

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NEUROCRINE BIOSCIENCES, INC.
Petitioner

v.

SPRUCE BIOSCIENCES, INC.
Patent Owner

Case PGR2021-00088
U.S. Patent 10,849,908

PETITION FOR POST GRANT REVIEW OF

U.S. PATENT NO. 10,849,908

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EXHIBITS

Petitioner Exhibit Number	Exhibit Description
1001	U.S. Patent No. 10,849,908 to Alexis Howerton, et al. (“the ’908 patent”).
1002	U.S. Prosecution History of the ’908 Patent.
1003	Application No. PCT/US2018/046760.
1004	U.S. Provisional Application Serial No. 62/545,406.
1005	Declaration of Robert M. Carey, M.D.
1006	U.S. Patent Application Publication No. 2017/0020877 to Grigoriadis et al. (“Grigoriadis”).
1007	U.S. Patent Application Publication No. 2005/0209250 to Romano (“Romano”).
1008	Turcu et al., “Single-Dose Study of a Corticotropin-Releasing Factor Receptor-1 Antagonist in Women With 21-Hydroxylase Deficiency,” <i>J. Clin. Endocrinol. Metab.</i> , 101(3):1174–1180 (March 2016) (“Turcu 2016”).
1009	Auchus et al., “Crinicerfont Lowers Elevated Biomarkers of Disease Control in Adults with Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency,” (submitted to <i>Lancet</i> journal April 30, 2021) (“Auchus 2021”).
1010	U.S. Patent Application Publication No. 2006/0078623 to Dhoot et al. (“Dhoot”).
1011	“Spruce Biosciences Presents Phase 1 and 2 Data for Tildacerfont in Adults with Congenital Adrenal Hyperplasia from Endocrine Society’s 2021 Annual Meeting,” Spruce Biosciences (Mar. 17, 2021) (“Spruce March 17, 2021 Press Release”).
1012	U.S. Patent No. 8,030,304 to Chen et al. (“Chen”).
1013	Speiser et al., “Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society

	Clinical Practice Guideline,” <i>J. Clin. Endocrinol. Metab.</i> , 95(9):4133–4160 (2010) (“Speiser 2010”)
1014	Turcu A.F. & Auchus R.J., “The Next 150 Years of Congenital Adrenal Hyperplasia,” <i>J. Steroid. Biochem. Mol. Biol.</i> 153:63–71 (Sep. 2015) (“Turcu & Auchus 2015”).
1015	El Maouche et al., “Congenital Adrenal Hyperplasia,” <i>Lancet</i> 390:2194–210 (2017) (“El Maouche 2017”).
1016	Merke D.P. & Bornstein S.R., “Congenital Adrenal Hyperplasia,” <i>Lancet</i> 365:2125–36 (2005) (“Merke & Bornstein 2005”).
1017	Speiser et al., “Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society Clinical Practice Guideline,” <i>J. Clin. Endocrinol. Metab.</i> , 103(11):4043–4088 (2018) (“Speiser 2018”).
1018	Fahmy et al., “Structure and Function of Small Non-Peptide CRF Antagonists and their Potential Clinical Use,” <i>Curr. Mol. Pharmacol.</i> 10(4): 270–281 (2017) (“Fahmy 2017”).
1019	Griebel et al., “4-(2-Chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]5-methyl-N-(2-propynyl)-1,3-thiazol-2-amine Hydrochloride (SSR125543A), a Potent and Selective Corticotrophin-Releasing Factor1 Receptor Antagonist. II. Characterization in Rodent Models of Stress-Related Disorders,” <i>J. Pharmacol. Exp. Ther.</i> 301(1):333–345 (2002) (“Griebel 2002”)
1020	Gully et al., “4-(2-Chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]5-methyl-N-(2-propynyl)-1,3-thiazol-2-amine Hydrochloride (SSR125543A): A Potent and Selective Corticotrophin-Releasing Factor1 Receptor Antagonist. I. Biochemical and Pharmacological Characterization,” <i>J. Pharmacol. Exp. Ther.</i> 301(1):322-332 (2002) (“Gully 2002”).
1021	Merke D.P. & Cutler G.B., “New Ideas for Medical Treatment of Congenital Adrenal Hyperplasia,” <i>Endocrinol. Metab. Clin. North. Am.</i> 30(1):121–135 (2001) (“Merke & Cutler 2001”).
1022	Merke et al., “Future Directions in the Study and Management of Congenital Adrenal Hyperplasia due to 21-

	Hydroxylase Deficiency,” <i>Ann. Intern. Med.</i> 136:320–334 (2002) (“Merke 2002”).
1023	“Microparticles Formulation as a Targeting Drug Delivery System,” <i>J. Nanomed. Res.</i> 6(2):00151, 1–4 (2017) (“Microparticles Formulation 2017”).
1024	Merke D.P. & Auchus R.J., “Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency,” <i>N. Engl. J. Med.</i> 383(13):1248–1261 (2020) (“Merke & Auchus 2020”).
1025	Turcu A.F. & Auchus R.J., “Novel Treatment Strategies in Congenital Adrenal Hyperplasia,” <i>Curr. Opin. Endocrinol. Diabetes Obes.</i> 23(3):225–232 (June 2016) (“Turcu & Auchus 2016”).
1026	Webb E.A. & Krone N., “Current and Novel Approaches to Children and Young People with Congenital Adrenal Hyperplasia and Adrenal Insufficiency,” <i>Best Pract. Res. Clin. Endocrinol. Metab.</i> 29:449–468 (2015) (“Webb & Krone 2015”).
1027	“Neurocrine Biosciences to Present New Data Analyses for Crinecerfont in Adults with Classical Congenital Adrenal Hyperplasia at ENDO 2021,” Neurocrine Biosciences (Mar. 20, 2021) (“Neurocrine March 20, 2021 Press Release”).
1028	“Neurocrine Biosciences Reports Positive Phase II Data for Crinecerfont in Adults with Congenital Adrenal Hyperplasia at ENDO Online 2020,” Neurocrine Biosciences (June 8, 2020) (“Neurocrine June 8, 2020 Press Release”).
1029	Williams, “Corticotropin-Releasing Factor 1 Receptor Antagonists: A Patent Review,” <i>Expert Opin. Ther. Pat.</i> 23(8):1057–68 (2013) (“Williams 2013”).
1030	Zorrilla E.P. & Koob G.F., “Progress in Corticotropin-Releasing Factor-1 Antagonist Development,” <i>Drug Discovery Today</i> 15(9/10):371–383 (2010) (“Zorrilla & Koob 2010”).
1031	Kehne J.H. & Cain C.K., “Therapeutic Utility of Non-Peptidic CRF1 Receptor Antagonists in Anxiety, Depression, and Stress-Related Disorders: Evidence from Animal Models,” <i>Pharmacol. Ther.</i> 128(3):460–487 (2010). (“Kehne & Cain 2010”).

1032	Goodman & Gilman's The Pharmacological Basis of Therapeutics (Brunton L.L. ed., 12th ed. 2011) ("Goodman & Gilman 2011).
1033	Shargel L. & Yu A., Applied Biopharmaceutics & Pharmacokinetics (7th ed. 2016) ("Shargel & Yu 2016").
1034	Shargel et al., Applied Biopharmaceutics & Pharmacokinetics (6th ed. 2012) ("Shargel 2012").
1035	Bale et al., "Overview on Therapeutic Applications of Microparticulate Drug Delivery Systems," <i>Crit. Rev. Ther. Drug Carrier Syst.</i> 33(4):309-361 (2016).

I. INTRODUCTION

Neurocrine Biosciences, Inc. (“Petitioner” or “Neurocrine”) petitions for Post Grant Review (“PGR”) under 35 U.S.C. §§ 321–326 and 37 C.F.R. § 42 of claims 1-25 (“the Challenged Claims”) of U.S. Patent No. 10,849,908 (“the ’908 patent;” Ex. 1001) assigned to Spruce Biosciences (“Spruce”). As explained in this petition, it is more likely than not that Neurocrine will prevail with respect to at least one of the Challenged Claims.

The ’908 patent broadly claims the use of CRF1 receptor antagonists to treat congenital adrenal hyperplasia (“CAH”), a group of genetic disorders impacting hormone production, but the specification describes only a single CRF1 receptor antagonist, unsurprisingly, the one compound Spruce is developing. The ’908 patent is invalid because of this insufficient disclosure, and because Neurocrine’s own work on the use of CRF1 receptor antagonists to treat CAH, which is prior art to the ’908 patent, anticipates Spruce’s broad claims or renders those claims obvious.

With respect to Neurocrine’s prior work, Published Application No. US 2017/0020877 (Ex. 1006; “Grigoriadis”), discloses the use of a number of CRF1 receptor antagonists to treat CAH, including crinecerfont, the compound Neurocrine is currently developing for the treatment of CAH, and NBI-77860, a

compound Neurocrine previously studied as a CAH treatment. Grigoriadis published several years before the application that issued as the '908 patent was filed, and the Patent Office rejected Spruce's application over Neurocrine's work.

The only basis for allowance of the '908 patent over Neurocrine's prior work was the Examiner's misunderstanding that the ability of the one CRF1 receptor antagonist disclosed in the '908 patent to maintain its effect for more than 24 hours was surprising and nonobvious. As detailed in this Petition, 1) the data presented by Spruce was not, in fact, surprising; 2) data relating to other CRF1 receptor antagonists that was not before the Examiner shows that the behavior of this single compound was not unique among CRF1 receptor antagonists, and; 3) most of the '908 patent claims do not even recite the post-24 hours requirement that was basis of the purportedly surprising result. Even if the results of this single compound were surprising or unexpected (which they are not), the results are not commensurate with the scope of the '908 patent claims, which cover a much larger class of compounds.

The broad '908 patent claims are also unpatentable under 35 U.S.C. § 112 in view of its limited disclosure. Although the patent claims the use of CRF1 receptor antagonists, the entire disclosure relates to only a single CRF1 receptor antagonist. The '908 patent repeatedly characterizes "the invention" as relating to this particular compound. The patent's disclosure does not allow persons of

ordinary skill in the art to recognize that the inventor invented what is claimed (the use of a class of compounds), and does not permit skilled artisans to make and use the full scope of the claims without undue experimentation.

Neurocrine respectfully submits that a PGR should be instituted, and that the Challenged Claims should be canceled as unpatentable.

II. REQUIREMENTS FOR PGR UNDER 37 C.F.R. § 42.204

A. Grounds for Standing Under 37 C.F.R. § 42.204(a)

Neurocrine certifies that the '908 Patent is available for PGR. The present petition is being filed within nine months of the issuance of the '908 patent on December 1, 2020. Neurocrine has not filed a civil action challenging the validity of any claim of the '908 patent. Neurocrine is not barred or estopped from requesting this review challenging claims 1-25 on the below-identified grounds.

B. Challenge Under 37 C.F.R. § 42.204(b) and Relief Requested

Neurocrine requests a PGR of the Challenged Claims on the grounds set forth in the table shown below, and requests that each of the Challenged Claims be found unpatentable.

Ground	'908 Patent Claims	Basis for Rejection
Ground 1	1-4, 7-9, 11-14, 17-19, 21-24	Anticipation under 35 U.S.C. § 102 by Grigoriadis et al., US 2017/0020877 (Ex. 1006; "Grigoriadis")
Ground 2	4, 10, 14, 20-22, 25	Obviousness under 35 U.S.C. § 103 in view of Grigoriadis and the knowledge of a skilled artisan

Ground	'908 Patent Claims	Basis for Rejection
Ground 3	5-6, 15-16	Obviousness under 35 U.S.C. § 103 in view of Grigoriadis in combination with US 2005/0209250 (Ex. 1007; “Romano”)
Ground 4	1-25	Lack of written description under 35 U.S.C. § 112
Ground 5	1-25	Lack of enablement under 35 U.S.C. § 112

Grigoriadis (Ex. 1006) qualifies as prior art under 35 U.S.C § 102(a).

Specifically, Grigoriadis is a patent application that published on January 26, 2017, names a different inventor than the inventors named on the '908 patent, and was published before August 14, 2017, which is the earliest possible effective filing date to which claims 1-25 of the '908 patent could be entitled.¹

Romano (Ex. 1007) qualifies as prior art under 35 U.S.C § 102(a).

Specifically, Romano is a patent application that published on September 22, 2005, names a different inventor than the inventors named on the '908 patent, and was published more than one year before the '908 patent's earliest effective filing date

¹ Claims 1-25 are entitled to an effective filing date no earlier than April 18, 2019, and are not entitled to claim priority to Provisional App. No. 62/545,406, filed on August 14, 2017. However, for purposes of this Petition it is not necessary to reach the priority issue.

of August 14, 2017. Thus, Romano is prior art to the '908 patent.

III. BACKGROUND OF THE TECHNOLOGY

A. Congenital Adrenal Hyperplasia (“CAH”)

Congenital adrenal hyperplasia (“CAH”) refers to a group of disorders encompassing enzyme deficiencies that impair a patient’s ability to synthesize cortisol.² Cortisol is a hormone that plays an important role in regulating blood sugar, immune responses, metabolism of fat, protein, and carbohydrates, and regulation of bone formation.³

Patients suffering from CAH typically have lower levels of cortisol than needed. These deficient cortisol levels cause the hypothalamus to increase production of a hormone called corticotropin-releasing factor (“CRF”).⁴ The production of CRF signals the pituitary gland to secrete another hormone, adrenocorticotrophic hormone (“ACTH”).⁵ ACTH stimulates the production of a number of precursor hormones, in particular 17- α -hydroxyprogesterone (“17-

² Ex. 1005, ¶ 13; Ex. 1013, 4134.

³ Ex. 1005, ¶ 14.

⁴ Ex. 1005, ¶ 16; Ex. 1014, 1.

⁵ *Id.*

OHP”), that ultimately lead to the production of cortisol.⁶ However, CAH patients cannot convert 17-OHP to cortisol.⁷ As a result, CAH patients produce excess 17-OHP that cannot be converted to cortisol.⁸ The continued cortisol deficiency in these patients creates a feedback loop whereby the body continues to produce CRF and ACTH, which results in the continued overproduction of 17-OHP.⁹

In addition to being a precursor hormone to cortisol, 17-OHP is also a precursor hormone to androgens.¹⁰ Androgens are a group of hormones, such as testosterone, that regulate the development of male characteristics and reproductive activity. Because CAH patients cannot synthesize cortisol, the 17-OHP is converted to androgens, which leads to excessive androgen production.¹¹ The overproduction of androgens in CAH patients leads to a number of physiological problems, including abnormalities in growth and development in children,

⁶ Ex. 1005, ¶¶ 15-16; Ex. 1014, 1.

⁷ *Id.*

⁸ Ex. 1005, ¶ 16; Ex. 1015, 2295-2296.

⁹ Ex. 1005, ¶¶ 15-16.

¹⁰ Ex. 1005, ¶¶ 15-17.

¹¹ Ex. 1005, ¶¶ 16-17; Ex. 1015, 2295-2296.

hirsutism (excessive hair growth), and in females, irregular or absent menstrual cycles and infertility.¹²

The objectives of CAH treatment are two-fold: to correct cortisol hormone deficiency and to control excess androgen production caused by elevated ACTH and 17-OHP hormones.¹³ Correcting cortisol deficiency while also controlling excess androgen production caused by elevated ACTH is challenging.¹⁴

Treating cortisol deficiency in CAH patients involves providing supplemental hormones, called glucocorticoids, as replacement for the cortisol.¹⁵ Glucocorticoid therapy can correct cortisol deficiency in CAH patients. However, the amount of glucocorticoids needed to replace deficient cortisol levels is often not sufficient to reduce ACTH in CAH patients, and thus control excess androgen production.¹⁶ This is particularly true in the early morning hours, because ACTH production

¹² Ex. 1005, ¶ 20; Ex. 1016, 2130-2132.

¹³ Ex. 1001, 11:1-5; Ex. 1005, ¶ 18; Ex. 1014, 7.

¹⁴ Ex. 1005, ¶¶ 19-21.

¹⁵ Ex. 1001, 11:1-5; Ex. 1005, ¶ 18; Ex. 1017, 4056; Ex. 1013, 4147.

¹⁶ Ex. 1001, 11:41-48; Ex. 1005, ¶ 19; Ex. 1006, ¶ [0066]; Ex. 1014, 8.

follows a circadian pattern where the highest ACTH production occurs in the early morning.¹⁷

To address the issue of excessive ACTH, and subsequently androgen, production in the early morning hours, physicians often prescribe higher glucocorticoid doses than is needed to replace the cortisol deficiency.¹⁸ However, increased glucocorticoid dosing over the long term can lead to increased cardiovascular risk, weight gain, increased blood pressure, glucose intolerance, and bone loss in CAH patients.¹⁹ High glucocorticoid dosing can also result in elevated cortisol levels and Cushing's syndrome, a disease characterized by obesity and an increased risk of heart attack, stroke, blood clots, bone loss, and type 2 diabetes.²⁰

There is no single standard treatment regimen for all CAH patients—the types of glucocorticoid treatments, and dosing of those treatments, vary according to a patient's age, symptoms, and the severity of androgen excess.²¹

¹⁷ *Id.*

¹⁸ Ex. 1005, ¶ 19; Ex. 1014, 8.

¹⁹ Ex. 1001, 11:45-48; Ex. 1005, ¶ 19; Ex. 1014, 8.

²⁰ Ex. 1005, ¶ 19; Ex. 1006, ¶ [0045].

²¹ Ex. 1001, 11:12-15; Ex. 1005, ¶ 18; Ex. 1017, 4056-57; Ex. 1013, 4140, 4147-4148.

B. The Use of CRF1 Receptor Antagonists to Treat CAH

As discussed above, CRF is a hormone that activates the synthesis and release of ACTH from the pituitary gland.²² The CRF receptor has two main subtypes, CRF1 and CRF2.²³ By 2002, the literature had reported CRF as the main regulator of the release of ACTH from the pituitary gland.²⁴

A CRF type 1 (“CRF1”) receptor antagonist is a specific type of antagonist that binds the CRF receptor and blocks or reduces the actions of CRF. By doing so, CRF1 receptor antagonists can directly inhibit ACTH synthesis and secretion.²⁵

Researchers proposed the use of CRF1 receptor antagonists as a potential treatment for CAH before the effective filing date of the '908 patent. For example, in 2001, several researchers suggested that CRF1 receptor antagonists could decrease CRF and ACTH secretion, and thus eliminate the need to rely solely on glucocorticoid negative feedback to prevent excessive adrenal androgen production in CAH patients.²⁶ These researchers made similar observations in journal articles

²² Ex. 1005, ¶ 22; Ex. 1006, ¶ [0006], Fig. 1.

²³ Ex. 1005, ¶ 22; Ex. 1018, 270.

²⁴ Ex. 1005, ¶ 22; Ex. 1019, 333; Ex. 1020, 322.

²⁵ Ex. 1005, ¶ 23; Ex. 1006, ¶¶ [0006], [0040].

²⁶ Ex. 1005, ¶ 24; Ex. 1021, 130-131; Ex. 1022, 331; Ex. 1016, 2132.

published in 2002 and 2005.²⁷ Beginning in 2013, Petitioner Neurocrine Biosciences embarked on an examination of the utility of CRF1 receptor antagonists for the treatment of CAH.

Neurocrine has developed and tested two CRF1 receptor antagonists, NBI-77860 and crinercerfont, for their ability to treat CAH by decreasing elevated ACTH, 17-OHP, and adrenal androgens. Neurocrine's Phase I clinical study, published in 2016, demonstrated that administration of 300 mg and 600 mg NBI-77860 reduced ACTH in the 6-10 a.m. timeframe (referred to as the "morning window" to note the time of peak ACTH elevation in CAH patients) by a mean of 43% and 41%, respectively, compared to placebo.²⁸ Administration of 600 mg NBI-77860 reduced mean 17-OHP levels by 27% compared to placebo.²⁹ Neurocrine's Phase II study demonstrated that compared to a pre-dose baseline, administering crinercerfont daily for 14 days reduced median ACTH and 17-OHP levels in the morning window between 53% to 66% in four dosing cohorts.³⁰

IV. THE '908 PATENT AND ITS PROSECUTION HISTORY

²⁷ *Id.*

²⁸ Ex. 1005, ¶ 25; Ex. 1008, 1177.

²⁹ Ex. 1005, ¶ 25; Ex. 1008, 1177.

³⁰ Ex. 1005, ¶ 61; Ex. 1009, Fig. 2.

A. The '908 Patent Disclosure

The '908 patent discloses the use of a single CRF1 receptor antagonist, 3-4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-a) pyrimidine or “Compound 1,” for treating CAH. This compound is also known as tildacerfont.³¹ Spruce is developing tildacerfont as a potential treatment for CAH.³² U.S. Patent No. 8,030,304 (Ex. 1012, “the '304 patent”), which issued on October 4, 2011, includes tildacerfont in a list of CRF1 receptor antagonists for treating various psychiatric and neuroendocrine disorders, neurological diseases, and metabolic syndromes, including CAH.³³

The '908 patent repeatedly characterizes the “present invention” or “present disclosure” as relating to Compound 1, i.e. tildacerfont. For example, the Abstract states:

The present invention provides novel pharmaceutical

³¹ The '908 patent discloses two chemical names that can be referred to as “Compound 1.” Ex. 1001, 14:15-42. These two chemical names are alternative names for the same compound, tildacerfont. *See*

<https://pubchem.ncbi.nlm.nih.gov/compound/Tildacerfont>; Ex. 1005, ¶ 31.

³² Ex. 1011, 1.

³³ Ex. 1005, ¶ 27; Ex. 1012, 2:10-62, 44:7-10.

compositions comprising *[3]-4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-a) pyrimidine* and methods of using the same for the treatment of adrenal hyperplasia (CAH).³⁴

The Summary of the Invention states:

The present invention provides novel pharmaceutical compositions comprising *3-4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-a) pyrimidine* and methods using such pharmaceutical compositions for treating congenital adrenal hyperplasia (CAH).

In one aspect, *the present disclosure* provides a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering a pharmaceutical composition comprising *Compound 1*³⁵

* * *

In one aspect, *the present disclosure* provides a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, the method comprising (i) measuring a hormone level in the subject in need thereof; (ii) administering *Compound 1* ... or a pharmaceutically acceptable salt or solvate thereof; and (iii) repeating steps (i) and (ii) until the hormone level reaches a pre-determined

³⁴ Ex. 1001, Abstract.

³⁵ Ex. 1001, 1:30-38 (emphasis added).

range followed by a maintenance therapy of a daily dosing of compound 1.³⁶

* * *

In one aspect, *the present disclosure* provides a method of improving hyperandrogenic symptoms in a subject in need thereof comprising administering a pharmaceutical composition comprising *Compound 1*³⁷

* * *

In one aspect, *the present disclosure* provides a method of treating menstrual irregularity, ovulatory dysfunction or infertility, in a subject in need thereof, comprising administering a pharmaceutical composition comprising *Compound 1*³⁸

* * *

In one aspect, *the present disclosure* provides a method of improving metabolic symptoms in a subject in need thereof, comprising administering a pharmaceutical composition comprising *Compound 1*³⁹

* * *

In one aspect, *the present disclosure* provides a method of improving the quality of life of a subject in need thereof, comprising

³⁶ *Id.*, 4:43-67 (emphasis added).

³⁷ *Id.*, 8:35-38 (emphasis added).

³⁸ *Id.*, 8:63-67 (emphasis added).

³⁹ *Id.*, 9:19-22 (emphasis added).

administering a pharmaceutical composition comprising ***Compound 1***

....⁴⁰

Each of the embodiments for the above-described aspects in the Summary of the Invention also refers to Compound 1.⁴¹ Nowhere does the '908 patent describe or disclose the use of any compound other than Compound 1 (tildacerfont) to treat CAH or any other condition.

Examples 3-8 of the '908 patent describe clinical studies related to Compound 1. Example 3 discloses the results of two Phase I clinical studies evaluating Compound 1 in healthy adults, and reports pharmacokinetic data from subjects after administration of Compound 1.⁴² Example 4 describes a 6-week Phase II clinical study of Compound I in adults with classic CAH.⁴³ The '908 patent reports that 8 of 10 subjects in the Phase II study (80%) demonstrated reduction in ACTH and 17-OHP levels, whereas two of the 10 subjects did not.⁴⁴

⁴⁰ *Id.*, 9:46-49 (emphasis added).

⁴¹ *See generally id.*, 1:30-10:2.

⁴² *Id.*, 36:32-41:49.

⁴³ *Id.*, 42:1-43:47.

⁴⁴ *Id.*, 42:49-65; Figs. 2-3.

70% of subjects in the study demonstrated a more than 25% reduction in ACTH, and 50% of subjects demonstrated more than a 25% reduction in 17-OHP.⁴⁵

Examples 5-8 describe clinical study protocols but do not disclose any data.⁴⁶

The '908 patent does not contain any description or data for any compound besides Compound 1 (tildacerfont).

B. The '908 Patent Claims

In contrast to the '908 patent specification, the '908 patent claims are not limited to the use of Compound 1 to treat CAH, but instead recite the use of a much broader class of CRF1 receptor antagonists for treating CAH.⁴⁷ Specifically, independent claim 1 recites a method of treating CAH by administering a therapeutically effective amount of a CRF1 receptor antagonist, or pharmaceutically acceptable salt thereof, wherein the ACTH level of a human is reduced by at least 10% from baseline.⁴⁸ Claim 11, the only other independent claim, recites the same treatment step but requires the 17-OHP level of a human to

⁴⁵ *Id.*

⁴⁶ *Id.*, 44:7-47:58.

⁴⁷ *Id.*, 48:6-49:15.

⁴⁸ *Id.*, 48:6-12.

be reduced by at least 10% from baseline.⁴⁹

Dependent claims 2-4 and 12-14 add dosing ranges or amounts of the CRF1 antagonist to the limitations of the independent claims.⁵⁰

Dependent claims 5 and 15 recite that the CRF1 receptor antagonist be in the form of microparticles, and claims 6 and 16 require that the average size of the microparticles be between about 1 μ m and about 20 μ m.⁵¹

Dependent claims 7 and 17 require the CRF1 receptor antagonist to be in the form of a pharmaceutical composition, and claims 8 and 18 specify that the pharmaceutical composition is a capsule or a tablet.⁵²

Dependent claims 9 and 19 recite that the treated condition is classic CAH, while claims 10 and 20 recite that the treated condition is the non-classical form of CAH.⁵³

Dependent claims 21 and 22 are the only '908 patent claims that require the

⁴⁹ *Id.*, 48:37-42.

⁵⁰ *Id.*, 48:13-23, 43-53.

⁵¹ *Id.*, 48:24-28, 54-58.

⁵² *Id.*, 48:29-33, 59-63.

⁵³ *Id.*, 48:34-35, 64-67.

hormone reduction be “maintained at a reduced level post 24 hours.”⁵⁴

Claim 23 adds administration of a glucocorticoid to the methods of claim 1 and claim 11, claim 25 requires that the glucocorticoid be administered within two hours of the CRF1 receptor antagonist, and claim 24 requires that the CRF1 receptor antagonist be administered “4 hours prior to sleeping.”⁵⁵

C. The '908 Patent Prosecution History

The '908 patent issued on December 1, 2020 from U.S. Patent Application No. 16/388,620 (“the ‘620 application”), which was filed on April 18, 2019 with 20 new claims replacing 180 originally filed claims.⁵⁶ All of the originally filed claims of the '620 application were limited to the administration of Compound 1 or a pharmaceutically acceptable salt or solvate thereof.⁵⁷

The '620 application is a continuation of Application No. PCT/US2018/046760 (“the '760 PCT;” Ex. 1003) filed August 14, 2018, which claims the benefit of US Provisional Serial No. 62/545,406 (“the '406 Provisional;” Ex. 1004) filed August 14, 2017. The claims of both the '760 PCT

⁵⁴ *Id.*, 49:1-6.

⁵⁵ *Id.*, 49:7-15.

⁵⁶ *See* Ex. 1002.

⁵⁷ *Id.*, 308-322.

and the '406 Provisional were also limited to the administration of Compound 1 or a pharmaceutically acceptable salt or solvate thereof.⁵⁸

The '760 PCT contains the same Phase II clinical data as the '620 application and the '908 patent.⁵⁹ The '406 Provisional, however, contains no Phase II clinical data, including no data on reduction of ACTH or 17-OHP levels after administration of a CRF1 receptor antagonist.

On April 18, 2019, the '908 patent applicants submitted a preliminary amendment in which they canceled all pending claims directed to the administration of Compound 1, and added claims 181-200.⁶⁰ The newly added claims recited methods of treating CAH by administering a CRF1 receptor antagonist, wherein the ACTH or 17-OHP level of a human was reduced by at least 10% from baseline.⁶¹ In remarks accompanying the amendment, the applicants asserted that “[s]upport for the claim amendments are found in the original claims and throughout the specification.”⁶² However, the specification and original claims

⁵⁸ Ex. 1003, 38-52; Ex. 1004, 52-61.

⁵⁹ Ex. 1003, 102-103.

⁶⁰ Ex. 1002, 328-329.

⁶¹ *Id.*

⁶² *Id.*, 330.

describe only one CRF1 receptor antagonist: Compound 1.⁶³

On July 15, 2019, the Examiner rejected pending claims 181-184, 187-194 and 197-200 as obvious in view of Neurocrine’s prior work on a particular CRF1 receptor antagonist, NBI-77860, as disclosed in Grigoriadis (Ex. 1006), and rejected pending claims 185-186 and 195-196 as obvious in view of Grigoriadis in combination with US 2006/0078623 to Dhoot et al. (“Dhoot;” Ex. 1010).⁶⁴ In response, the applicants attempted to distinguish Grigoriadis by arguing that the data on NBI-77860 disclosed in Grigoriadis demonstrated clinically significant reductions in ACTH and 17-OHP levels “relative to placebo,” whereas their claims recited ACTH and 17-OHP reductions “from baseline.”⁶⁵

The applicants’ argument relied on a false distinction. As described in greater detail *infra* at § VI.A, Grigoriadis describes the results of a single dose Phase I study in which the same 8 subjects were given placebo, a single dose of 300 mg of NBI-77860, and a single dose of 600 mg NBI-77860, with 21-day washout periods in between dosing periods.⁶⁶ “Baseline” is the subject’s ACTH or

⁶³ *Id.*, 252-325.

⁶⁴ *Id.*, 112-116.

⁶⁵ *Id.*, 100-102.

⁶⁶ Ex. 1005, ¶ 63; Ex. 1006, ¶ [0091], Fig. 4.

17-OHP levels in the absence of a study drug, here the value recorded after administration of placebo.⁶⁷ Grigoriadis thus discloses that administration of NBI-77860 resulted in a greater than 10% reduction in ACTH and 17-OHP compared to the subject's baseline levels throughout the measured time period.⁶⁸

On November 25, 2019, the Examiner again rejected claims 181-184, 187-194 and 197-200 over Grigoriadis, and rejected claims 185-186 and 195-196 over the combination of Grigoriadis and Dhoot.⁶⁹ To overcome this rejection, applicants submitted a supplemental response supported by the declaration of Chris Barnes, a Vice President and Project Team Leader at Spruce Biosciences.⁷⁰

Dr. Barnes presented additional data from Spruce's Phase II study evaluating tildacerfont (*i.e.*, "Compound 1") showing ACTH and 17-OHP levels measured after 14 days of repeated dosing with tildacerfont, and after 28 and 42 days of repeated dosing.⁷¹ Dr. Barnes concluded that this data "clearly showed" the reduction of the ACTH and 17-OHP levels from baseline was maintained post 24

⁶⁷ *Infra*, §§ V.A and VI.A; Ex. 1005, ¶¶ 36-43, 64.

⁶⁸ Ex. 1005, ¶ 65; Ex. 1006, ¶ [0093], Fig. 5.

⁶⁹ Ex. 1002, 86-91.

⁷⁰ *Id.*, 30-38.

⁷¹ *Id.*, 35-37.

hours.⁷² However, the data showed only that the reductions in ACTH and 17-OHP were maintained “post 24 hours” when tildacerfont was administered daily up to the measurement at day 14, day 28, or day 42.⁷³ In other words, the Barnes declaration merely showed that there is no decrease in the efficacy of tildacerfont over time—not that administration of a single dose maintains ACTH or 17-OHP reductions more than 24 hours.⁷⁴

The applicants relied on this data as purportedly demonstrating unexpected results that distinguished the claims from Grigoriadis.⁷⁵ Specifically, the applicants argued that these data “show a significant and practical advantage over Grigoriadis because it is beneficial to keep the ACTH and 17-OHP at a reduced level from baseline in CAH patients for more than 24 hours. Further, the above data demonstrate the superiority of the claimed method over Grigoriadis by maintaining the reduction of the ACTH and 17-OHP levels from baseline for weeks when Grigoriadis only discloses a reduction during a 24-hour period.”⁷⁶

⁷² *Id.*, 37; Ex. 1005, ¶ 48.

⁷³ Ex. 1002, 35-37; Ex. 1005, ¶¶ 48, 86.

⁷⁴ Ex. 1005, ¶¶ 48, 86.

⁷⁵ Ex. 1002, 30-32.

⁷⁶ *Id.*, 31-32.

The Examiner accepted the applicants' argument, stating in the notice of allowance that the applicants had shown "reduction in the adrenocorticotrophic (ACTH) and 17-hydroxyprogesterone (17-OHP) hormone levels in humans, wherein said hormone reductions were maintained over a 6-week period [see the Declaration at Figure A], in the treatment of congenital adrenal hyperplasia. These results appear unexpected over the closest prior art, Grigoriadis et al (US 2017/0020877)."⁷⁷

However, in allowing the claims on this basis, the Examiner overlooked the fact that only two of the 25 pending claims, now issued as claims 21 and 22, recited a "post 24 hours" limitation. Moreover, as discussed in detail *infra* at § VI.D.2.c, these results were not surprising based on the data for NBI-77860 presented in Grigoriadis.⁷⁸ Spruce's data merely showed that there is no decrease in the efficacy of tildacerfont over time, which was entirely expected.⁷⁹

In addition, the Examiner was unaware of clinical data for another CRF1 receptor antagonist disclosed in Grigoriadis, crinecerfont,⁸⁰ demonstrating that

⁷⁷ *Id.*, 12.

⁷⁸ *Infra*, § VI.D.2.c; Ex. 1005, ¶¶ 63-68.

⁷⁹ *Id.*

⁸⁰ Ex. 1006, ¶ [0054].

crinecerfont, when dosed as described in Grigoriadis, met the limitations of the '908 patent claims.⁸¹ Like Spruce's data, the crinecerfont clinical data was collected after 14 days of daily dosing, and demonstrates that reductions in ACTH and 17-OHP were maintained "post 24 hours" in the same way as Spruce's data.⁸²

V. CLAIM CONSTRUCTION UNDER 37 C.F.R. §§ 42.204(b)(3)

Claims are construed using the *Phillips* standard that aims to determine "the ordinary and customary meaning of [each] claim as understood by [a skilled artisan] and the prosecution history pertaining to the patent." 37 C.F.R. § 42.200; *see also Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-14 (Fed. Cir. 2005) (en banc). Claim terms are construed only to the extent necessary to resolve a controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).

For purposes of this proceeding only, Neurocrine submits constructions for the following terms. All remaining terms should be given their plain meaning.

A. "Baseline"/ "From Baseline"

Independent claims 1 and 11 recite a reduction of ACTH or 17-OHP by at least 10% "from baseline" after administering a CRF1 receptor antagonist to a

⁸¹ *Infra*, § VI.C.3.f; Ex. 1005, ¶¶ 53-62.

⁸² *Infra*, § VI.C.3.f; Ex. 1005, ¶¶ 53-62; Ex. 1009, 10.

CAH patient. Based upon the ordinary meaning of the claim language, “baseline” refers to a measurement prior to the administration of a study drug—in this case, a CRF1 receptor antagonist.⁸³ The intrinsic evidence supports this construction. The only clinical data in the ’908 patent relating to ACTH and 17-OHP describe measuring ACTH and 17-OHP levels “at baseline,” *i.e.* ACTH and 17-OHP levels before the administration of tildacerfont, a CRF1 receptor antagonist, and ACTH and 17-OHP levels after the administration of the first dose of tildacerfont.⁸⁴ Figures 2 and 3 of the ’908 patent present the measurements and show a reduction of ACTH and 17-OHP due to the administration of tildacerfont.⁸⁵ That is, Figures 2 and 3 present the change in ACTH and 17-OHP levels from “baseline,” consistent with the ordinary meaning of the term.

The claims do not require that the measurement be made at any particular point in time. Therefore, based upon the claim language, the baseline measurement for ACTH and 17-OHP levels may be made at any point in time prior to CRF1 receptor antagonist administration, and then compared to those levels

⁸³ Ex. 1005, ¶¶ 36-43.

⁸⁴ Ex. 1001, 42:1-16, 43:49-67, Figs. 2-3; Ex. 1005, ¶ 38.

⁸⁵ Ex. 1001, 43:49-67, Figs. 2-3; Ex. 1005, ¶ 39.

post-CRF1 receptor antagonist administration, measured at the same time point.⁸⁶

Furthermore, a person of ordinary skill would understand that “baseline” and “from baseline” allow for glucocorticoid administration during baseline measurements. When studying a new CAH drug like a CRF1 receptor antagonist, a person of ordinary skill would have allowed the patient to continue his or her usual glucocorticoid treatments during and after baseline measurements to avoid endangering the patient’s health.⁸⁷ This is consistent with the clinical example in the ’908 patent, which tracked the patients’ “background glucocorticoid regimens.”⁸⁸

B. “A Human”/ “The Human”

Independent claims 1 and 11 recite treating CAH in “a human” by administering a CRF1 receptor antagonist to “the human,” wherein the ACTH or 17-OHP level in “the human” is reduced. Based upon the ordinary meaning of the claim language, “a human”/“the human” refers to an individual patient.⁸⁹ This is supported by the intrinsic evidence, which presents changes in ACTH and 17-OHP

⁸⁶ Ex. 1005, ¶¶ 41-42.

⁸⁷ Ex. 1005, ¶ 40.

⁸⁸ Ex. 1001 at 42:26-32; Ex. 1005, ¶ 40.

⁸⁹ Ex. 1005, ¶ 44.

levels experienced by individual patients.⁹⁰ A person of ordinary skill would also understand that each CAH patient is unique in disease severity and treatment regimens.⁹¹

C. “Maintained at a Reduced Level Post 24 Hours”

Claims 21, which depends upon claim 1, recites a reduction of ACTH by at least 10% from baseline, which is “maintained at a reduced level post 24 hours.” Claim 22, which depends upon claim 11, recites a reduction of 17-OHP by at least 10% from baseline, which is “maintained at a reduced level post 24 hours.” The phrase “maintained at a reduced level post 24 hours” means that the ACTH or 17-OHP levels are maintained at a reduced level with repeated dosing.⁹² In other words, there is no loss of efficacy with repeated dosing.

The intrinsic evidence supports this interpretation. For example, Figures 2 and 3 of the '908 patent show the change in ACTH and 17-OHP levels after repeated administration of tildacerfont for 14, 28, or 42 days.⁹³ While prosecuting the '908 patent, Spruce presented additional figures showing reductions in ACTH

⁹⁰ Ex. 1001, Figs. 2-3; Ex. 1002, 36; Ex. 1005, ¶ 44.

⁹¹ Ex. 1005, ¶ 44.

⁹² Ex. 1005, ¶¶ 45-48.

⁹³ Ex. 1001, 10:21-26, Figs. 2-3; Ex. 1005, ¶ 46.

and 17-OHP levels from baseline after repeated administration of tildacerfont for 14, 28, or 42 days.⁹⁴ Notably, the intrinsic evidence contains no evidence that a single, non-repeated, dose of tildacerfont (or any other CRF1 receptor antagonist) would maintain reduced ACTH or 17-OHP levels for more than 24 hours.⁹⁵

D. “Administered 4 Hours Prior to Sleeping”

Claim 24 depends upon claim 23, which in turn depends upon claims 1 or 11. It recites that the CRF1 receptor antagonist is “administered 4 hours prior to sleeping.” The phrase “administered 4 hours prior to sleeping” means administered prior to the circadian release of ACTH.⁹⁶

As an initial matter, the intrinsic evidence does not disclose administering a CRF1 receptor antagonist “4 hours prior to sleeping.” Rather, the ’908 patent discloses administering a CRF1 receptor antagonist “less than about 4 hours before sleep,” “less than about 2 hours before sleep,” “less than about 30 mins before sleep,” or “about 10 pm.”⁹⁷ In the same paragraph, the ’908 patent states that, in some embodiments, the pharmaceutical composition is administered “at or before”

⁹⁴ Ex. 1002, 30-31, 35-38; Ex. 1005, ¶¶ 47-48.

⁹⁵ Ex. 1005, ¶ 48.

⁹⁶ Ex. 1005, ¶¶ 49-52.

⁹⁷ Ex. 1001, 4:25-35; Ex. 1005, ¶ 51.

(or “3-4 hours before”) the expected circadian release of ACTH.⁹⁸

A person of ordinary skill would know that the circadian release of ACTH typically occurs between 1-2 a.m. in most patients.⁹⁹ Thus, the administration times provided by the ’908 patent are consistent with an evening dose prior to the circadian release of ACTH. Accordingly, a person of ordinary skill would understand the phrase “4 hours prior to sleeping” to mean prior to the circadian release of ACTH.¹⁰⁰

VI. THE CLAIMS OF THE ’908 PATENT ARE UNPATENTABLE

The ’908 patent repeatedly characterizes its invention as relating to Compound 1.¹⁰¹ During prosecution, Spruce convinced the Examiner to allow claims 1-25 of the ’908 patent over one of the CRF1 receptor antagonists taught by Grigoriadis (NBI-7760) on the basis of allegedly surprising results related to Compound 1. At the same time, Spruce amended its claims to cover CRF1 receptor antagonists broadly. Spruce’s actions and arguments are inconsistent. Because claims 1-25 are not limited to Compound 1, they are unpatentable under

⁹⁸ Ex. 1001, 4:35-40; Ex. 1005, ¶ 51.

⁹⁹ Ex. 1005, ¶ 19; Ex. 1006, ¶ [0066].

¹⁰⁰ Ex. 1005, ¶ 52.

¹⁰¹ Ex. 1001, Abstract, 1:30-38, 4:43-67, 8:35-38, 8:63-67, 9:19-22, 9:46-49.

35 U.S.C. § 112, ¶ 1 for failure to meet both the written description and enablement requirements.

Claims 1-25 are also unpatentable over Grigoriadis, alone or in combination with Romano, under 35 U.S.C. §§ 102(a) and 103. As described in detail below, the Examiner made several errors in allowing claims 1-25, and did not have the benefit of new evidence presented in this petition.

A. Grigoriadis

Grigoriadis discloses treating CAH with a number of CRF1 receptor antagonists, including NBI-77860 and SSR-125543 (crinecerfont).¹⁰² Grigoriadis teaches administering the CRF1 receptor antagonist as a single dose ranging from 50-1000 mg.¹⁰³ The dose is preferably administered at bedtime “to deliver clinically relevant concentrations of the CRF1 antagonist at or before (such as 2-5 hours before) the expected circadian release of ACTH.”¹⁰⁴ Grigoriadis further explains that because the circadian release of ACTH typically occurs between 1 and 2 a.m., and most orally administered drugs have a T_{\max} of several hours,

¹⁰² Ex. 1006, ¶¶ [0051], [0054].

¹⁰³ *Id.*, ¶ [0063].

¹⁰⁴ *Id.*, ¶ [0066].

“dosing at 10 P.M., for example, which is 3-4 hours in advance of the expected circadian release of ACTH is desirable.”¹⁰⁵

1. Crinercerfont (SSR-125543)

Grigoriadis discloses that SSR-125543 is a CRF1 receptor antagonist, which is useful for the treatment of CAH.¹⁰⁶ SSR-125543 is also known as crinercerfont.¹⁰⁷ Crinercerfont is currently being developed by Petitioner, Neurocrine Biosciences, as a treatment for CAH.

The results of Neurocrine’s Phase II crinercerfont clinical study have been summarized in a manuscript that was submitted for publication in the scientific journal *Lancet* on April 30, 2021 (Ex. 1009; “Auchus 2021”).¹⁰⁸ The Phase II clinical study showed that the administration of crinercerfont to a patient with CAH resulted in at least a 10% reduction in ACTH and 17-OHP compared to the patient’s baseline levels prior to administration of crinercerfont.¹⁰⁹ This clinical study tested four dosing regimens, with patients in four cohorts receiving between

¹⁰⁵ *Id.*

¹⁰⁶ Ex. 1006, ¶ [0054].

¹⁰⁷ See <https://pubchem.ncbi.nlm.nih.gov/compound/5282340>; Ex. 1005, ¶¶ 28, 53.

¹⁰⁸ Ex. 1009.

¹⁰⁹ Ex. 1005, ¶¶ 54-62; Ex. 1009, 11, 13-19, Figs. 1-2, Table 2.

50 mg and 200 mg of crinecerfont per day, administered for 14 consecutive days.¹¹⁰ The study measured the patients' baseline ACTH and 17-OHP levels over a 24-hour period beginning in the evening of the seventh day before the study began (Day-7 to Day-6).¹¹¹ After 14 days of repeated dosing of crinecerfont, the patients' ACTH and 17-OHP levels were measured over a 24-hour period beginning in the evening of Day 14 and ending on Day 15.¹¹²

The reduction in ACTH and 17-OHP levels compared to baseline exceeded 10% for patients in all four cohorts after receiving crinecerfont for 14 days.¹¹³

Auchus 2021 Figure 1, an excerpt of which is reproduced below, presents 24-hour profiles of median patient ACTH and 17-OHP by cohort, at baseline and at Day 14.¹¹⁴ The results show that “[t]reatment with crinecerfont for 14 days led to substantial median reductions for ACTH, 17OHP, and androstenedione relative to baseline, especially during the morning window, across all cohorts (Figure 1).”¹¹⁵

¹¹⁰ Ex. 1005, ¶ 55; Ex. 1009, 10.

¹¹¹ Ex. 1005, ¶ 56; Ex. 1009, 10-11, Fig. 1.

¹¹² Ex. 1005, ¶ 56; Ex. 1009, 10-11, Fig. 1.

¹¹³ Ex. 1005, ¶ 57; Ex. 1009, 13-19, Figs. 1-2, Table 2.

¹¹⁴ Ex. 1005, ¶ 58; Ex. 1009, Fig. 1.

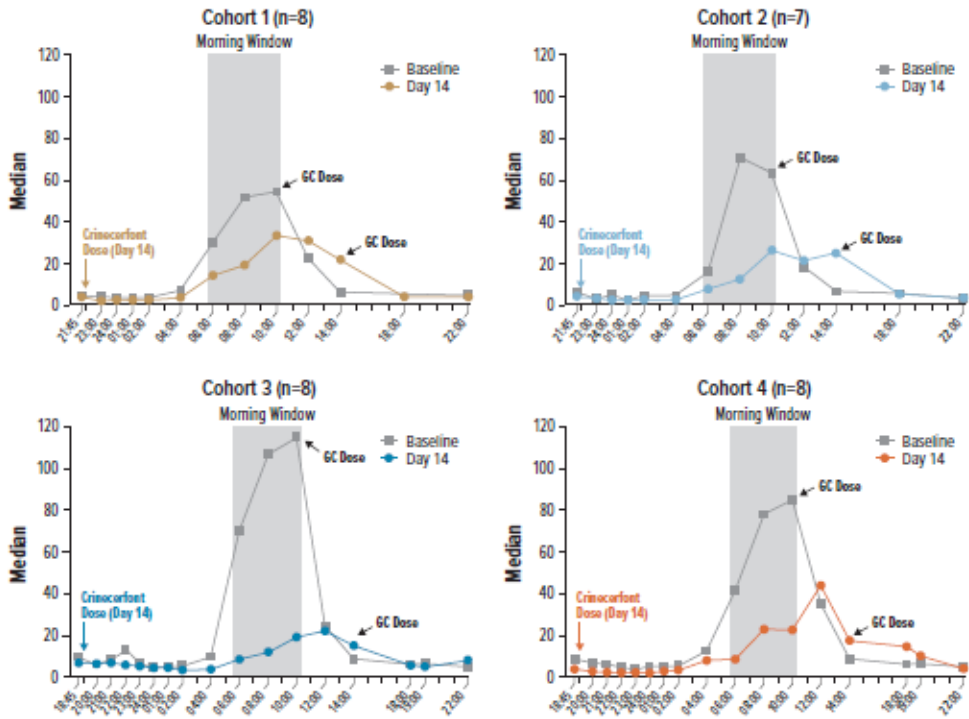
¹¹⁵ Ex. 1005, ¶ 58; Ex. 1009, 14.

The “morning window” is clinically relevant because the body’s natural circadian release of ACTH occurs in the early morning hours.¹¹⁶ In the absence of treatment, the highest ACTH and 17-OHP levels in CAH patients are observed in the morning; reducing ACTH and 17-OHP during this time period is an important objective of any CAH treatment.¹¹⁷

¹¹⁶ Ex. 1005, ¶ 19; Ex. 1006, ¶ [0066].

¹¹⁷ Ex. 1005, ¶¶ 19, 59; Ex. 1009, 11.

A. Plasma ACTH, pmol/L



B. Serum 17OHP, nmol/L

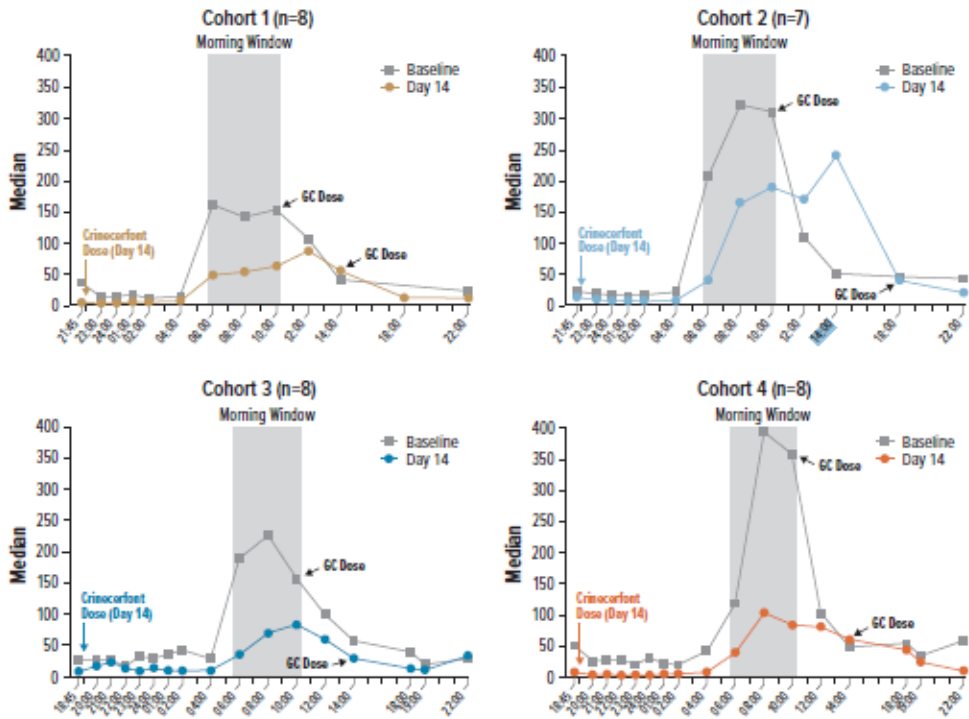


Figure 1: 24-hour profiles

For Cohorts 1 and 2, crinecerfont dosing was at 22:00 on Day 14; pre-dose sampling was at 21:45. For Cohorts 3 and 4, crinecerfont dosing was at 19:00 on Day 14; pre-dose sampling was at 18:45. 17OHP=17-hydroxyprogesterone; ACTH=adrenocorticotropic hormone; GC=glucocorticoid.

Ex. 1009, Excerpt of Figure 1

The Phase II clinical study reported in Auchus 2021 also examined median percent reductions in patient ACTH and 17-OHP levels during the clinically relevant morning window (6-10 a.m.) after 14 days of receiving crinecerfont compared to baseline morning window measurements.¹¹⁸ Auchus 2021 reports that in all cohorts, median ACTH and 17-OHP “were reduced from baseline to Day 14 whether based on samples collected during the morning window (06:00 to 10:00) or the 24-hour sampling period (Supplementary Table 1). For ACTH and 17OHP, median percent decreases from baseline were generally similar across cohorts, ranging from -53% to -66% (Figure 2).¹¹⁹

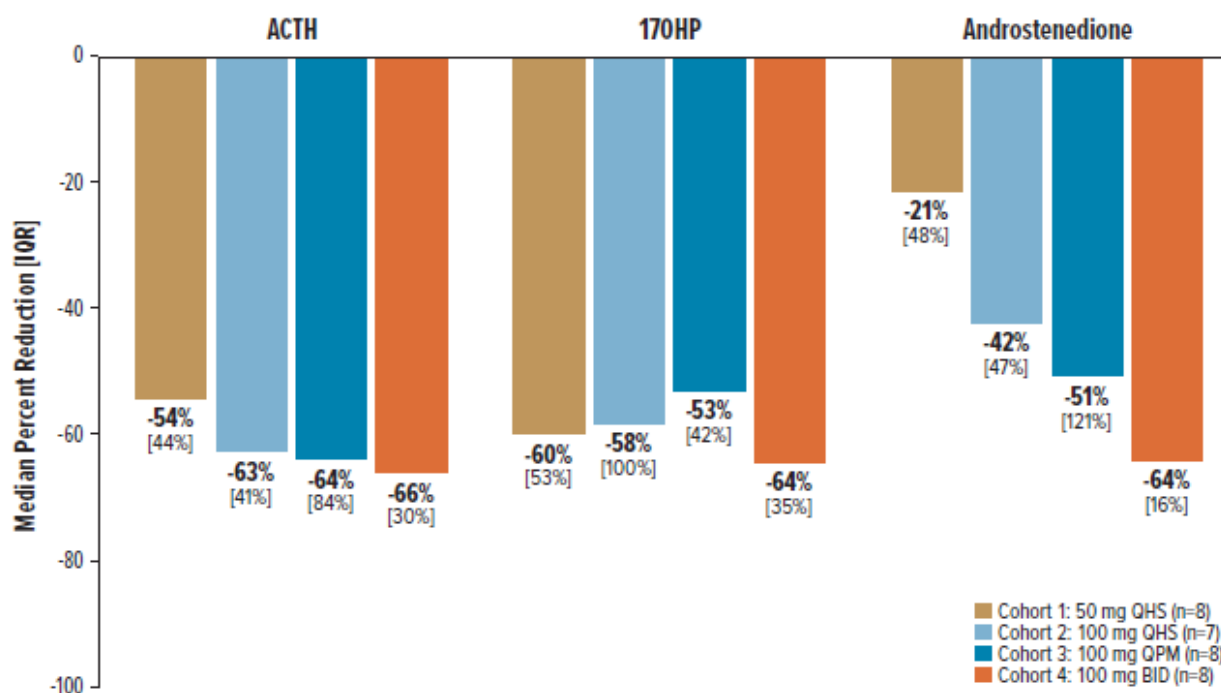
Auchus 2021 Figure 2, reproduced below, shows the median percent reduction in morning window ACTH and 17-OHP in all four cohorts exceeded

¹¹⁸ Ex. 1005, ¶ 59; Ex. 1009, 11, 14, Fig. 2, Table 2.

¹¹⁹ Ex. 1005, ¶ 60; Ex. 1009, 14.

10% after 14 days of receiving crinecerfont, compared to the patients' baseline.¹²⁰

Median morning window ACTH decreased from baseline by 54% in patients in Cohort 1, by 63% in patients in Cohort 2, by 64% in patients in Cohort 3, and by 66% in patients in Cohort 4.¹²¹ Median morning window 17-OHP decreased from baseline by 60% in patients in Cohort 1, by 58% in patients in Cohort 2, by 53% in patients in Cohort 3, and by 64% in patients in Cohort 4.¹²²



¹²⁰ Ex. 1005, ¶ 61; Ex. 1009, Fig. 2.

¹²¹ Ex. 1005, ¶ 61; Ex. 1009, Fig. 2.

¹²² Ex. 1005, ¶ 61; Ex. 1009, Fig. 2.

Figure 2: Median percent reductions from baseline to Day 14 based on morning window values

Based on each participant's values from the morning window timepoints (06:00, 08:00, 10:00).

The IQRs (absolute value of Q3-Q1) for median percent reductions are shown in brackets.

17OHP=17-hydroxyprogesterone; ACTH=adrenocorticotrophic hormone; BID=twice daily;

IQR=interquartile range; QHS=once daily at bedtime; QPM=once daily in the evening.

Ex. 1009, Figure 2

Auchus 2021 also reports the number of patients with a greater than 50% reduction in ACTH and 17-OHP at Day 14 compared to baseline levels.¹²³ Auchus 2021 Table 2, reproduced below, reports that 50% of patients in Cohort 1, 71% of patients in Cohort 2, 63% of patients in Cohort 3, and 75% of patients in Cohort 4 demonstrated a greater than 50% reduction in ACTH at Day 14 compared to the patient's baseline level.¹²⁴ 50% of patients in Cohort 1, 57% of patients in Cohort 2, 63% of patients in Cohort 3, and 75% of patients in Cohort 4 demonstrated a greater than 50% reduction in 17-OHP at Day 14 compared to the patient's baseline level.¹²⁵

¹²³ Ex. 1005, ¶ 62; Ex. 1009, Table 2.

¹²⁴ Ex. 1005, ¶ 62; Ex. 1009, Table 2.

¹²⁵ Ex. 1005, ¶ 62; Ex. 1009, Table 2.

Table 2: Proportion of participants having $\geq 50\%$ reduction in morning window hormone values from baseline to Day 14 and proportion achieving normal values

Participants, n/N (%)	Cohort 1: 50 mg QHS	Cohort 2: 100 mg QHS	Cohort 3: 100 mg QPM	Cohort 4: 100 mg BID
With $\geq 50\%$ reduction from baseline				
ACTH	4/8 (50)	5/7 (71)	5/8 (63)	6/8 (75)
17-hydroxyprogesterone	4/8 (50)	4/7 (57)	5/8 (63)	6/8 (75)
Androstenedione	2/8 (25)	3/7 (43)	4/8 (50)	6/8 (75)
Testosterone-females	2/4 (50)	3/5 (60)	2/3 (67)	3/4 (75)
Androstenedione/testosterone ratio-males	1/4 (25)	0/2 (0)	4/5 (80)	2/3 (67)
With return to normal values ^a				
Androstenedione	2/5 (40)	1/4 (25)	2/5 (40)	2/6 (33)
Testosterone-females	1/1 (100)	0/1 (0)	1/1 (100)	0/1 (0)
Androstenedione/testosterone ratio-males	1/3 (33)	0/2 (0)	2/4 (50)	2/3 (67)

^aIn the subset of participants who had baseline androstenedione or (in females) testosterone values that were >1.2 x upper limit of normal (age- and sex-matched) or androstenedione/testosterone ratio (in men) ≥ 0.5 .
ACTH=adrenocorticotrophic hormone; BID=twice daily; QHS=once daily at bedtime; QPM=once daily in the evening.

Ex. 1009, Table 2

2. NBI-77860

Example 6 of Grigoriadis describes a Phase I clinical study in which NBI-77860 was administered to 8 adult female patients with classical CAH, concurrently with the patients' usual steroidal treatment.¹²⁶ Each patient received single bedtime doses of placebo, 300 mg NBI-77860, and 600 mg NBI-77860,

¹²⁶ *Id.*, ¶¶ [0090]-[0091], Fig. 4.

each during a separate treatment period.¹²⁷ The study provided for a 21-day drug-free interval (washout period) in between each treatment.¹²⁸ After administering each dose, the patients' ACTH and 17-OHP level were collected over a 24-hour period.¹²⁹

In this Phase I study, the baseline measurement for each patient is that patient's ACTH and 17-OHP levels after the placebo dose.¹³⁰ A placebo dose by definition does not include the study drug. Due to the relatively few adult CAH patients available for clinical trials, some trials have administered the study drug and placebo to the same patients, with washout periods in between dosing.¹³¹ In such a study, where the same patients receive both the study drug and placebo, data taken after a patient receives placebo reflects that patient's baseline—a measurement taken in the absence of the study drug. In the Phase I study disclosed in Grigoriadis, the change from baseline for a given patient is the difference

¹²⁷ *Id.*, ¶ [0091], Fig. 4.

¹²⁸ *Id.*

¹²⁹ *Id.*, ¶¶ [0092]-[0093], Fig. 5.

¹³⁰ Ex. 1005, ¶¶ 43, 63.

¹³¹ Ex. 1005, ¶ 43.

between ACTH and 17-OHP levels after receiving placebo, and that patient's ACTH and 17-OHP levels after receiving NBI-77860, at a given time point.¹³²

Figure 5 of Grigoriadis shows the mean post-dose ACTH and 17-OHP levels of all patients after receiving the placebo dose, the 300 mg dose, and the 600 mg dose.¹³³ The mean data shows greater than 10% reductions in ACTH and 17-OHP when patients received 300 mg or 600 mg compared to baseline at multiple time points, including at 8 a.m. (10 hr time point in Figure 5),¹³⁴ which is a time point Spruce presented during prosecution of the '908 patent.¹³⁵

¹³² *Id.*, ¶¶ 40-42, 62-64.

¹³³ *Id.*

¹³⁴ Ex. 1005, ¶¶ 64-65; Ex. 1006, ¶¶ [0092]-[0093], Fig. 5.

¹³⁵ Ex. 1002, 35-38.

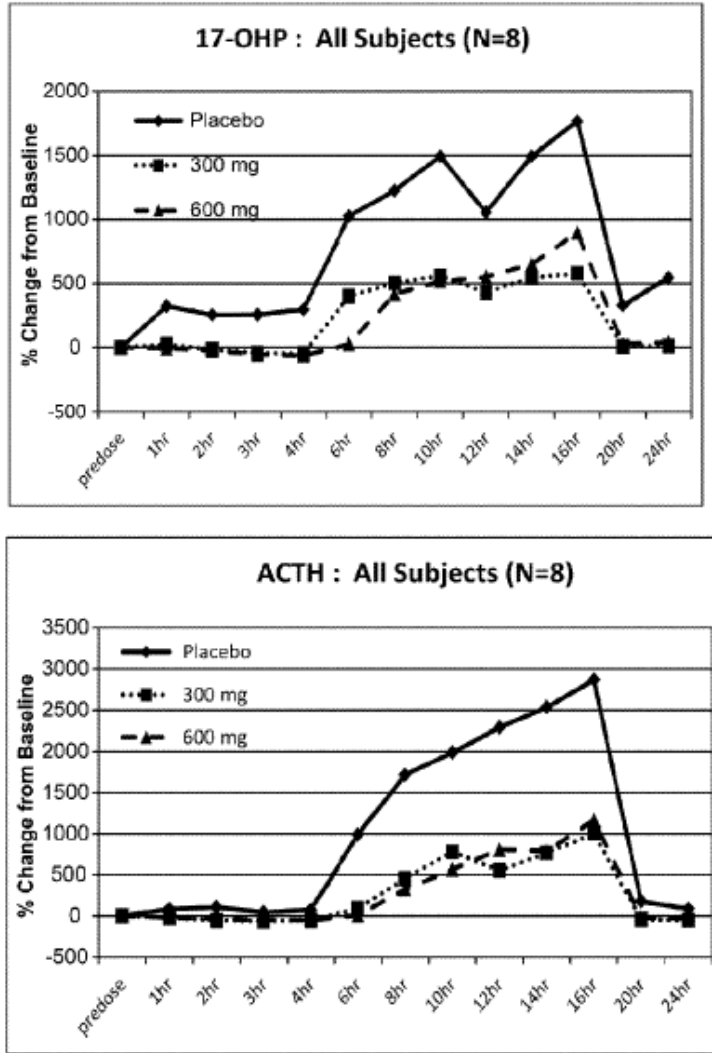


FIG. 5

Grigoriadis (Ex. 1006) at Fig. 5

Figure 6 presents data from an individual patient.¹³⁶ These individual patient data likewise show a greater than 10% reduction in the patient's ACTH and 17-

¹³⁶ Ex. 1006, Fig. 6, ¶ [0039].

OHP levels after taking either a 300 mg or 600 mg dose of NBI-77860 compared to the patient's baseline.¹³⁷

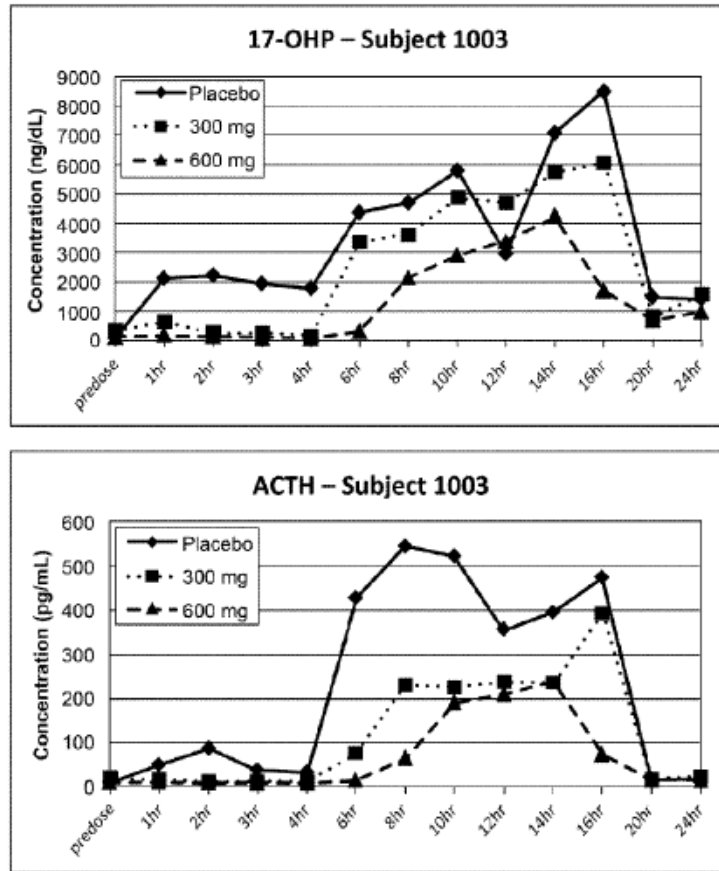


FIG. 6

Grigoriadis (Ex. 1006) at Fig. 6

Turcu (Ex. 1008) presents data from the same Phase I study disclosed in Example 6 of Grigoriadis. In addition to analyzing the change in ACTH and 17-OHP levels from baseline at time points throughout the 24 hour period as discussed in Grigoriadis, Turcu reports a comparison of ACTH and 17-OHP levels to

¹³⁷ Ex. 1005, ¶ 66; Ex. 1006, Fig. 6, ¶ [0093].

baseline in the clinically relevant morning window, an average of post-dose measurements taken between 6 a.m. and 10 a.m. (*i.e.*, the 8, 10, and 12 hour time points).¹³⁸

Turcu reports that administration of 300 mg and 600 mg doses of NBI-77860 in adult patients with 21-hydroxylase enzyme deficiency CAH “attenuated and delayed the rise in ACTH and 17OHP at both doses.”¹³⁹ Figure 2 of Turcu presents mean ACTH (Fig. 2A) and 17-OHP (Fig. 2B) levels in patients across the 24-hour period after administration of placebo, 300 mg NBI-77860, and 600 mg NBI-77860.¹⁴⁰ The bracket with asterisk indicates the defined 8-10a.m. morning window.¹⁴¹ As is shown in Grigoriadis, Figure 2 of Turcu demonstrates that mean patient ACTH and 17-OHP levels were reduced from baseline by greater than 10% at multiple time points after receiving 300 mg or 600 mg of NBI-77860.¹⁴²

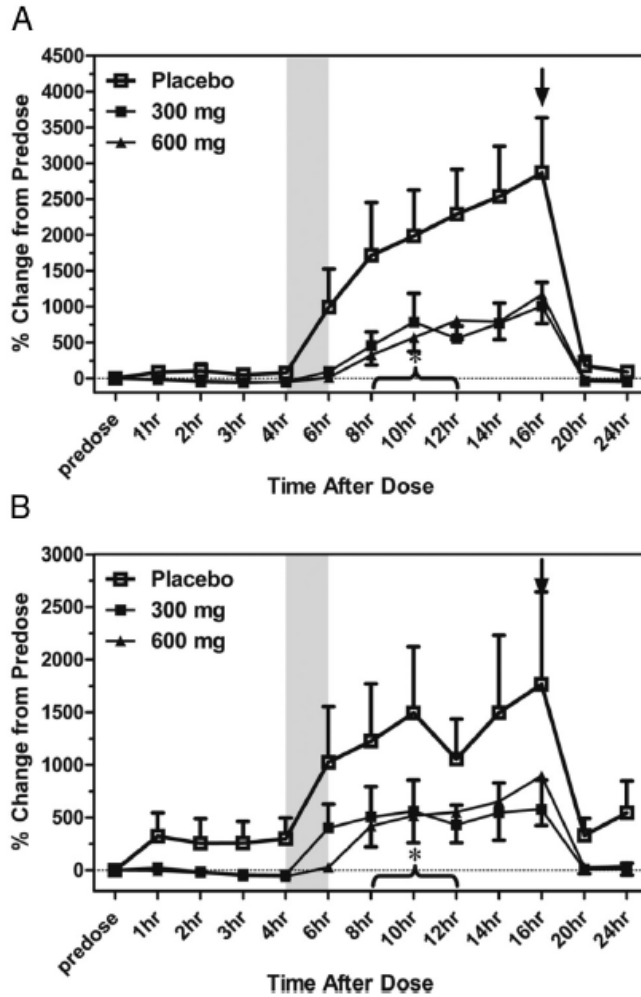
¹³⁸ Ex. 1008, 1176-77.

¹³⁹ Ex. 1008, 1177.

¹⁴⁰ *Id.*, 1176.

¹⁴¹ *Id.*

¹⁴² *Id.*



Turcu (Ex. 1008) at Fig. 2

Turcu also reports ACTH and 17-OHP data within the morning window (6-10 a.m.) for individual patients.¹⁴³ Patients were classified as “responders” if 17-OHP declined by at least 50% from placebo (*i.e.*, baseline) at one or more time points within the morning window after administration of NBI-77860.¹⁴⁴ Turcu

¹⁴³ *Id.*, 1177, Table 1.

¹⁴⁴ *Id.*, 1177.

reports that four of the eight patients achieved at least a 50% (*i.e.*, greater than 10%) reduction in 17-OHP levels from baseline at one more time points within the morning window after receiving NBI-77860.¹⁴⁵ Seven of the eight patients observed a greater than 10% reduction in ACTH within the morning window, calculated as a mean of the 6-10 a.m. time points.¹⁴⁶

Table 1. Plasma ACTH and 17OHP After Single Doses of NBI-77860

Participant	Age (y)	BMI (kg/m ²)	BSA (m ²)	Dose (mg)	ACTH % Change From Placebo (Mean of AM Timepoints)	17OHP % Change From Placebo			Responder/Nonresponder ^a
						6 AM	8 AM	10 AM	
1011001	58	29.4	1.62	300	-29.7	1.2	16.6	2.3	Nonresponder
				600	-32.9	-4.3	18.1	-52.4	
1011002	22	19.2	1.48	300	-42.8	-19.2	11.4	6.1	Responder
				600	-86.1	-60.7	-65.9	-73.0	
1011003	22	20.1	1.46	300	-51.3	-22.8	-16.0	58.4	Responder
				600	-67.1	-54.4	-49.6	13.6	
1011004	47	33.9	1.83	300	-13.0	29.3	-61.5	167.5	Nonresponder
				600	220	189.3	18.9	-29.0	
1011005	33	23.1	1.47	300	-43.2	-4.8	10.6	7.7	Nonresponder
				600	-54.9	-9.7	-17.1	84.0	
1011006	21	24.6	1.53	300	-89.1	-89.4	-97.1	-96.4	Responder
				600	-61.2	-94.3	-93.7	-49.0	
1011007	25	36.0	1.64	300	-64.9	139.3	63.6	49.8	Nonresponder
				600	-51.7	-11.9	9.8	23.3	
1011008	19	25.3	1.80	300	91.1	31.8	-9.4	-40.3	Responder
				600	11.5	-8.2	-40.3	-90.6	

^a Patients were classified as "responders" if they had at least a 50% reduction of 17OHP from placebo levels at one or more time points within the 6-10 AM window. BSA, body surface area.

Turcu (Ex. 1008) at Table 1

¹⁴⁵ *Id.*, Table 1.

¹⁴⁶ *Id.*

B. Romano

Romano discloses therapeutic combinations of atypical antipsychotics with CRF1 receptor antagonists.¹⁴⁷ Romano notes that CRF1 receptor antagonists have been described in the art as effective in the treatment of various conditions, and provides examples of CRF1 receptor antagonists known in the art.¹⁴⁸ Romano also discloses that the compositions of the invention can be administered orally in solid dosage forms, including capsules, tablets, pills, powders, granules, and the like.¹⁴⁹

Romano discloses that the active ingredients in the described compositions can “range in size from nanoparticles to microparticles.”¹⁵⁰ Romano also discloses that the CRF1 receptor antagonist can be in a sustained or controlled release form.¹⁵¹ The use of nanoparticles or microparticles is a common method of developing sustained or controlled release pharmaceutical formulations.¹⁵²

¹⁴⁷ Ex. 1007, Abstract and ¶ [0012].

¹⁴⁸ *Id.*, ¶¶ [0009]-[0010].

¹⁴⁹ *Id.*, ¶ [0526].

¹⁵⁰ *Id.*, ¶ [0531].

¹⁵¹ *Id.*

¹⁵² Ex. 1005, ¶ 76; Ex. 1023, 2; Ex. 1035, 309-310, 349-350.

C. Ground 1: Grigoriadis Anticipates Claims 1-4, 7-9, 11-14, 17-19, and 21-24.

A patent is invalid as anticipated under 35 U.S.C. § 102 if a prior art reference discloses every limitation of the claimed invention, either explicitly or inherently. *Liebel-Flarsheim Co. v. Medrad, Inc.*, 481 F.3d 1371, 1381 (Fed. Cir. 2007). Anticipation by inherency requires that the prior art reference necessarily disclose unstated limitations. *Monsanto Technology LLC v. E.I. DuPont de Nemours & Co.*, 878 F.3d 1336, 1343 (Fed. Cir. 2018). “Extrinsic evidence can be used to demonstrate what is ‘necessarily present’ in a prior art embodiment even if the extrinsic evidence is not itself prior art.” *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1329 (Fed. Cir. 2020).

1. The use of crinecerfont to treat CAH, as disclosed in Grigoriadis, inherently results in the ACTH and 17-OHP reductions from baseline recited in claims 1 and 11.

Claim 1 requires administering a therapeutically effective amount of a CRF1 receptor antagonist to a human, wherein ACTH levels in the human are reduced by at least 10% from baseline. Claim 11 requires administering a therapeutically effective amount of a CRF1 receptor antagonist to a human, wherein 17-OHP levels in the human are reduced by at least 10% from baseline.

As discussed in Section VI.A.1 above, Grigoriadis discloses crinecerfont (SSR-125543), a CRF1 receptor antagonist, as useful for the treatment of CAH.¹⁵³ Grigoriadis also discloses a range of therapeutically acceptable amounts of a CRF1 receptor antagonist, about 50-1000 mg.¹⁵⁴ The administration of a therapeutically effective amount of crinecerfont to a patient as taught in Grigoriadis inherently and necessarily results in an at least 10% reduction of the patient's ACTH compared to the patient's baseline, and inherently and necessarily results in an at least 10% reduction of the patient's 17-OHP level compared to the patient's baseline.¹⁵⁵

Specifically, after 14 days of administering crinecerfont, most patients in Neurocrine's Phase II clinical study experienced a greater than 50% reduction in ACTH and 17-OHP at Day 14 compared to baseline measurements, which were taken over a 24-hour period beginning in the evening of the seventh day before the study began (Day-7 to Day-6).¹⁵⁶ These data demonstrate that the administration of a therapeutically effective amount of crinecerfont necessarily resulted in at least a 10% reduction of ACTH and 17-OHP compared to baseline in "a patient", and

¹⁵³ *Infra*, § VI.A.2; Ex. 1006, ¶ [0054].

¹⁵⁴ Ex. 1006, ¶ [0063].

¹⁵⁵ Ex. 1005, ¶¶ 53-62; Ex. 1009, 10, 13-19, Figs. 1-2, Table 2.

¹⁵⁶ Ex. 1005, ¶ 56; Ex. 1009, 10-11, 13-19, Figs. 1-2, Table 2.

indeed in the majority of patients.¹⁵⁷ ACTH and 17-OHP measurements taken over 24 hours and within the morning window (6-10 a.m.) time points likewise showed that administration of a therapeutically effective amount of crinecerfont to a patient meets the at least 10% reduction from baseline requirement recited in '908 patent claims 1 and 11.¹⁵⁸

Administration of a therapeutically effective amount of crinecerfont to a patient, as taught by Grigoriadis, necessarily results in an at least 10% reduction in a patient's ACTH level from baseline, and necessarily results in an at least 10% reduction in a patient's ACTH level from baseline. Thus, Grigoriadis inherently anticipates '908 patent claims 1 and 11. *See Liebel-Flarsheim*, 481 F.3d at 1381; *Monsanto Technology*, 878 F.3d at 1343.

2. The use of NBI-77860 to treat CAH, as disclosed in Grigoriadis, results in the ACTH and 17-OHP reductions from baseline recited in claims 1 and 11.

As discussed in Section VI.A.2 above, Grigoriadis discloses NBI-77860, a CRF1 receptor antagonist, as useful for the treatment of CAH.¹⁵⁹ Grigoriadis also discloses the results of a clinical study wherein a therapeutically effective amount

¹⁵⁷ Ex 1005, ¶ 62; Ex. 1009, Table 2.

¹⁵⁸ Ex. 1005, ¶¶ 58-60; Ex. 1009, 14-15, Figs. 1-2.

¹⁵⁹ *Infra*, § VI.A.1; Ex. 1006, ¶¶ [0051], [0090]-[0093].

of NBI-77860, 300 mg and 600 mg doses, were administered to CAH patients.¹⁶⁰

The administration of a therapeutically effective amount of NBI-77860 to a patient as taught in Grigoriadis resulted in an at least 10% reduction of the patient's ACTH compared to the patient's baseline, and resulted in an at least 10% reduction of the patient's 17-OHP compared to the patient's baseline.¹⁶¹

Specifically, Grigoriadis discloses that “[c]onsistent and clinically meaningful reductions from predose levels of both 17-OHP and ACTH were observed throughout the postdose period following administration of NBI-77860 relative to placebo in these CAH patients.”¹⁶² Figure 5 of Grigoriadis shows that the administration of either 300 mg or 600 mg of NBI-77860 to a patient resulted in an at least a 10% reduction in ACTH and 17-OHP from the patient's baseline levels at multiple time points.¹⁶³ For example, at the 6 hour post-dose time point, there was an approximately 500% reduction in mean ACTH, and over a 500% reduction in mean 17-OHP, after administering NBI-77860 compared to

¹⁶⁰ Ex. 1006, ¶¶ [0090]-[0093].

¹⁶¹ Ex. 1005, ¶¶ 63-68; Ex. 1006, ¶ [0093], Figs. 5-6.

¹⁶² Ex. 1005, ¶ 65; Ex. 1006, ¶ [0093].

¹⁶³ Ex. 1005, ¶ 65; Ex. 1006, Fig. 5.

administration of placebo.¹⁶⁴ The differences in mean ACTH and 17-OHP between both the 300 mg and 600 mg NBI-77860 treatment groups and the placebo treatment group increased at the 8 hour and 10 hour time points.¹⁶⁵

Grigoriadis also reports that half of the eight individual patients studied achieved at least a 50% decrease in ACTH and 17-OHP from receiving NBI-77860 relative to placebo during the peak morning period.¹⁶⁶ Figure 6 of Grigoriadis presents data from an individual patient, and shows that the administration of 300 mg or 600 mg of NBI-77860 to that patient resulted in a greater than 10% reduction in ACTH and 17-OHP compared to the patient's baseline.¹⁶⁷ For example, at the 8 hour post-dose time point, this patient's ACTH was over 500 pg/mL at baseline (*i.e.*, the placebo measurement).¹⁶⁸ The patient's ACTH was reduced to under 300 pg/mL after receiving 300 mg of NBI-77860, and was reduced to under 100 pg/mL after receiving 600 mg NBI-77860.¹⁶⁹ At the 8 hour

¹⁶⁴ Ex. 1005, ¶ 65; Ex. 1006, Fig. 5.

¹⁶⁵ Ex. 1005, ¶ 65; Ex. 1006, Fig. 5.

¹⁶⁶ Ex. 1005, ¶ 66; Ex. 1006, ¶ [0093].

¹⁶⁷ Ex. 1005, ¶ 66; Ex. 1006, Fig. 6.

¹⁶⁸ Ex. 1005, ¶ 66; Ex. 1006, Fig. 6.

¹⁶⁹ Ex. 1005, ¶ 66; Ex. 1006, Fig. 6.

post-dose time point, this patient's 17-OHP was approaching 5000 ng/dL at baseline, and was reduced to under 4000 ng/dL after administration of 300 mg NBI-77860, and was reduced to approximately 2000 ng/dL after administering 600 mg NBI-77860.¹⁷⁰

As taught by Grigoriadis, the administration of a therapeutically effective amount of NBI-77860 to a patient resulted in an at least 10% reduction in the patient's ACTH and 17-OHP levels compared to the patient's baseline ACTH and 17-OHP levels.¹⁷¹ Grigoriadis discloses every element of '908 patent claims 1 and 11, and thus anticipates those claims. *See Liebel-Flarsheim*, 481 F.3d at 1381.

3. Grigoriadis discloses all of the limitations of dependent claims 2-4, 7-9, 12-14, 17-19, and 21-24.

a. Claims 2 and 12

In addition to the limitations of claims 1 and 11, claims 2 and 12 require administering the CRF1 receptor antagonist at a dose ranging from 50-1600 mg. Grigoriadis discloses administering a CRF1 receptor antagonist at a dose ranging from 50-1000 mg, which falls within the claimed range.¹⁷² Grigoriadis further

¹⁷⁰ Ex. 1005, ¶ 66; Ex. 1006, Fig. 6.

¹⁷¹ Ex. 1005, ¶¶ 63-68.

¹⁷² Ex. 1005, ¶ 70; Ex. 1006, ¶ [0063].

expressly teaches administering NBI-77860 at doses of 300 mg and 600 mg.¹⁷³ As discussed above, patients treated with both doses exhibited a greater than 10% reduction in ACTH and 17-OHP levels relative to baseline.¹⁷⁴ With respect to the disclosure of crinecerfont in Grigoriadis, Neurocrine's Phase II clinical trial results, set forth in Auchus 2021, demonstrate that administration of crinecerfont at doses falling within the claimed range (between 50 mg/day and 200 mg/day), resulted in at least a 10% reduction in a patient's ACTH and 17-OHP levels compared to baseline.¹⁷⁵ Grigoriadis meets every limitation of claims 2 and 12, and therefore anticipates those claims. *See Liebel-Flarsheim*, 481 F.3d at 1381.

b. Claims 3 and 13

In addition to the limitations of claims 1 and 11, claims 3 and 13 require administering the CRF1 receptor antagonist at a dose ranging from 100-600 mg. As discussed above, Grigoriadis discloses administering a CRF1 receptor antagonist at a dose ranging from 50-1000 mg, which encompasses the range recited in claims 3 and 13, and teaches administering NBI-77860 at doses of 300

¹⁷³ Ex. 1005, ¶ 70; Ex. 1006, ¶ [0091].

¹⁷⁴ Ex. 1005, ¶¶ 63-68, 69; Ex. 1006, ¶ [0093], Fig. 5.

¹⁷⁵ Ex. 1005, ¶¶ 53-62, 70; Ex. 1009, 10, 14-15, Figs. 1-2, Table 2.

and 600 mg, both of which fall within the claimed range.¹⁷⁶ Patients receiving both 300 mg and 600 mg doses of NBI-77860 exhibited a greater than 10% reduction in ACTH and 17-OHP relative to their baseline levels.¹⁷⁷ With respect to the disclosure of crinecerfont in Grigoriadis, Auchus 2021 shows the administration of crinecerfont at doses falling within the claimed range resulted in at least a 10% reduction in a patient's ACTH and 17-OHP levels compared to baseline.¹⁷⁸ Grigoriadis meets every limitation of claims 3 and 13, and therefore anticipates those claims. *See Liebel-Flarsheim*, 481 F.3d at 1381.

c. Claims 4 and 14

Claims 4 and 14 depend from claims 1 and 11, respectively, and require administering the CRF1 receptor antagonist at a dose of about 200 mg/day. Grigoriadis discloses administering a CFR1 receptor antagonist to treat CAH at a dose ranging from 50-1000 mg/day.¹⁷⁹ Grigoriadis also discloses crinecerfont as a CRF1 receptor antagonist useful in the treatment of CAH.¹⁸⁰

¹⁷⁶ Ex. 1005, ¶ 71; Ex. 1006, ¶¶ [0063], [0091].

¹⁷⁷ Ex. 1005, ¶¶ 63-68, 71; Ex. 1006, ¶ [0093], Fig. 5.

¹⁷⁸ Ex. 1005, ¶¶ 53-62, 71; Ex. 1009, 10, 14-15, Figs. 1-2, Table 2.

¹⁷⁹ Ex. 1005, ¶ 72; Ex. 1006, ¶ [0063].

¹⁸⁰ Ex. 1005, ¶ 72; Ex. 1006, ¶ [0054].

As shown in Neurocrine's Phase II clinical study, summarized in Auchus 2021, the administration of 200 mg/day crinecerfont results in a reduction of ACTH and 17-OHP by at least 10% relative to baseline.¹⁸¹ Specifically, patients in Cohort 4 of that study were administered 100 mg of crinecerfont twice per day, and thus at a total dose of 200 mg/day.¹⁸² Median ACTH and 17-OHP levels in Cohort 4 patients decreased from baseline by over 10% after receiving 200 mg/day of crinecerfont.¹⁸³ Thus, Grigoriadis meets every limitation of claims 4 and 14, and anticipates those claims. *See Liebel-Flarsheim*, 481 F.3d at 1381; *Hospira*, 946 F.3d at 1329.

d. Claims 7-8 and 17-18

Claims 7 and 17 require the CRF1 receptor antagonist to be in the form of a pharmaceutical composition, and claims 8 and 18 require the composition to be in the form of a capsule or a tablet. Grigoriadis expressly teaches pharmaceutical compositions that contain a CRF1 receptor antagonist, and further discloses that the pharmaceutical compositions described can be in the form of a tablet.¹⁸⁴

¹⁸¹ Ex. 1005, ¶¶ 53-62, 72-73; Ex. 1009, 10, 14-15, Figs. 1-2, Table 2.

¹⁸² Ex. 1005, ¶ 73; Ex. 1009, 10.

¹⁸³ Ex. 1005, ¶ 73; Ex. 1009, 14-15, Figs. 1-2, Table 2.

¹⁸⁴ Ex. 1005, ¶¶ 80-81; Ex. 1006, ¶¶ [0061], [0073], [0074].

Therefore, Grigoriadis meets every limitation of claims 7-8 and 17-18, and anticipates those claims. *See Liebel-Flarsheim*, 481 F.3d at 1381.

e. Claims 9 and 19

Claims 9 and 19 depend from claim 1 and 11, respectively, and require the treated condition to be classic CAH. Grigoriadis teaches that the most common form of CAH is 21-hydroxylase deficiency caused by mutations in the CYP21A2 gene, and that the more severe form of 21-hydroxylase deficiency is termed classical CAH.¹⁸⁵ Grigoriadis also expressly teaches administering NBI-77860 to treat patients with classic 21-hydroxylase deficiency CAH.¹⁸⁶ As discussed above, patients treated with NBI-77860 exhibited at least a 10% reduction in ACTH and 17-OHP relative to baseline.¹⁸⁷ Moreover, Grigoriadis also discloses the use of crinecerfont to treat CAH, and the data reported in Auchus 2021 demonstrated that when crinecerfont was administered to patients with classic 21-hydroxylase deficiency CAH, patients exhibited at least a 10% reduction in ACTH and 17-OHP

¹⁸⁵ Ex. 1005, ¶ 82; Ex. 1006, ¶¶ [0004], [0034], Fig 1.

¹⁸⁶ Ex. 1005, ¶ 82; Ex. 1006, ¶¶ [0091].

¹⁸⁷ Ex. 1005, ¶¶ 63-68, 82; Ex. 1006, ¶ [0093], Figs. 5-6.

relative to baseline.¹⁸⁸ Therefore, Grigoriadis meets every limitation of claims 9 and 19, and anticipates those claims. *See Liebel-Flarsheim*, 481 F.3d at 1381.

f. Claims 21 and 22

Claims 21 and 22 require that the at least 10% reduction in ACTH and 17-OHP from baseline recited in claims 1 and 11, respectively, is maintained at a reduced level post 24 hours. As discussed above, a skilled artisan would understand “maintained at a reduced level post 24 hours” to mean maintenance of reduced hormone level for more than 24 hours when a patient is dosed repeatedly.¹⁸⁹ Grigoriadis teaches the use of crinecerfont to treat CAH patients.¹⁹⁰ As reported in Auchus 2021, the administration of crinecerfont to a patient results in a reduction of the patient’s ACTH and 17-OHP by at least 10% compared baseline on Day 15, after 14 days of repeated dosing.¹⁹¹ In other words, the reduction in ACTH and 17-OHP after administering crinecerfont was maintained

¹⁸⁸ Ex. 1005, ¶¶ 53-62, 82; Ex. 1009, 10, 14-15, Figs. 1-2, Table 2.

¹⁸⁹ *Supra*, § V.C; Ex. 1005, ¶¶ 45-48.

¹⁹⁰ Ex. 1005, ¶ 85; Ex. 1006, ¶ [0051].

¹⁹¹ Ex. 1005, ¶¶ 53-62, 85; Ex. 1009, 10, 14-15, Figs. 1-2, Table 2.

for more than 24 hours.¹⁹² Grigoriadis thus meets every limitation of claims 21 and 22, and anticipates those claims. *See Liebel-Flarsheim*, 481 F.3d at 1381.

g. Claim 23

In addition to the limitations of claims 1 and 11, claim 23 further requires administering a glucocorticoid. Grigoriadis discloses that the use of glucocorticoids as maintenance therapy for CAH patients was known in the art.¹⁹³ Grigoriadis also discloses that a CRF1 receptor antagonist may lower the amount of glucocorticoids administered to a CAH patient, indicating co-administration.¹⁹⁴ Grigoriadis also discloses a clinical study in which glucocorticoids were co-administered with a CRF1 antagonist, NBI-77860, and a patient achieved an at least 10% reduction in ACTH and 17-OHP compared to baseline.¹⁹⁵ With respect to the use of crinecerfont to treat CAH as disclosed in Grigoriadis, patients in Neurocrine's Phase II study were kept on their existing glucocorticoid treatments throughout the study, and likewise achieved an at least 10% reduction in ACTH

¹⁹² Ex. 1005, ¶¶ 53-62, 85-88; Ex. 1009, 10, 14-15, Figs. 1-2, Table 2.

¹⁹³ Ex. 1005, ¶ 88; Ex. 1006, ¶¶ [0069].

¹⁹⁴ Ex. 1005, ¶ 88; Ex. 1006, ¶ [0070].

¹⁹⁵ Ex. 1005, ¶¶ 63-68, 88; Ex. 1006, ¶¶ [0091]-[0093].

and 17-OHP compared to baseline.¹⁹⁶ Grigoriadis thus meets every limitation of claim 23, and anticipates claim 23. *See Liebel-Flarsheim*, 481 F.3d at 1381.

h. Claim 24

In addition to the limitations of claim 23, claim 24 requires that the CRF1 receptor antagonist be administered 4 hours prior to sleeping. As discussed above, a skilled artisan would understand “administered 4 hours prior to sleeping” to mean administration of the CRF1 receptor antagonist prior to the circadian release of ACTH.¹⁹⁷ Grigoriadis discloses that “bedtime administration refers to dosing intended to deliver clinically relevant concentrations of the CRF antagonist at or before (such as 2-5 hours before) the expected circadian release of ACTH”, and teaches that “since most orally administered drugs have a Tmax of several hours, dosing at 10 P.M., for example, which is 3-4 hours in advance of the expected circadian release of ACTH is desirable.”¹⁹⁸ Therefore, Grigoriadis meets every limitation of claim 24, and anticipates claim 24. *See Liebel-Flarsheim*, 481 F.3d at 1381.

¹⁹⁶ Ex. 1005, ¶¶ 53-62, 88; Ex. 1009, 10, 14-15, Figs. 1-2, Table 2.

¹⁹⁷ *Supra*, § V.D; Ex. 1005, ¶¶ 49-52.

¹⁹⁸ Ex. 1005, ¶¶ 91-92; Ex. 1006, ¶ [0066].

D. Ground 2: Claims 4, 10, 14, 20-22, and 25 Would Have Been Obvious in View of Grigoriadis and the Knowledge of a Skilled Artisan.

The question of obviousness requires analyzing (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness.

Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966).

“When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.” *KSR Int’l Co. v. Teleflex, Inc.*, 550 U.S. 398, 421. “Conclusive proof of efficacy is not necessary to show obviousness. All that is required is a reasonable expectation of success.” *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014).

“[A] patent can be obvious in light of a single prior art reference if it would have been obvious to modify that reference to arrive at the patented invention.” *Game & Tech. Co. v. Activision Blizzard Inc.*, 926 F.3d 1370, 1381 (Fed. Cir. 2019); *see also SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp.*, 225 F.3d 1349, 1356 (Fed. Cir. 2000).

“When the prior art does not expressly disclose a claim limitation, ‘inherency may supply a missing claim limitation in an obviousness analysis.’” *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1329 (Fed. Cir. 2020) (affirming district court finding of obviousness by combining inherent teaching of prior art with knowledge of a skilled artisan). “An inherent characteristic of a formulation can be part of the prior art in an obviousness analysis even if the inherent characteristic was unrecognized or unappreciated by a skilled artisan.” *Persion Pharm. LLC v. Alvogen Malta Operations Ltd.*, 945 F.3d 1184, 1190 (Fed. Cir. 2019).

1. Level of Ordinary Skill in the Art

A hypothetical person of ordinary skill in the art of the '908 patent would have a medical degree or a Ph.D. in a field related to endocrinology, and would have knowledge of hormone regulation and disorders, as well as knowledge of the treatment regimens employed to treat such disorders. The hypothetical person of ordinary skill would also have at least three years of experience conducting research concerning endocrine disorders, including CAH or other adrenal disorders.¹⁹⁹

2. Claims 4, 10, 14, 20-22, and 25 Are Obvious

¹⁹⁹ Ex. 1005, ¶ 34.

a. Claims 4 and 14

As set forth in Section VI.C.3.c above, administering a CRF1 receptor antagonist at a dose of 200 mg/day is inherently anticipated by Grigoriadis's disclosure of crinecerfont to treat CAH, and Neurocrine's Phase II clinical data reported in Auchus 2021 demonstrating that administration of 200 mg/day crinecerfont results in the claimed ACTH and 17-OHP reductions from baseline.²⁰⁰ These claims are also obvious in view of the disclosure of NBI-77860 in Grigoriadis.

Grigoriadis discloses a dosing range for CFR1 receptor antagonists to treat CAH in a range from about 50-1000 mg/day.²⁰¹ The claimed 200 mg/day dose falls within this range. Grigoriadis also discloses administering a CRF1 receptor antagonist, NBI-77860, at doses of 300 mg/day and 600 mg/day, and data showing these doses are effective at reducing ACTH and 17-OHP in a patient by at least 10% from baseline.²⁰² Grigoriadis also teaches that "[t]he use of the minimum dose that is sufficient to provide effective therapy is usually preferred."²⁰³

²⁰⁰ *Supra*, § VI.C.3.c; Ex. 1005, ¶¶ 72-73.

²⁰¹ Ex. 1005, ¶ 72; Ex. 1006, ¶ [0063].

²⁰² Ex. 1005, ¶¶ 63-68, 74; Ex. 1006, ¶¶ [0091]-[0093].

²⁰³ Ex. 1005, ¶ 74; Ex. 1006, ¶ [0063].

“[W]here there is a range disclosed in the prior art, and the claimed invention falls within that range, the burden of production falls upon the patentee to come forward with evidence that (1) the prior art taught away from the claimed invention; (2) there were new and unexpected results relative to the prior art; or (3) there are other pertinent secondary considerations.” *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013). Here, the 200 mg/day dose recited in ’908 patent claims 4 and 14 is within the range disclosed in Grigoriadis. Grigoriadis does not teach away from administering the CRF1 receptor antagonist in a 200 mg/day dose. On the contrary, Grigoriadis presents data showing that a 300 mg/day dose of NBI-77860 was effective to reduce ACTH and 17-OHP in a patient, and teaches that the use of the minimum effective dose is preferred.²⁰⁴ A skilled artisan would be motivated to use a dose lower than 300 mg/day, such as 200 mg/day, in view of the teachings of Grigoriadis.²⁰⁵

Spruce presented no evidence during prosecution that the use of a 200 mg/day dose was new or unexpected relative to the prior art, and no evidence of any other pertinent secondary considerations.²⁰⁶ Thus, claims 4 and 14 would have

²⁰⁴ Ex. 1005, ¶ 74; Ex. 1006, ¶¶ [0063], [0093], Figs. 5-6.

²⁰⁵ Ex. 1005, ¶ 74.

²⁰⁶ Ex. 1002, 30-38, 53, 70-72, 100-102.

been obvious in view of Grigoriadis and the knowledge of a skilled artisan. *See Galderma*, 737 F.3d at 738.

b. Claims 10 and 20

Claims 10 and 20 depend on claims 1 and 11, respectively, and require treating non-classic CAH. Grigoriadis teaches that 21-hydroxylase deficiency CAH is a continuum, wherein the more severe form is termed classic CAH, and the milder form is known as non-classic CAH.²⁰⁷ Grigoriadis also teaches that CRF1 receptor antagonists are useful to treat CAH, and presents data showing that NBI-77860 is effective in treating patients with classic CAH.²⁰⁸

A skilled artisan would understand that the endocrinological mechanism for classic CAH and non-classic CAH—21-hydroxylase deficiency—is the same.²⁰⁹ In view of that knowledge, the disclosure of Grigoriadis that CRF1 receptor antagonists are useful to treat CAH, and the data showing a CRF1 receptor antagonist was effective in treating patients with classic CAH, a skilled artisan would be motivated to use these CRF1 receptor antagonists to treat patients with

²⁰⁷ Ex. 1005, ¶ 83; Ex. 1006, ¶ [0004].

²⁰⁸ Ex. 1005, ¶¶ 63-68, 84; Ex. 1006, ¶¶ [0090]-[0093], Figs. 5-6.

²⁰⁹ Ex. 1005, ¶ 83.

non-classic CAH.²¹⁰ A skilled artisan would also expect these CRF1 receptor antagonists would be effective in treating non-classic CAH, based on data showing their effectiveness in classic CAH patients.²¹¹ Therefore, claims 10 and 20 would have been obvious in view of Grigoriadis and the knowledge of a skilled artisan. *See Hoffmann-La Roche*, 748 F.3d at 1331.

c. Claims 21 and 22

Claims 21 and 22 require that the at least 10% reduction in ACTH and 17-OHP levels, respectively, from baseline are maintained at a reduced level post 24 hours. As set forth in Section VI.C.3.f above, Grigoriadis teaches the use of crinecerfont to treat CAH patients, and the administration of crinecerfont to a patient inherently results in a reduction of the patient's ACTH and 17-OHP by at least 10% after 14 days of repeated dosing—*i.e.*, the ACTH and 17-OHP reductions are maintained for more than 24 hours.²¹² These claims also would have been obvious in view of in the disclosure of NBI-77860 in Grigoriadis.

²¹⁰ *Id.*, ¶ 84.

²¹¹ *Id.*

²¹² *Supra*, § VI.C.3.f; Ex. 1005, ¶¶ 53-62, 85; Ex. 1006, ¶ [0054]; Ex. 1009, 10, 14-15, Figs. 1-2, Table 2.

As discussed in Section VI.C.2 above, Grigoriadis discloses that administration of a single dose of 300 mg or 600 mg NBI-77860 reduced ACTH and 17-OHP in a CAH patient by at least 10% compared to the patient's baseline over a 24-hour period post-dose.²¹³ In view of the disclosure of Grigoriadis, it would have been obvious to a skilled artisan that the at least 10% reduction in ACTH and 17-OHP from baseline would be maintained for more than 24 hours with repeated dosing.²¹⁴

As set forth in Section V.C above, "maintained at a reduced level post 24 hours" refers to maintaining reduced ACTH and 17-OHP with repeated dosing.²¹⁵ A skilled artisan would expect a drug to maintain its efficacy over time with repeated dosing.²¹⁶ A reduction in efficacy of a drug over time is relatively rare.²¹⁷ A skilled artisan would have reasonably expected the ACTH and 17-OHP

²¹³ *Supra*, § VI.C.2; Ex. 1005, ¶¶ 63-68, 88; Ex. 1006, ¶¶ [0091]-[0093], Figs. 5-6.

²¹⁴ Ex. 1005, ¶¶ 85-88.

²¹⁵ *Supra*, § V.C; Ex. 1005, ¶¶ 45-48.

²¹⁶ Ex. 1005, ¶¶ 86-87; Ex. 1032 at 36; Ex. 1032, 35-36; Ex. 1033, 205; Ex. 1034, 153.

²¹⁷ Ex. 1005, ¶¶ 86-87; Ex. 1032 at 36; Ex. 1032, 35-36; Ex. 1033, 205; Ex. 1034, 153.

reductions over 24 hours after administration of NBI-77860 disclosed in Grigoriadis to extend beyond 24 hours with repeated dosing of NBI-77860.²¹⁸

Moreover, any evidence of nonobviousness must be commensurate with the scope of the claims. *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 965 (Fed. Cir. 2014) (“It is the established rule that “objective evidence of non-obviousness must be commensurate in scope with the claims which the evidence is offered to support”); *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003) (“Establishing that one (or a small number of) species gives unexpected results is inadequate proof, for ‘it is the view of this court that objective evidence of non-obviousness must be commensurate in scope with the claims which the evidence is offered to support.’”). Spruce has presented alleged evidence of non-obviousness of one compound, tildacerfont. That is not commensurate with the scope of claims 21-22, which recite the administration of CRF1 receptor antagonists broadly. *Id.*

Accordingly, claims 21-22 would have been obvious over Grigoriadis and the knowledge of a skilled artisan. *See KSR*, 550 U.S. at 421.

d. Claim 25

²¹⁸ Ex. 1005, ¶¶ 86-87; Ex. 1032 at 36; Ex. 1032, 35-36; Ex. 1033, 205; Ex. 1034, 153.

Claim 25 depends from claim 23, and further requires that the glucocorticoid be administered concurrently or sequentially within two hours of the CRF1 receptor antagonist. As discussed in Section VI.C.3.g above, Grigoriadis teaches co-administration of a CRF1 antagonist and a glucocorticoid.²¹⁹ It would be obvious to a skilled artisan to administer a glucocorticoid concurrently or within two hours of administering the CRF1 receptor antagonist based on the knowledge in the field regarding treatment of CAH.²²⁰

Both glucocorticoid and CRF1 receptor antagonists treat CAH by reducing ACTH.²²¹ Moreover, Grigoriadis discloses that one objective of administering a CRF1 receptor antagonist is to reduce the amount of glucocorticoids needed by a CAH patient.²²² Accordingly, a skilled artisan would have been motivated to administer the glucocorticoid either concurrently with the CRF1 receptor antagonist or shortly thereafter to maximize the extent of ACTH reduction.²²³

²¹⁹ *Supra*, § VI.C.3.g; Ex. 1005, ¶¶ 89, 97; Ex. 1006, ¶¶ [0069]-[0070], [0091].

²²⁰ Ex. 1005, ¶¶ 93-97.

²²¹ Ex. 1005, ¶¶ 93-95; Ex. 1006, ¶¶ [0006], [0040], [0069]-[0070].

²²² Ex. 1005, ¶ 94; Ex. 1006, ¶ [0070].

²²³ Ex. 1005, ¶¶ 93-97.

Based on the results in Grigoriadis showing that the CRF1 receptor antagonist alone could reduce ACTH and 17-OHP levels by at least 10% relative to baseline, the skilled artisan would have expected that administering the glucocorticoid as claimed also would have successfully reduced these levels by at least 10% relative to baseline.²²⁴ Accordingly, claim 25 would have been obvious over Grigoriadis and the knowledge of a skilled artisan. *See KSR*, 550 U.S. at 421.

E. Ground 3: Claims 5-6 and 15-16 Would Have Been Obvious in View of Grigoriadis in Combination with Romano.

Claims 5 and 15 depend on claims 1 and 11, respectively, and require the CRF1 receptor antagonist to be in the form of microparticles. Claims 6 and 16 depend on claims 5 and 15, respectively, and require the average size of the CRF1 receptor antagonist microparticles to be between about 1 μm and about 20 μm .

Grigoriadis does not explicitly disclose administering the CRF1 receptor antagonist in the form of microparticles. In view of Romano, however, it would have been obvious to formulate the CRF1 receptor antagonists disclosed by Grigoriadis as microparticles with an average size of between about 1-20 μm . As discussed above, Romano explicitly teaches that the active ingredients of Romano's claimed compositions, a CRF1 receptor antagonist and an atypical

²²⁴ *Supra*, § VI.C.1-2.

antipsychotic, can range in size from nanoparticles to microparticles.²²⁵ A person of ordinary skill would understand Romano to teach the use of small particle sizes with CRF1 receptor antagonists, such as the claimed range of between about 1-20 μm .²²⁶

A person of ordinary skill would have been motivated to combine the teachings of Grigoriadis with Romano because both relate to pharmaceutical compositions comprising a CRF1 receptor antagonist.²²⁷ In addition, a person of ordinary skill would have known that microparticles could be used to create sustained release formulations, and would have been motivated to combine Grigoriadis and Romano because both disclose using a CRF1 receptor antagonist in a sustained release formulation.²²⁸ Further, Grigoriadis teaches that CRF1 receptor antagonist compositions could generally be prepared using well-known technology, and a person of ordinary skill would have been familiar with microparticles as a common form of administering a pharmaceutical active

²²⁵ Ex. 1005, ¶¶ 76-77; Ex. 1007, Abstract, ¶ [0531].

²²⁶ Ex. 1005, ¶¶ 78-79.

²²⁷ Ex. 1005, ¶ 77; Ex. 1006, ¶ [0061]; Ex. 1007, ¶ [0531].

²²⁸ Ex. 1005, ¶ 77; Ex. 1006, ¶ [0073]; Ex. 1007, ¶ [0531]; Ex. 1023, 2; Ex. 1035, 309-310, 349-350.

ingredient.²²⁹ Thus, it would have been obvious to formulate the CRF1 receptor antagonists disclosed by Grigoriadis as microparticles.

In addition, a skilled artisan would have been motivated to use a small particle size range in view of Romano's teaching that the CRF1 receptor antagonist in the compositions of Romano can range in size from nanoparticles to microparticles.²³⁰ The claimed 1-20 μm particle size represents, at best, a simple matter of routine optimization.²³¹ Accordingly, claims 5, 6, 15, and 16 would have been obvious in view of Grigoriadis in combination with Romano. *See KSR*, 550 U.S. at 421.

F. Ground 4: Claims 1-25 of the '908 Patent are Unpatentable for Lack of Written Description.

"The written description requirement requires the inventor to disclose the claimed invention so as to 'allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.'" *Billups-Rothenberg, Inc. v. ARUP Labs., Inc.*, 642 F.3d 1031, 1036 (Fed. Cir. 2011) (quoting *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc)). The Federal Circuit has held that when a genus is claimed functionally, the specification must

²²⁹ Ex. 1005, ¶ 77; Ex. 1006, ¶ [0073]; Ex. 1023, 2; Ex. 1035, 309-310, 349-350.

²³⁰ Ex. 1005, ¶¶ 78-79.

²³¹ *Id.*

disclose “either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can ‘visualize or recognize’ the members of the genus.” *Ariad Pharm., Inc.* 598 F.3d at 1350. In *Ariad*, the Court found claims invalid for failing to satisfy the written description requirement where the specification failed to describe a sufficient number of species that could accomplish the claimed result:

The claims here recite methods encompassing a genus of materials achieving a stated useful result, i.e., reducing NF-eB binding to NF-eB recognition sites in response to external influences. But the specification does not disclose a variety of species that accomplish the result. *See Eli Lilly*, 119 F.3d at 1568 (“The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention.”). Thus, as indicated *infra*, that specification fails to meet the written description requirement by describing only a generic invention that it purports to claim.

Id.

The Federal Circuit has also held that a patent’s characterization of “the invention” is “strong evidence” of the scope of written description. *SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc.*, 242 F.3d 1337, 1343 (Fed. Cir. 2001) (“[T]he characterization of the coaxial configuration as part of the ‘present invention’ is strong evidence that the claims should not be read to encompass the

opposite structure.”); *see also Gentry Gallery Inc. v. Berkline Corp.*, 134 F.3d 1473, 1478-80 (Fed. Cir. 1998) (claims that did not restrict the location of controls invalid for lack of written description where disclosure identified console as only possible location for controls); *In re Lew*, 257 F. App’x 281, 285 (Fed. Cir. 2007) (non-precedential) (“There is no language in the original written description that would suggest that using ‘ball bearings’ was only one specific embodiment of Lew’s invention. To the contrary, each time ‘the invention’ is described, including in the summary of the invention and the abstract, it is stated to include ‘ball bearings.’ This court has consistently viewed such language as ‘strong evidence’ that the inventor intended his invention to be limited to embodiments containing such an element.”) (citations omitted).

Here, the claims of the ’908 patent fail the written description requirement because the ’908 patent does not show possession of the claimed subject matter. As noted above, the claims are extremely broad and recite methods of treating CAH that employ a “CRF1 receptor antagonist or a pharmaceutically acceptable salt thereof” that reduces ACTH or 17-OHP by at least 10% from baseline. These “functionally defined” claims are unbounded structurally and are limited only by the effect—the desired outcome—on ACTH and/or 17-OHP. Therefore, *Ariad* requires that the patent must disclose either a representative number of species or

common structural features. *Ariad Pharm., Inc.* 598 F.3d at 1350. The '908 patent does neither.

Even though CRF1 receptor antagonists represent a large, structurally diverse class of over 100 compounds, the '908 patent discloses only a single CRF1 receptor antagonist, tildacerfont (Compound 1).²³² The '908 patent repeatedly characterizes the “present invention” or “present disclosure” as relating to Compound 1. For example, the Summary of the Invention states:

The present invention provides novel pharmaceutical compositions comprising *3-4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-a) pyrimidine* and methods using such pharmaceutical compositions for treating congenital adrenal hyperplasia (CAH).

In one aspect, *the present disclosure* provides a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering a pharmaceutical composition comprising *Compound 1*²³³

Moreover, all of the Examples and clinical data in the '908 patent relate to tildacerfont.²³⁴ The '908 patent does not disclose the use of any other CRF1

²³² *Supra*, § IV.A; Ex. 1005, ¶¶ 98-100.

²³³ Ex. 1001, 1:30-38 (emphasis added).

²³⁴ *Id.*, 34:5-47:58, Tables 5-8.

receptor antagonist to treat CAH. Nor does the '908 patent disclose structural features common to the members of the genus so that one of skill in the art can visualize or recognize the members of the genus.

Notably, the original claims in the '406 Provisional and the '760 PCT were limited to tildacerfont.²³⁵ In an April 18, 2019 Preliminary Amendment, Spruce expanded the scope of the claims to include the entire genus of CRF1 receptor antagonists.²³⁶ However, Spruce failed to provide any specific support for the newly added, generic claims. Rather, Spruce simply stated “[s]upport for the claim amendments are found in the original claims and throughout the specification. The amendments provided herein do not constitute new matter.”²³⁷

During prosecution, Spruce relied on the allegedly unexpected results of administering a single CRF1 receptor antagonist—tildacerfont—to overcome rejections over Grigoriadis. As discussed above, Spruce’s tildacerfont data are not commensurate with the breadth of the claims and cannot be used as evidence of nonobviousness. On the other hand, if it was well-within the skill of a skilled artisan to identify other CFR1 receptor antagonists that performed the recited

²³⁵ Ex. 1003, 38-52; Ex. 1004, 52-61.

²³⁶ Ex. 1002, 328-329.

²³⁷ *Id.*, 330.

function, then the claims must be unpatentable over earlier Neurocrine art, which showed a different CRF1 receptor antagonist that performed the same function.

For at least these reasons, claims 1-25 are unpatentable under 35 U.S.C. § 112, para. 1 because there is no written description support for all CRF1 receptor antagonists.

G. Ground 5: Claims 1-25 of the '908 Patent are Unpatentable for Lack of Enablement.

35 U.S.C. § 112 ¶ 1 requires that the patent enable one of skill in the art to make and use the claimed invention. “The scope of the claims must be less than or equal to the scope of the enablement.” *Nat’l Recovery Techs., Inc. v. Magnetic Separation Sys., Inc.* 166 F.3d 1190, 1196 (Fed. Cir. 1999). “The scope of enablement, in turn, is that which is disclosed in the specification plus the scope of what would be known to one of ordinary skill in the art without undue experimentation.” *Id.* “A patentee who chooses broad claim language must make sure the broad claims are fully enabled.” *Sitrick v. Dreamworks, LLC*, 516 F.3d 993, 999 (Fed. Cir. 2008). A skilled artisan’s knowledge or skill is “not a substitute for a basic enabling disclosure.” *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997).

Whether undue experimentation is needed is “not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations.” *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Those factual

considerations, known as the “*Wands* factors,” are: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. *Id.*

Spruce fails to enable the full scope of the claims because the claims recite CRF1 antagonists broadly, but the patent provides only a single example, tildacerfont (Compound 1). During prosecution, Spruce singled out tildacerfont by alleging that tildacerfont’s ability to maintain the claimed ACTH and 17-OHP reductions was unexpected.²³⁸ Moreover, Spruce relied on this argument to distinguish another CRF1 receptor antagonist, Neurocrine’s NBI-77860.²³⁹

The genus of CRF1 receptor antagonists included over 100 structurally diverse compounds prior to the filing of the ’908 patent.²⁴⁰ Given the large scope of the CRF1 receptor antagonist genus, and given Spruce’s arguments that the ability of a single agent (tildacerfont) to perform the claimed reduction was unexpected relative to a different CRF1 antagonist, Spruce fails to enable the full scope of the claims. It would require undue experimentation to determine which

²³⁸ Ex. 1002, 30-38.

²³⁹ *Id.*

²⁴⁰ Ex. 1005, ¶ 99.

CRF1 antagonists from among the members of this large genus could achieve the claimed reductions.

VII. DISCRETIONARY DENIAL IS NOT WARRANTED

Under 35 U.S.C. § 325(d), the Board may deny institution if “the same or substantially the same prior art or arguments previously were presented to the Office.” 35 U.S.C. § 325(d). In making this determination, the Board considers two issues:

(1) whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and (2) if either condition of [the] first part of the framework is satisfied, whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.

Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH, IPR2019-01469, Paper 6 at 8 (PTAB Feb. 13, 2020) (precedential).

With respect to the second part of the test, *i.e.*, whether the petitioner has demonstrated material error, the Board considers “whether the petitioner has pointed out sufficiently how the examiner erred in its evaluation of the asserted prior art” and “the extent to which additional evidence and facts presented in the petition warrant reconsideration of the prior art or arguments.” *Id.*, 9 n.10, citing *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17-18 (PTAB Dec. 15, 2017).

Discretionary denial is not appropriate here. First, the petition raises two grounds, lack of written description and enablement, which the Examiner did not consider during prosecution. The petition, with support from its expert, Dr. Carey, demonstrates how the Examiner erred in failing to reject the claims on these grounds when Spruce amended its claims to cover CRF1 receptor antagonists broadly, even though its entire application was directed towards a single CRF1 receptor antagonist (tildacerfont/Compound 1).

Second, the petition, again with the aid of Dr. Carey, demonstrates how the Examiner erred in allowing the claims over Grigoriadis. The Examiner's first error arose when she overlooked the fact that Grigoriadis' data showing reduction in hormone levels relative to placebo was, in fact, demonstrating reduction relative to baseline because placebo reflected the same patient's performance in the absence of a CRF1 receptor antagonist. The Examiner's second error arose when she allowed claims 1-25 over Grigoriadis on the basis of the post-24 data presented in the Barnes declaration, despite the fact that only two of the claims (issued claims 21 and 22) included this limitation.

The Examiner also erred because she did not have important information available to her during examination. For example, when the Examiner was evaluating the data and statements presented in the Barnes declaration, she did not have the benefit of Dr. Carey's declaration, which demonstrates that the results

were not surprising to a person of skill in the art. The Examiner was also unaware of Neurocrine's Phase II clinical data relating to a second CRF1 receptor antagonist disclosed in Grigoriadis (crinecerfont/SSR-125543), which demonstrated that this CRF1 receptor antagonist inherently met the post-24 hour limitations of claims 21 and 22, as well as other claims, thereby rendering them anticipated.

For at least these reasons, Neurocrine submits that discretionary denial is not appropriate in this case.

VIII. PAYMENT OF FEES – 37 C.F.R. § 42.203

Neurocrine authorizes the Patent and Trademark Office to charge Deposit Account No. 06-1050 for the fee set in 37 C.F.R. § 42.15(a) for this Petition and further authorizes payment for any additional fees to be charged to this Deposit Account.

IX. CONCLUSION

For the above-described reasons, claims 1-25 are unpatentable on a number of grounds. Accordingly, Petitioner requests that the Board grant the petition Petitioner and find claims 1-25 unpatentable.

X. MANDATORY NOTICES UNDER 37 C.F.R § 42.8(a)(1)

A. Real Party-In-Interest Under 37 C.F.R. § 42.8(b)(1)

Petitioner Neurocrine Biosciences, Inc. is the real party-in-interest.

B. Related Matters Under 37 C.F.R. § 42.8(b)(2)

Petitioner is not aware of any disclaimers, reexamination certificates, or petitions for inter partes or post grant review for the '908 Patent, nor is Petitioner aware of any pending civil actions involving the '908 patent.

C. Lead And Back-Up Counsel Under 37 C.F.R. § 42.8(b)(3)

Neurocrine provides the following designation of counsel.

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D. Service Information

Please address correspondence/service to the above-listed address.

Neurocrine consents to email service at PGR47291-0002PS1@fr.com (referencing No. 47291-0002PS1 and cc'ing PTABInbound@fr.com, whelan@fr.com and oakes@fr.com).

Respectfully submitted,

Dated May 28, 2021

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CERTIFICATION UNDER 37 CFR § 42.24

Under the provisions of 37 CFR § 42.24(d), the undersigned hereby certifies that the word count for the foregoing Petition for Post Grant Review totals 14,064 words, which is less than the 18,700 allowed under 37 CFR § 42.24.

Dated May 28, 2021

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