

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**218808Orig1s000, 218820Orig1s000**

**OTHER REVIEW(S)**



**Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)  
ARIA Sufficiency Memorandum for Pregnancy Safety Concerns  
Version: 2024-09-13**

Date: December 13, 2024  
Product Name(s): CRENESSITY (Crinecerfont)  
Application Type/Number(s): NDA 218808, NDA 218820  
Submission Number:  
Sponsor/Applicant: Neurocrine Biosciences, Inc.  
NEXUS Task Tracking Tool ID #:  
Reviewer(s): Po-Yin Chang, PhD  
Division of Epidemiology I  
Team Lead: Yandong Qiang, MD, PhD, MPH, MHS  
Division of Epidemiology I  
Division Leadership: Wei Hua, MD, PhD, MHS, MS  
Division of Epidemiology I  
Sub-Office Director: Judith Zander, MD  
Office of Pharmacovigilance and  
Epidemiology  
Sentinel Program Lead: Sarah Dutcher, PhD  
Regulatory Science Staff  
Office of Surveillance & Epidemiology



## Expedited ARIA Sufficiency Template for Pregnancy Safety Concerns

### 1. BACKGROUND INFORMATION

#### 1.1. Medical Product

On April 29, 2024, Neurocrine Biosciences Inc. submitted a New Drug Application (NDA 218808) for CRENESSITY (crinecerfont) 25 mg, 50 mg, and 100 mg capsules. On April 30, 2024, the Applicant submitted NDA 218820 for CRENESSITY (crinecerfont) 50 mg/mL oral solution. NDAs 218808 and 218820 are 505(b)(1) applications.

Crinecerfont, a new molecular entity, is a selective corticotropin releasing factor 1 (CRF1) receptor antagonist. On the CRENESSITY labeling, the proposed indication of CRENESSITY as an adjunctive treatment to glucocorticoid replacement to control androgens in adults and pediatric patients 4 years of age and older with classic congenital adrenal hyperplasia (CAH).

The proposed dosage of crinecerfont for adults aged 18 years and older is 100 mg twice daily. For pediatric patients aged 4 to 17 years, crinecerfont dosage is based on body weight (see Table 1).

**Table 1. Recommended CRENESSITY Weight-Based Dosage for Pediatric Patients 4 Years of Age and Older**

| Weight                         | Dosage regimen            |
|--------------------------------|---------------------------|
| 10 kg to less than 20 kg       | 25 mg orally twice daily  |
| 20 kg to less than 55 kg       | 50 mg orally twice daily  |
| Greater than or equal to 55 kg | 100 mg orally twice daily |

Source: Table 1, draft labeling of CRENESSITY as of December 12, 2024

Crinecerfont was granted Orphan Drug Designation on March 15, 2019,<sup>1</sup> Rare Pediatric Disease Designation on September 27, 2020,<sup>2</sup> Fast Track Designation on June 15, 2021,<sup>3</sup> and Breakthrough Therapy Designation on December 1, 2023.<sup>4</sup>

#### Classic Congenital Adrenal Hyperplasia (CAH)

Classic CAH is a rare, autosomal recessive disorder, affecting approximately one in every 10,000 livebirths.<sup>5</sup> The most common cause of classic CAH is 21-hydroxylase deficiency (21OHD) due to mutations in the *CYP21A2* gene.<sup>5,6</sup> In classic CAH, conversion of 17-hydroxyprogesterone (17OHP) to 11-deoxycortisol is defected, leading to decreased cortisol synthesis, loss of negative feedback, and therefore increased corticotropin secretion. The resulting adrenal stimulation creates an increased production of adrenal-derived androgens and a variable degree of aldosterone deficiency.<sup>6</sup> Patients with classic CAH need lifelong hydrocortisone and/or long-acting glucocorticoids plus mineralocorticoids as clinically indicated.<sup>7</sup>

#### 1.2. Describe the Safety Concern

##### Preclinical data

In animal models, embryo-fetal developmental toxicity was not observed at crinecerfont tosylate doses up to 2000 mg/kg/day in pregnant rats [i.e., 3.7-fold the maximum recommended human dose (MRHD) based on area under the curve (AUC)] and up to 500 mg/kg/day in pregnant rabbits



(2.9-fold the MRHD based on AUC).<sup>a</sup> In rabbits treated with crinecerfont at approximately 2-fold the MRHD, three incidences of poly-malformations (craniofacial defects) and slightly lower mean fetal weights were observed. In rabbits exposed to 1000 mg/kg/day, slightly decreased fetal weights were observed.

The review team of Division of General Endocrinology (DGE) and Division of Pediatrics and Maternal Health (DPMH) considers the nonclinical findings with crinecerfont were inconclusive as these findings occurred in a small number of rabbits. The team concludes that the nonclinical findings do not rise to the level of a Contraindication or a Warning and Precaution for embryofetal toxicity, and do not preclude conducting a postmarketing pregnancy safety study in pregnant individuals. Please refer to the Pregnancy and Lactation Labeling review (PLLR) by Dr. Katherine Kratz of DPMH for details.<sup>8</sup>

### Clinical Experience

According to the PLLR,<sup>8</sup> there were three pregnancies reported in the clinical development program.

Two pregnancies occurred in healthy volunteers who participated in the phase 1 study of QT/QTc evaluations.

- A 22-year-old female subject received a single dose of 300 mg crinecerfont and a single dose of moxifloxacin. She became pregnant during the study based on urine and serum pregnancy test. The estimated date of conception was approximately 10 days after receiving the single dose of crinecerfont and approximately one month after receiving moxifloxacin. Study treatment was discontinued. The subject was subsequently lost to follow-up. There was no available information for additional laboratory assessment and pregnancy outcome.
- A female of unreported age was reported to be pregnant based on positive urine and serum pregnancy tests; however, ultrasound showed no evidence of pregnancy. The subject subsequently had decreasing beta human chorionic gonadotropin (hCG) levels, consistent with a spontaneous abortion.

One pregnancy was reported in a 32-year-old female subject with classic CAH during the open-label period in phase 3 study CAH3003. Crinecerfont was discontinued on the day of pregnancy diagnosed. This subject underwent an uncomplicated C-section and delivered a healthy infant at 38 weeks of gestation.

With only three pregnancies and no pattern to the outcomes, the PLLR concludes that conclusions cannot be drawn regarding the impact of crinecerfont on pregnancy outcomes.

### Lactation

In nonclinical study, crinecerfont was present in rat milk. Toxicity was not observed in rats exposed to crinecerfont via milk through lactation day 20. According to the PLLR, when a drug is present in animal milk, it is likely that the drug will be present in human milk.<sup>8</sup> The DPMH review team is concerned that “healthy neonates exposed to crinecerfont via breast milk could develop adrenal insufficiency” and recommends “monitoring infants exposed to crinecerfont through breast milk for symptoms of adrenal insufficiency, such as weakness, decreased feeding and weight loss.”<sup>8</sup>

### Postmarketing Requirements (PMRs) for Descriptive Pregnancy Safety Study

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<sup>a</sup> NDA 218820, Module 2.4, Nonclinical Overview, p 18.



The PLLR concludes that nonclinical and clinical data related to crinecerfont use during pregnancy are insufficient to inform labeling and that a PMR may provide necessary pregnancy safety data. Given that classic CAH is a rare disease, the number of pregnant patients who use crinecerfont is likely to be small. The DPHM team recommends issuance of a descriptive pregnancy safety PMR to assess risk of pregnancy and maternal complications, and adverse effects on the developing fetus, neonate, and infant in women exposed to Crenessity during pregnancy.

### Relevant Labeling

As of December 12, 2024, the draft labeling of CRENESSITY states:

#### *8.1. Pregnancy*

##### *Risk Summary*

*Available data from reports of pregnancy in clinical trials with CRENESSITY are insufficient to identify a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes.*

*No developmental toxicity was observed in rats at 4-fold higher than human exposure at the maximum recommended human dose (MRHD) based on area under the concentration-time curve (AUC). Crinecerfont was associated with a low incidence of poly-malformations (craniofacial defects) in rabbits at 2-fold higher than human exposure at the MRHD. In a pre- and postnatal developmental toxicity study, no developmental toxicity was observed in rats at 4-fold higher than human exposure at the MRHD (see Data).*

*The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.*

*If CRENESSITY is administered during pregnancy, or if a patient becomes pregnant while receiving CRENESSITY, health care providers should report exposure to CRENESSITY by calling 1-855-CRNSITY (1-855-276-7489).*

##### *Data*

#### *Animal Data*

*Crinecerfont was administered orally to pregnant rabbits at doses of 100, 500, and 1000 mg/kg/day, and to pregnant rats at doses of 150, 500, and 2000 mg/kg/day during the period of organogenesis. No crinecerfont-related malformations were observed in rats at 4-fold higher than human exposure at the MRHD based on AUC. Low incidence of poly-malformations (craniofacial defects) and slightly lower mean fetal weights were observed in rabbits treated with crinecerfont at 2-fold higher than human exposure at the MRHD based on AUC.*

*In a pre- and postnatal developmental toxicity study, crinecerfont was administered orally to pregnant rats at doses of 15, 50, and 250 mg/kg/day during the period of organogenesis and lactation through Day 20 postpartum. No changes in pup mortality, growth, sexual maturation, behavior, mating and fertility, or ovarian and uterine parameters were observed. The exposure in dams at the No Observed Adverse Effect Level (NOAEL) of 250 mg/kg/day was approximately 4-fold higher than human exposure at the MRHD based on AUC.*

#### *8.2. Lactation*



### Risk Summary

*There are no data on the presence of crinecerfont in human milk, the effects on the breastfed infant, or the effects on milk production. Crinecerfont is present in animal milk (see Data). When a drug is present in animal milk, it is likely that the drug will be present in human milk. Infants exposed to CRENESSITY through breast milk should be monitored for signs of adrenal insufficiency such as weakness, decreased feeding and weight loss.*

*The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CRENESSITY and any potential adverse effects on the breastfed child from CRENESSITY or from the underlying maternal condition.*

### Data

*Crinecerfont was excreted in the milk of rats, with milk-to-plasma concentration ratios ranging from 1.5 to 12. No effects on postnatal development were observed in a pre- and postnatal development study, in which female rats were treated orally with up to 250 mg/kg/day (4-fold higher than human exposure at the MRHD based on AUC) during organogenesis through lactation.*

## **1.3. FDAAA Purpose (per Section 505(o)(3)(B))**

*Ensure that the selected purpose(s) is consistent with the other PMR documents in DARRTS. More than one purpose may be chosen.*

- ☐ Assess a known serious risk
- ☐ Assess signals of serious risk
- ☒ Identify unexpected serious risk when available data indicate potential for serious risk

## **2. REVIEW QUESTIONS**

### **2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.**

- ☐ Specific FDA-approved indication in pregnant individuals exists and exposure is expected
- ☐ No approved indication in pregnant individuals, but practitioners may use product off-label in pregnant individuals
- ☒ No approved indication in pregnant individuals, but there is the potential for inadvertent exposure before a pregnancy is recognized
- ☒ No approved indication in pregnant individuals, but use in individuals of childbearing age is a general concern

### **2.2. Regulatory Goal<sup>b</sup>**

- ☐ Signal evaluation of specific outcome(s) – *implementation of a full epidemiological analysis to thoroughly evaluate the causal relationship between exposure to the medical*

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<sup>b</sup> Definitions adapted from: Robb MA, Racoosin JA, Sherman RE, Gross TP, Ball R, Reichman ME, Midthun K, Woodcock J. The US Food and Drug Administration's Sentinel Initiative: expanding the horizons of medical product safety. *Pharmacoepidemiol Drug Saf.* 2012 Jan;21 Suppl 1:9-11. doi: 10.1002/pds.2311. PMID: 22262587.



- product and the health outcome of interest.*
- ☐ Signal refinement of specific outcome(s) – *further investigation of an identified potential safety signal to determine whether evidence exists to support a relationship between the medical product exposure and the health outcome.*
  - ☒ Signal identification – *detection of new and unexpected potential medical product safety concerns and may be for a **targeted or multiple** safety concern(s)/health outcome(s).*
    - ☐ Targeted evaluation of specific safety concern
    - ☒ Simultaneous identification of multiple unspecified adverse outcomes

**2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.**

- ☐ Pregnancy registry with internal comparison group
- ☐ Pregnancy registry with external comparison group
- ☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
- ☐ Electronic database study with chart review
- ☐ Electronic database study without chart review
- ☒ Other, please specify: A worldwide descriptive study that collects prospective and retrospective data in women exposed to crinicerfont during pregnancy and/or lactation to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant.

**2.4. Identify the epidemiologic domain(s) where ARIA is not sufficient and provide a rationale on ARIA insufficiency for those epidemiologic domain(s). Then, provide an assessment of the overall ARIA sufficiency.**

| <b>Epidemiologic Domain</b>                          | <b>Explanation on ARIA insufficiency</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input checked="" type="checkbox"/> Study Population | The ARIA system cannot reliably identify the study population of classic CAH using claims data. Although ICD-10 code E25.0 can be used to identify CAH associated with enzyme deficiency, the diagnosis code lacks the specific enzyme deficiency and thus is not specific for classic CAH. <sup>9</sup>                                                                                                                                                                                                                                                                                 |
| <input type="checkbox"/> Exposures (and Comparators) |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <input checked="" type="checkbox"/> Outcomes         | ARIA lacks access to detailed narratives regarding pregnancy-related outcomes. The study being considered for broad-based surveillance is descriptive, without sample size requirements or a comparison group. Therefore, having detailed narratives are deemed necessary to identify and validate outcomes, assess exposure-outcome temporality, and to conduct causality assessments for individual cases. In addition, pregnancy and lactation outcomes may require medical chart validation and independent review of primary sources by physicians with expertise in birth defects. |
| <input checked="" type="checkbox"/> Covariates       | The ARIA system is unlikely to provide complete and reliable information about critical covariates that are potentially                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |



|                                                                                         |                                                                                                                                                     |
|-----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                         | associated with various pregnancy and lactation outcomes, such as over the counter medications, smoking, alcohol consumption, and illicit drug use. |
| <input type="checkbox"/> Analytic Tools                                                 |                                                                                                                                                     |
| <b>Overall ARIA sufficiency determination</b>                                           |                                                                                                                                                     |
| <input checked="" type="checkbox"/> Insufficient<br><input type="checkbox"/> Sufficient |                                                                                                                                                     |

**2.5. If ARIA is deemed insufficient, include the PMR language to be included in the approval letter.**

Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to Crenessity during pregnancy to assess risk of pregnancy and maternal complications, and adverse effects on the developing fetus, neonate, and infant. Assess infant outcomes through at least the first year of life. The study should also collect adverse event data for lactating women and infants exposed to Crenessity through breastfeeding to assess for any potential risks to the infant from breastfeeding. The minimum number of patients will be specified in the protocol.



## REFERENCE

1. U.S. Food and Drug Administration. Orphan Drug Designations and Approvals: Crinercerfont. March 15, 2019.  
<https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=639018>
2. U.S. Food and Drug Administration. *Rare Pediatric Disease Designation # RPD-2020-410 of Crinercerfont for Treatment of Classic Congenital Adrenal Hyperplasia due to 21-hydroxylase Deficiency*. September 27, 2020.
3. U.S. Food and Drug Administration. *IND 132849 Crinercerfont, Correspondence: Grant Fast Track*. DARRTS Reference ID: 4811769. June 15, 2021.
4. U.S. Food and Drug Administration. *IND 132849 Crinercerfont, Correspondence: Grant Breakthrough Therapy Designation*. DARRTS Reference ID: 5285815. December 1, 2023.
5. Congenital adrenal hyperplasia on OrphaNet. Accessed November 1, 2024.  
<https://www.orpha.net/en/disease/detail/418?name=Congenital%20adrenal%20hyperplasias&mcode=name>
6. Merke DP, Auchus RJ. UpToDate: Clinical manifestations and diagnosis of classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency in infants and children. Accessed November 1, 2024. <https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-classic-congenital-adrenal-hyperplasia-due-to-21-hydroxylase-deficiency-in-infants-and-children>
7. Speiser PW, Arlt W, Auchus RJ, et al. Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society\* Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism*. 2018;103(11):4043-4088. doi:10.1210/jc.2018-01865
8. Kratz K. *NDA 218808 and 218820. Pregnancy and Lactation Labeling for CRENESSITY (crinercerfont)*. DARRTS Reference ID: 5446420. September 13, 2024.
9. Harasymiw LA, Grosse SD, Sarafoglou K. Attention-Deficit/Hyperactivity Disorder Among US Children and Adolescents With Congenital Adrenal Hyperplasia. *Journal of the Endocrine Society*. 2020;4(12)doi:10.1210/jendso/bvaa152

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YANDONG QIANG on behalf of PO YIN CHANG  
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YANDONG QIANG  
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SUKHMINDER K SANDHU on behalf of WEI HUA  
12/12/2024 04:01:30 PM

JUDITH W ZANDER  
12/12/2024 04:03:22 PM

PATRICIA L BRIGHT on behalf of SARAH K DUTCHER  
12/13/2024 12:15:12 PM

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy**

**PATIENT LABELING REVIEW**

Date: December 4, 2024

To: Dana Smith, BS  
Regulatory Health Project Manager  
**Division of General Endocrinology (DGE)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Nyedra Booker, PharmD, MPH  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**  
Charuni Shah, PharmD  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Patient Package Insert (PPI)  
and Instructions for Use (IFU)

Drug Name (established name) and Dosage Form and Route: CRENESSITY (crinecerfont) capsules, for oral use  
CRENESSITY (crinecerfont) oral solution, for oral use

Application Type/Number: 218808  
218820

Applicant: Neurocrine Biosciences, Inc.

## 1 INTRODUCTION

On April 29, 2024, Neurocrine Biosciences, Inc. submitted for the Agency's review an original New Drug Application (NDA) for CRENESSITY (crinecerfont) capsules for oral use (NDA 218808) and CRENESSITY (crinecerfont) oral solution, for oral use (NDA 218820). The proposed indication for CRENESSITY (crinecerfont) is (b) (4)

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of General Endocrinology (DGE) on June 7, 2024, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for CRENESSITY (crinecerfont).

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on September 23, 2024.

## 2 MATERIAL REVIEWED

- Draft CRENESSITY (crinecerfont) PPI and IFU received on April 29, 2024, revised by the Review Division throughout the review cycle, and received by DMPP on November 22, 2024.
- Draft CRENESSITY (crinecerfont) PPI and IFU received on April 29, 2024, revised by the Review Division throughout the review cycle, and received by OPDP on November 22, 2024.
- Draft CRENESSITY (crinecerfont) Prescribing Information (PI) received on April 29, 2024, revised by the Review Division throughout the review cycle, and received by DMPP on November 22, 2024.
- Draft CRENESSITY (crinecerfont) Prescribing Information (PI) received on April 29, 2024, revised by the Review Division throughout the review cycle, and received by OPDP on November 22, 2024.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APhont to make medical information more accessible for patients with vision loss. We reformatted the IFU document using the Arial font, size 11.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the PI
- removed unnecessary or redundant information

- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the IFU meets the criteria as specified in both the FDA Guidance for Useful Written Consumer Medication Information (published July 2006) and Instructions for Use-Patient Labeling for Human Prescription Drug and Biological Products (published July 2022)

#### **4 CONCLUSIONS**

The PPI and IFU are acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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NYEDRA W BOOKER  
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CHARUNI P SHAH  
12/04/2024 04:43:07 PM

LASHAWN M GRIFFITHS  
12/05/2024 07:15:38 AM

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

**\*\*\*\*Pre-decisional Agency Information\*\*\*\***

**Memorandum**

**Date:** December 3, 2024

**To:** Dana Smith, Regulatory Project Manager  
Division of General Endocrinology (DGE)

**From:** Charuni Shah, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**CC:** Sapna Shah, Team Leader, OPDP

**Subject:** OPDP Labeling Comments for CRENESSITY (crinecerfont) capsules, for oral use

**NDA:** 218808; 218820

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**Background:**

In response to DGE's consult request dated June 7, 2024, OPDP has reviewed the proposed Prescribing Information (PI) and Patient Package Insert (PPI), and Instructions for Use (IFU) for original NDA for CRENESSITY (crinecerfont) capsules, for oral use (Crenessity).

**PI/PPI/IFU:**

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on November 22, 2024, and we do not have any comments at this time.

OPDP comments on the proposed PPI and IFU will be sent under separate cover, as a combined OPDP and Division of Medical Policy Programs (DMPP) review.

Thank you for your consult. If you have any questions, please contact Charuni Shah at (240) 402-4997 or [charuni.shah@fda.hhs.gov](mailto:charuni.shah@fda.hhs.gov).

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CHARUNI P SHAH  
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MEMORANDUM  
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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|                                          |                                                                      |
|------------------------------------------|----------------------------------------------------------------------|
| Date of This Review:                     | November 4, 2024                                                     |
| Requesting Office or Division:           | Division of General Endocrinology (DGE)                              |
| Application Type and Number:             | NDA 218808                                                           |
| Product Name, Dosage Form, and Strength: | Crenessity (crinecerfont), Oral Capsules<br>25 mg, 50 mg, and 100 mg |
| Applicant Name:                          | Neurocrine Biosciences (Neurocrine)                                  |
| FDA Received Date:                       | October 29, 2024                                                     |
| TTT ID #:                                | 2024-9301-1                                                          |
| DMEPA 1 Safety Evaluator:                | Peggy Rahbani, PharmD, BCPS                                          |
| DMEPA 1 Team Leader:                     | Yevgeniya Kogan, PharmD, BCSCP                                       |

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## 1 PURPOSE OF MEMORANDUM

Neurocrine Biosciences (Neurocrine) submitted revised container labels received on October 29, 2024 for Crenessity. The Division of General Endocrinology (DGE) requested that we review the revised container labels for Crenessity (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.<sup>a</sup>

## 2 CONCLUSION

Neurocrine Biosciences (Neurocrine) implemented all of our recommendations and we have no additional recommendations at this time.

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<sup>a</sup> Rahbani P. Label and Labeling Review for Crenessity (NDA 218808). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 Sep 23. TTT ID: 2024-9301.

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/s/  
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PEGGY M RAHBANI  
11/04/2024 07:33:08 AM

YEVGENIYA M KOGAN  
11/04/2024 08:20:59 AM

## Clinical Inspection Summary

|                                  |                                                                                                                                                                                                                                                                     |
|----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Date</b>                      | October 28, 2024                                                                                                                                                                                                                                                    |
| <b>From</b>                      | Ling Yang, M.D., Ph.D., FAAFP<br>Min Lu, M.D., M.P.H., Team Leader<br>Jenn Sellers, M.D., Ph.D., Branch Chief<br>Good Clinical Practice Assessment Branch (GCPAB)<br>Division of Clinical Compliance Evaluation (DCCE)<br>Office of Scientific Investigations (OSI) |
| <b>To</b>                        | Karen Vogt, M.D., Clinical Reviewer<br>Shannon Sullivan, M.D., Clinical Team Leader<br>Dana Smith, Consumer Safety Officer, RPM<br>Division of General Endocrinology (DGE)                                                                                          |
| <b>NDA #</b>                     | 218808 & 218820                                                                                                                                                                                                                                                     |
| <b>Applicant</b>                 | Neurocrine Biosciences Inc.                                                                                                                                                                                                                                         |
| <b>Drug</b>                      | Crinecerfont                                                                                                                                                                                                                                                        |
| <b>NME (Yes/No)</b>              | Yes                                                                                                                                                                                                                                                                 |
| <b>Review Priority</b>           | Priority                                                                                                                                                                                                                                                            |
| <b>Proposed Indication(s)</b>    | (b) (4)                                                                                                                                                                                                                                                             |
| <b>Consultation Request Date</b> | May 22, 2024                                                                                                                                                                                                                                                        |
| <b>Summary Goal Date</b>         | November 27, 2024                                                                                                                                                                                                                                                   |
| <b>Action Goal Date</b>          | December 27, 2024                                                                                                                                                                                                                                                   |
| <b>PDUFA Date</b>                | December 29, 2024                                                                                                                                                                                                                                                   |

### I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from studies **NBI-74788-CAH2006** 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” and **NBI-74788-CAH3003** 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” were submitted in the original new drug applications (NDAs) 218808 (25 mg, 50 mg, and 100 mg soft gelatin capsules) and 218820 (50 mg/mL oral solution) for Crinecerfont, a selective corticotropin releasing factor 1 (CRF1) receptor antagonist, (b) (4)

Three domestic clinical investigators (CIs): Drs. Eric Felner (Site #1076), Mimi Kim (Site #1080) for both studies, and Oksana Hamidi (Site #1083 for Study NBI-74788-CAH3003 only) were inspected.

Based on the overall inspection results of these CIs and the regulatory assessments, data generated by the CIs and submitted by the sponsor are verifiable. Studies NBI-74788-CAH2006 and NBI-74788-CAH3003 appear to have been conducted adequately and the clinical data submitted by the sponsor appear acceptable in support of the respective indication.

## II. BACKGROUND

Crinecerfont is a selective corticotropin releasing factor 1 (CRF1) receptor antagonist developed (b) (4)

Fast Track Designation was granted to crinecerfont in June 2021.

On 04/29/2024, Neurocrine Biosciences, Inc. (NBI) submitted an original NDA 218808 for crinecerfont 25 mg, 50 mg, and 100 mg soft gelatin capsules; and NDA 218820 for crinecerfont 50 mg/mL oral solution. Data from two Phase 3 studies NBI-74788-CAH2006 and NBI-74788-CAH3003 were submitted to support the approval.

### **Study NBI-74788-CAH2006**

Study NBI-74788-CAH2006 was a randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of crinecerfont (NBI-74788) in pediatric subjects with classic CAH, followed by an open-label treatment period.

The primary study objective was to evaluate the efficacy of crinecerfont, compared with placebo, in reducing adrenal steroid levels during a glucocorticoid-stable period.

The primary efficacy endpoint was the change from baseline (CFB) in serum androstenedione at Week 4.

### **Study Design:**

The study consisted of the following periods:

- **Randomized, Double-Blind, Placebo-Controlled Treatment Period:** Day 1 - Week 28

#### Glucocorticoid-Stable Period (Day 1 - Week 4)

- Eligible subjects were randomized at a 2:1 ratio to receive either crinecerfont or placebo.
- Randomization was stratified by pubertal stage (Tanner stage 1 or 2 versus 3, 4, or 5) and sex. All subjects received blinded study drug based on their Day 1 weight. Treatment was administered bid (12 hours apart) with breakfast and evening meals.
- Subjects maintained a stable glucocorticoid regimen, except for stress dosing as needed for illness or other significant physical stress, to assess the direct effect of study drug on adrenal androgens and precursors. Stress dosing was based on guidance provided by the investigator, the subject's treating physician, or guidelines provided in the protocol.

#### Glucocorticoid-Adjustment Period (Week 4 - 28)

- Subject's glucocorticoid dose was adjusted (in 4 or fewer steps) according to their androstenedione levels, with the goal to reach a target dose of 8-10 mg/m<sup>2</sup>/day (in hydrocortisone dose equivalents adjusted for body surface area [BSA]) at Week 28, while androstenedione was controlled, i.e., ≤ 120% of the baseline value or ≤ ULN, based on sex and either age (for Tanner stage 1) or pubertal stage (for Tanner stages 2 to 5), and as long as there was no evidence of glucocorticoid insufficiency.

- **Open-Label Treatment Period:** Week 28 - 52
  - Subjects received crinecerfont oral solution bid at doses based on their Week 28 body weight (25 mg for subjects 10 - < 20 kg, 50 mg for subjects 20 - < 55 kg, or 100 mg for subjects  $\geq$  55 kg) with breakfast and evening meals.
  - Subjects maintained their stable glucocorticoid regimen, except for sick-day guidelines as needed.
  - For subjects who were on  $>11$  mg/m<sup>2</sup>/day glucocorticoid dose (in hydrocortisone dose equivalents adjusted for BSA based on weight and height at Week 28) at Week 32, further adjustments in glucocorticoid dose were made following guidelines similar to those used during the double-blind period, with the goal to reach a target dose of 8-10 mg/m<sup>2</sup>/day in hydrocortisone dose equivalents adjusted for BSA at Week 52, while androstenedione was controlled.
  - The first glucocorticoid dose adjustment step during this period (if done) was guided by the serum androstenedione change at Week 32 (compared with Week 28), after the subject was on open-label active study drug as well as stable glucocorticoid regimen for 4 weeks.
- **Open-Label Extension (OLE) Treatment Period:** Week 52 onwards
  - Subjects continued to receive crinecerfont bid at the dose based on their body weight at each study visit (25 mg if weight 10 - < 20 kg, 50 mg if weight 20 - < 55 kg, 100 mg if weight  $\geq$  55 kg), unless the subject had inadequate efficacy. The crinecerfont dose was increased per the protocol-specified guidelines.
  - Subjects could have their glucocorticoid doses adjusted as appropriate and tolerated to achieve the lowest glucocorticoid dose that maintained adequate disease control.
  - At Week 52, subjects taking crinecerfont 50 mg bid or higher could elect to switch the crinecerfont formulation (oral solution or capsule) based on preference.
- **Follow-Up Period:** 4 weeks after the last dose.

The study screened 174 subjects, randomized 103 (69 in crinecerfont group and 34 in placebo group) subjects at 37 study sites in the US (19); Canada (3) and Europe (15). The first subject was randomized on 06/25/2021 and the last subject was still in the open-label period of the study with the data cutoff date on 08/09/2023. A total of 97 subjects (66 in crinecerfont group and 31 in placebo group) completed the study through Week 28 (double-blind period).

### **Study NBI-74788-CAH3003**

Study NBI-74788-CAH3003 was a randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of crinecerfont (NBI-74788) in adult subjects with classic CAH, followed by an open-label treatment period.

The primary study objective was to evaluate the efficacy of crinecerfont (100 mg bid), compared with placebo, in reducing daily glucocorticoid dosage while maintaining adrenal androgen control.

The primary efficacy endpoint was the percent change from baseline in glucocorticoid daily dose (in hydrocortisone equivalents adjusted for BSA [mg/m<sup>2</sup>/day]) at Week 24, while Week 24 androstenedione was adequately controlled at  $\leq$  120% of baseline or  $\leq$  ULN for age and sex.

### **Study Design:**

The study consisted of the following periods:

- **Randomized, Double-Blind, Placebo-Controlled Treatment Period:** Day 1 - Week 24
  - **4-Week Glucocorticoid Stable Period** (Day 1 up to Week 4): Eligible subjects were randomized at a 2:1 ratio to receive crinecerfont 100 mg or placebo. Randomization was stratified by total daily glucocorticoid dose/type, and sex. Study treatment was administered bid with the subject's breakfast and evening meal (separated by 12 hours). Subjects maintained their baseline glucocorticoid regimen.
  - **8-Week Glucocorticoid Reduction Period** (Week 4 - 12): Subjects underwent a down-titration (in 4 or fewer steps) of their glucocorticoid dose with the goal to reach a target dose of 8-10 mg/m<sup>2</sup>/day (hydrocortisone equivalents adjusted for BSA) by Week 12, unless the subject had signs or symptoms suggestive of clinically relevant glucocorticoid insufficiency (unexplained hyponatremia, orthostatic hypotension, or severe nausea, food aversion, or vomiting) or unacceptable symptoms of hyperandrogenism (e.g., hirsutism, acne, amenorrhea).
  - **12-Week Glucocorticoid Optimization Period** (Week 12 - 24): At the Week 12 visit, the investigator determined the appropriate dose of glucocorticoid to continue past Week 12 to achieve adequate control of androgen levels (i.e., androstenedione ≤ 120% of the subject's baseline or ≤ ULN for age and sex). The glucocorticoid dose was adjusted as needed based on androstenedione levels and signs or symptoms of glucocorticoid insufficiency or hyperandrogenism.
- **Open-Label Treatment Period:** Week 24 to Month 12
  - **1-Month Glucocorticoid Stable Period** (Week 24 to Month 7): Subjects maintained on the same glucocorticoid regimen as at on Week 24.
  - **3-Month Glucocorticoid Reduction Period** (Month 7 - 10): If the androstenedione level was controlled, glucocorticoid doses can be decreased as tolerated in subjects whose glucocorticoid dose was still >11 mg/m<sup>2</sup>/day at Month 7, with the goal to achieve a dose of 8-10 mg/m<sup>2</sup>/day by Month 10.
  - **2-Month Glucocorticoid Maintenance Period** (Month 10 - 12): The goal was to maintain stable glucocorticoid doses; however, the dose could be adjusted as needed based on androstenedione levels and signs or symptoms of glucocorticoid insufficiency or hyperandrogenism.
- **Open-Label or Double-Blind Active-Controlled Treatment Period:** Month 12 - 18
  - At Month 12, subjects with a glucocorticoid dose >11 mg/m<sup>2</sup>/day were re-randomized (2:1) to receive crinecerfont at an increased dosage of 100 mg every morning and 200 mg every evening, or to continue 100 mg bid.
  - Subjects maintained a stable glucocorticoid regimen for the first month. After Months 13, 14, and 16, the glucocorticoid doses were decreased as tolerated, with the goal to achieve a dose of 8-10 mg/m<sup>2</sup>/day by Month 18. Subjects who reduced their glucocorticoid dose to ≤ 11 mg/m<sup>2</sup>/day by Month 12 continued to receive open label crinecerfont 100 mg bid. The goal was to maintain stable glucocorticoid doses while androstenedione levels were controlled, but the glucocorticoid dose could be adjusted as needed based on androstenedione levels and signs or symptoms of glucocorticoid insufficiency or hyperandrogenism.
- **Open-Label Extension (OLE) Treatment Period:** Month 18 onwards
  - Subjects had their glucocorticoid doses adjusted as appropriate and tolerated to achieve the lowest glucocorticoid dose that maintains adequate disease control.

- All subjects started with open label crinecerfont 100 mg bid. If the subject had inadequate disease control, then the crinecerfont dose was increased to 100 mg every morning and 200 mg every evening. If this increased dosage was not well tolerated, then the crinecerfont dose was reduced back to 100 mg bid.
- After the Month 24 visit, an alternative crinecerfont dosing regimen of once daily 200 mg in the PM could be considered.
- **Follow-Up Period:** 4 weeks after the last dose.

The study screened 300 subjects, randomized 182 (122 in crinecerfont group and 60 in placebo group) subjects at 54 study sites in the US (18), Canada (1), Europe (34) and Israel (1). The first subject was randomized on 11/16/2020 and the last subject was still in the open-label period of the study with the data cutoff date on 07/19/2023. A total of 174 subjects (117 in crinecerfont group and 57 in placebo group) completed the study through Week 24 (double-blind period).

### III. RESULTS

#### 1. Eric Felner, M.D. (Site # 1076)

2174 N Druid Hills Road, NE  
Atlanta, GA 30329-2309

This CI was inspected on 07/29-08/02/2024 as a data audit for studies NBI-74788-CAH2006 and NBI-74788-CAH3003. This was the first FDA inspection of Dr. Felner.

For Study NBI-74788-CAH2006, the site screened 7 subjects and enrolled 5 subjects, who were still in the Open-Label Treatment Period. The first subject consented on 02/18/2022. Source records for all 7 screened subjects were reviewed.

For Study NBI-74788-CAH3003, the site screened 4 subjects and enrolled 2 subjects, who were still in the Open-Label Treatment Period. The first subject consented on 06/01/2021. Source records for all 4 screened subjects were reviewed.

The inspection reviewed the studies' protocols and amendments, Informed Consent Forms (ICFs) and versions, documentation of eligibility criteria and enrollment logs, medical records [including visit data, laboratory tests reports, physical exam results, concomitant medications, adverse events (AEs) and serious AEs (SAEs) reports], investigational product (IP) accountability records, both paper and electronic Case Report Forms (eCRFs) and electronic data capture (EDC) system, protocol deviations and related regulatory documents [e.g., Institutional Review Board (IRB) approvals and communications, staff trainings, monitoring log, records retention, financial disclosures and delegation of authority].

The submitted data were verifiable with source records at the study site. The primary efficacy endpoint data glucocorticoid daily dose (weights were confirmed for dose adjustments); and serum androstenedione levels were verified with no discrepancies noted. There were no underreporting of AEs or SAEs.

In general, the inspection verified adequate source data for the inspected studies' subjects, with no deficiencies reported.

**2. Mimi Kim, M.D. (Site # 1080)**

4650 W Sunset Blvd., MS 61  
Los Angeles, CA 90027-6062

This CI was inspected on 07/22-25/2024 as a data audit for Studies NBI-74788-CAH2006 and NBI-74788-CAH3003. This was the first FDA inspection of Dr. Kim.

For Study NBI-74788-CAH2006, the site screened 9 subjects and enrolled 7 subjects. Six (6) subjects were still in the Open-Label Treatment Period. The first subject consented on 11/10/2021. Source records for all 9 screened subjects were reviewed.

For Study NBI-74788-CAH3003, the site screened 4 subjects and enrolled 3 subjects, who were still in the Open-Label Treatment Period. The first subject consented on 10/30/2021. Source records for all 4 screened subjects were reviewed.

The inspection reviewed the studies' protocol and amendments, ICFs and versions, documentation of eligibility criteria and enrollment logs, medical records (including visit data, laboratory tests, concomitant medications, AEs and SAEs reports), IP accountability records, paper CRFs with eCRF entries and audit trails, protocol deviations and related regulatory documents (e.g., IRB approvals and communications, staff trainings, monitoring procedure and logs, records retention, financial disclosures and delegation of authority).

The submitted data were verifiable with source records at the study site. For both studies, the primary efficacy endpoint data glucocorticoid daily dose (weights were confirmed for dose adjustments); and serum androstenedione levels were verified with no discrepancies noted. There were no underreporting of AEs or SAEs.

In general, the inspection verified adequate source data for the inspected studies subjects, with no significant deficiencies noted.

**3. Oksana Hamidi, D.O. (Site #1083)**

5323 Harry Hines Blvd., U9.134  
Dallas, TX 75390-7208

This CI was inspected on 07/15-18/2024 as a data audit for Study NBI-74788-CAH3003. This was the first FDA inspection of Dr. Hamidi.

For the inspected study, the site screened 25 subjects and enrolled 13 subjects, who were still in the Open-Label Treatment Period. The first subject consented on 04/16/2021. Source records for all 25 screened subjects were reviewed.

The inspection reviewed the studies' protocol and amendments, ICFs and versions, documentation of eligibility criteria and enrollment logs, medical records (including visit data, laboratory tests, AEs and SAEs reports), IP accountability records, paper CRFs with eCRFs entries and audit trails, EDC system, protocol deviations and related regulatory documents (e.g.,

IRB approvals and communications, staff trainings, monitoring procedure and logs, records retention, financial disclosures and delegation of authority).

The submitted data were verifiable with source records at the study site. The primary efficacy endpoint data of glucocorticoid daily dose (weights were confirmed for dose adjustments); and serum androstenedione were verified with no discrepancies noted. There were no underreporting of AEs or SAEs.

In general, the inspection verified adequate source data for the inspected studies subjects, with no significant deficiencies noted.

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**MEMORANDUM**  
**Department of Health and Human Services**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**

**Date:** October 22, 2024

**To:** Theresa Kehoe, M.D., Director  
Division of General Endocrinology (DGE)

**Through:** Dominic Chiapperino, PhD, Director  
Chad J. Reissig, PhD, Supervisory Pharmacologist  
Controlled Substance Staff

**From:** Yohanka Caro, Pharm.D., Pharmacist  
Controlled Substance Staff

**Subject:** **NDA 218808, 218820 (IND 132849):** Crenessity (crinecerfont) - Capsules  
& Oral solution

**Indication:** (b) (4)  
(b) (4)

**Dosage and Route:** Adults & Pediatric patients weighing  $\geq 55$  kg-100 mg  
twice daily; 20 kg to <55 kg-50 mg twice daily; 10 kg to <20 kg 25 mg -  
twice daily - Oral

**Sponsor:** Neurocrine Biosciences, Inc. (NBI)  
**PDUFA Goal Date:** December 30, 2024

**Materials Reviewed:**

- Date of submission: April 29, 2024 (NDA 218808), April 30, 2024 (NDA 218820)
- Drug Abuse Liability Assessment of crinecerfont (NBI-74788)

**Table of Contents**

**I. SUMMARY.....2**

    1. Background.....2

    2. Conclusions.....3

    3. Recommendations (to the Division) .....3

**II. DISCUSSION.....4**

    1. Chemistry.....4

        1.1 Drug Substance and Product Information .....4

    2. Nonclinical Pharmacology.....5

        2.1 Receptor Binding and Functional Assays .....5

        2.2 Animal Behavioral Studies.....6

        2.3 Tolerance and Physical Dependence Studies in Animals .....8

    3. Clinical Studies.....8

        3.1 Human Abuse Potential Studies .....8

        3.2 Adverse Event Profile Through all Phases of Development.....8

        3.3 Evidence of Abuse, Misuse, and Diversion in Clinical Trials .....10

## I. SUMMARY

### 1. Background

This memorandum is in response to a consult request dated June 7, 2024 from the Division of General Endocrinology (DGE) pertaining to NDA 218808 and NDA 218820 for crinecerfont softgelatin capsules and crinecerfont oral solution, respectively. The Sponsor, Neurocrine Biosciences, Inc., is developing crinecerfont, a selective corticotropin releasing factor-1 (CRF<sub>1</sub>) receptor antagonist, (b) (4)

Crinecerfont was granted Orphan Drug designation; Fast Track designation; Rare Pediatric Disease Designation (RPDD); and Breakthrough Therapy designation. DGE requested that the Controlled Substance Staff (CSS) review the Applicant's NDA from an abuse potential perspective. CSS has not previously reviewed crinecerfont.

Crinecerfont is a new molecular entity (NME) currently under investigation in pediatric and adult patients with classic congenital adrenal hyperplasia but has also been evaluated for the treatment of major depressive disorder (MDD) and generalized anxiety disorder under IND (b) (4) (Division of Psychiatry Products (DPP)). IND (b) (4) was withdrawn (b) (4). Neurocrine Biosciences acquired the development of this product from Sanofi (formerly Sanofi-Synthelabo, Inc. and then Sanofi Aventis US Inc.) in May 2015.

CAH is a rare disorder in which deficiency of 21-hydroxylase results in glucocorticoid (cortisol) and mineralocorticoid (aldosterone) deficiencies. These deficiencies result in loss of negative feedback on the hypothalamus and pituitary, leading to increased corticotropin-releasing factor (CRF) and adrenocorticotrophic hormone (ACTH) secretion and consequently excess adrenal androgen production. Current standard of care therapies for CAH include glucocorticoid (e.g., hydrocortisone) and mineralocorticoid (e.g., fludrocortisone) replacement, and salt supplementation (in infants). However, supraphysiological doses of glucocorticoids are often required, creating a clinical management challenge of balancing disease control (by normalizing adrenal androgen levels) while avoiding Cushing's syndrome (due to excess glucocorticoid exposure).

Crinecerfont, a selective corticotropin releasing factor-1 (CRF<sub>1</sub>) receptor antagonist, reduces pituitary ACTH production and thereby helps to improve control of adrenal androgen levels and reduce the total daily glucocorticoid dose required to manage the disease. The Sponsor hypothesizes that inhibition of ACTH release in patients with CAH will decrease adrenal androgen production sufficiently to allow lower, more physiologic doses of glucocorticoids, thus minimizing the complications associated with glucocorticoid therapy.

According to the Sponsor, crinecerfont exhibits limited distribution to the brain at concentrations demonstrated to engage pituitary CRF<sub>1</sub> and there were no observed CNS effects associated with abuse in pharmacology and toxicology studies. Crinecerfont was also determined to have no significant activity in a broad panel of receptors, transporters, enzymes, and ion channels, including those associated with abuse. Therefore, additional studies including non-clinical abuse potential assessments and a human abuse potential study were not conducted.

Overall, CSS has not identified any abuse- or dependence-related concerns with crinecerfont and did not identify any evidence to suggest that crinecerfont poses risks of addiction liability in humans. CSS concludes that crinecerfont is unlikely to be abused and therefore should not be controlled under the Controlled Substance Act (CSA). The proposed drug product, if approved under this NDA will not require Section 9 (Drug Abuse and Dependence section) in its label.

## 2. Conclusions

- The receptor binding and activity data indicate that crinecerfont is a selective corticotropin releasing factor-1 (CRF<sub>1</sub>) receptor antagonist. Receptor binding studies demonstrated that crinecerfont did not bind to any receptors, transporters, or ion channels typically associated with drugs having a potential for abuse.
- Additional studies including non-clinical abuse potential assessments and a human abuse potential study were not requested.
- A review of TEAEs in clinical studies did not reveal any evidence to suggest that crinecerfont has a potential for abuse or physical dependence. The most prevalent AEs observed in clinical trials were fatigue, headache, and pyrexia.
- The proposed drug product, if approved under this NDA, will not require a Drug Abuse and Dependence section in its label.

## 3. Recommendations (to the Division)

- Based on crinecerfont low permeability, limited brain penetration and the lack of CNS activity, and the lack of abuse related AEs, crinecerfont does not appear to have abuse potential and should not be controlled under the Controlled Substances Act (CSA).
- Crinecerfont does not require a section 9 (Drug Abuse and Dependence section) in its label.

# II. DISCUSSION

## 1. Chemistry

### 1.1 Drug Substance and Product Information

#### *Drug Substance*

The IUPAC chemical name for crinecerfont is 2-thiazolamine, 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-2-propyn-1-yl. It has a molecular formula of C<sub>27</sub>H<sub>28</sub>ClFN<sub>2</sub>OS and a molecular weight of 483.04 g/mol. The chemical structure of crinecerfont is shown in **Figure 1**. The chemical properties of crinecerfont are listed in **Table 1**.

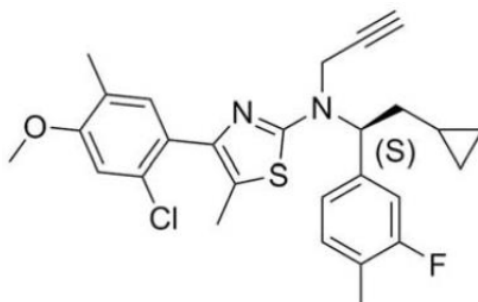


**Figure 1.** Chemical structure of crinecerfont

| <b>Table 1.</b> Summary of Crinecerfont Physicochemical Properties |                                                                                                                                          |
|--------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Property or Identifier</b>                                      | <b>Description</b>                                                                                                                       |
| Chemical CA Index Name                                             | 2-Thiazolamine, 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-2-propyn-1-yl   |
| IUPAC Name                                                         | 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine |
| Molecular Formula                                                  | C <sub>27</sub> H <sub>28</sub> ClFN <sub>2</sub> OS                                                                                     |
| Molecular Weight                                                   | 483.04 g/mol                                                                                                                             |
| Chemical Abstracts Service Registry Number                         | 752253-39-7                                                                                                                              |
| Appearance                                                         | White to light yellow solid                                                                                                              |
| Melting Point                                                      | Melt endotherm with an onset of approximately 87°C                                                                                       |
| Dissociation constant <sup>a</sup>                                 | pKa = 4.11 (calculated)                                                                                                                  |
| Partition coefficient <sup>a</sup>                                 | Log P = 7.75 (calculated)                                                                                                                |
| Solubility:                                                        | <0.01 mg/mL (aqueous)                                                                                                                    |

<sup>a</sup> Due to low aqueous solubility of crinecerfont, pKa, logP and logD could not be experimentally determined and logD could not be calculated.

## Drug Product

The proposed commercial formulations of crinecerfont free base (referred to as crinecerfont) capsule or oral solution is (b) (4) Crenessity (crinecerfont, NBI-74788) will be available as 25 mg, 50 mg, and 100 mg soft-gelatin capsules and an oral solution of 50 mg/mL for commercial use.

## 2. Nonclinical Pharmacology

### 2.1 Receptor Binding and Functional Assays

The Sponsor conducted several in vitro studies to assess the binding and functional activity of crinecerfont. The receptor binding assay included receptors, transporters, and ion channels associated with abuse as well as various individualized studies conducted to determine

crinecerfont's mechanism of action. The data, summarized below, indicate that crinecerfont is a selective CRF<sub>1</sub> antagonist that inhibits CRF-stimulated ACTH secretion.

Studies EVT0106 and EVT0147 were binding assays to determine the binding affinity of crinecerfont to receptors, ion channels, enzymes, and transporters, including those associated with abuse potential. The results of the studies indicate that crinecerfont at a fixed concentration of 10 µM (4830 ng/mL) demonstrated ≤50% inhibition of ligand binding or enzyme activity for all receptors and enzymes tested, including those potentially associated with abuse. The targets for which crinecerfont demonstrated >50% inhibition of ligand binding included: 88% inhibition of acetylcholinesterase activity, 54% inhibition of sigma-1 receptor binding, and 66% inhibition of the serotonin transporter. Follow-up assays on the serotonin transporter were conducted across a range of concentrations, with the result indicating that secondary activity was not clinically relevant. These off-target effects are considered negligible compared to the nanomolar affinity of crinecerfont for CRF<sub>1</sub> receptor.

A series of studies (Table 2) were conducted to characterize the affinity and selectivity of crinecerfont for CRF<sub>1</sub>. These studies demonstrated that crinecerfont selectively binds to CRF<sub>1</sub> with IC<sub>50</sub> values between 0.6 and 2.5 nM (0.290 and 1.21 ng/mL) in human cell lines, mouse, rat, and gerbil brain tissue. There were no apparent species differences in its affinity. In Chinese Hamster Ovary (CHO) cells transfected with hCRF<sub>1</sub>, the IC<sub>50</sub> value was 3.99 nM (1.93 ng/mL). Crinecerfont showed no affinity for hCRF<sub>2a</sub> or hCRF-BP.

In addition, the binding affinity of NBI-756179, a minor human metabolite (representing approximately 6% of crinecerfont in human steady state), was characterized for its affinity for CRF<sub>1</sub> (Study 23-74788-001-PH). According to the Sponsor, given the low abundance of NBI-756179, it is not expected to significantly contribute to the clinical CRF<sub>1</sub> receptor antagonist activity following administration of crinecerfont. Therefore, all of the pharmacodynamic activity is assumed to be through the parent drug.

**Table 2: Overview of Studies Evaluating Affinity of Crinecerfont for CRF Binding Sites (NDA 218808; Module 2.6.2P; pg. 13)**

| Study Number | Test System                                              | Crinecerfont Concentration Range Tested         |
|--------------|----------------------------------------------------------|-------------------------------------------------|
| EVT0103      | CHO cells transfected with hCRF <sub>1</sub>             | 0.01 nM to 10 µM<br>(4.83 pg/mL to 4830 ng/mL)  |
| EVT0104      | Human Y79 cells constitutively expressing CRF1           | 0.01 nM to 0.2 µM<br>(4.83 pg/mL to 96.6 ng/mL) |
| EVT0107      | Mouse brain membranes                                    | 1 pM to 1 µM<br>(483 fg/mL to 483 ng/mL)        |
| EVT0107      | Rat brain membranes                                      | 1 pM to 0.5 µM<br>(483 fg/mL to 242 ng/mL)      |
| EVT0107      | Gerbil brain membranes                                   | 1 pM to 0.03 µM<br>(483 fg/mL to 14.5 ng/mL)    |
| EVT0105      | CHO cells transfected with hCRF <sub>2a</sub> or hCRF-BP | 0.01 nM to 10 µM<br>(4.83 pg/mL to 4830 ng/mL)  |

CHO=Chinese hamster ovary; CRF=corticotropin-releasing factor; CRF1=corticotropin-releasing factor type 1 receptor; hCRF1=human corticotropin-releasing factor type 1 receptor; hCRF2a=human corticotropin-releasing factor type 2a receptor; hCRF-BP=human corticotropin-releasing factor binding protein

## 2.2 Animal Behavioral Studies

### *Safety Pharmacology*

The Sponsor evaluated CNS/behavioral, and pulmonary effects of crinecerfont in a battery of safety pharmacology studies. The effect of crinecerfont on CNS function was assessed in mouse after single oral administration at doses up to 1000 mg/kg in 3 different studies: a modified Irwin test (Study: SNX0237), a barbitol-induced sleeping time study (Study: SNX0240), and a PTZ-induced convulsive activity and mortality study (Study: SNX0239). The effect of crinecerfont on the CNS was also assessed in Sprague Dawley rats after single oral administration at doses up to 1230 mg/kg in a rotarod test (Study: SNX0241) and a locomotor and rearing study (Study: SNX0734).

#### CNS effects:

- Study: SNX0237 - The Sponsor conducted a modified Irwin study to evaluate crinecerfont tosylate for its CNS mediated behavioral effects and effects on body temperature. Male Swiss mice (N = 5/group) were administered crinecerfont tosylate at a dose of 10, 100, or 1000 mg/kg. Additional groups of mice were also treated with 10 mg/kg haloperidol as a positive control, along with its vehicle. According to the sponsor, all animals who received haloperidol decreased spontaneous motor activity and showed slowed irregular breathing within 30 minutes of administration, demonstrating the validity of the test. In contrast, all animals who received crinecerfont at doses of 10, 100, or 1000 mg/kg exhibited normal behavior and normal spontaneous motor activity. There were also no effects on body temperature at any dose observed up to 24 hours after administration.
- Study: SNX0240 - The effect of crinecerfont on barbitol-induced sleeping time was assessed following single oral doses of 10, 100, or 1000 mg/kg in male mice (n=10 animals/group). A group of mice was also treated with caffeine (8 mg/kg) or diazepam (8 mg/kg) as positive controls. Barbitol (200 mg/kg) was administered intraperitoneally 1 hour after the crinecerfont dose, and the latency to fall asleep and sleeping time were evaluated. According to the Sponsor, crinecerfont at doses up to 1000 mg/kg po did not significantly increase or decrease latency to fall asleep or sleeping time in barbitol-treated male mice, indicating that crinecerfont has no sedative or stimulant effect. Under the same conditions, caffeine increased the latency to fall asleep and statistically significantly decreased the sleeping time, while diazepam statistically significantly decreased the latency to fall asleep and statistically significantly increased the sleeping time relative to vehicle control.

- Study: SNX0241 - The purpose of this study was to evaluate the potential effects of a single oral dose of crinecerfont on motor coordination and muscle tone in male Sprague Dawley rats using the rotarod test. Sprague Dawley rats (N = 8/group) were administered crinecerfont tosylate at a dose of 10, 100, or 1230 mg/kg. A group of rats was also treated with diazepam (12 mg/kg) as a positive control. At 1-hour post-dose, the time the animals successfully remained on a rod rotating at a constant speed of 12 rpm was recorded for a maximum of 180 seconds. According to the Sponsor, crinecerfont did not induce any significant modification of the performance time on the rotarod test in male rats, indicating that crinecerfont did not impair motor performance.
- Study: SNX0734 - The purpose of this study was to evaluate the potential effects of a single oral dose of crinecerfont on locomotor and rearing activities in Sprague Dawley rats. Rats (n=8/group) were administered crinecerfont free base at 15, 250, or 1000 mg/kg. A group of rats was also treated with haloperidol (3 mg/kg) as a positive control. At approximately 4 hours post-dose, rats were individually placed in actimeters equipped with infrared light beams to monitor their spontaneous activity for 24 hours. According to the Sponsor, haloperidol significantly decreased exploratory locomotor and rearing during the first 30 minutes of recording. In contrast, single po administration of crinecerfont at doses of 15, 250, and 1000 mg/kg did not change exploratory behavior of male rats and did not change overall spontaneous locomotor activity up to 28 hours post-dose. Thus, crinecerfont did not have psychostimulant or depressant effects at doses up to 1000 mg/kg.

Pulmonary effects:

- The cardiovascular and respiratory effects of crinecerfont were tested (studies CVE0009 and RCV0031). In the cardiovascular study, beagle dogs were administered crinecerfont tosylate orally at 10, 100, or 1000 mg/kg in a dose-escalating design. Parameters evaluated included morbidity, mortality, clinical observations, body weight, body temperature, and cardiovascular assessment (arterial blood pressure, heart rate, and ECG parameters). There were no observed CNS-related clinical signs; clinical observations were restricted to intermittent vomiting in some animals. In the respiratory study, crinecerfont was administered orally at single doses of 10, 100, or 1000 mg/kg in male guinea pigs (n=8 animals/group). According to the Sponsor, crinecerfont at 10 and 100 mg/kg free base had no significant effects on any of the respiratory parameters measured. At 1000 mg/kg free base, crinecerfont induced long-lasting changes in respiratory parameters suggestive of a moderate respiratory depressant effect (increase in inspiratory, expiratory and relaxation times associated with an increase in peak expiratory flow and in tidal volume). However, these signs were likely associated with a poor clinical tolerance of the compound in guinea pigs, and not a CNS-depressant effect. Overall, the results of both studies indicate that, at these doses, crinecerfont does not appear to produce significant cardiovascular or respiratory effects.

### *Animal Abuse Potential Studies*

No animal studies were conducted by the Sponsor to assess the abuse potential of crinecerfont.

## **2.3 Tolerance and Physical Dependence Studies in Animals**

According to the Sponsor, data collected during the recovery periods of 6 repeat-dose toxicity studies (DIV0937, TXC1412, TXC1269, DIV0999, 20113112, and TXC1204) in rats and dogs showed no evidence of a withdrawal syndrome when crinecerfont was abruptly discontinued in animals, indicating no potential for physical dependence of crinecerfont. Therefore, no animal studies were conducted by the Sponsor to assess the tolerance or physical dependence of crinecerfont.

## **3. Clinical Studies**

The crinecerfont clinical development program for the CAH indication includes twenty-four studies: twenty-two Phase 1 and Phase 2 studies, and two pivotal Phase 3 studies (1 adult, 1 pediatric) in subjects with CAH.

### **3.1 Human Abuse Potential Studies**

The Sponsor was not required to conduct a human abuse potential study to assess the abuse liability of crinecerfont.

### **3.2 Adverse Event Profile Through all Phases of Development**

The Sponsor's analysis of abuse-related AEs (e.g., CNS-related, drug abuse related, etc.) is based on data from nineteen Phase 1 studies, three Phase 2 studies (2 in subjects with CAH and 1 in subjects with major depressive disorder), and two Phase 3 studies (subjects with CAH).

#### Phase 1 Studies

Based on the Sponsor's analysis of AEs captured in Phase 1 studies, very few healthy volunteers reported potential abuse-related AEs at single crinecerfont doses up to 800 mg (8-fold higher than a therapeutic single dose) or with multiple doses up to 400 mg/day. Crinecerfont produced sedative-type effects in several open-label trials, most notably somnolence and hypersomnia. However, the incidence rate of these events was similar to, or less than that of placebo in placebo-controlled trials. Additionally, there were no events of particular concern, such as euphoric mood, feeling drunk, hallucinations, or AEs related to actual abuse, misuse, dependence, or withdrawal involving crinecerfont.

#### Phase 3 Studies

The primary evaluation of the safety and efficacy of crinecerfont for the treatment of CAH comes from the randomized, double-blind, placebo-controlled, multicenter Phase 3 studies in adult subjects with CAH (Study CAH3003) and pediatric subjects with CAH (Study CAH2006).

- Study CAH3003 - was a Phase 3, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of crinecerfont 100 mg bid (fed) in adult female and male subjects with classic CAH due to 21-hydroxylase deficiency, followed by open-label treatment. The study was conducted at 54 sites in the United States (US), Canada, Europe, and Israel with 182 subjects enrolled. The most common neurological TEAEs ( $\geq 10\%$  in either treatment group) were fatigue (24.6% crinecerfont; 15.3% placebo), headache (15.6%; 15.3%), and pyrexia (5.7%; 10.2%). The incidence of potentially abuse-related TEAEs (consisting primarily of mood effects) in the double-blind period was similar or lower with crinecerfont compared to placebo. None of the TEAEs were of particular interest for abuse and are commonly observed in subjects with CAH.
- Study CAH2006 - was a Phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of crinecerfont in subjects 2 to 17 years of age with classic CAH due to 21-hydroxylase deficiency. The study was conducted at approximately 39 sites in the United States, Canada, Europe, and United Kingdom. A total of 103 subjects (69 crinecerfont and 34 placebo) were randomized into the study, of whom 102 subjects (69 crinecerfont and 33 placebo) received at least 1 dose of crinecerfont. In this study four crinecerfont-treated subjects (5.8%) experienced potential abuse-related TEAEs in the double-blind period of this study compared to one (3.0%) placebo-treated subject. However, most of these events were not considered related to study treatment. One subject experienced TEAEs of depression, anxiety, and suicidal ideation that were considered possibly related to study treatment, however, these are unlikely to contribute to abuse potential.

### *Conclusion*

Adverse events from multiple clinical studies indicate that crinecerfont does not produce pharmacodynamic effects that are typically associated with abuse. These data support the in vitro data indicating that crinecerfont does not have abuse potential.

### **3.3 Evidence of Abuse, Misuse, and Diversion in Clinical Trials**

There were no reports of misuse, abuse, or diversion of crinecerfont in clinical trials.

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## LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

\*\*\* This document contains proprietary information that cannot be released to the public\*\*\*

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|                                          |                                                                |
|------------------------------------------|----------------------------------------------------------------|
| Date of This Review:                     | September 23, 2024                                             |
| Requesting Office or Division:           | Division of General Endocrinology (DGE)                        |
| Application Type and Number:             | NDA 218820                                                     |
| Product Name, Dosage Form, and Strength: | Crenessity (crinecerfont) <sup>a</sup> Oral Solution, 50 mg/mL |
| Product Type:                            | Single Ingredient Product                                      |
| Rx or OTC:                               | Prescription (Rx)                                              |
| Applicant Name:                          | Neurocrine Biosciences (Neurocrine)                            |
| FDA Received Date:                       | April 30, 2024                                                 |
| TTT ID #:                                | 2024-9304                                                      |
| DMEPA 1 Safety Evaluator:                | Peggy Rahbani, PharmD, BCPS                                    |
| DMEPA 1 Team Leader:                     | Yevgeniya Kogan, PharmD, BCSCP                                 |

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<sup>a</sup> The proprietary name for this NDA, Crenessity, was found conditionally acceptable on July 15, 2024. Crenessity is used throughout this review.

## 1 INTRODUCTION

As part of the approval process for Crenessity (crinecerfont) Oral Solution, the Division of General Endocrinology (DGE) requested that we review the proposed Crenessity Prescribing Information (PI), Patient Package Insert (PPI), Instructions for Use (IFU), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

## 2 MATERIALS REVIEWED

This section lists the materials considered for our review of NDA 218820.

| Table 1. Materials Considered for this Label and Labeling Review |                  |
|------------------------------------------------------------------|------------------|
| Material(s) Reviewed                                             | Appendix Section |
| Relevant Product Information                                     | A                |
| Labels and Labeling                                              | B                |

## 3 CONCLUSION

The proposed Crenessity Prescribing Information (PI), Patient Package Insert (PPI), Instructions for Use (IFU), container label, and carton labeling may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of General Endocrinology (DGE) in Section 4 and for Neurocrine Biosciences in Section 5.

## 4 RECOMMENDATIONS FOR THE DIVISION OF GENERAL ENDOCRINOLOGY (DGE)

| Table 2. Identified Issues and Recommendations for the Division of General Endocrinology (DGE) |                                                                        |                                                                         |                                                                                                                                                                                                                    |
|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|-------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                | IDENTIFIED ISSUE                                                       | RATIONALE FOR CONCERN                                                   | RECOMMENDATION                                                                                                                                                                                                     |
| Full Prescribing Information – Section 2 Dosage and Administration                             |                                                                        |                                                                         |                                                                                                                                                                                                                    |
| 1.                                                                                             | As currently presented, tables 1 and 2 contain symbols (i.e., $\geq$ ) | Error prone symbols may lead to misinterpretation and medication error. | We recommend replacing the symbols with their intended meanings.<br><br>See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022). |
| Full Prescribing Information – Section 16 How Supplied/Storage and Handling                    |                                                                        |                                                                         |                                                                                                                                                                                                                    |
| 1.                                                                                             | As currently presented this Section states the                         | The inclusion of the physical container closure volume                  | We recommend revising the total volume to “30 mL” and                                                                                                                                                              |

**Table 2. Identified Issues and Recommendations for the Division of General Endocrinology (DGE)**

|                                     | IDENTIFIED ISSUE                                                                                                                                                                                                              | RATIONALE FOR CONCERN                                                                                                                      | RECOMMENDATION                                                                                                                                                                                                                                        |
|-------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                     | physical container closure bottle size (b) (4) mL instead of the actual drug product volume which is 30 mL.                                                                                                                   | (b) (4) could be misinterpreted as the volume of the drug product in the bottle which could cause confusion and lead to medication errors. | ensuring it is consistent throughout labeling.                                                                                                                                                                                                        |
| 2.                                  | The statement "Once a bottle is opened for use, it may be stored .... for up to 30 days." lacks clarity and the discard instructions need to align with recommendations in the IFU, PPI, carton labeling and container label. | Unclear discard instructions may increase the risk for deteriorated drug medication errors.                                                | For clarity, we recommend revising the statement to read: "Once a bottle is opened, it may be stored under refrigeration...." and add the language "Discard any unused oral solution after 30 days of first opening the bottle."                      |
| <b>Patient Package Insert (PPI)</b> |                                                                                                                                                                                                                               |                                                                                                                                            |                                                                                                                                                                                                                                                       |
| 1.                                  | As currently presented, the storage statement is (b) (4) " (b) (4) (b) (4) (b) (4) (b) (4) ." The units of measurement following the first numbers in the temperature ranges are missing.                                     | The storage statement should be clearly stated to mitigate the risk of storage error.                                                      | To provide clarity and consistency with the storage statement as presented on the proposed container labels and carton labeling, add the Centigrade symbol (C) following "2°" and Fahrenheit symbol (F) following "36°" within the storage statement. |
| 2.                                  | The statement "store in original container" is not included in the PPI.                                                                                                                                                       | Adding the storage information ensure appropriate storage of the medication and aligns with the labeling instructions                      | We recommend adding the storage statement for the bottle: "Store in original container and in upright position" in the "How should I store Crenessity?" Section.                                                                                      |
| <b>Instructions for Use (IFU)</b>   |                                                                                                                                                                                                                               |                                                                                                                                            |                                                                                                                                                                                                                                                       |
| 1.                                  | The statement "Store in original container and in                                                                                                                                                                             | The storage statement should be consistent across                                                                                          | To reduce the risk of storage errors and administration of                                                                                                                                                                                            |

| Table 2. Identified Issues and Recommendations for the Division of General Endocrinology (DGE) |                                               |                                                                                                                                                                                                                                           |                                                                                                                                                                       |
|------------------------------------------------------------------------------------------------|-----------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                | IDENTIFIED ISSUE                              | RATIONALE FOR CONCERN                                                                                                                                                                                                                     | RECOMMENDATION                                                                                                                                                        |
|                                                                                                | upright position” is not included in the IFU. | all labels and labeling to minimize the risk of improper storage and handling. Specific information for appropriate dispensing of the drug product to maintain its identity, strength, quality, and purity should be included in the IFU. | deteriorated drug, we recommend adding the statement “Store in original container and in upright position.” to Section “How should I store CRENESSITY oral solution?” |

## 5 RECOMMENDATIONS FOR NEUROCRINE BIOSCIENCES

| Table 3. Identified Issues and Recommendations for Neurocrine Biosciences<br>(entire table to be conveyed to Applicant) |                                                                                                                                                                    |                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                          |
|-------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                         | IDENTIFIED ISSUE                                                                                                                                                   | RATIONALE FOR CONCERN                                                                                                                              | RECOMMENDATION                                                                                                                                                                                                                                                                                                                                                                                                           |
| Container Label and Carton Labeling                                                                                     |                                                                                                                                                                    |                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 1.                                                                                                                      | The statement “Store in original container” does not align with the revised PI which states that the product should be stored and dispensed in original container. | The storage statement should be consistent across all labels and labeling to minimize the risk of improper storage and handling.                   | To ensure appropriate storage and dispensing of the medication and for consistency between the labeling, we recommend revising the statement to read: “Store and dispense in original container and in upright position.”                                                                                                                                                                                                |
| 2.                                                                                                                      | As currently presented, the proprietary name and established name are displayed using the same color (b) (4) that is used to emphasize the strength.               | The proprietary name and established name lack prominence on the principal display panel.                                                          | We recommend increasing the prominence of the proprietary name and established name by considering the use of a different color to display the proprietary name and the established name, so it does not coincide with (b) (4) that is used to emphasize the strength.<br><br>See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022). |
| 3.                                                                                                                      | As currently presented the net quantity (30 mL) on the principal display panel competes in prominence with the product strength.                                   | The prominence of the net quantity may result in numerical confusion with the product strength and may lead to product selection or dosing errors. | We recommend decreasing the prominence of the net quantity (30 mL) by decreasing the font size and unbolding it.<br><br>See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).                                                                                                                                                       |

**Table 3. Identified Issues and Recommendations for Neurocrine Biosciences**  
(entire table to be conveyed to Applicant)

|                    | IDENTIFIED ISSUE                                                                                                                                                                                                                                                                                                                                                                            | RATIONALE FOR CONCERN                                                                                                                                                                                                                                                                                                                                                  | RECOMMENDATION                                                                                                                                                                                                                                                                                                            |
|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 4.                 | <p>The terminology within the statement of dosage statement “ (b) (4) ” is inconsistent with the terminology in the Prescribing Information.</p>                                                                                                                                                                                                                                            | To ensure consistency with the terminology in the Prescribing Information.                                                                                                                                                                                                                                                                                             | We recommend revising the statement of dosage statement to read, “Recommended Dosage: see Prescribing Information.”                                                                                                                                                                                                       |
| 5.                 | The storage statement lacks clarity because it does not specify that the unopened bottle should be stored refrigerated, and an opened bottle can be stored either refrigerated or at room temperature.                                                                                                                                                                                      | Unclear instructions can lead to improperly storing this product and deteriorated drug medication errors.                                                                                                                                                                                                                                                              | Revise the storage statement for clarity and to align with the PI, PPI, and IFU for example: “Store unopened bottles under refrigeration at 2°C to 8°C (36°F to 46°F). Opened bottle may be stored under refrigeration at 2°C to 8°C (36°F to 46°F) or at room temperature 15°C to 25°C [59°F to 77°F] for up to 30 days. |
| 6.                 | <p>As currently presented, there is no space for end-users to write the beyond-use date which is the [date or time] the opened product must be discarded (30 days after first opening the)</p> <p>Additionally, the label includes the statement/space to write “ (b) (4) ” which appears in a different location to the statement “Discard unused portion 30 days after first opening”</p> | <p>Since the product has a different expiration date after opening, the label should have a designated space and format for end-users to write the beyond-use date to minimize the risk of deteriorated drug medication errors.</p> <p>Additionally, the inclusion of a statement/space for the “ (b) (4) ” is not necessary, creates confusion, and adds clutter.</p> | <p>We recommend adding a space for end-users to write the beyond-use date underneath the statement “Discard unused portion 30 days after first opening the bottle” for example:</p> <p>Discard after ____/____/____<br/>[Time ____]</p> <p>Remove the space to write “ (b) (4) ”.</p>                                     |
| Container Label(s) |                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                           |

**Table 3. Identified Issues and Recommendations for Neurocrine Biosciences**  
(entire table to be conveyed to Applicant)

|    | IDENTIFIED ISSUE                                                                                                                                                                                                                                                 | RATIONALE FOR CONCERN                                                                                                                                                        | RECOMMENDATION                                                                                                                                                                                              |
|----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. | The manufacturer information (manufacturer name and logo) competes in prominence with other important information on the side panel.                                                                                                                             | Manufacturer information should not be the most prominent information on the side panel and as currently presented it distracts the reader from other important information. | Decrease prominence of the manufacturer information on the side panel so it does not compete with the prominence of important product information.                                                          |
| 2. | The placeholder (XXXXXX) is unclear.                                                                                                                                                                                                                             | Undefined codes may cause confusion and add clutter to the label.                                                                                                            | Define the meaning of the undefined code (XXXXXX) and we recommend removal if it is not required information.                                                                                               |
| 3. | The NDC number, “Rx only” statement, and route of administration statement ““for oral administration only” appear prominent and compete with other critical information (e.g., proprietary name, established name, and strength) on the principal display panel. | Critical product information should appear as the most prominent information on the PDP in accordance with 21 CFR 201.15.                                                    | We recommend decreasing the size of the NDC number, “Rx only”, and route of administration statement so they do not compete in size or prominence with critical information on the principal display panel. |

## APPENDICES: METHODS AND RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 4 presents relevant product information for Crenessity received on April 30, 2024, from Neurocrine Biosciences.

| Table 4. Relevant Product Information for Crenessity |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Initial Approval Date                                | N/A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Active Ingredient                                    | crinecerfont                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Indication                                           | (b) (4)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Dosage Form                                          | Oral Solution                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Strength                                             | 50 mg/mL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Route of Administration                              | oral                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Dose and Frequency                                   | <p>Adults (18 years and older): 100 mg twice daily</p> <p>Pediatric Patients (4 to 17 years): Based on body weight as follows:</p> <p>10 kg to &lt; 20 kg: 25 mg twice daily</p> <p>20 kg to &lt; 55 kg: 50 mg twice daily</p> <p>≥55 kg: 100 mg twice daily</p> <p>Patients Taking Strong CYP3A4 Inducers</p> <p>10 kg to &lt; 20 kg (pediatric): 50 mg twice daily</p> <p>20 kg to &lt; 55 kg (pediatric): 100 mg twice daily</p> <p>≥55 kg (adult &amp; pediatric): 200 mg twice daily</p> |
| How Supplied                                         | light yellow to orange oral solution containing 50 mg/mL crinecerfont in an orange-flavored liquid. It is supplied in amber polyethylene terephthalate (PET) bottles.                                                                                                                                                                                                                                                                                                                         |
| Storage                                              | <p>Store unopened bottles under refrigeration at 2°C to 8°C (36°F to 46°F). Do not freeze.</p> <p>Once a bottle is opened for use, it may be stored under refrigeration at 2°C to 8°C (36°F to 46°F) or at room temperature (15°C to 25°C [59°F to 77°F]) for up to 30 days.</p>                                                                                                                                                                                                              |
| Container Closure                                    | Oral Solution-Bottle of 30 mL                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

## APPENDIX B. LABELS AND LABELING

### B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>b</sup> along with postmarket medication error data, we reviewed the following Crenessity labels and labeling submitted by Neurocrine Biosciences.

- Prescribing Information received on April 30, 2024, available from <\\CDSESUB1\EVSPROD\nda218808\0001\m1\us\m1-14-1-3-draft-labeling-text-uspi.docx>
- Patient Package Insert received on April 30, 2024, available from <\\CDSESUB1\EVSPROD\nda218808\0001\m1\us\m1-14-1-3-draft-labeling-text-pil.docx>
- Instructions for Use received on April 30, 2024, available from <\\CDSESUB1\EVSPROD\nda218808\0001\m1\us\m1-14-1-3-draft-labeling-text-ifu.docx>
- Container labels received on April 30, 2024
- Carton labeling received on April 30, 2024

### B.2 Container Label(s) and Carton Labeling Images

Container label



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<sup>b</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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## LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

\*\*\* This document contains proprietary information that cannot be released to the public\*\*\*

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|                                          |                                                                                    |
|------------------------------------------|------------------------------------------------------------------------------------|
| Date of This Review:                     | September 23, 2024                                                                 |
| Requesting Office or Division:           | Division of General Endocrinology (DGE)                                            |
| Application Type and Number:             | NDA 218808                                                                         |
| Product Name, Dosage Form, and Strength: | Crenessity (crinecerfont) <sup>a</sup> , Oral Capsules<br>25 mg, 50 mg, and 100 mg |
| Product Type:                            | Single Ingredient Product                                                          |
| Rx or OTC:                               | Prescription (Rx)                                                                  |
| Applicant Name:                          | Neurocrine Biosciences (Neurocrine)                                                |
| FDA Received Date:                       | April 29, 2024                                                                     |
| TTT ID #:                                | 2024-9301                                                                          |
| DMEPA 1 Safety Evaluator:                | Peggy Rahbani, PharmD, BCPS                                                        |
| DMEPA 1 Team Leader:                     | Yevgeniya Kogan, PharmD, BCSCP                                                     |

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<sup>a</sup> The proprietary name for this NDA, Crenessity, was found conditionally acceptable on July 15, 2024. Crenessity is used throughout this review.

## 1 INTRODUCTION

As part of the approval process for Crenessity (crinecerfont) oral capsules, the Division of General Endocrinology (DGE) requested that we review the proposed Crenessity Prescribing Information (PI), Patient Prescribing Information (PPI), and container labels for areas of vulnerability that may lead to medication errors.

## 2 MATERIALS REVIEWED

This section lists the materials considered for our review of NDA 218808.

| Table 1. Materials Considered for this Label and Labeling Review |                  |
|------------------------------------------------------------------|------------------|
| Material(s) Reviewed                                             | Appendix Section |
| Relevant Product Information                                     | A                |
| Labels and Labeling                                              | B                |

## 3 CONCLUSION

The proposed Crenessity Prescribing Information (PI), Patient Prescribing Information (PPI), and container labels may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of General Endocrinology (DGE) in Section 4 and for Neurocrine Biosciences (Neurocrine) in Section 5.

#### 4 RECOMMENDATIONS FOR THE DIVISION OF GENERAL ENDOCRINOLOGY (DGE)

| Table 2. Identified Issues and Recommendations for the Division of General Endocrinology (DGE) |                                                                                                                                                          |                                                                                                                                                                                           |                                                                                                                                                                                                                            |
|------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                | IDENTIFIED ISSUE                                                                                                                                         | RATIONALE FOR CONCERN                                                                                                                                                                     | RECOMMENDATION                                                                                                                                                                                                             |
| Full Prescribing Information – Section 2 Dosage and Administration                             |                                                                                                                                                          |                                                                                                                                                                                           |                                                                                                                                                                                                                            |
| 1.                                                                                             | As currently presented, tables 1 and 2 contain symbols (i.e. ≥)                                                                                          | Error prone symbols may lead to misinterpretation and medication error.                                                                                                                   | We recommend replacing the symbols with their intended meanings.<br><br>See Guidance for Industry: <i>Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i> . |
| Patient Prescribing Information                                                                |                                                                                                                                                          |                                                                                                                                                                                           |                                                                                                                                                                                                                            |
| 1.                                                                                             | The storage condition instruction for the capsule: “Do not freeze” is missing in the “How should I store CRENESSITY?” and is not consistent with the PI. | Improperly storing this product (i.e., not protecting from freezing) could lead to deteriorated drug medication errors and storage information need to be consistent throughout labeling. | Add the storage condition instruction: “Do not freeze” after the statement, “Store CRENESSITY capsules at room temperature between 15°C to 25°C (59°F to 77°F).”                                                           |

## 5 RECOMMENDATIONS FOR NEUROCRINE BIOSCIENCES (NEUROCRINE)

| Table 3. Identified Issues and Recommendations for Neurocrine Biosciences (Neurocrine)<br>(entire table to be conveyed to Applicant) |                                                                                                                                                                                           |                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                          |
|--------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                      | IDENTIFIED ISSUE                                                                                                                                                                          | RATIONALE FOR CONCERN                                                                                                                                           | RECOMMENDATION                                                                                                                                                                                                                                                                                           |
| <b>Container Labels</b>                                                                                                              |                                                                                                                                                                                           |                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                          |
| 1.                                                                                                                                   | As currently presented the net quantity statement on the principal display panel (PDP) competes in prominence with the product strength.                                                  | The prominence of net quantity statement may result in numerical confusion with the product strength and may lead to product selection or dosing errors.        | We recommend decreasing the prominence of the net quantity statement (e.g., 60 (b) (4)) by decreasing the font size (height) and unbolding it.<br><br>See Guidance for Industry: <i>Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i> . |
| 2.                                                                                                                                   | The NDC number and “Rx only” statement appear prominent and compete with other critical information (e.g., proprietary name, established name, strength,) on the principal display panel. | Critical product information should appear as the most prominent information on the PDP in accordance with 21 CFR 201.15.                                       | We recommend decreasing the size of the NDC number and “Rx only” statement so they do not compete in size or prominence with critical information on the principal display panel.                                                                                                                        |
| 3.                                                                                                                                   | The terminology within the statement of dosage statement “ (b) (4) (b) (4) ” is inconsistent with the terminology in the Prescribing Information.                                         | To ensure consistency with the terminology in the Prescribing Information.                                                                                      | We recommend revising the statement of dosage statement to read, “Recommended Dosage: see Prescribing Information.”                                                                                                                                                                                      |
| 4.                                                                                                                                   | The manufacturer information (manufacturer name and logo) competes in prominence with other important information such as how to store the                                                | Manufacturer information should not be the most prominent information on the side panel and as currently presented it distracts the reader from other important | Decrease prominence of the manufacturer information on the side panel so it does not compete with the prominence of important product information.                                                                                                                                                       |

Table 3. Identified Issues and Recommendations for Neurocrine Biosciences (Neurocrine)  
(entire table to be conveyed to Applicant)

|    | IDENTIFIED ISSUE                                                                                                                                               | RATIONALE FOR CONCERN                                                                                                                                                                                                                                                                                                                                                  | RECOMMENDATION                                                                                                                                                                                                                                                                                                                                                                          |
|----|----------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    | product on the side panel.                                                                                                                                     | information such as the product storage information.                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                         |
| 5. | The placeholder (XXXXXX) located immediately above the Global Trade Item Number (GTIN) is unclear.                                                             | Undefined codes may cause confusion and/or add clutter to the label.                                                                                                                                                                                                                                                                                                   | Define the meaning of the undefined code (XXXXXX) and we recommend removal if it is not required information.                                                                                                                                                                                                                                                                           |
| 6. | For the 100 mg strength, the net quantity statement is in close proximity to the product strength and competes in prominence with other important information. | The net quantity statement should appear on the principal display panel (PDP) but should be separated from and less prominent than the statement of strength. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement. | We recommend that you relocate the net quantity statement (30 (b) (4)) away from the strength statement (100 mg) for example: by moving it to the top right side of the PDP, similar to the current 25 mg and 50 mg container labels.<br><br>See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022). |
| 7. | The 100 mg strength (b) (4) font) overlaps with the (b) (4) background color used for the 25 mg strength.                                                      | For products with multiple strengths, a lack of differentiation may contribute to wrong strength errors. Color differentiation is most effective when the color used has no association with a particular feature.                                                                                                                                                     | We recommend revising the font color of the 100 mg strength such that the strength appears in its own unique color that does not overlap with the (b) (4) color used for 25 mg strength.                                                                                                                                                                                                |
| 8. | For the 100 mg strength the proposed packaging size (30 capsules) is                                                                                           | As currently presented the packaging size (30 capsules) is incongruent with product                                                                                                                                                                                                                                                                                    | We recommend revising the proposed packaging size for                                                                                                                                                                                                                                                                                                                                   |

| Table 3. Identified Issues and Recommendations for Neurocrine Biosciences (Neurocrine)<br>(entire table to be conveyed to Applicant) |                                                                                                                                                                                                                                          |                                                                                                      |                                                                                                                                                       |
|--------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                      | IDENTIFIED ISSUE                                                                                                                                                                                                                         | RATIONALE FOR CONCERN                                                                                | RECOMMENDATION                                                                                                                                        |
|                                                                                                                                      | incongruent with the recommended dosing regimen which is 100 mg twice a day.                                                                                                                                                             | dosing regimen because patients would need to receive 60 capsules for a one-month supply of therapy. | the 100 mg strength to include 60 capsules.                                                                                                           |
| 9.                                                                                                                                   | As currently presented, the color <span style="background-color: black; color: black;">(b) (4)</span> used to display the net quantity for the 25 mg and 50 mg strengths is the same color that is used to emphasize the 25 mg strength. | Creates confusion for end users.                                                                     | We recommend using a different color that doesn't correlate to any particular strength to display the net quantity for the 25 mg and 50 mg strengths. |

## APPENDICES: METHODS AND RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 4 presents relevant product information for Crenessity received on April 29, 2024, from Neurocrine Biosciences (Neurocrine).

| Table 4. Relevant Product Information for Crenessity |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Initial Approval Date                                | N/A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Active Ingredient                                    | crinecerfont                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Indication                                           | (b) (4)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Dosage Form                                          | oral capsules                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Strength                                             | 25 mg, 50 mg, 100 mg                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Route of Administration                              | Oral                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Dose and Frequency                                   | <p>Adults (18 years and older): 100 mg twice daily</p> <p>Pediatric Patients (4 to 17 years): Based on body weight as follows:</p> <p>10 kg to &lt; 20 kg: 25 mg twice daily</p> <p>20 kg to &lt; 55 kg: 50 mg twice daily</p> <p>≥55 kg; 100 mg twice daily</p> <p>Patients Taking Strong CYP3A4 Inducers</p> <p>10 kg to &lt; 20 kg (pediatric): 50 mg twice daily</p> <p>20 kg to &lt; 55 kg (pediatric): 100 mg twice daily</p> <p>≥55 kg (adult &amp; pediatric): 200 mg twice daily</p> |
| How Supplied                                         | Oral Capsules-Bottle of 30 count (100 mg) or 60 count (25 mg and 50 mg)                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Storage                                              | Store at 15°C to 25°C (59°F to 77°F).                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Container Closure                                    | bottle                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

## APPENDIX B. LABELS AND LABELING

### B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>b</sup> along with postmarket medication error data, we reviewed the following Crenessity labels and labeling submitted by Neurocrine Biosciences (Neurocrine).

- Prescribing Information received on April 29, 2024, available from <\\CDSESUB1\EVSPROD\nda218808\0001\m1\us\m1-14-1-3-draft-labeling-text-uspi.pdf>
- Patient Prescribing Information received on April 29, 2024, available from <\\CDSESUB1\EVSPROD\nda218808\0001\m1\us\m1-14-1-3-draft-labeling-text-pil.pdf>
- Container labels received on April 29, 2024

### B.2 Container Labels Images

Container labels



1 Page of Draft Labeling has been Withheld in Full as  
b4 (CCI/TS) immediately following this page

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<sup>b</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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**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.**  
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/s/  
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PEGGY M RAHBANI  
09/24/2024 08:44:29 AM

YEVGENIYA M KOGAN  
09/24/2024 03:02:34 PM



**DEPARTMENT OF HEALTH & HUMAN SERVICES**      Public Health Service

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Division of Pediatrics and Maternal Health  
Office of Rare Diseases, Pediatrics, Urologic  
and Reproductive Medicine  
Office of New Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Silver Spring, MD 20993  
Tel 301-796-2200  
FAX 301-796-9744

**Division of Pediatrics and Maternal Health Review**

**Date:** 9/13/2024                      **Date consulted:** 6/10/2024

**From:** Katherine Kratz, MD, Medical Officer, Maternal Health  
Division of Pediatrics and Maternal Health (DPMH)

**Through:** Miriam Dinatale, DO, Team Leader, Maternal Health, DPMH  
  
Lynne P. Yao, MD, OND, Division Director, DPMH

**To:** Division of General Endocrinology (DGE)

**Drug:** Crenissity (crinecerfont)

**NDA:** 218808 and 218820

**Applicant:** Neurocrine Biosciences, Inc.

**Subject:** Pregnancy and Lactation Labeling

**Indication:** (b) (4)

**Materials  
Reviewed:**

- DPMH consult request dated 6/10/2024. DARRTS Reference ID: 5395059
- Applicant's submitted background package and proposed labeling for NDA 218808 and 218820, Sequence Numbers (SN) 0001, dated 4/29/2024 and 4/30/2024, respectively.

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<sup>1</sup> NDAs 218808s and 218820, SN 0001, Module 1.14.1.3, Draft Labeling Text. Under review by DGE.

**Consult Request:** “We ask DPMH to review and provide input or recommendations that will be useful for the review of this NDA including labeling. We specifically request input regarding use of crinecerfont in pregnancy and lactation and recommendations for labeling in section 8.”

## I. INTRODUCTION AND BACKGROUND

On April 29, 2024, the Applicant, Neurocrine Biosciences, Inc., submitted a 505(b)(1) New Drug Application (NDA) for a new molecular entity (NME) called Crenissity (crinecerfont) 25 mg, 50 mg, and 100 mg capsules under NDA 218808. On April 30, 2024, the Applicant submitted a second NDA for Crenissity (crinecerfont) for 50 mg/mL oral solution under NDA 218820.

Crinecerfont is a selective corticotropin releasing factor 1 (CRF1) receptor antagonist developed as a treatment to (b) (4)

classic congenital adrenal hyperplasia (CAH). DGE consulted the DPMH Maternal Health Team (MHT) on June 10, 2024 to assist with the Pregnancy and Lactation subsections of labeling.

### Relevant Regulatory History

- There are no other approved CRF1 receptor antagonists.
- Approved drugs to treat CAH include steroids.

### Drug Characteristics<sup>2</sup>

|                              |                                                                                                                                                                                                                                           |
|------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Drug class                   | CRF1 receptor antagonist                                                                                                                                                                                                                  |
| Mechanism of action          | Crinecerfont blocks the binding of CRF to CRF type 1 receptors in the pituitary and inhibits adrenocorticotrophic hormone (ACTH) secretion from the pituitary.                                                                            |
| Dosage forms                 | Capsules: 25 mg, 50 mg, 100 mg of free base<br>Oral Solution: 50 mg/mL of free base                                                                                                                                                       |
| Administration               | Adults (18 years and older): 100 mg twice daily<br>Pediatric Patients (4 to 17 years): dosage is based on body weight and is administered twice daily                                                                                     |
| Molecular weight             | 483.04 Daltons                                                                                                                                                                                                                            |
| Half-life                    | 14 hours                                                                                                                                                                                                                                  |
| % protein bound              | 99.9%                                                                                                                                                                                                                                     |
| Bioavailability <sup>3</sup> | Oral dosing of tosylate salt: <sup>4</sup> 53% (rats), 19% (dogs), 14% (rabbits)<br>Oral dosing of free base: 49% (monkeys)<br>Exposure did not increase in a dose-dependent manner.<br>Absorption ceilings were observed in all species. |

<sup>2</sup> NDAs 218808s and 218820, SN 0001, Module 1.14.1.3, Draft Labeling Text. Under review by DGE.

<sup>3</sup> DGE Pharmacology/Toxicology team, draft review, discussed with Dr. Mekonnen Lemma Dechassa, 8/8/2024.

<sup>4</sup> Three forms of crinecerfont drug substance were used in the nonclinical development program: crinecerfont free base and two salt forms- crinecerfont tosylate and crinecerfont hydrochloride. Crinecerfont tosylate was used in most safety pharmacology studies and initial toxicology studies. (b) (4)

Information obtained from 2.4 Nonclinical Overview of the Applicant’s submission.

|                          |                                               |
|--------------------------|-----------------------------------------------|
| Warnings and Precautions | Acute Adrenal Insufficiency or Adrenal Crisis |
|--------------------------|-----------------------------------------------|

## II. REVIEW

### ***PREGNANCY***

#### CAH and Pregnancy<sup>5,6</sup>

Congenital adrenal hyperplasias (CAHs) are rare, autosomal recessive disorders. In approximately 95 percent of cases, CAH is characterized by deficiency of 21-hydroxylase (21-OHD) due to mutations in the CYP21A2 gene, which is known as classic CAH. The estimated prevalence of classic CAH in the U.S. is 1/10,000.<sup>7</sup> 46,XX infants with 21-OHD are typically born with atypical genitalia characterized by clitoral enlargement, labial fusion, and formation of a urogenital sinus caused by the effects of in-utero androgen excess on the development of the external genitalia. Rarely, virilization may be so profound that genital atypia is unrecognized, and male sex assignment with undescended testes is made at birth in a 46,XX patient. Signs of classic CAH include adrenal insufficiency and salt wasting in the neonatal period or virilization in the first few years of life. Classic CAH is diagnosed at birth through newborn screening with a high serum concentration of 17-hydroxyprogesterone. In patients with classic CAH, sexual function and fertility are impaired; however, in individuals who receive proper treatment and have regular intercourse, pregnancy rates exceed 90 percent. In pregnancy, treatment with hydrocortisone/prednisolone and fludrocortisone therapy is recommended, with dosage adjustments if symptoms and signs of glucocorticoid insufficiency occur.<sup>8</sup>

#### Nonclinical Experience<sup>9</sup>

According to the Applicant, embryo-fetal developmental toxicity was not observed at crinecerfont tosylate doses up to 2000 mg/kg/day in pregnant female rats (3.7-fold than the maximum recommended human dose (MRHD) based on area under the curve (AUC)) and up to 500 mg/kg/day of in pregnant female rabbits (2.9-fold the MRHD based on AUC). A low incidence of poly-malformations (craniofacial defects) and slightly lower mean fetal weights were observed in rabbits treated with crinecerfont at 1.6-fold higher than exposures at the MRHD. However, the association of these findings with crinecerfont was not certain. At 1000 mg/kg/day in rabbits, slightly decreased fetal weights were observed.

Based on these nonclinical data, the Applicant concluded that crinecerfont is unlikely to cause teratogenicity and in humans.

<sup>5</sup> Merke, D, Auchus, R. Clinical Manifestations and diagnosis of classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency in infants and children. UpToDate. Topic 145, Version 23.0.

<sup>6</sup> Nieman, L, and Merke, D. Diagnosis and treatment of nonclassic (late-onset) congenital adrenal hyperplasia due to 21-hydroxylase deficiency. UpToDate. Topic 147, Version 24.0.

<sup>7</sup>[https://www.orpha.net/en/disease/detail/418#:~:text=The%20estimated%20prevalence%20is%201,%2Dclassical%20\(N\)%20types.](https://www.orpha.net/en/disease/detail/418#:~:text=The%20estimated%20prevalence%20is%201,%2Dclassical%20(N)%20types.) Accessed 8/20/24.

<sup>8</sup> Speiser PW, Arlt W, Auchus RJ, Baskin LS, Conway GS, Merke DP, Meyer-Bahlburg HFL, Miller WL, Murad MH, Oberfield SE, White PC. 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. doi: 10.1210/jc.2018-01865. Erratum in: J Clin Endocrinol Metab. 2019 Jan 1;104(1):39-40. doi: 10.1210/jc.2018-02371. PMID: 30272171; PMCID: PMC6456929.

<sup>9</sup> NDA 218820, Module 2.4, Nonclinical Overview, p 18.

The reader is referred to the Pharmacology/Toxicology review by Dr. Mekonnen Lemma Dechassa.

**Reviewer comment:**

*The nonclinical study findings were discussed with the DGE Pharmacology/Toxicology (P/T) and Clinical teams. Per the P/T team, the Applicant provided bridging data from toxicity studies that allow a comparison of toxicity data between the tosylate salt form and the free base form; there were no differences in toxicity trends. There was a saturation in exposure with crinecerfont that prevented high exposure multiples in animals. Craniofacial abnormalities were noted in three rabbits across different litters, which is slightly higher than historical controls; however, the association of these findings with crinecerfont was uncertain as they occurred in a small number of rabbits only. Due the uncertainty of the association with crinecerfont, the P/T team along with the Clinical and DPMH teams agreed that the nonclinical findings do not rise to the level of a Contraindication or a Warning and Precaution for embryofetal toxicity and do not preclude conducting a postmarketing pregnancy safety study in pregnant individuals. As crinecerfont is systemically absorbed, it will cross the placenta. Although the P/T team reported that no changes in hormones were observed in healthy animals treated with crinecerfont, it is unknown whether crinecerfont will suppress ACTH secretion in the human fetus. Given the potential for ACTH suppression in the human fetus, it is necessary to obtain data related to the impact of crinecerfont on the human fetus through a postmarketing pregnancy safety study. See the Discussion and Conclusions section below for more information on the recommended pregnancy safety study.*

Pregnancies during drug development clinical trials<sup>10</sup>

During drug development clinical trials, there were three reported pregnancies. Two pregnancies occurred in the phase 1 study of QT/QTc evaluations in healthy volunteers, involving single oral doses of 300 mg or 800 mg of crinecerfont, as follows:

- 1) Subject (b) (6): A 22-year-old female was administered a single dose of crinecerfont 300 mg and a single dose of moxifloxacin. She was confirmed to be pregnant during the study based on urine and serum pregnancy tests. The estimated date of conception was approximately 10 days after receiving the single dose of crinecerfont and approximately 1 month after receiving moxifloxacin. Study treatment was discontinued. The subject was subsequently lost to follow-up and no additional information, including additional laboratory assessments or the outcome of the pregnancy, is known.
- 2) Subject (b) (6): A female of unreported age was reported to be pregnant based on positive urine and serum pregnancy tests; however, ultrasound showed no evidence of pregnancy. The subject subsequently had decreasing beta human chorionic gonadotropin (hCG) levels, consistent with a spontaneous abortion (SAB).

One subject in study CAH3003 had a reported pregnancy as follows:

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<sup>10</sup> NDA 218820, Module 2.7.4 Summary of Clinical Safety, p 122.

- 3) Subject (b) (6): A 32-year-old female was found to be pregnant (approximately 5-6 weeks of gestation) during the open-label period and discontinued crinecerfont on the day that the pregnancy was diagnosed. The subject remained in the study until her Month 18 visit. Subsequently, she underwent an uncomplicated C-section and delivered a healthy infant at 38 weeks of gestation.

***Reviewer comment:***

*The data from the three pregnancies that occurred during the drug development program are not sufficient to inform labeling. There was one spontaneous abortion (SAB), one unknown outcome and one normal pregnancy outcome. With only three pregnancies and no pattern to the outcomes, conclusions cannot be drawn.*

Review of Literature

*Applicant's review:*

The Applicant did not provide a literature review related to crinecerfont and pregnancy.

*DPMH review:*

DPMH conducted a search of published human studies in PubMed, using the search terms “corticotropin releasing factor 1 receptor antagonist” AND “pregnancy,” “pregnancy outcomes,” “birth defects,” “malformations,” “stillbirth,” OR “spontaneous abortion.” No publications were found.

DPMH also searched Micromedex,<sup>11</sup> Reprotox,<sup>12</sup> TERIS,<sup>13</sup> and Shepard's<sup>14</sup> and no information was found.

***LACTATION***

Nonclinical Experience

Excretion of crinecerfont in milk was observed in lactating rats, with milk-to-plasma concentration ratios ranging from 1.5 to 12. Crinecerfont was well tolerated in a pre- and postnatal developmental toxicity study following daily oral administration to pregnant rats from Gestation Day 7 through Lactation Day 20 at doses up to 250 mg/kg/day (4.4-fold the MRHD based on the AUC). There were no effects on mortality, growth, sexual maturation, behavior and function, mating and fertility, or ovarian and uterine parameters.

The reader is referred to the Pharmacology/Toxicology review by Dr. Mekonnen Lemma Dechassa.

Lactation Cases During Drug Development

No cases related to crinecerfont use during lactation occurred during drug development.

Review of Literature

*Applicant's review:*

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<sup>11</sup> Truven Health Analytics information, <http://www.micromedexsolutions.com>. Accessed 7/29/24.

<sup>12</sup> Reprotox Website: [www.Reprotox.org](http://www.Reprotox.org). Accessed 8/3/22.

<sup>13</sup> TERIS database, Truven Health Analytics, Micromedex Solutions. Accessed 7/29/24.

<sup>14</sup> Shepard's database, Truven Health Analytics, Micromedex Solutions. Accessed 7/29/24.

The Applicant did not provide a literature review related to crinecerfont and lactation.

*DPMH review:*

DPMH conducted a search for published human studies in PubMed, using the search terms: “corticotropin releasing factor 1 receptor antagonist” AND “lactation” OR “breastfeeding.” DPMH also searched Micromedex, Hale’s *Medications and Mothers’ Milk*,<sup>15</sup> Reprotox, the Drugs and Lactation Database (LactMed),<sup>16</sup> and Briggs *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*.<sup>17</sup> No lactation information was found.

***Reviewer comment:***

*Nonclinical data indicate that crinecerfont is present in rat milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Although no toxicity was seen in rats exposed to crinecerfont via milk through lactation day 20, DPMH is concerned that healthy neonates exposed to crinecerfont via breast milk could develop adrenal insufficiency; therefore, infants exposed to crinecerfont through breast milk should be monitored for symptoms of adrenal insufficiency, such as weakness, decreased feeding and weight loss.*<sup>18</sup>

***FEMALES AND MALES OF REPRODUCTIVE POTENTIAL***

***Nonclinical Experience***<sup>19</sup>

According to the Applicant, crinecerfont tosylate did not affect fertility or reproductive performance of male or female rats following oral administration at doses up to 1000 mg/kg/day (1.9-fold the MRHD based on the AUC). Crinecerfont was not mutagenic or clastogenic in a standard battery of genotoxicity studies, including GLP in vitro bacterial reverse mutation (Ames) and mouse lymphoma forward mutation assays with or without metabolic activation and a GLP in vivo micronucleus assay in rats administered crinecerfont tosylate at oral doses up to 2000 mg/kg (3.6-fold the MRHD based on the AUC). The reader is referred to the Pharmacology/Toxicology review by Dr. Mekonnen Lemma Dechassa.

***Drug-Drug Interactions***<sup>20</sup>

According to the Applicant, crinecerfont was neither an inhibitor nor inducer of CYP3A4.

***Reviewer comment:***

*DPMH discussed drug-drug interactions (DDIs) with the DGE Clinical Pharmacology (CP) Team. The CP team confirmed that DDIs between crinecerfont and hormonal contraceptives are not likely.*

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<sup>15</sup> Hale, Thomas W. *Hale’s Medications & Mothers’ Milk 2021: A Manual of Lactational Pharmacology*. 19th ed. New York: Springer Publishing Company, 2020. [www.halesmeds.com](http://www.halesmeds.com)

<sup>16</sup> Drugs and Lactation Database (LactMed). Accessed 7/29/24.

<sup>17</sup> Briggs, Gerald G., Craig V. Towers, and Alicia B. Forinash. *Briggs Drugs in Pregnancy and Lactation: a Reference Guide to Fetal and Neonatal Risk*. 12th edition. Philadelphia, PA: Lippincott Williams & Wilkins, 2021. Print.

<sup>18</sup> Kim, M. Clinical manifestations and diagnosis of adrenal insufficiency in children. UpToDate. Topic5828, Version 26.0.

<sup>19</sup> NDA 218820, Module 2.4, Nonclinical Overview, p 18.

<sup>20</sup> NDA 218820, Module 2.7.4, Summary of Clinical Safety, p. 121.

### Clinical Experience

For female subjects, the Applicant reported that “in the crinecerfont group, a greater proportion of females with baseline progesterone >1.908 nmol/L achieved a progesterone level consistent with follicular phase levels (<1.908 nmol/L [0.6 ng/mL]) at Week 24 (13.5% [5/37] crinecerfont vs 5.9% [1/17] placebo) and a greater proportion of females with baseline testosterone  $\geq 1.2 \times \text{ULN}$  achieved normal testosterone levels at Week 24 (10.7% [3/28] crinecerfont vs 0% [0/11] placebo...).”<sup>21</sup>

For male subjects with a high ratio of androstenedione to testosterone at baseline, the Applicant reported “a decrease in the ratio to <0.5 was observed at Week 24 in a numerically higher proportion of males in the crinecerfont group compared to the placebo group (18.9% [7/37] crinecerfont vs 4.5% [1/22] placebo; nominal  $p=0.1233$ ). A numerically higher proportion of males with abnormal (i.e., low or high) luteinizing hormone (LH) levels at baseline achieved normal levels at Week 24 in the crinecerfont group versus the placebo group (47.4% [9/19] crinecerfont vs 22.2% [2/9] placebo; nominal  $p=0.2993$ ).”<sup>22</sup>

From these clinical findings, the Applicant concluded that “These findings are relevant to the pathophysiology of impaired fertility that often occurs in females with CAH and have relevance to the potential for improved fertility and unexpected pregnancy after initiating treatment with crinecerfont.”

Although there was a change in the progesterone and testosterone levels in crinecerfont-treated subjects, the Applicant reported that “At Week 24, there was no difference in menstrual regularity in female subjects, but this analysis was limited by the small number of subjects not on contraceptive treatment for whom this endpoint could be evaluated.”

#### ***Reviewer comment:***

*Based on the clinical data outlined above, the Applicant proposes to include the following in labeling:*



<sup>21</sup> NDA 218820, Module 2.5, Clinical Overview, pp. 45-46.

<sup>22</sup> NDA 218830, 2.7.3 Summary of Clinical Efficacy, pp. 64-65.

*Given that there are no available data to suggest that the changes in hormones with treatment of crinecerfont are associated with increased menstrual regularity (which signifies ovulatory cycles) or pregnancy rates or improved sperm function, DPMH does not agree with the Applicant's proposed labeling* (b) (4)

*DPMH discussed these findings with the DGE Clinical Review team who agreed that it was reasonable to report the hormonal findings in subsection 12.2 of labeling but noted that there was insufficient information to include the sections titled* (b) (4)

#### Review of Literature

##### *Applicant's review:*

The Applicant did not provide a literature review related to crinecerfont and fertility.

##### *DPMH review:*

DPMH conducted a literature search for studies in humans using PubMed, using the search terms "corticotropin releasing factor 1 receptor antagonist" AND "fertility," "contraception,"

“oral contraceptives,” OR “infertility.” DPMH also conducted a search in Micromedex, Reprotox, and TERIS.<sup>23</sup> No publications were found.

### III. DISCUSSION AND CONCLUSIONS

#### Pregnancy

Although craniofacial abnormalities were seen in rabbits in the nonclinical embryofetal development studies, the relationship of these findings to crinecerfont is uncertain. The animal data should be conveyed in subsection 8.1 of labeling under the “Risk Summary” and “Animal Data.” Clinical data related to crinecerfont use during pregnancy are insufficient to inform labeling, which should be explained in subsection 8.1 of labeling.

DPMH recommends issuing a post-marketing requirement (PMR) for a descriptive pregnancy safety study (DPSS) for the following reasons:

- 1) Three pregnancies occurred during the drug development program, indicating that females of reproductive potential with classic CAH may take crinecerfont. Although there were pregnancies that occurred during drug development, there are no data from these pregnancies to inform the use of crinecerfont during pregnancy. Thus, a DPSS would provide necessary pregnancy safety data.
- 2) Given that classic CAH is a rare disease, the number of pregnant patients who use crinecerfont is likely to be small. With a small number of pregnant patients using crinecerfont, a pregnancy exposure registry would be unlikely to adequately enroll patients; therefore, a DPSS is preferred.
- 3) Crinecerfont is systemically absorbed and will cross the placenta. Crinecerfont has the potential to inhibit ACTH secretion in the developing fetus thereby reducing cortisol levels in the fetus, which may result in fetal growth restriction, preterm delivery or demise.

#### Lactation

Nonclinical data demonstrated that crinecerfont was excreted in milk of lactating rats. Although there are no clinical data related to crinecerfont use during human lactation, when a drug is present in animal milk, it is likely that it will be present in human milk. This information should be included in the labeling of subsection 8.2.

Rats exposed to crinecerfont via milk did not experience adverse events; however, the nonclinical data are available until lactation day 20 only. This timeframe may not be sufficient to observe adrenal insufficiency in rats. Serious adverse events associated with crinecerfont include adrenal insufficiency or crisis, which is life-threatening. With anticipated use in lactating females and the potential for the severe adverse events of adrenal insufficiency or crisis in healthy neonates and infants exposed to crinecerfont via breast milk, DPMH recommends the inclusion of text in labeling about monitoring infants exposed through breast milk for signs and symptoms of adrenal insufficiency.

Due to the presence of crinecerfont in animal milk and the potential for adrenal insufficiency or crisis in healthy neonates and infants exposed to crinecerfont via breast milk, DPMH

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<sup>23</sup> TERIS database, Truven Health Analytics, Micromedex Solutions. Accessed 7/29/24.

recommends issuing a PMR for a clinical lactation study to determine the extent to which crinecerfont is present in human milk.

#### Females and Males of Reproductive Potential

Nonclinical data do not show an adverse effect of crinecerfont on fertility. The clinical data related to changes in hormones related to treatment with crinecerfont are not adequate to inform labeling (b) (4). A drug-drug interaction with hormonal contraceptives is not likely as crinecerfont is neither an inhibitor nor an inducer of CYP3A4. Crinecerfont does not cause embryofetal toxicity or genotoxicity; therefore, pregnancy testing and contraception are not recommended. Given that there are no known adverse effects of crinecerfont on fertility or contraceptives and that there was no evidence of embryofetal toxicity or genotoxicity, DPMH recommends omitting subsection 8.3.

#### **LABELING RECOMMENDATIONS**

DPMH recommends labeling subsections 8.1 and 8.2 and section 17 of labeling for compliance with the PLLR as shown below. DPMH refers to the final NDA action for final labeling.

#### **DPMH Proposed Pregnancy and Lactation Labeling**

#### **FULL PRESCRIBING INFORMATION**



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**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.**  
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/s/  
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KATHERINE G KRATZ  
09/13/2024 02:02:23 PM

MIRIAM C DINATALE  
09/13/2024 02:20:15 PM

LYNNE P YAO  
09/13/2024 03:06:57 PM

**Interdisciplinary Review Team for Cardiac Safety Studies**  
**QT Study Review**

|                       |                                                    |
|-----------------------|----------------------------------------------------|
| Submission            | NDA 218808 / 218820                                |
| Submission Number     | 1                                                  |
| Submission Date       | 4/29/2024                                          |
| Date Consult Received | 6/10/2024                                          |
| Drug Name             | Crinecerfont capsules/ oral solution, for oral use |
| Indication            | (b) (4)                                            |
| Therapeutic Dose      | 100 mg BID                                         |
| Clinical Division     | DGE                                                |
| Protocol Review       | <a href="#">Link</a>                               |

Note: Any text in the review with a light background should be considered to be copied from the applicant's document.

This review responds to your consult dated 6/10/2024 regarding the Applicant's QTc evaluation report. We reviewed the following materials:

- Previous IRT reviews dated [01/07/2022](#) and [07/19/2022](#) in DARRTS;
- QT Study Report [NBI-74788-1719](#) (NDA218808/SN0001);
- Pharmacometrics Report Number [2023-PM-136](#) (NDA218808/SN0001);
- Investigator's brochure Version 6.0 (IND132849/SN0139; [link](#));
- Highlights of clinical pharmacology and cardiac safety (NDA218808/SN0001; [link](#));
- Summary of Clinical Pharmacology (NDA 218808/ SN0001; [link](#)); and
- Draft labeling (NDA 218808/ SN0001; [link](#)).

## 1 SUMMARY

Crinecerfont did not prolong the QTc interval in this thorough QT study. Instead, crinecerfont shortened the QTc interval in a dose-dependent manner – see Table 1 for overall results. The small magnitude of QTc shortening at high clinical exposure (-5 msec) in the TQT study is unlikely to be clinically important.

The clinical study NBI-74788-1719 was a Phase 1, randomized, double-blind (with respect to crinecerfont/placebo only; moxifloxacin was open-labelled), placebo- and active-controlled, single-dose, 4-way crossover study. Forty-eight (48) healthy adult subjects were enrolled. The highest dose provided 3.3-fold high clinical exposure. Data

were analyzed using by-time analysis as the primary analysis, which did not suggest that crinecerfont is associated with QTc prolonging effect but has QTc shortening effect (section 4.3). Crinecerfont exhibited delayed QTc shortening effect in this study (~3-4 hours delay). Thus, concentration-QTc analysis was not evaluated.

The mechanism for QTc shortening is unknown because the applicant only evaluated the effects of crinecerfont on the hERG channel and not its effect on other cardiac ion channels (e.g., Nav1.5, Cav1.2). However, the delay between the timing of peak QTc shortening relative to peak crinecerfont concentrations and the lack of any major metabolites that could account for this delay do not suggest a direct effect of crinecerfont on cardiac ion channels.

**Table 1: Summary of findings**

|                            |                                                                                                                                                                                                                                            |                     |          |               |                 |
|----------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|----------|---------------|-----------------|
| QT assessment pathway      | <input checked="" type="checkbox"/> Thorough QT study<br><input type="checkbox"/> Substitute for thorough QT study (5.1)<br><input type="checkbox"/> Alternative QT study when a thorough QT study is not feasible (6.1)                   |                     |          |               |                 |
| Clinical QT study findings | <ul style="list-style-type: none"><li>High clinical exposure scenario is anticipated with concomitant strong CYP3A4 inhibitors (section 3.1)</li><li>The highest dose in the TQT study provides 3.3-fold the high clinical Cmax.</li></ul> |                     |          |               |                 |
|                            | ECG parameter                                                                                                                                                                                                                              | Treatment           | Time (h) | ΔΔQTcF (msec) | 90% CI (msec)   |
|                            | QTcF                                                                                                                                                                                                                                       | Crinecerfont 300 mg | 10.0     | -5.0          | (-7.2 to 2.8)   |
|                            | QTcF                                                                                                                                                                                                                                       | Crinecerfont 800 mg | 10.0     | -9.8          | (-12.0 to -7.6) |
| In vitro findings          | Integrated nonclinical risk assessment was not performed.                                                                                                                                                                                  |                     |          |               |                 |
| In vivo findings           |                                                                                                                                                                                                                                            |                     |          |               |                 |

## 2 RECOMMENDATIONS

### 2.1 PROPOSED LABEL

Below are proposed edits to the label submitted to eCTD 0001 ([link](#)).

Our changes are highlighted ([addition](#), ~~deletion~~). Each section is followed by a rationale for the changes made. Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

(b) (4)

*Reviewer's comment: We propose to use labeling language for this product consistent with the "QTc Information in Human Prescription Drug and Biological Product Labeling Guidance for Industry" draft guidance ([link](#)).*

### 3 APPLICANT'S SUBMISSION

#### 3.1 OVERVIEW

Neurocrine Biosciences is developing crinecerfont for the treatment of congenital adrenal hyperplasia (CAH; resulting from 21-hydroxylase deficiency). Crinecerfont (NBI-74788, SSR125543Q; MW: 483.04 g/mol) is an antagonist of corticotropin releasing factor 1 (CRF1) receptor. The crinecerfont treatment (b) (4)

The recommended dosage is 100 mg twice daily taken orally with food.

The applicant initially proposed (b) (4)

disagreed with this proposal (b) (4)

Subsequently the applicant submitted a TQT study protocol for a 4-way cross-over study for review. Overall, we found the study protocol to be acceptable but noted that the adequacy of the dose selection would be a review issue. (DARRTS [07/19/2022](#))

The protocol has not been changed after our previous review.

##### 3.1.1 Clinical pharmacology

See highlights of clinical pharmacology and cardiac safety.

Following oral administration of crinecerfont 100 mg BID with food, the median time to peak plasma concentration (T<sub>max</sub>) is 4.0 hours. Crinecerfont achieves steady state in approximately 7 days with a dose-proportional increase in systemic exposure over a dose range of 20 to 200 mg. Administration of crinecerfont with a high-fat, high-calorie meal significantly increases exposure, with an 8.2-fold increase of C<sub>max</sub> for the oral solution and a 3.3-fold increase of C<sub>max</sub> for the capsule formulation compared to the fasted state.

Crinecerfont exhibits high plasma protein binding of  $\geq 99.9\%$  and shows no affinity for blood cells, with a whole blood to plasma ratio of 0.5 to 0.7, independent of concentration. The drug is primarily metabolized by CYP3A4 and to a lesser extent by CYP2B6, with an effective half-life of approximately 14 hours. Concomitant administration of crinecerfont with a strong CYP3A4 inhibitor (ketoconazole 400 mg QD for 14 days) is expected to increase crinecerfont exposures (C<sub>max</sub>: 1.25-fold & AUC: 1.45-fold).

Excretion studies show that unchanged crinecerfont was the major component in human plasma. Recovered radioactivity accounted for 47.3% in feces and 2% in urine of the total administered dose. Hepatic impairment (mild, moderate, or severe) had no clinically

important effect on crinecerfont pharmacokinetics, with slight decreases in C<sub>max</sub> observed compared to subjects with normal hepatic function. No dedicated renal impairment study was conducted as renal elimination only accounts for approximately 2% of the administered dose, and the effects of severe renal impairment or end-stage renal disease on crinecerfont exposure remain unknown.

A QT study assessed the effect of single 300 mg and 800 mg doses of crinecerfont on QT interval prolongation, including placebo and positive control (moxifloxacin 400 mg). Crinecerfont plasma concentrations following administration of a single 800 mg dose in the fed state were expected to achieve supratherapeutic levels, exceeding the high clinical exposure scenario while accounting for intrinsic and extrinsic factors (See Table 2).

**Table 2: Summary of dose and exposure assessment**

|                                                             |                                          | <b>Mean C<sub>max</sub></b>       |
|-------------------------------------------------------------|------------------------------------------|-----------------------------------|
| <b>Highest therapeutic or clinical trial dosing regimen</b> | 100 mg BID with food                     | 5590 ng/mL (C <sub>max,ss</sub> ) |
| <b>Applicant's High clinical exposure scenario</b>          | 1.3-fold increase with CYP3A4 inhibition | 7267 ng/mL                        |
| <b>Highest dose in QT assessment</b>                        | 800 mg with food                         | 24230 ng/mL                       |
| <b>C<sub>max</sub> Ratio</b>                                | 24230 / 7267 ~ 3.3-fold                  |                                   |

### 3.1.2 Nonclinical Safety Pharmacology Assessments

**In vitro:** The applicant evaluated the effects of crinecerfont tosylate on hERG current in the study report (FSRFU-PAT006-EN-E01, [link](#)). The hERG current was induced by a step-step voltage protocol (from a holding potential of -80 mV to + 20 mV for 0.8 s, and then repolarized to -120 mV for 0.3 s to induced the negative deactivated tail current) that is different from the recommended voltage protocol by the FDA ([link](#)). While the voltage protocol has been rarely used across the academia and industry, the reviewer does not expect that the difference of voltage protocol will impact the drug pharmacology. Experimental temperature was not mentioned in the study report. However, based on the current trace at + 20 mV in Figure (4.)1, the hERG current was likely assessed at room temperature using manual patch clamp assay.

The reduction in hERG current at the highest concentration 10 µM tested was 5%. This concentration provides 66-fold (MW: 483 g/mol; PB: >99%) the high clinical exposure scenario (see Table 2). Assuming the hill coefficient is 1, IC<sub>50</sub> is estimated to be ~202 µM or 1348x high clinical exposure. However, this estimate should be interpreted with caution due to the minimal inhibition at the highest tested dose.

The effects of crinecerfont on other cardiac ion channels have not been evaluated.

**In vivo (conscious telemetrized dogs):** The in vivo QT study (FSRFU-CVE0009-EN-E01, [link](#)) assessed the effects of crinecerfont tosylate on ECG parameters following single oral doses to conscious telemetrized dogs (n=3/sex) in an escalating dose design. The free concentration at 6 h post-dose of the highest dose (1000 mg/kg) in the study is

23 ng/mL and 12 ng/mL for males and females, respectively. This corresponds to ~0.2-0.3-fold high clinical exposure scenario. No changes in QTc, HR, PR, or QRS were observed at the highest dose.

In vivo (anesthetized telemetrized dogs): The in vivo QT study (CVR0259, [link](#)) assessed the effects of crinecerfont tosylate on ECG parameters following single IV dose to anesthetized telemetrized dogs (n=3-4/sex) in parallel group design. The free concentration at the end of infusion for the highest group (30 mg/kg over 20 min) was 12365 and 12410 ng/mL for male and female dogs, respectively. This corresponds to ~1.7-fold high clinical exposure scenario. No changes in QTc, HR, PR, or QRS were observed at the highest dose.

## 3.2 APPLICANT'S RESULTS

### 3.2.1 By-Time Analysis

In the applicant's by-time analysis, crinecerfont excluded the 10 msec threshold at the therapeutic and supratherapeutic dose level of both 300 mg and 800 mg for  $\Delta\Delta\text{QTcF}$ . The applicant used the linear mixed-effect model to analyze the drug effect by-time for each biomarker (e.g.,  $\Delta\text{QTcF}$ ,  $\Delta\text{HR}$ ) independently. The upper bounds of the 90% CI of  $\Delta\Delta\text{QTcF}$  were well below the 10 msec threshold for all time points for crinecerfont treatment groups.

**Reviewer's comment:** Reviewer also used MMRM for by-time analysis. The results of the reviewer's analysis were similar to the applicant's analysis. Please see section 4.3 for details. However, crinecerfont showed shorting QTc effect based on  $\Delta\Delta\text{QTcF}$  that was dose dependent. The minimal mean  $\Delta\Delta\text{QTcF}$  in the treatment of crinecerfont 800 mg is -9.8 msec, and the lower bound of 90% CI is -12.0.

#### 3.2.1.1 Assay Sensitivity

Assay sensitivity was established by the moxifloxacin arm with by-time analysis. The results of the applicant's analysis show that using a Bonferroni adjustment, the largest 97.5% of lower bounds exceeding 5 msec for the 4 pre-specified timepoints (at 2, 3, 4, 5 hour) following administration of 400 mg moxifloxacin. The Applicant did not conduct an exposure-response analysis for 400 mg moxifloxacin.

**Reviewer's comment:** Reviewer's by-time analysis confirmed that assay sensitivity had been demonstrated. Please see section 4.3.1.1 for additional details.

### 3.2.3 Bias Assessment

Not applicable in this review.

### 3.2.2 Categorical Analysis

There were no significant outliers per the applicant's analysis for QTc (i.e., >500 msec or >60 msec over baseline), HR (<40 or >100 beats/min), PR (>220 msec and 25% over baseline), and QRS (>120 msec and 25% over baseline).

**Reviewer's comment:** Reviewer's analysis results are like the applicant's analysis results. Since the drug shortens the QTc interval, reviewers also report the minimum value for QTc. One subject exhibited a QTcF below 350 msec, and two subjects exhibited

a QTcF change from baseline of  $\leq -40$  msec in the crinecerfont 800 mg treatment group. Please see Section 4.4 for details.

### 3.2.3 Exposure-Response Analysis

The sponsor conducted C-QTc analysis using 43 subjects contributing 823 time matched  $\Delta\Delta$ QTc observations in the TQT study. Before modeling, the sponsor conducted exploratory analyses to examine the assumptions of the white paper model (i.e., linear mixed effect model). Crinecerfont caused small dose dependent increase in HR. Although the increase was  $< 10$  bpm (beats per minute) the sponsor assessed different HR correction methods for QT using drug free baseline data. According to the sponsor, population based, study-specific correction (QTcP) most effectively reduced correlations between QTc and RR. Therefore  $\Delta\Delta$ QTcP for assessment of QTc hysteresis and C-QTc modeling. Although a clockwise hysteresis was observed, indicating delayed QTc effect, the sponsor’s final model did not account for delayed QTc effects. Since the LOESS line of the exploratory  $\Delta\Delta$ QTcP vs concentration graph indicated a sigmoid relationship, the sponsor developed an Emax model to describe crinecerfont C-QTc relationship (Figure 1). The estimates of INT, Emax, and EC50 were 1.95 msec, -6.95 msec and 874 ng/mL respectively.

**Figure 1: C-QTc model equation**

$$\Delta\Delta QTc_{ij} = INT_i + \frac{Emax_i \cdot Conc_{ij}}{EC50_i + Conc_{ij}} + \epsilon_{ij}$$

where:

- $\Delta\Delta QTc_{ij}$  is the placebo-corrected change in QTc for subject i at time j;
- $INT_i$  is the individual intercept in the absence of a treatment effect in subject i;
- $Emax_i$  is the maximum drug effect in subject i;
- $EC50_i$  is the drug concentration that results in half the maximal effect in subject i;
- $Conc_{ij}$  is the observed concentration for subject i at time j;
- $\epsilon_{ij}$  is the residual error for subject i at time j (assumed independent normal with mean 0)

Source: Sponsor’s Pharmacometrics Report, Page 26

At the observed  $C_{max}$  following a 300 mg and 800 mg dose with high-fat meal, the mean model-predicted  $\Delta\Delta$ QTcP (90% CI) was -4.21 (-6.54 to -1.92) and -4.48 msec (-6.82 to -2.11), respectively.

At the observed  $C_{max ss}$  in Study NBI-74788-CAH2001 for 100 mg BID with standard meal, the mean model-predicted  $\Delta\Delta$ QTcP (90% CI) was -3.83 msec (-6.12 to -1.56).

**Reviewer’s comment:** One of the assumptions of linear C-QTc model is absence of delayed QT effects. Based on exploratory graphs, crinecerfont seems to exhibit delayed QTc shortening (~3-4 hours delay). Therefore, reviewers did not conduct linear mixed effects modeling (see section 4.5.1). Since sample size supports by-time analysis, reviewers characterized QT effects of crinecerfont using by-time analysis as the primary analysis (See section 4.3.1).

### 3.2.4 Safety Analysis

There were no deaths in the study. There were two serious AEs in the study: small intestinal obstruction and acute cholecystitis. Three participants discontinued due to a treatment-emergent AE (small intestinal obstruction, moderate intensity of PVCs with onset prior to treatment but not discontinued until after administration of first dose, decreased neutrophil count and decreased white blood cell count).

**Reviewer's comment:** *None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., seizure, significant ventricular arrhythmias, or sudden cardiac death) occurred in this study.*

## 4 REVIEWERS' ASSESSMENT

### 4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The applicant used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e.,  $|\text{mean}| > 10$  beats/min) were observed (see section 4.3.2).

### 4.2 ECG ASSESSMENTS

#### 4.2.1 Overall

Digital ECG waveforms were submitted for review. The ECGs were read semi-automatically by a central reader blinded to subject, administration conditions, time, and treatment group. Compared to the ECG warehouse algorithm, we did not observe significant bias in QT measurements and the ECG acquisition and interpretation for this study is therefore acceptable.

#### 4.2.2 QT Bias Assessment

Not applicable.

### 4.3 BY-TIME ANALYSIS

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG.

The statistical reviewer used a linear mixed model to analyze the drug effect by-time for each biomarker (e.g.,  $\Delta\text{QTcF}$ ,  $\Delta\text{HR}$ ) independently. The default model includes treatment, sequence, period, time (as a categorical variable), and treatment-by-time interaction as fixed effects, and baseline as a covariate. The default model also includes subject as a random effect and an unstructured covariance matrix to explain the associations among repeated measures within the period.

#### 4.3.1 QTc

Figure 1 displays the time profile of  $\Delta\Delta\text{QTcF}$  for different treatment groups. Since the drug shortens the QTc, significantly smaller than that of placebo, the minimum  $\Delta\Delta\text{QTcF}$  values by treatment are shown in Table 3. A significant decrease in LS mean of  $\Delta\Delta\text{QTcF}$  was observed at 10 hours post-dose in the crinecerfont 800 mg treatment group.

**Figure 2: Mean and 90% CI of  $\Delta\Delta\text{QTcF}$  Time-course (unadjusted CIs).**

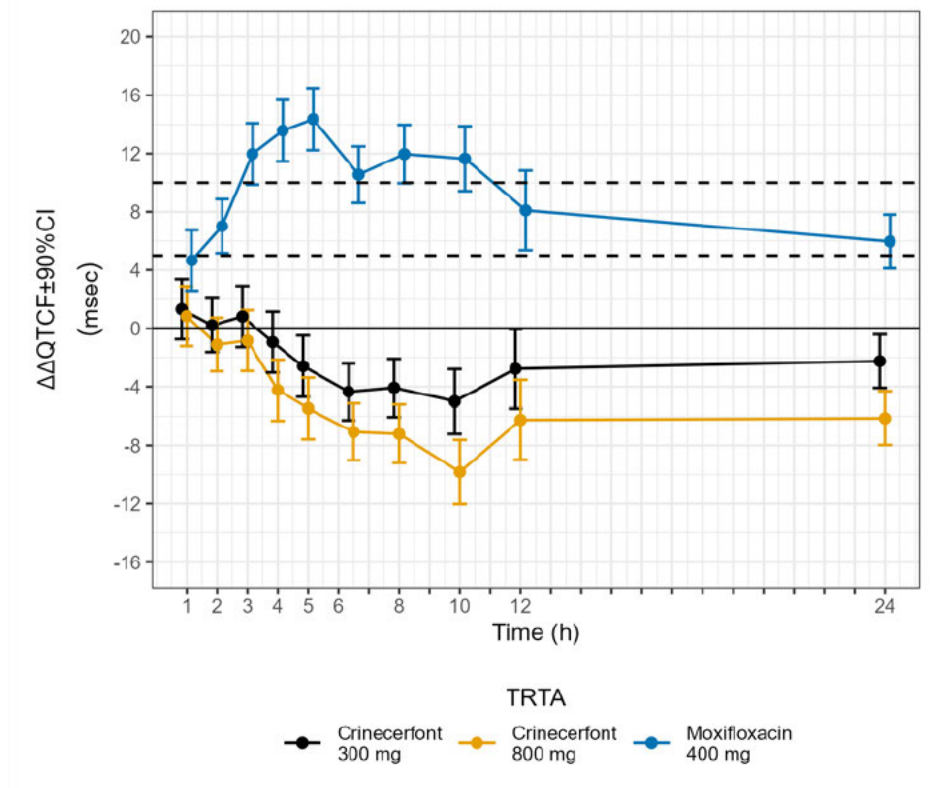


**Table 3: Point Estimates and the 90% CIs Corresponding to the Minimum Lower Bounds for  $\Delta\Delta\text{QTcF}$**

| Actual Treatment    | Nact / Npbo | Time (h) | $\Delta\Delta\text{QTcF}$ (msec) | 90.0% CI (msec) |
|---------------------|-------------|----------|----------------------------------|-----------------|
| Crinecerfont 300 mg | 45 / 43     | 10.0     | -5.0                             | (-7.2 to 2.8)   |
| Crinecerfont 800 mg | 45 / 43     | 10.0     | -9.8                             | (-12.0 to -7.6) |

#### 4.3.1.1 Assay Sensitivity

The assay sensitivity was established by by-time analysis. The model used for assay sensitivity is the same as the primary model. The time-course of changes in  $\Delta\Delta\text{QTcF}$  is shown in Figure 1 and includes the expected time-profile with a mean effect of  $>5$  msec after Bonferroni adjustment for 4 time points (Table 4).

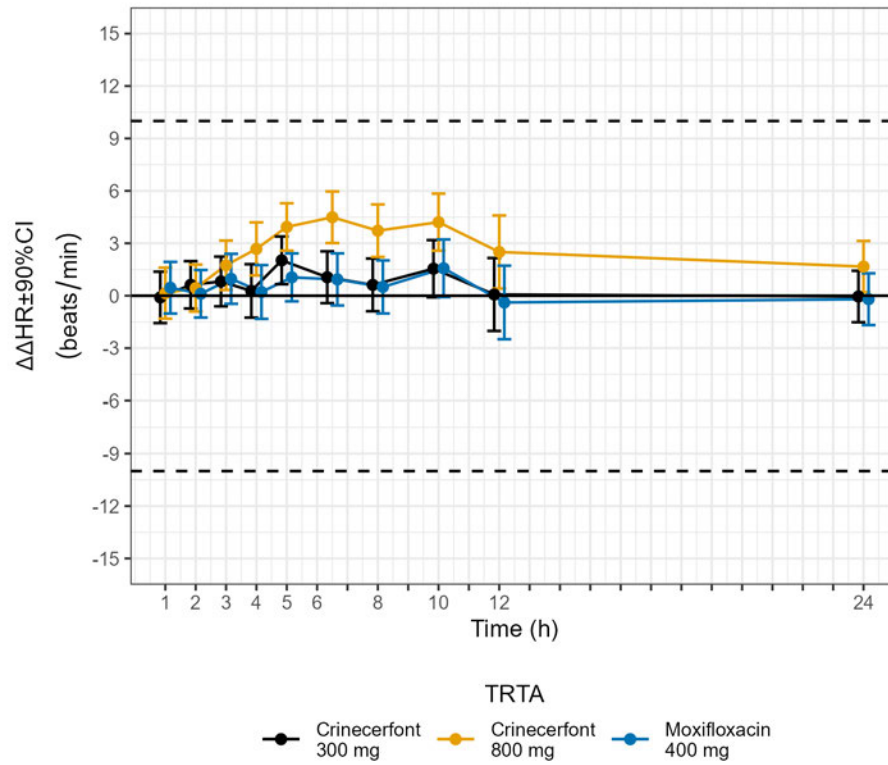
**Table 4: The Point Estimates and the 90% CIs Corresponding to the Largest Lower Bounds for  $\Delta\Delta\text{QTcF}$**

| Actual Treatment    | Nact / Npbo | Time (h) | $\Delta\Delta\text{QTcF}$ (msec) | 90.0% CI (msec) | 97.5% CI (msec) |
|---------------------|-------------|----------|----------------------------------|-----------------|-----------------|
| Moxifloxacin 400 mg | 43 / 43     | 5.0      | 14.4                             | (12.2 to 16.5)  | (11.5 to 17.3)  |

#### 4.3.2 HR

Figure 2 displays the time profile of  $\Delta\Delta\text{HR}$  for different treatment groups.

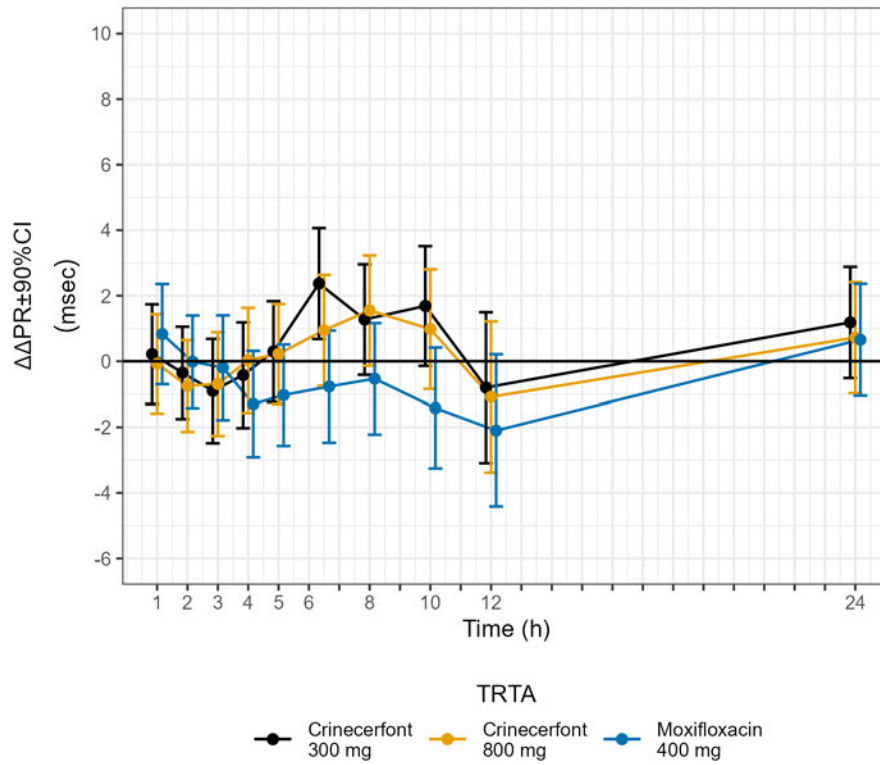
**Figure 3: Mean and 90% CI of  $\Delta\Delta HR$  Time-course**



### 4.3.3 PR

Figure 3 displays the time profile of  $\Delta\Delta PR$  for different treatment groups.

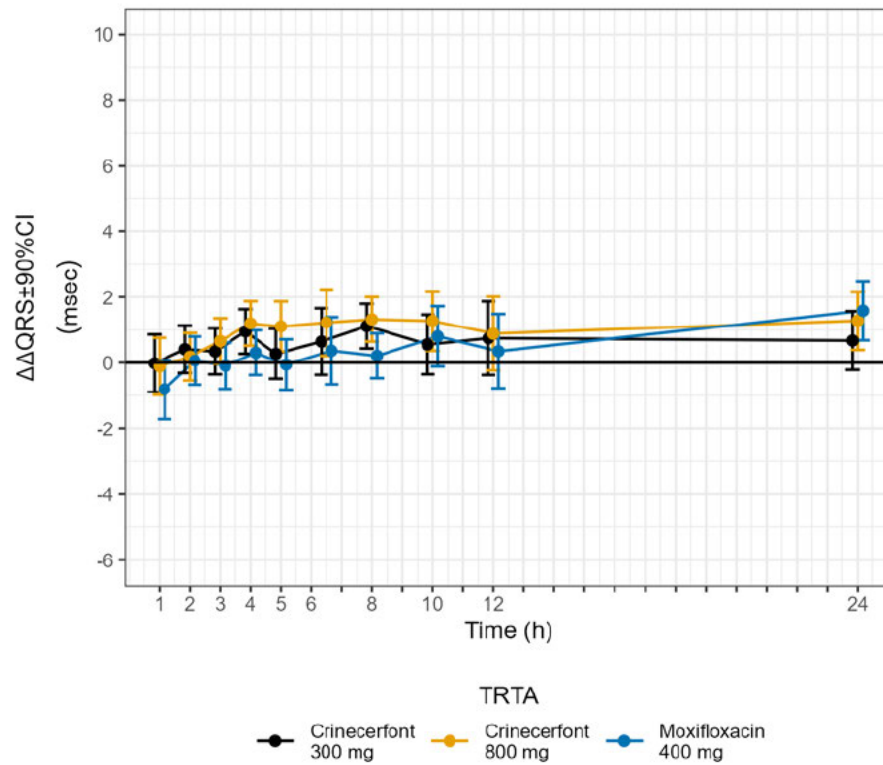
**Figure 4: Mean and 90% CI of  $\Delta\Delta PR$  Time-course**



#### 4.3.4 QRS

Figure 4 displays the time profile of  $\Delta\Delta QRS$  for different treatment groups.

**Figure 5: Mean and 90% CI of  $\Delta\Delta$ QRS Time-course**



#### 4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs.

##### 4.4.1 QTc

There were no subjects having observed QTcF above 450 msec or change from baseline above 30 msec. Table 5 lists the number of subjects, as well as the number of observations with QTcF values of  $>320$  and  $\leq 350$  msec,  $>350$  and  $\leq 400$  msec, and  $>400$  msec. Table 6 lists the categorical analysis results for  $\Delta$ QTcF ( $\leq -40$  msec,  $> -40$  and  $< -20$ , and  $> -20$  msec). There was one subject having observed QTcF below 350 msec and two subjects having observed QTcF with a change from baseline  $\leq -40$  msec in the crinecerfont 800 mg treatment group.

**Table 5: Categorical Analysis for QTcF (minimum)**

| Actual Treatment    | Total (N) |        | 320 msec < Value $\leq 350$ msec |           | 350 msec < Value $\leq 400$ msec |                | Value $> 400$ msec |                |
|---------------------|-----------|--------|----------------------------------|-----------|----------------------------------|----------------|--------------------|----------------|
|                     | # Subj.   | # Obs. | # Subj.                          | # Obs.    | # Subj.                          | # Obs.         | # Subj.            | # Obs.         |
| Crinecerfont 300 mg | 45        | 585    | 0<br>(0%)                        | 0<br>(0%) | 37<br>(82.2%)                    | 336<br>(57.4%) | 8<br>(17.8%)       | 249<br>(42.6%) |

| Actual Treatment    | Total (N) |        | 320 msec < Value<br>≤350 msec |             | 350 msec < Value<br>≤400 msec |                | Value >400 msec |                |
|---------------------|-----------|--------|-------------------------------|-------------|-------------------------------|----------------|-----------------|----------------|
|                     | # Subj.   | # Obs. | # Subj.                       | # Obs.      | # Subj.                       | # Obs.         | # Subj.         | # Obs.         |
| Crinecerfont 800 mg | 46        | 592    | 1<br>(2.2%)                   | 1<br>(0.2%) | 41<br>(89.1%)                 | 407<br>(68.8%) | 4<br>(8.7%)     | 184<br>(31.1%) |
| Placebo             | 43        | 557    | 0<br>(0%)                     | 0<br>(0%)   | 33<br>(76.7%)                 | 281<br>(50.4%) | 10<br>(23.3%)   | 276<br>(49.6%) |

**Table 6: Categorical Analysis for  $\Delta$ QTcF (minimum)**

| Actual Treatment    | Total (N) |        | Value ≤-40 msec |             | -40 msec < Value ≤-20 msec |                | Value >-20 msec |                |
|---------------------|-----------|--------|-----------------|-------------|----------------------------|----------------|-----------------|----------------|
|                     | # Subj.   | # Obs. | # Subj.         | # Obs.      | # Subj.                    | # Obs.         | # Subj.         | # Obs.         |
| Crinecerfont 300 mg | 45        | 585    | 0<br>(0%)       | 0<br>(0%)   | 13<br>(28.9%)              | 44<br>(7.5%)   | 32<br>(71.1%)   | 541<br>(92.5%) |
| Crinecerfont 800 mg | 46        | 592    | 2<br>(4.3%)     | 7<br>(1.2%) | 25<br>(54.3%)              | 104<br>(17.6%) | 19<br>(41.3%)   | 481<br>(81.2%) |
| Placebo             | 43        | 557    | 1<br>(2.3%)     | 2<br>(0.4%) | 12<br>(27.9%)              | 23<br>(4.1%)   | 30<br>(69.8%)   | 532<br>(95.5%) |

#### 4.4.2 HR

There were no subjects having observed maximum HR above 100 beats/min in any of the crinecerfont treatment groups.

#### 4.4.3 PR

None of the subjects experienced PR >220 msec in any of the treatment groups.

#### 4.4.4 QRS

None of the subjects experienced QRS >120 msec in any of the treatment groups.

### 4.5 EXPOSURE-RESPONSE ANALYSIS

Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG, with time-matched PK (n = 48).

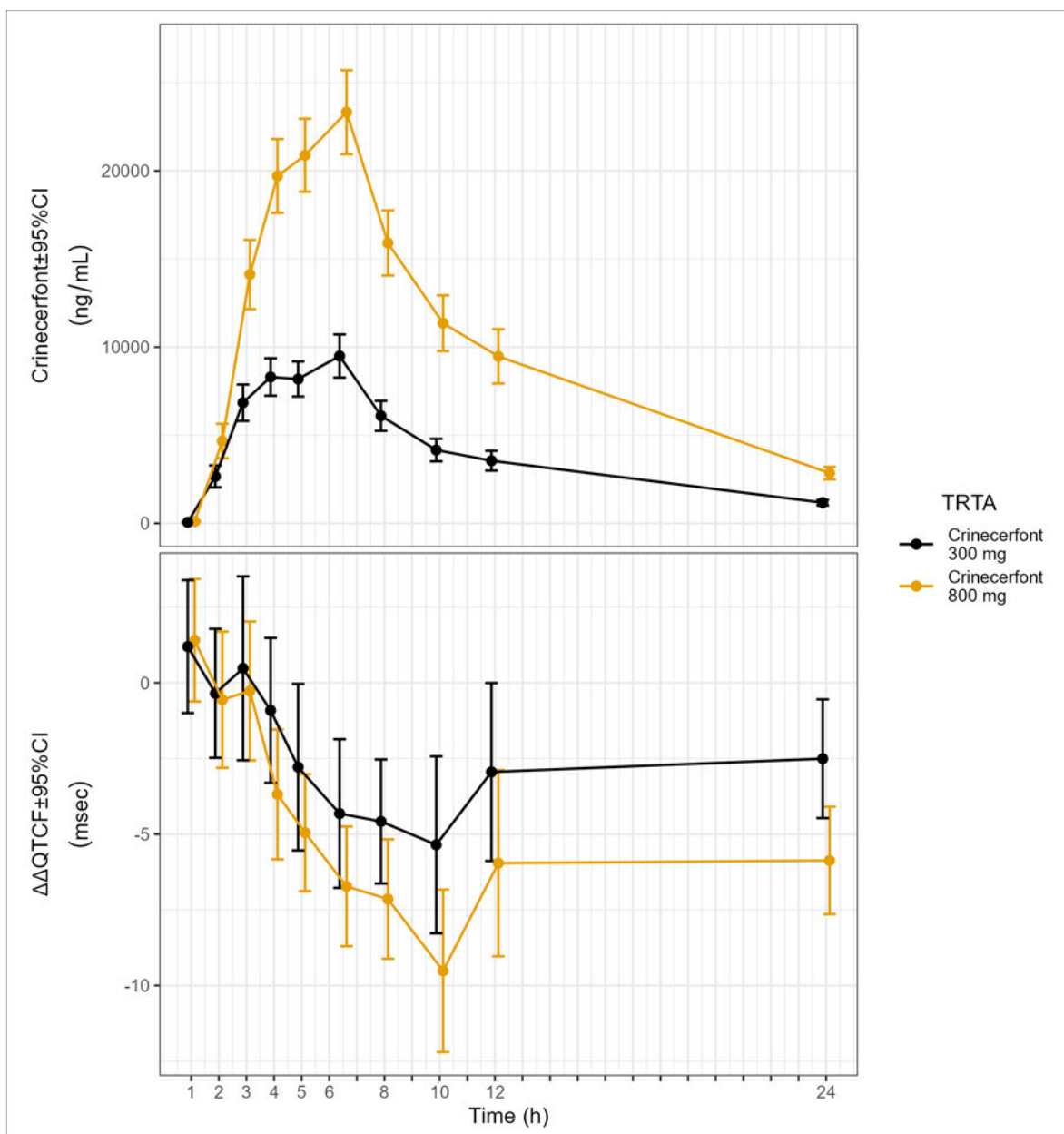
#### 4.5.1 QTc

Figure 2 shows the time-course of  $\Delta\Delta$ HR, with small dose-dependent HR increase. These HR changes are less than 10 bpm and therefore may not substantially impact characterization of QTc effects using HR corrected QT using Fridericia formula. Figure 5 offers an evaluation of the relationship between time-course of drug concentration and  $\Delta\Delta$ QTcF. The figure shows QT shortening over-time. While peak crinecerfont concentration occurs at 6.5-hours post-dose, maximum QT shortening is delayed and occurs at 10-hours post-dose. The delay in QTc shortening is approximately 3-4 hours after crinecerfont reach its peak plasma concentration (C<sub>max</sub>). Both 300 mg and 800 mg

crinecerfont treatments resulted in QTcF shortening with dose-dependent decrease in QTc interval. Although Figure 6 shows linear relationship between drug concentration and  $\Delta$ QTcF supporting linear model, linear mixed effects modeling was not conducted by the reviewers to the due to QTc hysteresis.

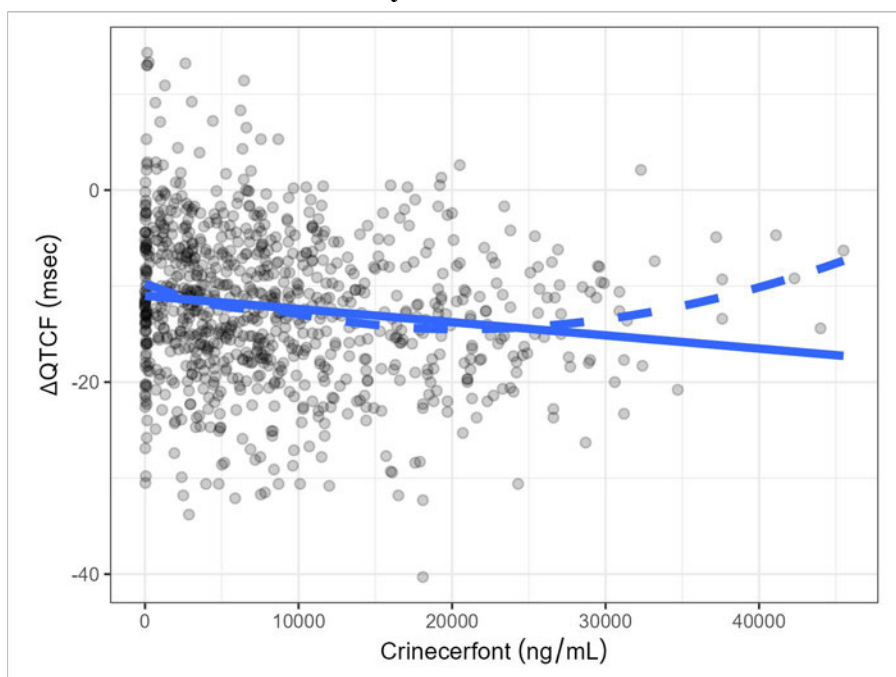
The underlying mechanism for the observed QTc shortening remains unclear. It is also unclear if the extent of crinecerfont induced QTc shortening at therapeutic dosing is clinically relevant.

**Figure 6: Time-course of Drug Concentration (top) and QTcF (bottom)<sup>1</sup>**



<sup>1</sup> ΔΔQTcF shown were obtained via descriptive statistics and might differ from Figure 1

**Figure 7: Assessment of Linearity of the Concentration-QTcF Relationship**



#### **4.5.1.1 Assay Sensitivity**

The applicant did not collect moxifloxacin concentrations for exposure-response analysis. Assay sensitivity was demonstrated using by-time analysis (Section 4.3.1.1).

#### **4.6 SAFETY ASSESSMENTS**

See section 3.2.4. No additional safety analyses were conducted.

## **5 APPENDIX**

### **5.1 EVALUATION OF THE APPLICANT'S CLINICAL QT STUDIES**

We previously reviewed the protocol. (DARRTS [07/19/2022](#))

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WEI LIU  
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DEVI KOZELI on behalf of JING SUN  
08/15/2024 01:20:39 PM

DALONG HUANG  
08/15/2024 01:50:22 PM

YANING SUN  
08/15/2024 04:23:33 PM

ELIFORD N KITABI  
08/15/2024 07:54:26 PM

DONGLIN GUO  
08/16/2024 08:31:33 PM

MICHAEL Y LI  
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LARS JOHANNESSEN  
08/19/2024 07:29:08 AM

CHRISTINE E GARNETT  
08/21/2024 07:26:27 AM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 7/12/2024

TO: Division of Pulmonology, Allergy, and Critical Care (DPACC)  
Office of Immunology and Inflammation (OII)

Division of General Endocrinology (DGE)  
Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)

Division of Rheumatology and Transplant Medicine (DRTM)  
Office of Immunology and Inflammation (OII)

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: non-responsive  
NDA 218808  
non-responsive

The Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not needed for the site listed below. The rationale for this decision is noted below.

**Rationale**

(b) (4) OSIS conducted a Remote Regulatory Assessment (RRA) for the site in (b) (4). The RRA was conducted under the following submission: NDA non-responsive.

OSIS concluded that data from the reviewed studies were reliable.

**Site**

| Facility Type | Facility Name                                           | Facility Address |
|---------------|---------------------------------------------------------|------------------|
| Analytical    | <span style="background-color: #cccccc;">(b) (4)</span> |                  |

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ADANMA S OJI  
07/15/2024 03:07:06 PM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

DATE: 7/12/2024

TO: Division of General Endocrinology (DGE)  
Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 218808

The Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not needed for the site listed below. The rationale for this decision is noted below.

**Rationale**

**Celerion, Tempe:** The Office of Regulatory Affairs (ORA) conducted an inspection for the site in April 2024. The inspection was conducted under the following submission: NDA 219008.

OSIS concluded that data from the reviewed studies were reliable.

Site

| Facility Type | Facility Name  | Facility Address                   |
|---------------|----------------|------------------------------------|
| Clinical      | Celerion, Inc. | 2420 West Baseline Road, Tempe, AZ |

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