

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NEUROCRINE BIOSCIENCES, INC.
Petitioner

v.

SPRUCE BIOSCIENCES, INC.
Patent Owner

Case PGR2022-00025
U.S. Patent 11,007,201

PETITION FOR POST GRANT REVIEW OF

U.S. PATENT NO. 11,007,201

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EXHIBITS

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1001	U.S. Patent No. 11,007,201 to Alexis Howerton, et al. (“the ’201 patent”).
1002	U.S. Prosecution History of the ’201 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 Hormone Markers in Adults With 21-Hydroxylase Deficiency Congenital Adrenal Hyperplasia,” <i>J. Clin. Endocrinol. Metab.</i> (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 <i>The Pharmacological Basis of Therapeutics</i> (Brunton L.L. ed., 12th ed. 2011) (“Goodman & Gilman 2011”).

1033	Shargel L. & Yu A., <i>Applied Biopharmaceutics & Pharmacokinetics</i> (7th ed. 2016) (“Shargel & Yu 2016”).
1034	Shargel et al., <i>Applied Biopharmaceutics & Pharmacokinetics</i> (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).
1036	U.S. Patent No. 10,849,908 to Alexis Howerton, et al. (“the ’908 patent”).
1037	U.S. Prosecution History of the ’908 Patent.
1038	Fuqua et al., “Duration of Suppression of Adrenal Steroids after Glucocorticoid Administration,” <i>International Journal of Pediatric Endocrinology</i> (2010) (“Fuqua 2010”).
1039	Sarafoglou et al., “Tildacerfont in Adults with Classic Congenital Adrenal Hyperplasia: Results from Two Phase 2 Studies,” <i>Journal of Clinical Endocrinology & Metabolism</i> (2021) (“Sarafoglou 2021”).
1040	Reif et al., “Mechanisms Involved in Placebo and Nocebo Responses and Implications for Drug Trials,” <i>Clinical Pharmacology and Therapeutics</i> (2011) (“Reif 2011”).

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 1-19 (“the Challenged Claims”) of U.S. Patent No. 11,007,201 (“the ’201 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.

Neurocrine is an innovator in the area of treatments for congenital adrenal hyperplasia (“CAH”), a group of genetic disorders impacting hormone production, and was the first company to study CRF1 receptor antagonists to treat CAH. Neurocrine is currently developing a specific CRF1 receptor antagonist, crinecerfont, as a treatment for CAH, and previously studied NBI-77860, a different CRF1 receptor antagonist, as a treatment for CAH. Later, Spruce began to develop treatments for CAH as well, and is currently studying a third CRF1 receptor antagonist, tildacerfont, to treat CAH. Spruce, however, has not been content to patent only its own work, and instead has filed serial applications claiming the use of a class of CRF1 receptor antagonists to treat CAH. The ’201 patent issued from one such application. These actions have the potential to artificially constrict the choices of patients and doctors in the treatment of this very

challenging disease.

The '201 patent broadly claims the use of CRF1 receptor antagonists to treat CAH, but the specification describes only a single CRF1 receptor antagonist, tildacerfont, which it repeatedly characterizes as “the invention.” The '201 patent claims are unpatentable 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 '201 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”) was published in January 2017, and discloses the use of a number of CRF1 receptor antagonists to treat CAH, including crinecerfont. The administration of crinecerfont to a patient inherently results in a reduced androstenedione level of the patient compared to baseline, which is maintained post 24 hours, as recited in the '201 patent claims, and thus anticipates the claims.

Grigoriadis also discloses the use of NBI-77860, the compound Neurocrine previously studied as a CAH treatment. Neurocrine’s work studying NBI-77860 as a treatment for CAH was also published in 2016 (Ex. 1008; “Turcu 2016”). These disclosures would render the '201 patent claims obvious to a person of ordinary skill in this art.

The broad '201 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, tildacerfont. The '201 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).

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 '201 Patent is available for PGR. The present petition is being filed within nine months of the issuance of the '201 patent on May 18, 2021. Neurocrine has not filed a civil action challenging the validity of any claim of the '201 patent. Neurocrine is not barred or estopped from requesting this review challenging claims 1-19 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	'201 Patent Claims	Basis for Rejection
Ground 1	1-4, 7-9, 11-15, 18	Anticipation under 35 U.S.C. § 102 by the disclosure of crinecerfont in Grigoriadis et al., US 2017/0020877 (Ex. 1006; “Grigoriadis”)
Ground 2	10, 16-17, 19	Obviousness under 35 U.S.C. § 103 by the disclosure of crinecerfont in Grigoriadis in view of the knowledge of a skilled artisan
Ground 3	5-6	Obviousness under 35 U.S.C. § 103 by the disclosure of crinecerfont in Grigoriadis in combination with US 2005/0209250 (Ex. 1007; “Romano”) and the knowledge of a skilled artisan
Ground 4	1-4, 7-19	Obviousness under 35 U.S.C. § 103 by the disclosure of NBI-77860 in Grigoriadis and Turcu 2016 (Ex. 1008), in view of the knowledge of a skilled artisan
Ground 5	5-6	Obviousness under 35 U.S.C. § 103 by the disclosure of NBI-77860 in Grigoriadis and Turcu 2016 in combination with Romano and the knowledge of a skilled artisan
Ground 6	1-19	Lack of written description 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 '201 patent, and was published before August 14, 2017, which is the earliest possible effective filing

date to which claims 1-19 of the '201 patent could be entitled.¹

Turcu 2016 (Ex. 1008) qualifies as prior art under 35 U.S.C. § 102(a). Specifically, Turcu 2016 is a printed publication that first published online on January 11, 2016,² names different authors than the inventors named on the '201 patent, and was published more than one year before the '201 patent's earliest effective filing date of August 14, 2017. Thus, Turcu 2016 is prior art to the '201 patent.

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 '201 patent, and was published more than one year before the '201 patent's earliest effective filing date of August 14, 2017. Thus, Romano is prior art to the '201 patent.

¹ Claims 1-19 are entitled to an effective filing date no earlier than April 18, 2019, which is the date its parent application, U.S. App. No. 16/388,620, was filed. The claims 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.

² Ex. 1008 at 1174.

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.³ 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.⁴

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”).⁵ The production of CRF signals the pituitary gland to secrete another hormone, adrenocorticotrophic hormone (“ACTH”).⁶ ACTH stimulates the production of a number of precursor hormones, in particular 17- α -hydroxyprogesterone (“17-OHP”), that ultimately lead to the production of both cortisol and androstenedione

³ Ex. 1005, ¶ 13; Ex. 1013, 4134.

⁴ Ex. 1005, ¶ 14.

⁵ Ex. 1005, ¶ 16; Ex. 1014, 1.

⁶ *Id.*

(“A4”), which is a common precursor of the androgen sex hormones.⁷ Androgens are a group of hormones, such as testosterone, that regulate the development of male characteristics and reproductive activity. CAH patients cannot convert 17-OHP to cortisol.⁸ As a result, CAH patients produce excess 17-OHP that cannot be converted to cortisol.⁹ Because CAH patients can convert 17-OHP to A4, the excess 17-OHP is sent down this pathway, resulting in the overproduction of A4 and the downstream androgens that A4 converts to, testosterone and dihydroxytestosterone.¹⁰ The overproduction of androgens in CAH patients leads to a number of physiological problems, including abnormalities in growth and development in children, hirsutism (excessive hair growth), and in females, irregular or absent menstrual cycles and infertility.¹¹

Moreover, the continued cortisol deficiency in these patients creates a feedback loop whereby the body continues to produce CRF and ACTH, which

⁷ Ex. 1005, ¶¶ 14-16; Ex. 1014, 1.

⁸ *Id.*

⁹ Ex. 1005, ¶ 16; Ex. 1015, 2195-2196.

¹⁰ Ex. 1005, ¶¶ 16-17; Ex. 1015, 2195-2196.

¹¹ Ex. 1005, ¶ 20; Ex. 1016, 2130-2132.

results in the continued overproduction of 17-OHP, the continued overproduction of A4 and downstream androgens, and a continued cortisol deficiency.¹²

The objectives of CAH treatment are two-fold: to correct cortisol hormone deficiency and to control excess androgen production caused by elevated ACTH, 17-OHP, and A4 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 A4 and downstream androgen production.¹⁶ This is particularly true in the early morning

¹² Ex. 1005, ¶¶ 15-16.

¹³ Ex. 1001, 11:1-5; Ex. 1005, ¶ 18; Ex. 1014, 7-8.

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.

hours, because ACTH and A4 production follows a circadian pattern where the highest ACTH and A4 production occurs in the early morning.¹⁷

To address the issue of excessive ACTH, and subsequently excessive downstream A4 and 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

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].

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

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 ’201 patent. For example,

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

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].

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 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, A4, and downstream 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

²⁶ Ex. 1005, ¶ 24; Ex. 1021, 130-131.

²⁷ Ex. 1005, ¶ 24; Ex. 1022, 331; Ex. 1016, 2132.

²⁸ Ex. 1005, ¶ 25; Ex. 1008, 1177.

27% compared to placebo.²⁹ Administration of 300 mg or 600 mg of NBI-77860 also reduced mean A4 levels in six of the eight patients studied.³⁰

Neurocrine's Phase II study demonstrated that compared to a pre-dose baseline, administering crinecerfont daily for 14 days reduced median ACTH and 17-OHP levels in the morning window between 53% to 66% in four dosing cohorts.³¹ Administration of crinecerfont daily for 14 days reduced median A4 levels in the morning window between 21% and 64% in four dosing cohorts.³²

IV. THE '201 PATENT AND ITS PROSECUTION HISTORY

A. The '201 Patent Disclosure

The '201 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.³³ Spruce is developing tildacerfont as a

²⁹ Ex. 1005, ¶ 25; Ex. 1008, 1177.

³⁰ Ex. 1005, ¶¶ 25, 58; Ex. 1008, Table 3.

³¹ Ex. 1005, ¶ 52; Ex. 1009, Fig. 3.

³² Ex. 1005, ¶ 52-55; Ex. 1009, Fig. 3.

³³ The '201 patent discloses two chemical names that can be referred to as "Compound 1." Ex. 1001, 14:15-42. These two chemical names are alternative

potential treatment for CAH.³⁴ U.S. Patent No. 8,030,304 (Ex. 1012, “the ’304 patent”), which issued on October 4, 2011, claims tildacerfont and discloses CRF1 receptor antagonists as useful for treating various psychiatric and neuroendocrine disorders, neurological diseases, and metabolic syndromes, including CAH.³⁵

The ’201 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 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 Congenital adrenal hyperplasia (CAH).³⁶

The Summary of the Invention states:

The present invention provides novel pharmaceutical compositions comprising 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-

names for the same compound, tildacerfont. *See*

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

³⁴ Ex. 1011, 1.

³⁵ Ex. 1005, ¶ 27; Ex. 1012, 2:10-62, 44:7-10.

³⁶ Ex. 1001, Abstract (emphasis added).

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*³⁷

* * *

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 range followed by a maintenance therapy of a daily dosing of compound 1.³⁸

* * *

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*³⁹

³⁷ Ex. 1001, 1:32-40 (emphasis added).

³⁸ *Id.*, 4:45-5:2 (emphasis added).

³⁹ *Id.*, 8:37-40 (emphasis added).

* * *

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*⁴⁰

* * *

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*⁴¹

* * *

In one aspect, *the present disclosure* provides a method of improving the quality of life of a subject in need thereof, comprising administering a pharmaceutical composition comprising *Compound 1*⁴²

Each of the embodiments for the above-described aspects in the Summary of the Invention also refers to Compound 1.⁴³ Nowhere does the '201 patent describe or disclose the use of any compound other than Compound 1 (tildacerfont) to treat

⁴⁰ *Id.*, 8:63-67 (emphasis added).

⁴¹ *Id.*, 9:19-22 (emphasis added).

⁴² *Id.*, 9:46-49 (emphasis added).

⁴³ *See generally id.*, 1:30-10:2.

CAH or any other condition.

Examples 3-8 of the '201 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 1.⁴⁴ Example 4 describes a 6-week Phase II clinical study of Compound I in adults with classic CAH.⁴⁵ The '201 patent reports that the subjects in the Phase II study demonstrated reduction in A4 levels.⁴⁶ 60% of subjects in the study demonstrated a more than 25% reduction in A4.⁴⁷ Examples 5-8 describe clinical study protocols but do not disclose any data.⁴⁸

The '201 patent does not contain any description or data for any compound besides Compound 1 (tildacerfont).

B. The '201 Patent Claims

In contrast to the '201 patent specification, the '201 patent claims are not

⁴⁴ *Id.*, 35:62-41:41.

⁴⁵ *Id.*, 41:43-43:53.

⁴⁶ *Id.*, 43:29-53; Fig. 4.

⁴⁷ *Id.*

⁴⁸ *Id.*, 43:55-47:49.

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.⁴⁹ Specifically, independent claim 1, the only independent claim, recites a method of treating CAH by administering a therapeutically effective amount of a CRF1 receptor antagonist, or pharmaceutically acceptable salt thereof, wherein the A4 level of a human is reduced from baseline and is maintained at a reduced level post 24 hours.⁵⁰

Dependent claims 2-4 add dosing ranges or amounts of the CRF1 antagonist to the limitations of the independent claims.⁵¹

Dependent claim 5 recites that the CRF1 receptor antagonist be in the form of microparticles, and claim 6 requires that the average size of the microparticles be between about 1 μ m and about 20 μ m.⁵²

Dependent claim 7 requires the CRF1 receptor antagonist to be in the form of a pharmaceutical composition, and claim 8 specifies that the pharmaceutical composition is a capsule or a tablet.⁵³

⁴⁹ *Id.*, 47:51-48:51.

⁵⁰ *Id.*, 47:51-48:5.

⁵¹ *Id.*, 48:6-16.

⁵² *Id.*, 48:17-21.

⁵³ *Id.*, 48:22-26.

Dependent claim 9 recites that the treated condition is classic CAH, while claim 10 recites that the treated condition is the non-classical form of CAH.⁵⁴

Dependent claims 11 to 15 require at least a 5%, 10%, 15%, 20%, and 25% reduction in A4 levels, respectively, from baseline.”⁵⁵

Dependent claim 16 requires that the A4 level be “reduced from baseline and is maintained at a reduced level post 4 weeks.”⁵⁶ Dependent claim 17 requires that the A4 level be “reduced from baseline and is maintained at a reduced level post 6 weeks.”⁵⁷

Claim 18 adds administration of a glucocorticoid to the method of claim 1, and claim 19 requires that the glucocorticoid be administered within two hours of the CRF1 receptor antagonist”⁵⁸

C. The '201 Patent Prosecution History

The '201 patent issued on May 18, 2021 from U.S. Patent Application No. 17/078,054 (“the '054 application”), which was filed on October 22, 2020 with 20

⁵⁴ *Id.*, 48:27-29.

⁵⁵ *Id.*, 48:30-39.

⁵⁶ *Id.*, 48:40-42.

⁵⁷ *Id.*, 48:43-45.

⁵⁸ *Id.*, 48:46-51.

claims.⁵⁹

The '054 application is a continuation of Application No. 16/388,620 (“the '620 application”), which issued as U.S. Patent No. 10,849,908 (“the '908 patent;” Ex. 1036). 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 and the '406 Provisional, as well as the original claims of the '620 application, were limited to the administration of Compound 1 or a pharmaceutically acceptable salt or solvate thereof.⁶⁰

The '760 PCT contains the same Phase II clinical data as the '201 patent and the '908 patent.⁶¹ The '406 Provisional, however, contains no Phase II clinical data, including no data on reduction of A4 levels after administration of a CRF1 receptor antagonist. The '908 patent and the '201 patent share the same specification.

On December 14, 2020, the Examiner rejected pending claims 1-4, 7-15, and

⁵⁹ See Ex. 1002, 303-304.

⁶⁰ Ex. 1003, 38-52; Ex. 1004, 52-61; Ex. 1037 at 308-322.

⁶¹ Ex. 1003, 102-103.

19-20 of the '054 application as obvious in view of Neurocrine's prior work on a particular CRF1 receptor antagonist, NBI-77860, as disclosed in Grigoriadis (Ex. 1006), in combination with Fuqua et al., "Duration of Suppression of Adrenal Steroids after Glucocorticoid Administration," *International Journal of Pediatric Endocrinology* (2010) ("Fuqua;" Ex. 1038).⁶² The Examiner also rejected pending claims 5-6 as obvious in view of Grigoriadis in combination with Fuqua and US 2006/0078623 to Dhoot et al. ("Dhoot;" Ex. 1010).⁶³ The Examiner further rejected claims 1-20 on the ground of nonstatutory double patenting over the claims of the '620 application in view of Fuqua.⁶⁴

In response, Spruce amended claim 1 to require the reduction in A4 level to be "maintained at a reduced level post 24 hours."⁶⁵ Spruce also canceled claim 16.⁶⁶ In remarks accompanying the amendment, Spruce asserted that amended claim 1, the only independent claim, "is not obvious over the asserted combination of Grigoriadis et al. and Fuqua et al. because these, references, alone or in

⁶² Ex. 1002, 202-205.

⁶³ *Id.*, 205-206.

⁶⁴ *Id.*, 206-208.

⁶⁵ *Id.*, 34, 36.

⁶⁶ *Id.*, 34.

combination, do not meet all of the elements of claim 1.”⁶⁷ The applicants also submitted a terminal disclaimer over the ’908 patent.⁶⁸ On March 9, 2021, the Examiner allowed the pending claims without comment.⁶⁹

The “maintained at a reduced level post 24 hours” limitation originated in the prosecution history of the parent of the ’201 patent, the ’620 application. During the prosecution of the ’620 application, the Examiner rejected then-pending claims 181-184, 187-194 and 197-200 of the ’620 application as obvious in view of Neurocrine’s prior work on NBI-77860, as disclosed in Grigoriadis (Ex. 1006), and rejected then-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).⁷⁰ In response, Spruce 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.”⁷¹

⁶⁷ *Id.*, 36.

⁶⁸ *Id.*, 37-38.

⁶⁹ *Id.*, 12.

⁷⁰ *Id.*, 112-116.

⁷¹ *Id.*, 100-102.

On November 25, 2019, the Examiner again rejected claims 181-184, 187-194 and 197-200 of the '620 application over Grigoriadis, and rejected claims 185-186 and 195-196 over the combination of Grigoriadis and Dhoot.⁷² To overcome this rejection, Spruce submitted a supplemental response supported by the declaration of Chris Barnes, a Vice President and Project Team Leader at Spruce.⁷³

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.⁷⁴ 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—not that administration of a single dose maintains ACTH or 17-OHP reductions more than 24 hours.⁷⁵ The Barnes declaration did not present any data regarding a reduction in A4 levels, or the maintenance of a reduction in A4 levels for more than 24 hours.⁷⁶

⁷² Ex. 1037, 86-91.

⁷³ *Id.*, 30-38.

⁷⁴ *Id.*, 35-37.

⁷⁵ Ex. 1005, ¶¶ 46, 61; Ex. 1037, 35-37.

⁷⁶ Ex. 1037, 34-38.

Spruce relied on this data as purportedly demonstrating unexpected results that distinguished the '620 application claims from Grigoriadis.⁷⁷ The Examiner accepted Spruce's argument during prosecution of the '620 application.⁷⁸ The Examiner accepted the same argument during the prosecution of the '201 patent—after Spruce added the “maintained at a reduced level post 24 hours” limitation to independent claim 1, the Examiner allowed the claims without further comment.⁷⁹

However, in allowing the claims of both the '201 patent and the '908 patent on this basis, the Examiner overlooked the fact that these results were not surprising based on the data for NBI-77860 presented in Grigoriadis.⁸⁰ Spruce's data merely showed that there is no decrease in the efficacy of tildacerfont over time, which was entirely expected.⁸¹

In addition, the Examiner was unaware, during prosecution of both the '201 patent and the '908 patent, of clinical data for another CRF1 receptor antagonist

⁷⁷ Ex. 1037, 30-32.

⁷⁸ Ex. 1037, 12.

⁷⁹ Ex. 1002, 12, 34.

⁸⁰ *Infra*, § VII.G.1; Ex. 1005, ¶¶ 57-64.

⁸¹ *Id.*

disclosed in Grigoriadis, crinecerfont,⁸² demonstrating that crinecerfont, when dosed as described in Grigoriadis, met the limitations of these patent claims.⁸³ Like Spruce’s data, the crinecerfont clinical data was collected after 14 days of daily dosing, and demonstrates that reductions in A4, ACTH and 17-OHP from baseline were maintained “post 24 hours” in the same way as Spruce’s data.⁸⁴

V. LEGAL STANDARDS

A. Anticipation

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 of a genus requires only that the prior art disclose a single species within the genus. *Eli Lilly & Co. v. Barr Lab’ys, Inc.*, 251 F.3d 955, 971 (Fed. Cir. 2001). 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

⁸² Ex. 1006, ¶ [0054].

⁸³ *Infra*, § VII.D; Ex. 1005, ¶¶ 47-56.

⁸⁴ *Infra*, § VII.D; Ex. 1005, ¶¶ 47-56; Ex. 1009, 3.

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).

B. Obviousness

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). A patent can also be obvious in view of multiple references, provided those references provide a teaching or motivation for a person of ordinary skill to combine them in a way that leads to the patented invention. *Canfield Sci., Inc. v. Melanoscan, LLC*, 987 F.3d 1375, 1378 (Fed. Cir. 2021) (citing *KSR*, 550 U.S. at 400–01).

“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 ’201 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.⁸⁵

VI. 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 claim 1 recites a reduction in A4 level “from baseline” after administering a CRF1 receptor antagonist to a CAH patient. Dependent claims 11-15 require a reduction in A4 level of at least 5%, at least 10%, at least 15%, at least 20%, or at least 25%, respectively, from baseline. The only clinical data in the ’201 patent relating to A4 describe measuring A4 level before the administration of

⁸⁵ Ex. 1005, ¶ 34.

tildacerfont, a CRF1 receptor antagonist, and measuring A4 level after the administration of the first dose of tildacerfont.⁸⁶ Figure 4 of the '201 patent presents the measurements and shows a reduction of A4 due to the administration of tildacerfont, i.e., a change from baseline.⁸⁷

The Board has previously construed a related term “reduced by at least 10% from baseline” in the '908 patent, which issued from the parent application of the '201 patent. The Board construed this term in the '908 patent as meaning “a reduction of at least 10% in the level of ACTH (claim 1) or 17-OHP (claim 11) compared to measurements of ACTH or 17-OHP made prior to, and/or at the beginning of, administration of the drug.”⁸⁸ Petitioner applies this definition of “from baseline”—a measurement made prior to, and/or at the beginning of, administration of the drug—in this petition.

B. “A Human”/“The Human”

Independent claim 1 recites treating CAH in “a human” by administering a CRF1 receptor antagonist to “the human,” wherein the A4 level in “the human” is reduced. Based upon the ordinary meaning of the claim language, “a human”/“the

⁸⁶ Ex. 1001, 41:45-59, 43:47-53, Fig. 4; Ex. 1005, ¶ 37.

⁸⁷ Ex. 1001, 43:47-53, Fig. 4; Ex. 1005, ¶ 37.

⁸⁸ PGR2021-00088, Paper 11 at 9.

human” refers to an individual patient.⁸⁹ This is supported by the intrinsic evidence, which presents changes in A4 level 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”,
“Maintained at a Reduced Level Post 4 Weeks”,
“Maintained at a Reduced Level Post 6 Weeks”**

Independent claim 1 recites a reduction in A4 level from baseline, which is “maintained at a reduced level post 24 hours.” Claim 16 requires the reduction in A4 level to be maintained at a reduced level post 4 weeks, and claim 17 requires the reduction in A4 level to be maintained at a reduced level post 6 weeks. The phrases “maintained at a reduced level post 24 hours,” “maintained at a reduced level post 4 weeks,” and “maintained at a reduced level post 6 weeks” mean that the A4 level is maintained at a reduced level for the specified period of time with repeated dosing.⁹² In other words, there is no loss of efficacy with repeated dosing.

The intrinsic evidence supports this interpretation. For example, Figure 4 of

⁸⁹ Ex. 1005, ¶ 42.

⁹⁰ Ex. 1001, Fig. 4; Ex. 1005, ¶ 42.

⁹¹ Ex. 1005, ¶ 42.

⁹² Ex. 1005, ¶¶ 43-46.

the '201 patent shows the change in A4 level after repeated administration of tildacerfont for up to 6 weeks.⁹³ Notably, the intrinsic record contains no evidence that a single, non-repeated, dose of tildacerfont (or any other CRF1 receptor antagonist) would maintain a reduced A4 level for more than 24 hours, for more than 4 weeks, or for more than 6 weeks.⁹⁴

VII. THE CLAIMS OF THE '201 PATENT ARE UNPATENTABLE

The '201 patent repeatedly characterizes its invention as relating to Compound 1.⁹⁵ During prosecution of the parent '908 patent, Spruce convinced the Examiner to allow the '908 patent claims over one of the CRF1 receptor antagonists taught by Grigoriadis (NBI-77860) 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. These faulty arguments carried through to the '201 patent, which similarly claims the use of all CRF1 receptor antagonists, and which the Examiner similarly allowed based on a mistaken understanding that maintaining reduced hormone levels with repeated dosing was unexpected.

⁹³ Ex. 1001, 10:27-28, 41:51-62, Fig. 4; Ex. 1005, ¶ 44.

⁹⁴ Ex. 1005, ¶ 46.

⁹⁵ Ex. 1001, Abstract, 1:32-40, 4:45-5:2, 8:37-40, 8:63-67, 9:19-22, 9:46-49, 35:62-41:41, 41:43-43:53.

Spruce's actions and arguments are inconsistent. Because claims 1-19 of the '201 patent are not limited to Compound 1, they are unpatentable under 35 U.S.C. § 112, ¶ 1 for failure to meet the written description requirement.

As set forth in detail below, claims 1-19 of the '201 patent are also unpatentable over Grigoriadis' disclosure of crinecerfont under 35 U.S.C. §§ 102(a) and 103, alone or in combination with Romano. Separately, claims 1-19 are unpatentable under 35 U.S.C. § 103 over the disclosure of NBI-77860 in Grigoriadis and Turcu 2016, alone or in combination with Romano. As described in detail below, the Examiner made several errors in allowing claims 1-19, 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 crinecerfont (SSR-125543) and NBI-77860.⁹⁶ Grigoriadis teaches administering the CRF1 receptor antagonist as a single dose ranging from 50-1000 mg.⁹⁷ Grigoriadis discloses the dose is administered at bedtime "to deliver clinically relevant concentrations of the CRF1 antagonist at or before (such

⁹⁶ Ex. 1006, ¶¶ [0051], [0054].

⁹⁷ *Id.*, ¶ [0063].

as 2-5 hours before) the expected circadian release of ACTH.”⁹⁸ As a downstream hormone of ACTH, A4 follows a similar circadian pattern as ACTH.⁹⁹

1. Grigoriadis’ Disclosure of Crinercerfont (SSR-125543)

Grigoriadis discloses that SSR-125543 is a CRF1 receptor antagonist, which is useful for the treatment of CAH.¹⁰⁰ Specifically, Grigoriadis states that in one embodiment, the CRF1 receptor antagonist is one of a limited list of compounds that specifically includes SSR-125543.¹⁰¹ SSR-125543 is also known as crinercerfont.¹⁰² Crinercerfont is currently being developed by Petitioner, Neurocrine Biosciences, as a treatment for CAH.

The results of Neurocrine’s Phase II crinercerfont clinical study were summarized in an article published in *The Journal of Clinical Endocrinology & Metabolism* on October 15, 2021 (Ex. 1009; “Auchus 2021”).¹⁰³ Auchus 2021 is not prior art, but is used in this petition to demonstrate what necessarily occurs

⁹⁸ *Id.*, ¶ [0066].

⁹⁹ Ex. 1005, ¶ 40.

¹⁰⁰ Ex. 1006, ¶ [0054].

¹⁰¹ *Id.*, ¶ [0054].

¹⁰² See <https://pubchem.ncbi.nlm.nih.gov/compound/5282340>; Ex. 1005, ¶¶ 28, 47.

¹⁰³ Ex. 1009.

upon administration of crinecerfont to a CAH patient as disclosed in Grigoriadis, which is permitted by controlling Federal Circuit precedent. *See Hospira*, 946 F.3d at 1329.

The Phase II clinical study showed that the administration of crinecerfont to a patient with CAH resulted in a reduction in A4 (androstenedione) level compared to the patient's baseline level prior to administration of crinecerfont, which was maintained at a reduced level post 24 hours.¹⁰⁴ This clinical study tested four dosing regimens, with patients in four cohorts receiving between 50 mg and 200 mg of crinecerfont per day, administered for 14 consecutive days.¹⁰⁵ The study measured the patients' baseline A4 levels over a 24-hour period beginning in the evening of the seventh day before the study began (Day-7 to Day-6).¹⁰⁶ After 14 days of repeated dosing of crinecerfont, the patients' A4 levels were measured over a 24-hour period beginning in the evening of Day 14 and ending on Day 15.¹⁰⁷

¹⁰⁴ Ex. 1005, ¶¶ 48-56; Ex. 1009, 3-11, Tables 2-3, Figs. 2-4.

¹⁰⁵ Ex. 1005, ¶ 49; Ex. 1009, 3.

¹⁰⁶ Ex. 1005, ¶ 50; Ex. 1009, 3, Figs. 1-2.

¹⁰⁷ Ex. 1005, ¶ 50; Ex. 1009, 3, Figs. 1-2.

A4 levels compared to baseline were reduced for patients in all four cohorts after receiving crinecerfont for 14 days.¹⁰⁸ Auchus 2021 Table 2 presents the median change from baseline in A4 level after administration of crinecerfont in the four cohorts.¹⁰⁹ Figure 2, an excerpt of which is reproduced below, presents 24-hour profiles of median patient A4 by cohort, at baseline and at Day 14.¹¹⁰ 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 (see Fig. 2). The decrease in androstenedione was most pronounced for cohort 4 (100 mg twice a day).”¹¹¹ Auchus 2021 also reported that “[d]ose-related decreases in androstenedione were also observed, ranging from a 21% reduction in cohort 1 (50 mg once daily at bedtime) to a 64% reduction in cohort 4 (100 mg twice a day).”¹¹²

¹⁰⁸ Ex. 1005, ¶ 51; Ex. 1009, 3-11, Tables 2-3, Figs. 2-4.

¹⁰⁹ Ex. 1005, ¶ 52; Ex. 1009, Table 2.

¹¹⁰ Ex. 1005, ¶ 52; Ex. 1009, Fig. 2.

¹¹¹ Ex. 1005, ¶ 52; Ex. 1009, 5.

¹¹² Ex. 1005, ¶ 54; Ex. 1009, 5.

C. Serum androstenedione, nmol/L

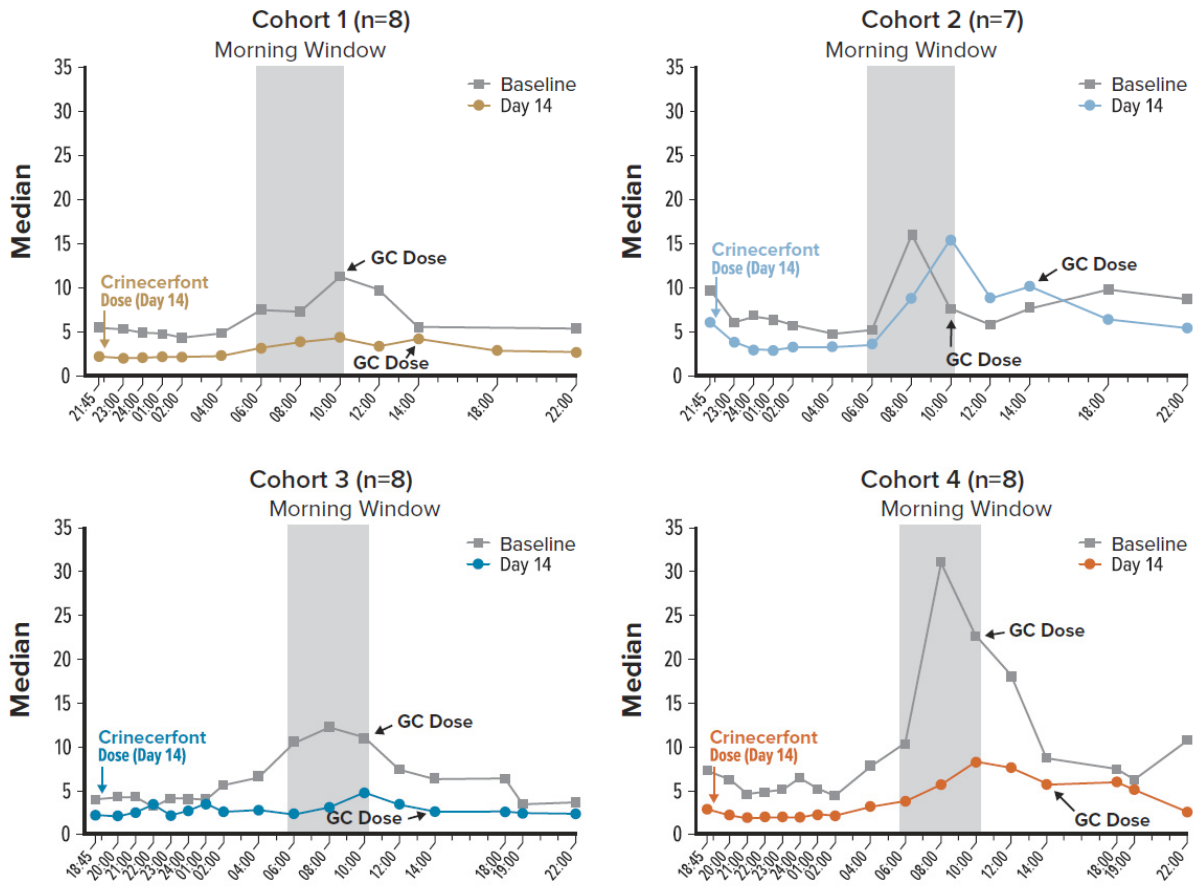


Figure 2. Twenty-four-hour profiles. For cohorts 1 and 2, crinecerfont dosing was at 22:00 on day 14; predose sampling was at 21:45. For cohorts 3 and 4, crinecerfont dosing was at 19:00 on day 14; predose sampling was at 18:45. 17OHP, 17-hydroxyprogesterone; ACTH, adrenocorticotropic; GC, glucocorticoid.

Ex. 1009, Excerpt of Figure 2

Table 2. Effects of crinecerfont on adrenal androgens and precursors^{a,b}

Median (IQR)	Cohort 1: 50 mg once daily at bedtime (n = 8)		Cohort 2: 100 mg once daily at bedtime (n = 7)		Cohort 3: 100 mg once daily in evening (n = 8)		Cohort 4: 100 mg twice a day (n = 8)	
	Morning window ^c	24-h period ^d	Morning window ^c	24-h period ^d	Morning window ^c	24-h period ^d	Morning window ^c	24-h period ^d
ACTH, pmol/L								
At baseline	33 (103)	20 (69)	43 (83)	16 (21)	98 (104)	28 (26)	68 (86)	22 (25)
Change from baseline to day 14	-24 (48)	-7.6 (48)	-34 (42)	-9.2 (16)	-85 (101)	-18 (29)	-45 (57)	-5.8 (15)
17OHP, nmol/L								
At baseline	162 (77)	69 (89)	299 (452)	114 (260)	197 (292)	89 (150)	327 (425)	103 (175)
Change from baseline to day 14	-81 (43)	-20 (43)	-135 (281)	-38 (104)	-102 (208)	-59 (94)	-171 (330)	-41 (74)
Androstenedione, nmol/L								
At baseline	9.4 (12)	7.5 (6.5)	7.8 (51)	7.2 (38)	11 (19)	6.4 (13)	27 (41)	9.9 (27)
Change from baseline to day 14	-3.8 (4.8)	-0.9 (4.2)	-5.8 (12)	-3.5 (8.5)	-8.1 (13)	-4.8 (9.7)	-14 (33)	-4.2 (16)

Ex. 1009, Excerpt of Table 2

The “morning window” is clinically relevant because the body’s natural circadian release of ACTH, and consequently the release of downstream hormones such as A4, occurs in the early morning hours.¹¹³ In the absence of treatment, the highest ACTH and A4 levels in CAH patients are observed in the morning; reducing ACTH and A4 during this time period is an important objective of any CAH treatment.¹¹⁴

The Phase II clinical study reported in Auchus 2021 also examined median percent reductions in patient A4 levels during the clinically relevant morning window (6-10 a.m.) after 14 days of receiving crinecerfont compared to baseline

¹¹³ Ex. 1005, ¶¶ 19, 53; Ex. 1006, ¶ [0066].

¹¹⁴ Ex. 1005, ¶¶ 19, 53; Ex. 1009, 3.

morning window measurements.¹¹⁵ Auchus 2021 Figure 3, reproduced below, shows the median percent reduction in morning window A4 in all four cohorts exceeded 21% after 14 days of receiving crinecerfont, compared to the patients' baseline.¹¹⁶ As indicated in the right-hand panel of Figure 3, median morning window A4 decreased from baseline by 21% in patients in Cohort 1, by 42% in patients in Cohort 2, by 51% in patients in Cohort 3, and by 64% in patients in Cohort 4.¹¹⁷

¹¹⁵ Ex. 1005, ¶ 53; Ex. 1009, 5, Fig. 3, Table 3.

¹¹⁶ Ex. 1005, ¶ 55; Ex. 1009, Fig. 3.

¹¹⁷ Ex. 1005, ¶ 55; Ex. 1009, Fig. 3.

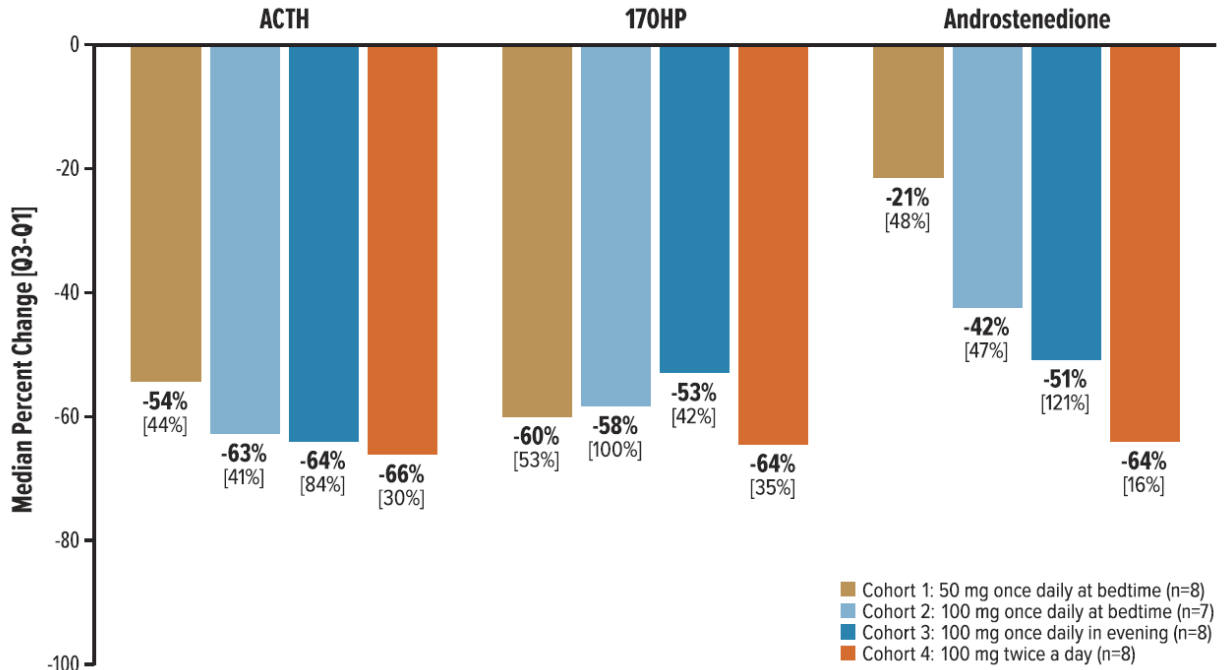


Figure 3. Median percent reductions from baseline to day 14 based on morning window values. Based on each participant's values from the morning window time points (06:00, 08:00, 10:00). The interquartile ranges (absolute value of Q3-Q1) for median percent reductions are shown in brackets. 17OHP, 17-hydroxyprogesterone; ACTH, adrenocorticotropin.

Ex. 1009, Figure 3

Auchus 2021 also reports the number of patients with a greater than 50% reduction in A4 at Day 14 compared to baseline levels.¹¹⁸ Auchus 2021 Table 3, reproduced below, reports that 25% of patients in Cohort 1, 43% of patients in Cohort 2, 50% of patients in Cohort 3, and 75% of patients in Cohort 4 demonstrated a greater than 50% reduction in A4 at Day 14 compared to the patient's baseline level.¹¹⁹

¹¹⁸ Ex. 1005, ¶ 56; Ex. 1009, Table 3.

¹¹⁹ Ex. 1005, ¶ 56; Ex. 1009, Table 3.

Table 3. Proportion of participants having 50% or greater reduction in morning window hormone values from baseline to day 14 and proportion achieving normal values

Participants, n/N (%)	Cohort 1: 50 mg once daily at bedtime	Cohort 2: 100 mg once daily at bedtime	Cohort 3: 100 mg once daily in evening	Cohort 4: 100 mg twice a day
With ≥ 50% reduction from baseline				
ACTH	4/8 (50)	5/7 (71)	5/8 (63)	6/8 (75)
17OHP	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 for women	2/4 (50)	3/5 (60)	2/3 (67)	3/4 (75)
Androstenedione/testosterone ratio for men	1/4 (25)	0/2 (0)	4/5 (80)	2/3 (67)
With return to normal values^d				
Androstenedione	2/5 (40)	1/4 (25)	2/5 (40)	2/6 (33)
Testosterone for women	1/1 (100)	0/1 (0)	1/1 (100)	0/1 (0)
Androstenedione/testosterone ratio for men	1/3 (33)	0/2 (0)	2/4 (50)	2/3 (67)

Abbreviations: 17OHP, 17-hydroxyprogesterone; ACTH, adrenocorticotropic.

^dIn the subset of participants who had baseline androstenedione or (in women) testosterone values that were greater than 1.2 × upper limit of normal (age- and sex-matched) or androstenedione/testosterone ratio (in men) greater than or equal to 0.5.

Ex. 1009, Table 3

2. Grigoriadis' Disclosure of 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.¹²⁰ Each patient received single bedtime doses of placebo, 300 mg NBI-77860, and 600 mg NBI-77860, each during a separate treatment period.¹²¹ The study provided for a 21-day drug-free interval (washout period) in between each treatment.¹²² Grigoriadis discloses

¹²⁰ Ex. 1006, ¶¶ [0090]-[0091], Fig. 4.

¹²¹ *Id.*, ¶ [0091], Fig. 4.

¹²² *Id.*

that “[t]he PD endpoints for this study included the HPA axis biomarkers of interest in this patient population; namely, 17-hydroxyprogesterone (17-OHP; as the primary PD endpoint), adrenocorticotrophic hormone (ACTH), androstenedione, testosterone, and serum cortisol levels.”¹²³

B. Turcu 2016

Turcu 2016 (Ex. 1008) presents data from the same Phase I study disclosed in Example 6 of Grigoriadis. Turcu 2016 discloses that “[p]lasma drug concentrations and the hypothalamic-pituitary adrenal axis biomarkers ACTH, 17OHP, androstenedione, testosterone, and cortisol were measured in all samples.”¹²⁴ Table 3 of Turcu 2016 reports A4 (androstenedione) data within the morning window (6-10 a.m.) for individual patients.¹²⁵ Turcu 2016 states that “[r]eductions in serum testosterone and androstenedione were observed in some participants during one or both treatment periods (Table 3).”¹²⁶ Six of the eight

¹²³ *Id.*, ¶ [0091].

¹²⁴ Ex. 1008, 1175.

¹²⁵ *Id.*, 1179.

¹²⁶ *Id.*, 1177, Table 3.

patients observed a reduction in A4 within the morning window, calculated as a mean of the 6-10 a.m. time points.¹²⁷

Table 3. Serum Androstenedione and Testosterone After Single Doses of NBI-77860, Mean, and Percent Change From Placebo During the Morning Window (6–10 AM)

Participant	Dose	Androstenedione		Testosterone	
		Mean (ng/dl)	% Change From Placebo	Mean (ng/dl)	% Change From Placebo
1011001	Placebo	303.0	0	105.3	0
	300	295.3	-2.5	131.7	25.0
	600	265.7	-12.3	122.7	16.5
1011002	Placebo	185.3	0	49.7	0
	300	190.7	2.9	42.7	-14.1
	600	78.0	-57.9	23.0	-53.7
1011003	Placebo	146.0	0	35.0	0
	300	132.7	-9.1	32.3	-7.6
	600	147.7	1.1	34.0	-2.9
1011004	Placebo	820.0	0	169.3	0
	300	747.7	-8.8	158.7	-6.3
	600	934.0	13.9	164.0	-3.1
1011005	Placebo	308.0	0	76.3	0
	300	377.0	22.4	107.3	40.6
	600	420.3	36.5	83.0	8.7
1011006	Placebo	195.7	0	59.7	0
	300	141.0	-27.9	36.7	-38.5
	600	173.3	-11.4	50.7	-15.1
1011007	Placebo	145.3	0	47.3	0
	300	135.3	-6.9	32.3	-31.7
	600	84.7	-41.7	19.0	-59.9
1011008	Placebo	914.0	0	127.0	0
	300	973.3	6.5	147.3	16.0
	600	1366.3	49.5	194.3	53.0

Turcu 2016 (Ex. 1008) at Table 3

C. Romano

Romano discloses therapeutic combinations of atypical antipsychotics with CRF1 receptor antagonists.¹²⁸ Romano notes that CRF1 receptor antagonists have been described in the art as effective in the treatment of various conditions, and

¹²⁷ *Id.*

¹²⁸ Ex. 1007, Abstract and ¶ [0012].

provides examples of CRF1 receptor antagonists known in the art.¹²⁹ 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.¹³⁰

Romano discloses that the active ingredients in the described compositions can “range in size from nanoparticles to microparticles.”¹³¹ Romano also discloses that the CRF1 receptor antagonist can be in a sustained or controlled release form.¹³² The use of nanoparticles or microparticles is a common method of developing sustained or controlled release pharmaceutical formulations.¹³³

D. Ground 1: Grigoriadis’ Disclosure of Crinecerfont Anticipates Claims 1-4, 7-9, 11-15, and 18.

- 1. The use of crinecerfont to treat CAH, as disclosed in Grigoriadis, inherently results in an A4 reduction from baseline that is maintained post 24 hours as recited in claim 1.**

¹²⁹ *Id.*, ¶¶ [0009]-[0010].

¹³⁰ *Id.*, ¶ [0526].

¹³¹ *Id.*, ¶ [0531].

¹³² *Id.*

¹³³ Ex. 1005, ¶ 75; Ex. 1023, 2; Ex. 1035, 309-310, 349-350.

Claim 1 requires administering a therapeutically effective amount of a CRF1 receptor antagonist to a human, wherein an A4 level in the human is reduced from baseline and is maintained at a reduced level post 24 hours.

As discussed in Section VII.A.1 above, Grigoriadis discloses crinecerfont (SSR-125543), a CRF1 receptor antagonist, as useful for the treatment of CAH.¹³⁴ Grigoriadis also discloses a range of therapeutically acceptable amounts of a CRF1 receptor antagonist, about 50-1000 mg.¹³⁵ The administration of a therapeutically effective amount of crinecerfont to a patient as taught in Grigoriadis inherently and necessarily results in a reduction of a patient's A4 level compared to the patient's baseline level, and that reduction is maintained post 24 hours.¹³⁶

As discussed above, a skilled artisan would understand “maintained at a reduced level post 24 hours” to mean maintenance of reduced hormone levels for more than 24 hours when a patient is dosed repeatedly.¹³⁷ After 14 days of administering crinecerfont once or twice daily, a patient, and indeed most patients, in the clinical study reported in Auchus 2021 experienced a reduction in A4 levels

¹³⁴ Ex. 1006, ¶ [0054].

¹³⁵ Ex. 1006, ¶ [0063].

¹³⁶ Ex. 1005, ¶¶ 47-56; Ex. 1009, 3-11, Tables 2-3, Figs. 2-4.

¹³⁷ *Supra*, § V.C; Ex. 1005, ¶¶ 43-46.

at Day 14 compared to baseline measurements.¹³⁸ Specifically, median A4 measurements taken over 24 hours and within the morning window (6-10 a.m.) time points showed that administration of a therapeutically effective amount of crinecerfont to a patient meets the reduction in A4 level from baseline requirement recited in '201 patent claim 1 at Day 14, *i.e.*, post 24 hours.¹³⁹ Baseline measurement were taken over a 24-hour period beginning in the evening of the seventh day before the study began (Day-7 to Day-6),¹⁴⁰ and thus were made prior to administration of the study drug.¹⁴¹

Administration of a therapeutically effective amount of crinecerfont to a patient, as taught by Grigoriadis, necessarily results in a reduction in a patient's A4 level from baseline after 14 days of repeated dosing—*i.e.*, the A4 reduction is maintained for more than 24 hours. Thus, Grigoriadis inherently anticipates '201 patent claim 1. *See Liebel-Flarsheim*, 481 F.3d at 1381; *Monsanto Technology*, 878 F.3d at 1343.

¹³⁸ Ex. 1005, ¶¶ 50-51; Ex. 1009, 3-11, Tables 2-3, Figs. 2-4.

¹³⁹ Ex. 1005, ¶¶ 52-54, 62; Ex. 1009, 3-11, Tables 2-3, Figs. 2-4.

¹⁴⁰ *Id.*

¹⁴¹ *See* Section VI.A, *supra*.

2. Grigoriadis discloses all of the limitations of dependent claims 2-4, 7-9, 11-15, and 18.

a. Claim 2

In addition to the limitations of claim 1, claim 2 requires administering the CRF1 receptor antagonist at a dose ranging from about 50 mg/day and about 1600 mg/day. Grigoriadis discloses “pharmaceutical compositions comprising any one of the CRF antagonist compounds described herein [which includes crinecerfont] and a pharmaceutically acceptable excipient for use in the methods for treating CAH.”¹⁴² Grigoriadis discloses administering the CRF1 receptor antagonist in such compositions at a dose ranging from 50-1000 mg, which falls within the range recited in ’201 patent claim 2.¹⁴³ Moreover, Auchus 2021 demonstrates that repeated administration of crinecerfont at doses falling within the claimed range (between 50 mg/day and 200 mg/day), resulted in a reduction in a patient’s A4 level compared to baseline that is maintained after 14 days of crinecerfont administration.¹⁴⁴ Grigoriadis meets every limitation of claim 2, and therefore anticipates claim 2. *See Liebel-Flarsheim*, 481 F.3d at 1381.

¹⁴² Ex. 1006, ¶ [0061].

¹⁴³ Ex. 1005, ¶ 66; Ex. 1006, ¶ [0063].

¹⁴⁴ Ex. 1005, ¶¶ 47-56, 66; Ex. 1009, 3-11, Tables 2-3, Figs. 2-4.

b. Claim 3

In addition to the limitations of claim 1, claim 3 requires administering the CRF1 receptor antagonist at a dose ranging from about 100 mg/day and about 600 mg/day. As discussed with respect to claim 2 above, Grigoriadis discloses administering a CRF1 receptor antagonist at a dose ranging from 50-1000 mg, which encompasses the range recited in claim 3.¹⁴⁵ Moreover, Auchus 2021 shows the repeated administration of crinecerfont at doses falling within the claimed range (between 50 mg/day and 200 mg/day) resulted in a reduction in a patient's A4 level compared to baseline that is maintained after 14 days of crinecerfont administration.¹⁴⁶ Grigoriadis meets every limitation of claim 3, and therefore anticipates claim 3. *See Liebel-Flarsheim*, 481 F.3d at 1381.

c. Claim 4

Claim 4 depends from claim 1, and requires administering the CRF1 receptor antagonist at a dose of about 200 mg/day. Grigoriadis discloses crinecerfont as a CRF1 receptor antagonist useful in the treatment of CAH.¹⁴⁷ Grigoriadis also discloses administering CFR1 receptor antagonists of the

¹⁴⁵ Ex. 1005, ¶ 68; Ex. 1006, ¶ [0063].

¹⁴⁶ Ex. 1005, ¶¶ 47-56, 71; Ex. 1009, 3-11, Tables 2-3, Figs. 2-4.

¹⁴⁷ Ex. 1005, ¶ 70; Ex. 1006, ¶¶ [0051], [0054].

invention, which includes crinecerfont, to treat CAH at a dose ranging from 50-1000 mg.¹⁴⁸

Auchus 2021 demonstrates that the repeated administration of 200 mg/day crinecerfont results in a reduction of A4 relative to baseline that is maintained after 14 days of crinecerfont administration.¹⁴⁹ 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.¹⁵⁰ Median A4 levels in Cohort 4 patients decreased from baseline after receiving 200 mg/day of crinecerfont for 14 days—patients in this cohort had a 64% median percent reduction in A4 level from baseline.¹⁵¹ These data demonstrate that a patient, and indeed most patients, experienced a reduction in A4 compared to baseline, and that this reduction was maintained after 14 days, i.e., post 24 hours.¹⁵² Thus, Grigoriadis meets every limitation of claim 4, and anticipates claim 4. *See Liebel-Flarsheim*, 481 F.3d at 1381; *Hospira*, 946 F.3d at 1329.

¹⁴⁸ Ex. 1005, ¶ 70; Ex. 1006, ¶¶ [0061], [0063].

¹⁴⁹ Ex. 1005, ¶¶ 47-56, 72-73; Ex. 1009, 3-11, Tables 2-3, Figs. 2-4.

¹⁵⁰ Ex. 1005, ¶ 71; Ex. 1009, 3.

¹⁵¹ Ex. 1005, ¶ 71; Ex. 1009, 5, Fig. 3.

¹⁵² *Id.*

d. Claims 7-8

Claim 7 requires the CRF1 receptor antagonist to be in the form of a pharmaceutical composition, and claim 8 requires the composition to be in the form of a capsule or a tablet. Grigoriadis expressly teaches pharmaceutical compositions that contain “any one of the CRF1 receptor antagonists described herein,” which includes crinecerfont, for use in methods of treating CAH, and further discloses that the pharmaceutical compositions described can be in the form of a tablet.¹⁵³ Therefore, Grigoriadis meets every limitation of claims 7-8, and anticipates those claims. *See Liebel-Flarsheim*, 481 F.3d at 1381.

e. Claim 9

Claim 9 depends from claim 1, and requires 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.¹⁵⁴ As discussed above, Grigoriadis also discloses the use of crinecerfont to treat CAH, and Auchus 2021 reports that when crinecerfont was administered to patients with classic 21-hydroxylase deficiency CAH, patients exhibited a reduction in A4

¹⁵³ Ex. 1005, ¶¶ 78-79; Ex. 1006, ¶¶ [0054], [0061], [0073], [0074].

¹⁵⁴ Ex. 1005, ¶ 80; Ex. 1006, ¶¶ [0004], [0034], Fig 1.

relative to baseline that was maintained after 14 days of crinecerfont administration, i.e., post 24 hours.¹⁵⁵ Therefore, Grigoriadis meets every limitation of claim 9, and anticipates claim 9. *See Liebel-Flarsheim*, 481 F.3d at 1381.

f. Claims 11-15

Claims 11-15 require that the reduction in A4 from baseline recited in claim 1 to be at least 5%, 10%, 15%, 20%, or 25% from baseline, respectively. Grigoriadis teaches the use of crinecerfont to treat CAH patients.¹⁵⁶ As reported in Auchus 2021, the administration of crinecerfont to a patient results in a reduction of the patient's A4 level by at least 25% compared to baseline after 14 days of repeated dosing.¹⁵⁷ Specifically, Auchus 2021 reports that dose-related decreases from baseline were observed, "ranging from a 21% reduction in cohort 1 (50 mg once daily at bedtime) to a 64% reduction in cohort 4 (100 mg twice a day)."¹⁵⁸ Median morning window A4 decreased from baseline by 21% in patients in Cohort 1, by 42% in patients in Cohort 2, by 51% in patients in Cohort 3, and by 64% in

¹⁵⁵ Ex. 1005, ¶¶ 47-56, 80; Ex. 1009, 3-11, Tables 2-3, Figs. 2-4.

¹⁵⁶ Ex. 1005, ¶ 85; Ex. 1006, ¶ [0051].

¹⁵⁷ Ex. 1005, ¶¶ 47-56, 85; Ex. 1009, 3-11, Tables 2-3, Figs. 2-4.

¹⁵⁸ Ex. 1005, ¶ 54, 85, Ex. 1009, 5.

patients in Cohort 4.¹⁵⁹ Auchus 2021 also reports that after 14 days of receiving crinecerfont, 25% of patients in Cohort 1, 43% of patients in Cohort 2, 50% of patients in Cohort 3, and 75% of patients in Cohort 4 demonstrated a greater than 50% reduction in A4 at Day 14 compared to the patient's baseline level.¹⁶⁰ These data demonstrate that at least one patient, and indeed most patients, achieved an at least 25% reduction in A4 compared to the patient's baseline after day 14—i.e., post 24 hours.

The use of crinecerfont to treat CAH as taught by Grigoriadis will reduce the A4 level of a patient by at least 5%, 10%, 15%, 20%, and 25% compared to the patient's baseline, and thus Grigoriadis thus meets every limitation of claims 11-15, and anticipates those claims. *See Liebel-Flarsheim*, 481 F.3d at 1381.

g. Claim 18

In addition to the limitations of claim 1, claim 18 further requires administering a glucocorticoid. Grigoriadis discloses that the use of glucocorticoids as maintenance therapy for CAH patients was known in the art.¹⁶¹ Grigoriadis also discloses that a CRF1 receptor antagonist may lower the amount

¹⁵⁹ Ex. 1005, ¶ 55, Ex. 1009, Fig. 3.

¹⁶⁰ Ex. 1005, ¶ 56, Ex. 1009, Table 3.

¹⁶¹ Ex. 1005, ¶ 89; Ex. 1006, ¶¶ [0069].

of glucocorticoids administered to a CAH patient, indicating co-administration.¹⁶²

As reported in Auchus 2021, patients in Neurocrine’s Phase II study evaluating crinecerfont were kept on their existing glucocorticoid treatments throughout the study, and achieved a reduction in A4 levels compared to baseline after 14 days of crinecerfont administration.¹⁶³ Grigoriadis thus meets every limitation of claim 18, and anticipates claim 18. *See Liebel-Flarsheim*, 481 F.3d at 1381.

E. Ground 2: Claims 10, 16-17, and 19 Would Have Been Obvious in View of Grigoriadis’ Disclosure of Crinecerfont and the Knowledge of a Skilled Artisan.

1. Claim 10

Claim 10 of the ’201 patent depends on claim 1 and requires 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.¹⁶⁴ Grigoriadis also teaches that CRF1 receptor antagonists, including crinecerfont, are useful to treat CAH.¹⁶⁵

¹⁶² Ex. 1005, ¶ 89; Ex. 1006, ¶ [0070].

¹⁶³ Ex. 1005, ¶¶ 47-56, 88; Ex. 1009, 3-11, Tables 2-3, Figs. 2-4.

¹⁶⁴ Ex. 1005, ¶ 82; Ex. 1006, ¶ [0004].

¹⁶⁵ Ex. 1005, ¶ 82; Ex. 1006, ¶¶ [0051], [0054].

A skilled artisan would understand that the endocrinological mechanism for classic CAH and non-classic CAH—21-hydroxylase deficiency—is the same.¹⁶⁶ In view of that knowledge, and the disclosure of Grigoriadis that CRF1 receptor antagonists, including crinecerfont, are useful to treat CAH, including by reducing A4 levels, a skilled artisan would be motivated to use these CRF1 receptor antagonists, including crinecerfont, to treat patients with non-classic CAH.¹⁶⁷ A skilled artisan would also reasonably expect CRF1 receptor antagonists to be effective in treating non-classic CAH, based on data showing their effectiveness in classic CAH patients.¹⁶⁸ Therefore, claim 10 would have been obvious in view of Grigoriadis and the knowledge of a skilled artisan. *See Hoffmann-La Roche*, 748 F.3d at 1331.

2. Claims 16-17

Claim 16 depends from claim 1 and requires that the reduction in A4 from baseline is maintained at a reduced level post 4 weeks. Claim 17 depends from claim 1 and requires that the reduction in A4 from baseline is maintained at a reduced level post 6 weeks.

¹⁶⁶ Ex. 1005, ¶ 82, 84.

¹⁶⁷ *Id.*, ¶ 84.

¹⁶⁸ *Id.*

As set forth in Section VII.D.1 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 A4 level after 14 days of repeated dosing—*i.e.*, the A4 reduction is maintained for more than 2 weeks.¹⁶⁹ In view of the disclosure of Grigoriadis, it would have been obvious to a skilled artisan that the reduction in patient A4 levels would be maintained for more than four weeks, or for more than six weeks, with continuous dosing.¹⁷⁰ A skilled artisan would reasonably expect a drug to maintain its efficacy over time with repeated dosing.¹⁷¹ Therefore, the use of crinecerfont to treat CAH as taught by Grigoriadis and the knowledge of a skilled artisan would render claim 16 and claim 17 obvious. *See KSR*, 550 U.S. at 421.

3. Claim 19

Claim 19 depends from claim 18. Claim 18 requires administering a glucocorticoid to the method of claim 1. Claim 19 further requires that the glucocorticoid be administered concurrently or sequentially within two hours of

¹⁶⁹ Ex. 1005, ¶¶ 47-56, 87; Ex. 1006, ¶ [0054]; Ex. 1009, 3-11, Tables 2-3, Figs. 2-4.

¹⁷⁰ Ex. 1005, ¶¶ 87-88.

¹⁷¹ Ex. 1005, ¶ 62.

the CRF1 receptor antagonist. Grigoriadis teaches that the use of glucocorticoids as maintenance therapy for CAH patients was known in the art, and that a CRF1 receptor antagonist may lower the amount of glucocorticoids administered to a CAH patient, indicating co-administration.¹⁷² 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.¹⁷³

Both glucocorticoids and CRF1 receptor antagonists treat CAH by reducing ACTH and downstream hormones, such as A4.¹⁷⁴ Moreover, Grigoriadis discloses that one objective of administering a CRF1 receptor antagonist is to reduce the amount of glucocorticoids needed by a CAH patient.¹⁷⁵ 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 A4 reduction.¹⁷⁶ Accordingly, claim 19 would have been obvious

¹⁷² Ex. 1005, ¶ 92; Ex. 1006, ¶¶ [0069]-[0070].

¹⁷³ Ex. 1005, ¶¶ 91-95.

¹⁷⁴ Ex. 1005, ¶¶ 91-93; Ex. 1006, ¶¶ [0006], [0040], [0069]-[0070].

¹⁷⁵ Ex. 1005, ¶ 92; Ex. 1006, ¶ [0070].

¹⁷⁶ Ex. 1005, ¶¶ 91-95.

over Grigoriadis in combination with the knowledge of a skilled artisan. *See KSR*, 550 U.S. at 421.

F. Ground 3: Claims 5-6 Would Have Been Obvious in View of Grigoriadis' Disclosure of Crinecerfont in Combination with Romano and the Knowledge of a Skilled Artisan.

Claim 5 depends on claim 1 and requires the CRF1 receptor antagonist to be in the form of microparticles. Claim 6 depends on claim 5 and requires 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, which include crinecerfont, 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 antipsychotic, can range in size from nanoparticles to microparticles.¹⁷⁷ A person of ordinary skill would understand Romano to teach

¹⁷⁷ Ex. 1005, ¶¶ 74-75; Ex. 1007, Abstract, ¶ [0531].

the use of small particle sizes with CRF1 receptor antagonists, such as the claimed range of between about 1-20 μm .¹⁷⁸

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.¹⁷⁹ 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.¹⁸⁰ 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

¹⁷⁸ Ex. 1005, ¶¶ 76-77.

¹⁷⁹ Ex. 1005, ¶ 75; Ex. 1006, ¶ [0061]; Ex. 1007, ¶ [0531].

¹⁸⁰ Ex. 1005, ¶ 75; Ex. 1006, ¶ [0073]; Ex. 1007, ¶ [0531]; Ex. 1023, 2; Ex. 1035, 309-310, 349-350.

ingredient.¹⁸¹ Thus, it would have been obvious to formulate the CRF1 receptor antagonists disclosed by Grigoriadis, including crinecerfont, 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.¹⁸² The claimed 1-20 μm particle size represents, at best, a simple matter of routine optimization.¹⁸³ Accordingly, claims 5 and 6 would have been obvious in view of Grigoriadis in combination with Romano and the knowledge of a skilled artisan. *See KSR*, 550 U.S. at 421.

G. Ground 4: Claims 1-4 and 7-19 Would Have Been Obvious in View of Grigoriadis' and Turcu 2016's Disclosure of NBI-77860 and the Knowledge of a Skilled Artisan.

1. Claim 1 would have been obvious in view of Grigoriadis' and Turcu 2016's disclosure of NBI-77860 reducing A4 in a patient compared to placebo measurement

Claim 1 requires administering a therapeutically effective amount of a CRF1 receptor antagonist to a human, wherein an A4 level in the human is reduced from

¹⁸¹ Ex. 1005, ¶ 73, 75; Ex. 1006, ¶ [0073]; Ex. 1023, 2; Ex. 1035, 309-310, 349-350.

¹⁸² Ex. 1005, ¶¶ 76-77.

¹⁸³ *Id.*

baseline and is maintained at a reduced level post 24 hours. Claim 1 would have been obvious in view of in the disclosure of NBI-77860 in Grigoriadis and Turcu 2016.

As discussed in Sections VII.A.2 and VII.B above, both Grigoriadis and Turcu 2016 report the results of a Phase I study in which a single dose of 300 mg or 600 mg NBI-77860, a CRF1 receptor antagonist, was administered to patients.¹⁸⁴ A skilled artisan would understand that these references discuss the same study, and would therefore be motivated to combine the teachings of Grigoriadis and Turcu 2016, and to consider their teachings together.¹⁸⁵ Turcu 2016 reports that 300 mg or 600 mg of NBI-77860 reduced A4 levels in six of the eight CAH patients studied compared to placebo over a 24-hour period post-dose.¹⁸⁶

As set forth in Section VI.A above, “reduced from baseline” refers to a reduction in a patient’s A4 level compared to a measurement made prior to

¹⁸⁴ Ex. 1005, ¶ 57.

¹⁸⁵ Ex. 1005, ¶ 64.

¹⁸⁶ Ex. 1005, ¶¶ 58-60, 86; Ex. 1006, ¶¶ [0091]-[0093], Figs. 5-6; Ex. 1008, Table 3.

administration of the drug.¹⁸⁷ The clinical study reported in Grigoriadis Example 6 and in Turcu 2016 provided patients with a placebo, then 300 mg of NBI-77860, then 600 mg of NBI-77860, in three separate treatment periods.¹⁸⁸ Turcu 2016 reports the change in A4 level for each patient after receiving 300 mg and 600 mg of NBI-77860 compared to the patient's A4 level after receiving placebo.¹⁸⁹

It would be obvious to a skilled artisan, based on the disclosure of Grigoriadis Example 6 and Turcu 2016, that administering NBI-77860 to a patient would reduce that patient's A4 level compared to the patient's baseline—i.e., the patient's A4 level before receiving any drug.¹⁹⁰ A skilled artisan would be aware that a placebo is a treatment which does not contain any drug.¹⁹¹ Therefore, a skilled artisan would reasonably expect, based on data showing administration of NBI-77860 reduced A4 in a patient compared to a placebo measurement, that administration of NBI-77860 would also reduce the patient's A4 level compared to baseline. To the extent that a placebo treatment elevated levels of A4 or its

¹⁸⁷ Ex. 1005, ¶ 37.

¹⁸⁸ Ex. 1005, ¶ 57; Ex. 1006, ¶ [0091], Fig. 1; Ex. 1008, 3, Fig. 1A.

¹⁸⁹ Ex. 1005, ¶ 58; Ex. 1008, Table 3.

¹⁹⁰ Ex. 1005, ¶ 59.

¹⁹¹ *Id.*

precursor hormones, the reduction in A4 from administration of NBI-77860 compared to placebo disclosed in Turcu 2016 would further indicate to a skilled artisan that administration of NBI-77860 would reduce A4 in a patient compared to the patient's baseline level.¹⁹²

As set forth in Section VI.C above, “maintained at a reduced level post 24 hours” refers to maintaining reduced A4 levels with repeated dosing.¹⁹³ A skilled artisan would expect a drug to maintain its efficacy over time with repeated dosing.¹⁹⁴ A reduction in efficacy of a drug over time is relatively rare.¹⁹⁵ A skilled artisan would have reasonably expected the A4 reductions over 24 hours after administration of NBI-77860 disclosed in Turcu 2016 to extend beyond 24 hours with repeated dosing of NBI-77860.¹⁹⁶ In view of the disclosure of

¹⁹² Ex. 1005, ¶ 59; Ex. 1040 at 722-23.

¹⁹³ Ex. 1005, ¶¶ 43-46.

¹⁹⁴ Ex. 1005, ¶¶ 62-63, 87-88; Ex. 1032 at 36; Ex. 1032, 35-36; Ex. 1033, 205; Ex. 1034, 153.

¹⁹⁵ Ex. 1005, ¶¶ 62-63, 87-88; Ex. 1032 at 36; Ex. 1032, 35-36; Ex. 1033, 205; Ex. 1034, 153.

¹⁹⁶ Ex. 1005, ¶¶ 62-63, 87-88; Ex. 1032 at 36; Ex. 1032, 35-36; Ex. 1033, 205; Ex. 1034, 153.

Grigoriadis and Turcu 2016, it would have been obvious to a skilled artisan that the reduction in A4 level from baseline would be maintained for more than 24 hours with repeated dosing.¹⁹⁷

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 presented no objective evidence of non-obviousness during prosecution of the ’201 patent. In prosecuting the ’908 patent, the parent of the ’201 patent, Spruce presented alleged evidence of non-obviousness of maintaining reductions of different hormone biomarkers, ACTH and 17-OHP, for more than 24 hours after repeated dosing of one compound, tildacerfont. That is not commensurate with the scope of claim 1 of the ’201 patent, which recites the

¹⁹⁷ Ex. 1005, ¶¶ 62-63, 87-88.

administration of CRF1 receptor antagonists broadly, and which recites a reduction in A4, not ACTH or 17-OHP. *Id.*

Accordingly, claim 1 of the '201 patent would have been obvious over Grigoriadis, Turcu 2016, and the knowledge of a skilled artisan. *See KSR*, 550 U.S. at 421.

2. Claim 2-4 and 7-19 would have been obvious in view of Grigoriadis' and Turcu 2016's disclosure of NBI-77860 and the knowledge of a skilled artisan

a. Claim 2

In addition to the limitations of claim 1, claim 2 requires administering the CRF1 receptor antagonist at a dose ranging from about 50 mg/day to about 1600 mg/day. Grigoriadis discloses a dosing range for CFR1 receptor antagonists to treat CAH in a range from about 50-1000 mg.¹⁹⁸ Grigoriadis further expressly teaches administering NBI-77860 at doses of 300 mg and 600 mg.¹⁹⁹ Turcu 2016 presents data showing these doses are effective at reducing an A4 level in a patient.²⁰⁰ As discussed in Section VII.G.1 above, in view of Grigoriadis and Turcu 2016, it would have been obvious to a skilled artisan that the reduction in

¹⁹⁸ Ex. 1005, ¶ 70; Ex. 1006, ¶ [0063].

¹⁹⁹ Ex. 1005, ¶ 57; Ex. 1006, ¶ [0091].

²⁰⁰ Ex. 1005, ¶¶ 57-64, 74; Ex. 1006, ¶¶ [0091]-[0093]; Ex. 1008, Table 3.

A4 level from baseline would be maintained for more than 24 hours with repeated dosing.²⁰¹

Accordingly, claim 2 would have been obvious over Grigoriadis, Turcu 2016, and the knowledge of a skilled artisan. *See KSR*, 550 U.S. at 421.

b. Claim 3

In addition to the limitations of claim 1, claim 3 requires administering the CRF1 receptor antagonist at a dose ranging from about 100 mg/day to about 600 mg/day. Grigoriadis discloses a dosing range for CFR1 receptor antagonists to treat CAH in a range from about 50-1000 mg.²⁰² Grigoriadis further expressly teaches administering NBI-77860 at doses of 300 mg and 600 mg.²⁰³ Turcu 2016 presents data showing these doses are effective at reducing an A4 level in a patient.²⁰⁴ As discussed in Section VII.G.1 above, in view of Grigoriadis and Turcu 2016, it would have been obvious to a skilled artisan that the reduction in

²⁰¹ Ex. 1005, ¶ 61.

²⁰² Ex. 1005, ¶ 70; Ex. 1006, ¶ [0063].

²⁰³ Ex. 1005, ¶ 57; Ex. 1006, ¶ [0091].

²⁰⁴ Ex. 1005, ¶¶ 57-64, 74; Ex. 1006, ¶¶ [0091]-[0093]; Ex. 1008, Table 3.

A4 level from baseline would be maintained for more than 24 hours with repeated dosing.²⁰⁵

Accordingly, claim 3 would have been obvious over Grigoriadis, Turcu 2016, and the knowledge of a skilled artisan. *See KSR*, 550 U.S. at 421.

c. Claim 4

Claim 4 depends from claim 1, and requires administering the CRF1 receptor antagonist at a dose of about 200 mg/day. Grigoriadis discloses a dosing range for CFR1 receptor antagonists to treat CAH in a range from about 50-1000 mg.²⁰⁶ The claimed 200 mg/day dose falls within this range. Grigoriadis also discloses administering NBI-77860 at doses of 300 mg/day and 600 mg/day, and Turcu 2016 presents data showing these doses are effective at reducing an A4 level in a patient.²⁰⁷ Grigoriadis also teaches that “[t]he use of the minimum dose that is sufficient to provide effective therapy is usually preferred.”²⁰⁸

“[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

²⁰⁵ Ex. 1005, ¶ 61.

²⁰⁶ Ex. 1005, ¶ 70; Ex. 1006, ¶ [0063].

²⁰⁷ Ex. 1005, ¶¶ 57-64, 74; Ex. 1006, ¶¶ [0091]-[0093]; Ex. 1008, Table 3.

²⁰⁸ Ex. 1005, ¶ 72; Ex. 1006, ¶ [0063].

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 ’201 patent claim 4 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 teaches that the use of the minimum effective dose is preferred.²⁰⁹ Turcu 2016 presents data showing that a 300 mg/day dose of NBI-77860 was effective to reduce an A4 level in a patient.²¹⁰ 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 in combination with Turcu 2016 and the knowledge of a skilled artisan.²¹¹

Spruce presented no evidence during prosecution of the ’201 patent, or its parent ’908 patent, 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

²⁰⁹ Ex. 1005, ¶ 72; Ex. 1006, ¶ [0063].

²¹⁰ Ex. 1008, Table 3; Ex. 1005, ¶ 60.

²¹¹ Ex. 1005, ¶ 72.

considerations.²¹² Thus, claim 4 would have been obvious in view of Grigoriadis in combination with Turcu 2016 and the knowledge of a skilled artisan. *See Galderma*, 737 F.3d at 738.

d. Claims 7-8

Claim 7 requires the CRF1 receptor antagonist to be in the form of a pharmaceutical composition, and claim 8 requires the composition to be in the form of a capsule or a tablet. As set forth in Section VII.D.2.d above, Grigoriadis expressly teaches pharmaceutical compositions that contain a CRF1 receptor antagonist as required by claim 7, and further discloses that the pharmaceutical compositions described can be in the form of a tablet as required by claim 8.²¹³ For the same reasons, these claims are rendered obvious in view of the disclosure of NBI-77860 in Grigoriadis, the disclosure of Turcu 2016, and the knowledge of a skilled artisan. *See KSR*, 550 U.S. at 421.

e. Claim 9

Claim 9 depends from claim 1, and requires the treated condition to be classic CAH. As set forth in Section VII.D.2.e above, Grigoriadis teaches that the most common form of CAH is 21-hydroxylase deficiency caused by mutations in

²¹² Ex. 1002, 33-39; Ex. 1037, 30-38, 53, 70-72, 100-102.

²¹³ Ex. 1005, ¶¶ 78-79; Ex. 1006, ¶¶ [0061], [0073], [0074].

the CYP21A2 gene, and that the more severe form of 21-hydroxylase deficiency is termed classical CAH.²¹⁴ Grigoriadis also expressly teaches administering NBI-77860 to treat patients with classic 21-hydroxylase deficiency CAH.²¹⁵ Turcu 2016 reports that the administration of NBI-77860 to a patient with classic 21-hydroxylase deficiency CAH reduced A4 level in the patient.²¹⁶

Therefore, claim 9 is rendered obvious in view of the disclosure of NBI-77860 in Grigoriadis and Turcu 2016, and the knowledge of a skilled artisan. *See KSR*, 550 U.S. at 421.

f. Claim 10

Claim 10 depends on claim 1 and requires 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.²¹⁷ Grigoriadis and Turcu 2016 present data showing that NBI-77860 is effective in treating patients with classic CAH.²¹⁸

²¹⁴ Ex. 1005, ¶ 80; Ex. 1006, ¶¶ [0004], [0034], Fig 1.

²¹⁵ Ex. 1005, ¶ 80; Ex. 1006, ¶¶ [0091].

²¹⁶ Ex. 1008, Table 3; Ex. 1005, ¶ 58.

²¹⁷ Ex. 1005, ¶ 82; Ex. 1006, ¶ [0004].

²¹⁸ Ex. 1005, ¶¶ 57-64, 83; Ex. 1006, ¶¶ [0090]-[0093], Figs. 5-6.

A skilled artisan would understand that the endocrinological mechanism for classic CAH and non-classic CAH—21-hydroxylase deficiency—is the same.²¹⁹ In view of that knowledge, the disclosure of Grigoriadis and Turcu 2016 that CRF1 receptor antagonists including NBI-77860 are useful to treat CAH, including by reducing A4 levels, and the data showing NBI-77860 was effective in treating patients with classic CAH, a skilled artisan would be motivated to use NBI-77860 to treat patients with non-classic CAH.²²⁰ A skilled artisan would also reasonably expect NBI-77860 to be effective in treating non-classic CAH, based on data showing its effectiveness in classic CAH patients.²²¹ Therefore, claim 10 would have been obvious in view of Grigoriadis, Turcu 2016, and the knowledge of a skilled artisan. *See Hoffmann-La Roche*, 748 F.3d at 1331.

g. Claims 11-15

Claims 11-15 require that the reduction in A4 from baseline recited in claim 1 to be at least 5%, 10%, 15%, 20%, or 25% from baseline, respectively. As discussed in Sections VII.A.2 and VII.B above, Grigoriadis and Turcu 2016 describe a clinical study in which eight patients were given 300 mg, and 600 mg of

²¹⁹ Ex. 1005, ¶ 82.

²²⁰ *Id.*, ¶ 84.

²²¹ *Id.*

NBI-77860.²²² Turcu 2016 disclose that administration of a single dose of 300 mg or 600 mg NBI-77860 reduced A4 by at least 5% in five of the eight patients studied, by at least 10% in three of the eight patients studied, by at least 15% in three of the eight patients studied, by at least 20% in three of the eight patients studied and by at least 25% in three of the eight patients studied.²²³ As set forth in Section VII.G.1 above, it would have been obvious to a skilled artisan that the reduction in A4 from baseline would be maintained for more than 24 hours with repeated dosing.²²⁴

Therefore, claims 11-15 are rendered obvious in view of the disclosure of NBI-77860 in Grigoriadis and Turcu 2016, and the knowledge of a skilled artisan. *See KSR*, 550 U.S. at 421.

h. Claims 16-17

Claim 16 depends from claim 1 and requires that the reduction in A4 from baseline is maintained at a reduced level post 4 weeks. Claim 17 depends from claim 1 and requires that the reduction in A4 from baseline is maintained at a reduced level post 6 weeks.

²²² Ex. 1005, ¶ 57; Ex. 1006, ¶ [0091].

²²³ Ex. 1008, Table 3; Ex. 1005, ¶ 85.

²²⁴ Ex. 1005, ¶¶ 85-88.

As discussed in Sections VII.A.2 and VII.B above, Grigoriadis and Turcu 2016 disclose the use of NBI-77860 to treat CAH, and Turcu 2016 reports that administration of a single dose of 300 mg or 600 mg NBI-77860 reduced A4 in a CAH patient over a 24-hour period post-dose.²²⁵ A skilled artisan would expect a drug to maintain its efficacy over time with repeated dosing.²²⁶ Thus, a skilled artisan would have reasonably expected that the A4 reductions disclosed in Grigoriadis and Turcu 2016 would be maintained post four weeks and post six weeks with repeated dosing of NBI-77860.²²⁷ Therefore, the use of NBI-77860 to treat CAH as taught by Grigoriadis and Turcu 2016 would render claim 16 and claim 17 obvious. *See KSR*, 550 U.S. at 421.

i. Claim 18

In addition to the limitations of claim 1, claim 18 further requires administering a glucocorticoid. As set forth in Section VII.D.2.g above, Grigoriadis teaches that the use of glucocorticoids as maintenance therapy for CAH patients was known in the art.²²⁸ Grigoriadis also discloses that a CRF1

²²⁵ Ex. 1005, ¶¶ 57-64; Ex. 1006, ¶¶ [0091]-[0093], Figs. 5-6; Turcu, Table 3.

²²⁶ Ex. 1005, ¶ 88.

²²⁷ Ex. 1005, ¶¶ 85-88.

²²⁸ Ex. 1005, ¶ 89; Ex. 1006, ¶¶ [0069].

receptor antagonist may lower the amount of glucocorticoids administered to a CAH patient, indicating co-administration.²²⁹ Grigoriadis and Turcu 2016 also discloses a clinical study in which glucocorticoids were co-administered with NBI-77860.²³⁰ For the same reasons as set forth in Section VII.D.2.g, claim 18 is rendered obvious in view of the disclosure of NBI-77860 in Grigoriadis and Turcu 2016, and the knowledge of a skilled artisan. *See KSR*, 550 U.S. at 421.

j. Claim 19

Claim 19 depends from claim 18, and further requires that the glucocorticoid be administered concurrently or sequentially within two hours of the CRF1 receptor antagonist. As discussed in Section VII.E.c above, Grigoriadis teaches co-administration of a CRF1 antagonist and a glucocorticoid.²³¹ 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.²³²

²²⁹ Ex. 1005, ¶ 89; Ex. 1006, ¶ [0070].

²³⁰ Ex. 1005, ¶¶ 57-64, 89-90; Ex. 1006, ¶¶ [0091]-[0093].

²³¹ Ex. 1005, ¶¶ 91, 95; Ex. 1006, ¶¶ [0069]-[0070], [0091].

²³² Ex. 1005, ¶¶ 91-95.

Both glucocorticoid and CRF1 receptor antagonists treat CAH by reducing ACTH and downstream hormones, such as A4.²³³ Moreover, Grigoriadis discloses that one objective of administering a CRF1 receptor antagonist is to reduce the amount of glucocorticoids needed by a CAH patient.²³⁴ 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 A4 reduction.²³⁵

Based on the results in Turcu 2016 showing that NBI-77860 alone could reduce A4 levels, the skilled artisan would have reasonably expected that administering the glucocorticoid as claimed also would successfully reduce A4 levels relative to baseline.²³⁶ Accordingly, claim 19 would have been obvious over Grigoriadis in combination with Turcu 2016 and the knowledge of a skilled artisan. *See KSR*, 550 U.S. at 421.

²³³ Ex. 1005, ¶¶ 91-95; Ex. 1006, ¶¶ [0006], [0040], [0069]-[0070].

²³⁴ Ex. 1005, ¶ 92; Ex. 1006, ¶ [0070].

²³⁵ Ex. 1005, ¶¶ 91-95.

²³⁶ *Supra*, § VII.B.

H. Ground 5: Claims 5-6 Would Have Been Obvious in View of Grigoriadis and Turcu 2016 in Combination with Romano and the Knowledge of a Skilled Artisan.

Claim 5 depends on claim 1 and requires the CRF1 receptor antagonist to be in the form of microparticles. Claim 6 depends on claim 5 and requires the average size of the CRF1 receptor antagonist microparticles to be between about 1 μm and about 20 μm .

Grigoriadis and Turcu 2016 do not explicitly disclose administering NBI-77860 in the form of microparticles. In view of Romano, however, it would have been obvious to formulate NBI-77860, the CRF1 receptor antagonist disclosed by Grigoriadis and Turcu 2016, 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 antipsychotic, can range in size from nanoparticles to microparticles.²³⁷ 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 .²³⁸

²³⁷ Ex. 1005, ¶¶ 76-77; Ex. 1007, Abstract, ¶ [0531].

²³⁸ Ex. 1005, ¶¶ 76-77.

A person of ordinary skill would have been motivated to combine the teachings of Grigoriadis and Turcu 2016 with Romano because they all relate to pharmaceutical compositions comprising a CRF1 receptor antagonist.²³⁹ Both Grigoriadis and Turcu 2016 report results of the same study evaluating the use of NBI-77860 to treat CAH patients. 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.²⁴⁰ 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 ingredient.²⁴¹ Thus, it would have been obvious to formulate NBI-77860, the CRF1 receptor antagonist disclosed by Grigoriadis and Turcu 2016, as microparticles.

²³⁹ Ex. 1005, ¶ 77; Ex. 1006, ¶ [0061]; Ex. 1007, ¶ [0531].

²⁴⁰ Ex. 1005, ¶ 75; Ex. 1006, ¶ [0073]; Ex. 1007, ¶ [0531]; Ex. 1023, 2; Ex. 1035, 309-310, 349-350.

²⁴¹ Ex. 1005, ¶ 75; Ex. 1006, ¶ [0073]; Ex. 1023, 2; Ex. 1035, 309-310, 349-350.

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.²⁴² The claimed 1-20 μm particle size represents, at best, a simple matter of routine optimization.²⁴³ Accordingly, claims 5 and 6 would have been obvious in view of Grigoriadis and Turcu 2016 in combination with Romano and the knowledge of a skilled artisan. *See KSR*, 550 U.S. at 421.

I. Ground 6: Claims 1-19 of the ’201 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. Associated Reg’l & Univ. Pathologists, 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 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

²⁴² Ex. 1005, ¶¶ 76-77.

²⁴³ *Id.*

‘present invention’ is strong evidence that the claims should not be read to encompass the opposite structure.”); *see also Gentry Gallery Inc. v. Berklinc 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 ’201 patent fail the written description requirement because the ’201 patent does not show possession of the claimed subject matter. The ’201 patent discloses only a single CRF1 receptor antagonist, tildacerfont (Compound 1).²⁴⁴ As set forth in Section IV.A above, the ’201 patent repeatedly characterizes the “present invention” or “present disclosure” as relating to Compound 1. For example, the Summary of the Invention states:

²⁴⁴ *Supra*, § IV.A; Ex. 1005, ¶ 96.

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*²⁴⁵

Moreover, all of the Examples and clinical data in the '201 patent relate to tildacerfont.²⁴⁶ The '201 patent does not disclose the use of any other CRF1 receptor antagonist to treat CAH. Nor does the '201 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. Moreover, Spruce has distinguished the features of tildacerfont from other CRF1 receptor antagonists in its scientific publications, stating that tildacerfont “was developed with structurally unique features that lower the lipophilicity and volume of distribution of the compound and improve solubility resulting in more predictable pharmacokinetic

²⁴⁵ Ex. 1001, 1:30-38 (emphasis added).

²⁴⁶ *Id.*, 34:5-47:58, Tables 5-8.

properties” compared to other, “first generation” CRF1 receptor antagonists.²⁴⁷

Notably, the original claims in the ’406 Provisional, the ’760 PCT, and the ’908 patent were limited to tildacerfont.²⁴⁸ During prosecution of the parent ’908 patent, Spruce expanded the scope of the claims to include the entire genus of CRF1 receptor antagonists.²⁴⁹ 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.”²⁵⁰ Spruce filed the application that issued as the ’201 patent as a continuation of the ’908 patent, and the ’201 patent likewise claims the entire genus of CRF1 receptor antagonists without any support in the specification for the breadth of the claims.

During prosecution of the ’908 patent, 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

²⁴⁷ Ex. 1039 at 2.

²⁴⁸ Ex. 1003, 38-52; Ex. 1004, 52-61.

²⁴⁹ Ex. 1037, 328-329.

²⁵⁰ *Id.*, 330.

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 function, then the claims must be unpatentable over earlier
Neurocrine art, Grigoriadis and Turcu 2016, which disclosed different CFR1
receptor antagonists that performed the same function.

For at least these reasons, claims 1-19 are unpatentable under 35 U.S.C. §
112, para. 1 because there is no written description support for all CRF1 receptor
antagonists.

VIII. 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 one ground, lack of written description, 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 claimed 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 and Turcu 2016. As set forth above, Dr. Carey has explained that the '201 patent claims are anticipated or obvious in view of the disclosure of crinecerfont in Grigoriadis, or are obvious in view of the disclosure of NBI-77860 in Grigoriadis and Turcu 2016, in combination with Romano and the knowledge of a skilled artisan.

When the Examiner was considering the '201 patent claims, she did not have the benefit of Dr. Carey's declaration, which demonstrates that the claimed 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 crinecerfont (SSR-125543), which demonstrated that this CRF1 receptor antagonist inherently met the post-24 hour limitation of claim 1, as well as the other claims.

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

IX. 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.

X. CONCLUSION

For the above-described reasons, claims 1-19 are unpatentable on a number of grounds. Accordingly, Petitioner requests that the Board grant the petition and find claims 1-19 unpatentable.

XI. 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 '201 Patent, nor is Petitioner aware of any pending civil actions involving the '201 patent.

On May 28, 2021, Petitioner filed a petition for post grant review (PGR2021-00088) of the '908 Patent, the parent of the '201 Patent. On December 10, 2021, the Board denied institution of this petition. Petitioner has filed a request for rehearing and a request for precedential opinion panel review, which are pending.

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

Neurocrine provides the following designation of counsel.

Lead Counsel	Backup counsel
Dorothy Whelan, Reg. No. 33,814 Fish & Richardson P.C. 3200 RBC Plaza 60 South Sixth Street Minneapolis, MN 55402 Tel: 612-335-5070 Fax: 877-769-7945 Email: PGR47291-0005PS1@fr.com	Robert Oakes, Reg. No. 62,189 Fish & Richardson P.C. 3200 RBC Plaza 60 South Sixth Street Minneapolis, MN 55402 Tel: 302-778-8477 Fax: 877-769-7945 Email: PTABInbound@fr.com

D. Service Information

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

Neurocrine consents to email service at PGR47291-0005PS1@fr.com (referencing No. 47291-0005PS1 and cc'ing PTABInbound@fr.com, whelan@fr.com and oakes@fr.com).

Respectfully submitted,

Dated: February 18, 2022

/Dorothy Whelan/

Dorothy Whelan, Reg. No. 33,814
Robert Oakes, Reg. No. 62,189
Fish & Richardson P.C.
3200 RBC Plaza, 60 South Sixth Street
Minneapolis, MN 55402
T: 612-335-5070
F: 877-769-7945

(Control No. PGR2022-00025)

Attorneys for Petitioner

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 15,199 words, which is less than the 18,700 allowed under 37 CFR § 42.24.

Dated : February 18, 2022

/Dorothy Whelan/
Dorothy Whelan, Reg. No. 33,814
Robert Oakes, Reg. No. 62,189
Fish & Richardson P.C.
3200 RBC Plaza, 60 South Sixth Street
Minneapolis, MN 55402
T: 612-335-5070
F: 877-769-7945

Attorneys for Petitioner

