presented separately in Module 2.7.3 Summary of Clinical Efficacy (SCE) and that no additional content is needed in the Integrated Summary of Efficacy (ISE).

Additionally, to allow an adequate assessment of persistence of therapeutic response to crinecerfont, we recommend including a separate analysis of the following endpoints at Week 52 of the Open Label Extension (OLE) for subjects with available data from both trials:

1. **The proportion of subjects who achieved physiologic glucocorticoid daily dose (i.e., ≤11 mg/m^2/day), while androstenedione control was maintained (i.e., ≤120% of baseline or ≤ ULN).**

2. **Absolute and percent change from baseline in glucocorticoid daily dose, while androstenedione control was maintained.**

Sponsor Response for Question 5: *Sponsor acknowledges the FDA's feedback and will address these recommendations in the NDA submissions; no additional discussion is needed.*

Discussion for Question 5: ***No discussion occurred.***

Question 6: Does the FDA agree that the cumulative exposures from clinical studies with crinecerfont planned for the NDA submission, including the proposed number of subjects with approximately 12 months of exposure in CAH3003 and CAH2006, are sufficient to characterize the safety profile of crinecerfont for the treatment of CAH?

FDA Response to Question 6:
You have proposed that at the time of the NDA submission, the safety database will include 200 subjects (136 adult and 64 pediatric) who will have been exposed to crinecerfont for at least 6 months and 62 subjects (41 adult and 21 pediatric) who will have been exposed to crinecerfont for at least 1 year. Your proposal seems reasonable in this rare disease population.

Sponsor Response for Question 6: *No additional discussion is needed.*

Discussion for Question 6: ***No discussion occurred.***

Question 7:

a. Does the FDA agree that the only pooling of safety data in the NDA submission will be for exposure to crinecerfont?

b. Does the FDA agree that the safety data for the Phase 1 and Phase 2 studies will be provided as brief summaries for the individual studies located in Module 2.7.4 SCS?

c. Does the FDA agree that the safety results from CAH3003 and CAH2006 will be presented separately for each study in Module 2.7.4 SCS?

d. Does the FDA agree that the Integrated Summary of Safety (ISS) can be split across Module 2 and Module 5, with the narrative portion located in the Module 2.7.4 SCS, and the ISS appendices of tables, figures, and datasets located in Module 5.3.5.3?

FDA Response to Question 7 (a-d):
Your proposals seem reasonable.

Sponsor Response for Question 7: *No additional discussion is needed.*

Discussion for Question 7: ***No discussion occurred.***

Question 8: Does the FDA agree with the proposal for the submission of narratives, completed case report forms, and patient profiles for subjects who died, discontinued study treatment due to an AE, or experienced a serious AE (SAE)?

a. Does the FDA agree that completed case report forms, narratives, and patient profiles will be submitted for subjects with these events in the Phase 3 studies CAH3003 and CAH2006?

b. Does the FDA agree that only narratives and completed case report forms will be submitted for subjects with these events in the Phase 2 studies in subjects with CAH?

FDA Response to Question 8 (a-b):
Your proposal seems reasonable. In addition, include narratives and case report forms for all adverse events related to adrenal insufficiency/adrenal crisis that occurred during the phase 2 and phase 3 trials in subjects with CAH. We also recommend that you include a separate analysis in which all preferred terms potentially related to adrenal insufficiency/adrenal crisis are grouped together in order to adequately assess the risk of acute adrenal insufficiency associated with crinecerfont treatment. This analysis should be done separately for each trial.

Sponsor Response for Question 8: *The Sponsor acknowledges the FDA's feedback; no discussion is needed at this time.*

- *The CAH2001 and CAH2008 Phase 2 studies in subjects with CAH were uncontrolled trials of short duration (2 weeks) that did not include a glucocorticoid dose reduction component. There were no cases of adrenal insufficiency or adrenal crisis in these studies and there are therefore no applicable narratives or case report forms for inclusion in the NDA. The Sponsor will provide narratives and case report forms in the NDA for all adverse events related to adrenal insufficiency/adrenal crisis that occurred during the Phase 3 studies (CAH3003 and CAH2006) in subjects with CAH. Analysis to assess the risk of acute adrenal insufficiency will also be provided for the two Phase 3 studies.*

Does the FDA agree with the Sponsor's proposal for narratives and case report forms to be provided for all adverse events related to adrenal insufficiency/adrenal crisis that occurred only during the Phase 3 trials in subjects with CAH in the NDA?

Does the FDA agree with the plan to provide the additional analysis of acute adrenal insufficiency for only the Phase 3 studies?

Discussion for Question 8: ***FDA agreed with the Sponsor's proposal.***

2.2. 120-Day Safety Update

Question 9: Does the FDA agree with the content, format, and proposed data cut-off dates for the datasets to be included in the Day 120 Update?

FDA Response to Question 9:

You have proposed that the 120-day update will include Open Label Extension (OLE) efficacy and safety data from approximately 131 adult subjects in Trial CAH3003 and 77 pediatric subjects in Trial CAH2006 with at least 12 months of exposure to crinecerfont, and additional safety data beyond Month 12 of the trials. We agree with your proposal to include the updated safety data from the ongoing OLE in the 120-day update.

Note that any efficacy data that are intended to support approval of your NDA should be included at the time of the initial NDA submission. Additional efficacy information submitted during the review cycle cannot be used to support the primary analysis or substantial evidence of effectiveness.

Sponsor Response for Question 9: *The Sponsor acknowledges the FDA's comment; no efficacy data will be included in the 120-day update. No additional discussion is needed.*

Discussion for Question 9: ***No discussion occurred.***

2.3 120-Day NDA STRUCTURE AND CONTENTS

Question 10: Does the FDA agree with the proposed plans for crosslinking from the IND?

a. Does the FDA agree that all Module 4 reports, Standard for Exchange of Nonclinical Data (SEND) datasets for specified studies, and references can be crosslinked from the IND?

b. Does the FDA agree that the 11 CSRs for clinical studies conducted by Sanofi to be submitted in Module 5 can be cross-linked from the IND?

FDA Response to Question 10 (a-b):

No, we do not agree. All datasets and clinical study reports will need to be submitted to the NDA to constitute a complete application.

Sponsor Response for Question 10: *The Sponsor acknowledges the FDA's feedback to Question 10 and the General Comment that NDA 218808 and NDA 218820 will be tentatively classified as Type 1 NME products. The Sponsor*

seeks to clarify if the following proposal for crosslinking would be acceptable to FDA.

Sponsor will include all documents, datasets and clinical study reports in NDA 218808 (soft gelatin capsules) and proposes to crosslink NDA 218820 (oral solution) to NDA 21808 (soft gelatin capsules) for the following sections:

- *Module 2:*
  - *Module 2.3.S*
  - *Module 2.4*
  - *Module 2.5*
  - *Module 2.6*
  - *Module 2.7.2 through 2.7.4*
- *Module 4*
- *Module 5*

Does the FDA agree that the proposal for creating crosslinks between the 2 NDAs can be deemed to constitute complete applications for both submissions?

Discussion for Question 10: ***FDA agreed with the Sponsor's proposal.***

Question 11: Does the FDA agree that the proposed location of the data packages and the content within the electronic Common Technical Document (eCTD) structure for the proposed NDA constitute a fileable marketing application?

FDA Response to Question 11: **Yes, we agree.**

Sponsor Response for Question 11: *No additional discussion is needed.*

Discussion for Question 11: ***No discussion occurred.***

Question 12: Does the FDA agree with the proposal to submit all programs for the creation of Analysis Data Model (ADaM) datasets and for the primary analyses of the primary and key secondary endpoints for CAH3003 and CAH2006?

FDA Response to Question 12:
Yes, we agree. In addition, submit all programs for the sensitivity and the supplementary analyses of the primary and key secondary endpoints for studies. Also submit the programs for the primary and sensitivity analyses of the proportion of subjects who achieved physiologic glucocorticoid daily dose at Week 28 in Trial CAH2006.

Sponsor Response for Question 12:*The Sponsor acknowledges the FDA's comment and will submit all programs requested. No additional discussion is needed.*

Discussion for Question 12: ***No discussion occurred.***

Question 13: Does the FDA agree with the Sponsor's plans to submit Bioresearch Monitoring (BIMO) clinical data listings for pivotal studies CAH3003 and CAH2006 in Module 5.3.5.4?

FDA Response to Question 13:
Yes, we agree with your plan to submit Bioresearch Monitoring (BIMO) clinical data listings for studies CAH3003 and CAH2006 in Module 5.3.5.4.

In addition to the summary-level clinical site dataset for the two pivotal studies, clinical study-level information and subject-level data line listings by clinical site for both studies should also be submitted. Please refer to the following guidances for industry:[6]

- ***Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring Inspections for CDER Submissions***

- ***Bioresearch Monitoring Technical Conformance Guide*****.**

Sponsor Response for Question 13: *The Sponsor acknowledges the FDA's comment and will provide the summary-level clinical site dataset, as well as clinical study-level information and subject-level data line listings by clinical site for the 2 pivotal studies, CAH3003 and CAH2006. No additional discussion is needed.*

Discussion for Question 13: ***No discussion occurred.***

Question 14: Does the FDA agree with the proposed Study Data Standardization Plan (SDSP) and the presentation of electronic datasets and documentation in the NDA?

a. Does the FDA agree that submission of legacy tabulation data and Study Data Tabulation Model (SDTM) are sufficient to support study BEX5094, a Phase 1 study in healthy subjects?

b. Does the FDA confirm their agreement with the proposal to submit the legacy tabulation data, along with a subset of 3 domains (demographics, exposure, and trial summary data), for TDU5091, FED5615 (a pilot food

[6] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

effect arm of TDU5091), and TDR5092, which are Phase 1 studies in healthy subjects?

c. Does the FDA agree that ADSL and ADaM define.xml are not required for Study NBI-74788-1601, a Phase 1 food effect study in healthy subjects, performed using Analysis Legacy Data?

FDA Response to Question 14 (a-c): Yes, we agree.

Sponsor Response for Question 14 (a-c): *No additional discussion is needed.*

Discussion for Question 14 (a-c): ***No discussion occurred.***

Question 15: Does the FDA agree with the proposed plan to include both reported (eg, United States [US] conventional) units and Systeme International (SI) units in the clinical study datasets, SI units only in the CAH2006 and CAH3003 clinical study report (CSRs), both US conventional and SI units for selected analytes in the Module 2 clinical summary documents, and US conventional units in labeling?

FDA Response to Question 15:
We request that the clinical study reports (CSRs) for Trials CAH2006 and CAH3003 include both US conventional units and SI units to allow adequate review of the data by the US FDA.

Sponsor Response for Question 15:*The Sponsor acknowledges the FDA's request and will include both US conventional units and SI units in the CSRs for Study CAH2006 and CAH3003. No additional discussion is needed.*

Discussion for Question 15: ***No discussion occurred.***

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission.

You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

In addition, we note that written responses for a chemistry pre-submission meeting were issued on November 14, 2023. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[7] and Pregnancy and Lactation Labeling Final Rule[8] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

- Regulations and related guidance documents.

[7] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[8] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

- A sample tool illustrating the format for Highlights and Contents, and

- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[9] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[10]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

[9] https://www.fda.gov/media/84223/download
[10] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[11]

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no items requiring further action.

6.0 ATTACHMENTS AND HANDOUTS

Sponsor's emailed responses are attached.

[11] https://www.fda.gov/media/85061/download

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHANNON D SULLIVAN
12/08/2023 02:43:08 PM

IND 132849

MEETING MINUTES

Neurocrine Biosciences, Inc.
Attention: Kristine Kim
Senior Director, Regulatory Affairs
12780 El Camino Real
San Diego, CA 92130

Dear Ms. Kim:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for crinecerfont (NBI-74788).

We also refer to the telecon between representatives of your firm and the FDA on March 17, 2020. The purpose of the meeting was to discuss and obtain agreement on the adequacy of the proposed registration study and completed studies and planned assessments to characterize the human and metabolite profile to support the marketing application for this product.

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jennifer Johnson, Regulatory Health Project Manager, at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Lisa Yanoff, M.D.
Director (Acting)
Division of Diabetes, Lipid Disorders and Obesity
Office of Cardiology, Hematology Endocrinology and Nephrology
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: March 17, 2020; 12:00 – 1:00 pm
Meeting Location: Teleconference

Application Number: IND 132849
Product Name: crinecerfont (NBI-74788)
Indication: Treatment of congenital adrenal hyperplasia
Sponsor Name: Neurocrine Biosciences, Inc.

Meeting Chair: Shannon Sullivan, M.D., Ph.D.
Meeting Recorder: Jennifer Johnson

FDA ATTENDEES

Office of New Drugs

Mary Thanh Hai, M.D.	Acting Deputy Director

Office of Cardiology, Hematology, Endocrinology and Nephrology

Division of Diabetes, Lipid Disorders and Obesity

Lisa Yanoff, M.D.	Acting Director

Division of General Endocrinology

Theresa E. Kehoe, M.D.	Acting Director
Shannon Sullivan, M.D., Ph.D.	Clinical Team Leader
Marina Zemskova, M.D.	Clinical Team Leader
William Lubas, M.D., Ph.D.	Clinical Reviewer
Shivangi Vachhani, M.D.	Clinical Reviewer

Division of Pharmacology and Toxicology

Geeta Negi, Ph.D.	Nonclinical Reviewer

Office of Regulatory Operations

Division of Regulatory Operations for Cardiology, Hematology, Endocrinology and Nephrology

Pam Lucarelli	Chief, Project Management Staff
Jennifer Johnson	Regulatory Health Project Manager
Dana Smith	Regulatory Project Manager

Office of Clinical Pharmacology, Division of Cardiometabolic and Endocrine Pharmacology

S.W. Johnny Lau, Ph.D.	Clinical Pharmacology Reviewer
Jaya Vaidyanathan, Ph.D.	Clinical Pharmacology Team Leader

Office of Biostatistics, Division of Biometrics 2

Kyunghee Song, Ph.D.	Statistics Reviewer
Feng Li, Ph.D.	Acting Statistics Team Leader

SPONSOR ATTENDEES

Eiry Roberts, MD	Chief Medical Officer
Malcolm Lloyd-Smith, MSc	Chief Regulatory Officer
Robert Farber, PhD	Vice President, Clinical Development
Jean L. Chan, MD	Vice President, Clinical Development – Endocrinology
Arline Nakanishi, MS	Vice President, Biometrics
Nagdeep Giri, PhD	Director, Clinical Pharmacology
Kristine Kim, MS	Senior Director, Regulatory Affairs
(b) (4)	Consultant

1.0 BACKGROUND

The investigational new drug (IND) application for crinecerfont for the treatment of CAH was submitted to the Food and Drug Administration (FDA) on December 23, 2016. Following review of the initial IND, the FDA issued non-hold comments and requests for additional information regarding quality, nonclinical, and clinical topics in a letter dated March 16, 2017.

The sponsor requested a Type C Written Responses Only (WRO) meeting on November 7, 2018, to address the FDA nonclinical comment regarding the use of new excipients in drug formulations used in the IND-opening study and to obtain FDA agreement on the appropriateness of the drug product formulation proposed for use in the long-duration phase 3 clinical studies and in a commercial setting in adult and pediatric subjects. A Meeting Request – Written Responses letter was issued on January 18, 2019; the WRO expressed the FDA concordance with the proposed formulation for both long-duration clinical study and commercial use.

The sponsor submitted a fast track designation request on April 24, 2019, and a denial letter was issued on June 20, 2019. The basis for the fast track denial was the limited data provided at the time from the ongoing phase 2 Study NBI-74788-CAH2001 (hereafter Study CAH2001) regarding the potential of crinecerfont to provide a clinically meaningful benefit, or to address an unmet medical need in the CAH patient population, or to address a serious aspect of CAH.

The sponsor requested a Type C meeting on May 29, 2019, to discuss and obtain FDA agreement on the nonclinical and clinical development plan to support a new drug

application (NDA) for the treatment of CAH. A Meeting Granted – WRO letter was issued on August 12, 2019. The FDA communicated in the Type C WRO the agreement that glucocorticoid dose reduction may be clinically beneficial in patients with CAH and that assessment of glucocorticoid dose reduction and control of adrenal steroid hormone levels was an acceptable approach for the planned phase 3 study to support the registration of crinecerfont. The WRO also expressed FDA agreement that the nonclinical program as described in the meeting briefing materials, as well as the number of subjects and duration of exposures in the clinical safety database, were sufficient to support an NDA submission, provided no new safety signals are identified that require further evaluation. It was clear from the feedback that further discussion was needed regarding the adequacy of the human mass balance study and certain aspects of the registrational study CAH3003 (e.g., definition of endpoints, statistical analysis, and dose selection). These topics are the subject of this EOP2 meeting request.

FDA sent Preliminary Comments to Neurocrine Biosciences, Inc. on March 12, 2020. Neurocrine Biosciences sent responses to our preliminary comments on March 14, 2020, received March 16, 2020. These are indicated as 'Sponsor Follow-Up' in this document.

2.0 DISCUSSION

The sponsor's questions are repeated below, followed by the FDA preliminary response, followed by the sponsor's follow-up response and meeting discussion (where applicable).

Clinical

Question 1: The Sponsor's development plan for crinecerfont for classic CAH in adult patients includes a single registrational Phase 3 trial, Study CAH3003. Does the FDA agree with the planned design of Study CAH3003 for the demonstration of efficacy in adult subjects with classic CAH?

FDA Response to Question 1:
Your proposal to conduct a 24-week, double-blind, randomized (2:1), placebo-controlled trial, followed by a 12-month open-label extension period as your pivotal trial, is reasonable for this rare disease. We have the following additional comments and requests regarding the proposed phase 3 trial:

1. **At least 12 months of data (6 months blinded trial period, 6 months of open-label extension) will need to be available for review at the time of NDA submission to monitor for long-term safety and durability. The open label extension will need to continue to monitor change in GC dose from baseline for each individual patient.**

Sponsor Follow-Up: *No additional discussion needed*

2. **We recommend comparing both absolute and percent change in GC daily dose (in HC equivalents) between study drug and placebo as part of the efficacy assessment. Clarify which of these you plan to use as the primary endpoint. In either case, the efficacy analyses should adjust for baseline GC dose.**

   Sponsor Follow-Up:
   We appreciate the recommendation to look at both absolute and percent change; and agree that both approaches provide important, complementary information. We will provide clarity on which of these approaches is selected as the primary endpoint in the final protocol. ***To inform this decision, does the FDA have a preference as to which approach should be used for the primary endpoint?*** *We also agree that the efficacy analyses should adjust for baseline GC dose.*

   Meeting Discussion: ***FDA confirmed that percent change is preferred.***

3. **Regarding your key secondary endpoint of achievement of physiologic GC daily dosing, clarify your rationale for choosing ≤11mg/m^2/day in hydrocortisone equivalents adjusted for BSA as a physiologic replacement dose. According to Endocrine Society Guidelines for treatment of adrenal insufficiency, physiologic GC replacement is considered to be 5-8 mg/m^2/day in HC equivalents adjusted for BSA.[1] Further, you state in your study protocol that subjects will undergo GC dose down-titration "with the goal to reach a target dose of** (b) (4) **mg/m^2/day," suggesting that achievement of physiologic GC dosing would require GC dose down-titration to <10 mg/m^2/day.**

   Sponsor Follow-Up:
   The Sponsor agrees that the Endocrine Society guidelines for treatment of primary adrenal insufficiency are relevant for defining physiologic replacement doses, given that treatment of primary adrenal insufficiency is based on replacing the deficient hormone. These guidelines indicate that the mean cortisol production rates reported in the literature ranged from 5 to 8 mg/m^2/day, which they note as "equivalent" to an oral replacement of hydrocortisone 15 to 25 mg/day (in 2 or 3 divided doses), with a recommendation towards the lower end of this range to avoid overtreatment. However, hydrocortisone 15 to 25 mg/day corresponds to 8.8 to 14.7 mg/m^2/day (for an average sized adult with a body surface area of 1.7 m^2), which is considerably higher than the cited 5 to 8 mg/m^2/day for cortisol production rate (even accounting for the slight adjustment

[1]Bornstein SR et al. JCEM 2016; 101:364-389.

needed based on 95%, i.e. <100%, bioavailability for hydrocortisone). It is also relevant to note that the Endocrine Society guidelines for treatment of CAH also recommend glucocorticoid treatment with hydrocortisone 15 to 25 mg/day, despite the general understanding that higher doses are typically required to control androgen excess in CAH (in addition to treating the adrenal insufficiency). The Sponsor surmises that the intent of the recommendation to use hydrocortisone 15 mg in primary adrenal insufficiency at the lower end of the range is to target a level that would provide sufficient replacement doses for the large majority of the patient population.

This forms the basis for the Sponsor's proposal to use a more conservative target of (b) (4) *mg/m^2/day hydrocortisone dose equivalents (which corresponds to hydrocortisone 15 mg for an average-sized person) in the CAH3003 protocol in order to achieve the best balance between demonstrating efficacy for achieving physiologic glucocorticoid doses while ensuring subject safety. Targeting a glucocorticoid dose of 5 to 8 mg/m^2/day (8.5 to 13.6 mg hydrocortisone for BSA of 1.7 m^2) could increase the risk of precipitating glucocorticoid insufficiency in a substantial number of patients, especially if the lower end of the range is targeted in a smaller individual. In fact, based on discussions with key experts and information about the glucocorticoid dosage strengths that are readily available in the ~15 countries in which Study CAH3003 will be conducted, the Sponsor intends to adjust the glucocorticoid target to 8 to 10 mg/m^2/day to facilitate the operational aspects of implementing the glucocorticoid dose reduction.*

The potential concern with targeting a glucocorticoid dose of 5 to 8 mg/m^2/day is further illustrated by examining the papers cited in the Endocrine Society guidelines for the estimated cortisol production rate, specifically three studies using stable isotope methodology (Linder et al J Ped 1990; Purnell et al JCEM 2004; Esteban et al JCEM 1991) and one study using deconvolution analysis of 24-hr serum cortisol profiles (Kerrigan et al JCEM 1993), which were performed in healthy subjects (children and adults, male and female). Figures are presented below from the 2 studies with the most subjects (Linder et al with N=33, age 8 to 17, and Purnell et al with N=54, age 19 to 70) that were performed using stable isotopes (which could be considered the more reliable method of estimating cortisol production rate since it is based on direct measurement) and that included plots showing the distribution of cortisol production rates.

Distribution of Cortisol Production Rates (Purnell et al 2004, Linder et al 1990)

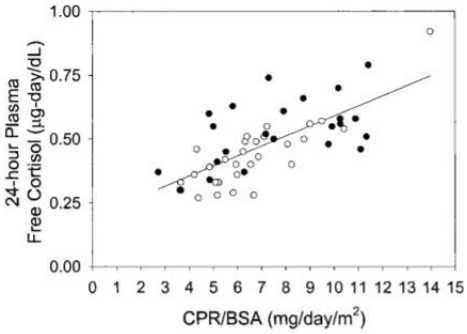

FIG. 1. Correlation between CPR/BSA and 24-h plasma free cortisol levels ($r = 0.71$; $P < 0.001$). Men are shown in *closed circles*, women in *open circles*. To convert cortisol values from metric (milligrams per deciliter) to SI (nanomoles per liter), multiply by 27.59.

Reference: Purnell et al JCEM 2004

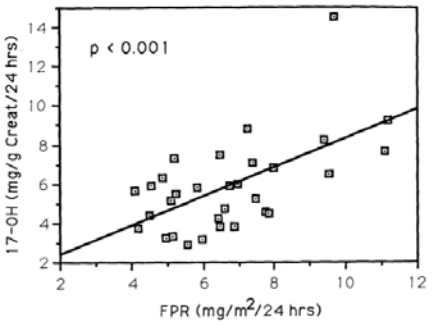

Fig. 2. Correlation between FPR and urinary 17-hydroxysteroid excretion, corrected for creatinine value, in normal children and adolescents.

Reference: Linder et al J Ped 1990

It is worthwhile to note that the range of cortisol production rates (adjusted for body surface area) was similar across a broad range of age (8 to 70 years old) with similar mean values for children (6.8 mg/m^2/day) as for adults (7.0 mg/m^2/day [7.6 male vs. 6.6 female]). Importantly, the normal cortisol production rate had a broad range (~4 to 12 mg/m^2/day, i.e. approximately 3-fold range). Based on the Linder et al publication, 5 to 8 mg/m^2/day would correspond to the 20th to 80th percentile, while 10 and 11 mg/m^2/day corresponds to the 90th and 95th percentiles, respectively.

The Sponsor believes that defining the achievement of physiologic dose as ≤ 11 mg/m^2/day is appropriate since this threshold represents the 95th percentile of normal cortisol production. Given that patients enrolled in the study must be on >14 mg/m^2/day (i.e. approximately twice the <u>average</u> cortisol production rate) at baseline, achieving this definition of physiologic glucocorticoid dose corresponds to a decrease of at least 3 mg/m^2/day (~5 mg hydrocortisone for an average size person, which based on discussions with multiple experts is viewed as a clinically meaningful reduction in glucocorticoid dose in the setting of maintaining stable androgen levels). Since 14 mg/m^2/day reflects the minimum glucocorticoid dose that a subject could be on to qualify for the study, the vast majority of subjects will likely be on higher doses (some considerably higher), and thus achieving a glucocorticoid dose of ≤11 mg/m^2/day would represent an even greater dose reduction.

The rationale for targeting a glucocorticoid dose range during the down-titration phase that is slightly less than the criteria for defining achievement of physiologic dose is based on the likely distribution of glucocorticoid dose reduction values when aiming for a specific target. Targeting a dose that is slightly lower than the success criteria maximizes the chance for detecting efficacy by accommodating more of the right tail of the glucocorticoid dose distribution.

Meeting Discussion: ***FDA stated that no additional discussion was needed following review of the Sponsor's justification regarding the glucocorticoid dose reduction target (to be updated*** (b) (4) ***to 8-10 mg/m^2/day) or the criteria for achieving physiologic glucocorticoid dose (≤11 mg/m^2/day); both were found to be acceptable. FDA acknowledged the importance of preventing significant study discontinuation due to patients experiencing adrenal insufficiency.***

Question 2: Does the FDA agree with the proposed primary endpoint and key secondary endpoints, the planned methods for analysis, and multiplicity adjustment for Study CAH3003?

FDA Response to Question 2:
We acknowledge that many patients with CAH may have a reduction in GC dose that does not reach a physiologic level but that is still clinically meaningful. Therefore, your proposed primary endpoint of change from baseline in GC daily dose at Week 24, while maintaining androstenedione levels (Week 24 androstenedione ≤120% of baseline or ≤ULN for age and sex), may be acceptable if you can provide adequate justification that the specific GC dose reduction achieved is clinically meaningful; i.e., you should scientifically justify a minimum effect size that is clinically meaningful. Ultimately, a final approval decision will be based on a risk-benefit analysis of the totality of the data.

Sponsor Follow-Up: *No additional discussion needed.*

We have the following additional comments:

(1) The efficacy analysis for GC dose reduction should depend on the final, stable tolerated GC dose. Thus, it is inappropriate to use GC data from Week 12 and Week 16 given that the protocol continues to permit GC dose adjustments during these visits. We recommend analyzing the final GC dose at Week 24 in the efficacy analyses for GC dose reduction with an ANCOVA analysis. In addition, you may consider pre-specifying that Week 20 data can be used in patients with missing Week 24 data as a sensitivity analysis for the primary analysis.

Sponsor Follow-Up: *No additional discussion needed.*

(2) Your full analysis set (FAS) should include all randomized subjects.

Sponsor Follow-Up: *No additional discussion needed.*

(3) You have proposed a Hochberg procedure for multiplicity control of some secondary endpoints. We note that Hochberg procedure is valid for controlling overall type-I error when the tests are independent or positively

correlated. However, it is unclear whether your tests for the secondary endpoints are independent or positively correlated. You may consider the Holm's stepdown procedure instead.

Sponsor Follow-Up: *No additional discussion needed.*

(4) It appears that you have proposed to impute missing primary and key continuous secondary endpoints using (b) (4) that is generally not acceptable unless scientifically justified.

Sponsor Follow-Up:
We understand the concerns (b) (4), specifically the potential for deflation of variance. In light of this comment on imputation and the earlier comment on the mixed-effect model repeated measures, we are proposing a change to multiple imputation methodology for missing data used in the derivation of the primary and key secondary endpoints.

We agree with FDA and are including procedures to minimize missing data in this study. Section 9.10 of the protocol specifies that subjects who discontinue study drug should remain in the study and complete important efficacy and safety assessments in the study, at least through the completion of the Week 24 visit.

When data are missing, we propose to implement multiple imputation using observed data from subjects in the placebo treatment group with similar baseline characteristics. The multiple imputation approach will be described in the final protocol with additional details in the statistical analysis plan; this approach will restore variance in the data, (b) (4)

During the glucocorticoid optimization period (see Section 7 of the protocol), glucocorticoid dose levels should be adjusted to ensure maintenance of the androstenedione levels relative to baseline (defined as ≤120% of baseline or ≤upper limit of normal [ULN] for age and sex). As such, it is likely that androstenedione levels relative to baseline will be maintained at Week 24. Nevertheless, the primary endpoint derivation will need to account for subjects who are not able to maintain androstenedione levels at Week 24. We continue to propose that these subjects be considered as having a zero change from baseline in the glucocorticoid daily dose at Week 24. (b) (4) However, this is an endpoint definition intended to appropriately reflect any observed glucocorticoid dose reduction at Week 24 that has failed to maintain the subject's androstenedione level.

The proposed changes to the handling of missing data, the thoughtful use of sensitivity analyses to assess the impact of missing data, and the diligence in

avoiding missing data should provide a complete and robust outcome from this study.

We would appreciate discussion and guidance with the review team if there are further comments or recommendations based on this revised proposal.

Meeting Discussion: FDA agreed that the Sponsor's proposal for multiple imputation based on observed data from the placebo group is acceptable. FDA stated that in the scenario where the androstenedione level is not controlled at Week 24, the Sponsor's proposal to impute a 0 change for glucocorticoid dose is clinically acceptable. FDA also recommended conducting a sensitivity analysis based on observed data for glucocorticoid dose at Week 24 regardless of androstenedione control. FDA encouraged submission of the statistical analysis plan for review.

(5) Missing data should be kept to a minimum. We recommend making continued efforts to measure efficacy and safety endpoints on all subjects, even those who may have discontinued protocol treatment.

Sponsor Follow-Up: *No additional discussion needed; refer to Q2(4) response.*

(6) It is important to study the limitation of the primary analysis using sensitivity analyses. For each sensitivity analysis, describe what limitation(s) of the data or assumption(s) of the primary analysis are being evaluated and how the sensitivity analysis achieves this.

Sponsor Follow-Up: *No additional discussion needed. A SAP will be provided for review well in advance of database lock for the Week 24 timepoint.*

Question 3: Does the FDA agree with the selected daily dose of 100 mg bid for the registration Study CAH3003 in adult subjects with classic CAH?

FDA Response to Question 3:

We do not agree that you have sufficient data to identify the optimal dose of crinecerfont to assess in Study CAH3003. The EC_{80} of crinecerfont, 1500 ng/mL, to suppress CRF-stimulated ACTH from baseline (Figure 4 of the Briefing Materials) may not fully apply to patients with CAH because Study TDR10671 assessed a single-dose in healthy male volunteers, whereas Study CAH3003 will assess female and male patients with CAH treated for 24 weeks.

The data in Table 3 of the Briefing Materials (Study CAH2001) do not clearly show a dose-response relationship for doses between 50 mg qhs and 100 mg BID of crinecerfont, suggesting that efficacy may not be directly related to AUC24. In addition, your latest data with dosing at 100mg of crinecerfont BID continue to show an ACTH peak in individual patients at the time of the normal morning peak.

Do you have data to support that higher crinecerfont levels at or just prior to the normal morning ACTH peak may be more efficacious?

It may be helpful to conduct a 14-day pharmacokinetic and pharmacodynamic study, similar to Study CAH2001, to better assess the optimal dosing regimen of crinecerfont prior to the phase 3 trial. This study may assess higher total daily doses or higher doses of crinecerfont at bedtime to maximally suppress the morning peak of ACTH.

Sponsor Follow-Up:

The Sponsor requests to refer to Table 2 of the Addendum to the End of Phase 2 Meeting Briefing Document, which shows ACTH, 17-OHP, and androstenedione changes for the peak morning window by dosing cohort, with the updated and complete data (N=8) for Cohort 4 (100 mg bid dosing). While similar median reductions from baseline were observed across dosing cohorts for ACTH and 17-OHP, androstenedione demonstrated evidence of a dose-response relationship with greater median reductions as crinecerfont dose increased from 50 mg qd (-21%) to 100 mg qd (-43 to -47%) to 100 mg bid (-64%).

While reductions in ACTH provide evidence of target engagement, the Sponsor considers androstenedione to not only be the more clinically relevant marker (being more downstream) but also the more reliable and stable pharmacodynamic measure given the pulsatile and/or more variable nature of ACTH levels. According to the study design, the morning glucocorticoid dose was withheld until completion of blood sampling during the peak morning window in order to better assess the direct effect of CRF-1 receptor antagonism on the HPA axis. Thus, the ACTH profile did not reflect the effect of usual glucocorticoid dosing; the morning peak of ACTH would be expected to be further attenuated in the typical clinical setting of administration with the patient's usual glucocorticoid regimen. As presented in Figure 4 of the Addendum to the EOP2 meeting briefing materials, the evaluation of the exposure-response relationship between crinecerfont PK parameters and hormone levels (ACTH, 17OHP, androstenedione) focused on $AUC_{0\text{-}24}$. However, the exposure-response relationship between $AUC_{0\text{-}24}$, C_{max}, $AUC_{partial}$, and change from baseline in hormone levels were all evaluated and found to be similar across all 3 hormone parameters.

Although the corticorelin stimulation test in healthy subjects, which was important in establishing proof of mechanism, was performed in male subjects only, the Phase 2 CAH2001 study enrolled both female and male CAH patients (n=11 female, n=7 male) and demonstrated meaningful decreases in hormone levels regardless of sex. In addition, there is no reason to believe that the response to CRF-1 receptor antagonism would differ fundamentally according to sex.

The Sponsor appreciates the recommendation to consider further detailed PK/PD evaluation to better optimize the dosing regimen, including strategies using a higher evening dose. Given the practical considerations of recruiting subjects with a rare

disease for these intensive studies, the Sponsor considers that the Phase 2 Study CAH2001 provided a reasonable and robust evaluation of a range of doses and regimen that demonstrated the ability of crinecerfont to suppress CRF-stimulated ACTH and cortisol secretion. As discussed in the End of Phase 2 Meeting Briefing Document, distributing the 200 mg total daily dose as two 100 mg doses administered twice daily provides the greatest likelihood of maximal suppression of excess adrenal androgen production throughout the day. Although the early morning peak of ACTH stimulates the majority of adrenal androgen production, a substantial minority of adrenal androgens is still produced during the first half of the day and could benefit from a morning dose of a CRF-1 receptor antagonist. Importantly, the Phase 2 Study CAH2001 demonstrated that crinecerfont administered 100 mg bid resulted in clinically meaningful reductions in androstenedione that would be expected to allow for reduced glucocorticoid dosing.

Meeting Discussion: ***FDA agreed that androstenedione is an appropriate pharmacodynamic marker but requested that ACTH levels continue to be collected. FDA also agreed with the sponsor's rationale that morning dosing, as part of a bid regimen, is needed for maximal suppression of excess adrenal androgen production throughout the day. FDA noted that following evening administration (qhs or at mealtime), the exposure of crinecerfont prior to the morning surge of ACTH appeared to be at trough levels, thus perhaps not maximizing the efficacy of crinecerfont. The FDA agreed that a 100 mg bid regimen was reasonable for the 6-month placebo-controlled portion of the study. However, the FDA also encouraged the Sponsor to consider modification of the open-label extension phase to explore a higher total daily dose and/or an alternate dosing regimen (such as a higher dose in the evening and a lower dose in the morning to maximally suppress the morning ACTH peak) in patients who do not have optimal/adequate response with the 100 mg bid dose. The FDA recommendation to evaluate higher doses and/or alternate dosing regimens of crinecerfont in the open-label extension period was based on an effort to potentially maximize efficacy beyond that which may be seen with the 100 mg bid dose, as well as safeguard against an unsuccessful registration study in an orphan patient population over a long period of evaluation (18 months). The Sponsor referred FDA to prior Type C meeting responses from August 2019, in which the FDA indicated that chronic toxicology studies appeared to be adequate to support long term administration of total daily crinecerfont doses up to 200 mg in adult patients. In support of exploring a higher dose in the registration trial, FDA cited their understanding that a 300 mg total daily dose would have acceptable safety margins. The FDA pointed out that dose selection, and the decision whether or not to explore higher doses, is the Sponsor's risk.***

The FDA also stressed the importance of documenting adverse events of infection and adverse events of use of rescue and/or stress dosing of

glucocorticoids in Study CAH3003; the Sponsor agreed with this recommendation.

Clinical Pharmacology

Question 4: Does the FDA agree that the completed mass balance study and proposed additional assessments in ongoing and planned studies will be sufficient to adequately characterize the crinecerfont human disposition and metabolite profile and support an NDA filing?

FDA Response to Question 4:
In general, your explanations for the incomplete recovery and relatively low accumulation of crinecerfont appear reasonable for future NDA filing. However, the acceptability of these data will depend on review of the NDA. Quantify the M6 metabolite of crinecerfont and consider quantifying the M11 metabolite as well in the ongoing and planned studies, in addition to quantifying the M4 and M9 metabolites of crinecerfont.

Crinecerfont has a chiral center. You will need to address whether metabolic chiral inversion occurs for crinecerfont in humans and the potential impact on the efficacy and safety of crinecerfont and include this information in the future crinecerfont NDA submission.

Sponsor Follow-Up: *No additional discussion needed.*

3.0 ADDITIONAL INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.[2]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format--- Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide,[3] as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[4] that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan

[2] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
[3] https://www.fda.gov/media/88173/download
[4] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

(see the FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov.[5] For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide[6] (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site.[7] When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.[8]

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled Study Data Standards Resources[9] and the CDER/CBER Position on Use of SI Units for

[5] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
[6] https://www.fda.gov/media/88173/download
[7] https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[8] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
[9] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

Lab Tests website.[10]

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims.*

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

(1) Study phase

(2) Statement of whether the study is intended to support marketing and/or labeling changes

(3) Study objectives (e.g., dose finding)

(4) Population

(5) A brief description of the study design (e.g., placebo or active controlled)

(6) Specific concerns for which you anticipate the Division will have comments

(7) For changes to protocols only, also include the following information:

- A brief summary of the substantive change(s) to the protocol (e.g., changes to

[10] https://www.fda.gov/media/109533/download

endpoint measures, dose, and/or population)

- Other significant changes
- Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials* for more information.

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

- Sponsor PowerPoint presentation.

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/s/

LISA B YANOFF
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