

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NEUROCRINE BIOSCIENCES, INC.,

Petitioner

v.

SPRUCE BIOSCIENCES, INC.,

Patent Owner

Case PGR2021-00088

U.S. Patent 10,849,908

PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE

TABLE OF CONTENTS

I. INTRODUCTION.....	1
II. THE BOARD SHOULD REBUKE SPRUCE’S PERSONAL ATTACKS AGAINST DR. CUTLER	2
III. CLAIMS 1–25 ARE UNPATENTABLE FOR LACK OF WRITTEN DESCRIPTION (GROUND 4).....	4
A. The Specification Does Not Show Possession of Using a Class of CRF1 Receptor Antagonists to Treat CAH.....	6
B. The Prior Art Did Not Teach a Class of CRF1 Receptor Antagonists Could Treat CAH, or Reduce ACTH or 17-OHP by At Least 10%	7
C. The Specification Does Not Describe Common Structural Features of CRF1 Receptor Antagonists that Achieve the Claimed Reductions in ACTH or 17-OHP	9
IV. CLAIM CONSTRUCTION RELEVANT TO ANTICIPATION AND OBVIOUSNESS GROUNDS.....	12
A. Spruce Has Not Disputed Neurocrine’s Proposed Construction of “A Human”/ “The Human”	12
B. The Board’s Construction of “Baseline” Includes Comparisons From Placebo	13
C. Neurocrine’s Construction of “4 Hours Prior to Sleeping” Should Be Adopted.....	15
V. GRIGORIADIS’ DISCLOSURES ANTICIPATE CLAIMS 1-4,7-9,11-14,17- 19, AND 20-24 (Ground 1).....	15
A. Grigoriadis’ Disclosure of Crinecerfont Inherently Anticipate Claims 1 and 11.....	16
1. Unrecited claim elements are irrelevant to anticipation.	17

2. Auchus demonstrates the 10% reduction in ACTH and 17-OHP from baseline inevitably flows from the disclosure in Grigoriadis.....	19
B.Grigoriadis’ Disclosure of Verucerfont Anticipates Claims 1 and 11	21
1. Variability among patients does not undermine Grigoriadis’ disclosure of the claimed ACTH and 17-OHP reductions.	21
2. Grigoriadis’ verucerfont study was appropriately designed to demonstrate the claimed reductions.	24
C.Grigoriadis Anticipates Claims 2-4, 7-9, 12-14, 17-19, and 21-24.....	25
VI. GRIGORIADIS’ DISCLOSURE RENDERS CLAIMS 4, 10, 14, 20-22 AND 25 OBVIOUS (GROUND 2)	26
VII.THE COMBINATION OF GRIGORIADIS AND ROMANO RENDERS CLAIMS 5, 6, 15, AND 16 OBVIOUS (Ground 3)	26
VIII..... CLAIMS 1–25 ARE UNPATENTABLE FOR LACK OF ENABLEMENT (GROUND 5)	27

PETITIONER’S UPDATED EXHIBIT LIST

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

Exhibit Number	Exhibit Description
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”)

Exhibit Number	Exhibit Description
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”).

Exhibit Number	Exhibit Description
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	Declaration of Gordon B. Cutler, JR., M.D.

Exhibit Number	Exhibit Description
1037	Auchus et al., “Crinecerfont Lowers Elevated Hormone Markers in Adults with 21-Hydroxylase Deficiency Congenital Adrenal Hyperplasia,” <i>Journal of Clinical Endocrinology & Metabolism</i> (2021) (“Auchus”).
1038	Transcript of June 5, 2024 Deposition of Dr. Adrian Dobs.
1039	December 14, 2023 Email from Counsel Regarding Dr. Carey’s health status.
1040	Spierling & Zorilla, “Don’t stress about CRF: Assessing the translational failures of CRF1 antagonists,” <i>Psychopharmacology (Berl)</i> . 2017 May; 234(9-10): 1467–1481 (“Spierling”).
1041	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”).
1042	Recto et al., “Comparison of the Efficacy and Tolerability of Simvastatin and Atorvastatin in the Treatment of Hypercholesterolemia,” <i>Clin. Cardiol.</i> 23,682-688 (2000) (“Recto”).
1043	Auchus et al., “Phase 3 Trial of Crinecerfont in Adult Congenital Adrenal Hyperplasia,” <i>The New England Journal of Medicine</i> (2024) (“Auchus 2024”).
1044	Reply Declaration of Gordon B. Cutler, Jr., M.D.

I. INTRODUCTION

Spruce’s Patent Owner Response (“POR”) recycles arguments the Board and the Director have already rejected and provides no reason to deviate from the Board’s Institution Decision (“DI”). Grigoriadis’ disclosure of crinecerfont inherently anticipates the challenged claims because the recited ACTH and 17-OHP reductions inevitably flow from Grigoriadis’ disclosure, as shown by the Auchus reference. Spruce’s argument that the methods of these references are not the same injects unrecited features into the claims and has already been rejected in the DI and the Director’s Decision. DI, 29-31; Decision, 10. Spruce’s characterization of Auchus as an “unpublished manuscript” ignores that Auchus was published in a peer-reviewed journal and submitted with the Board’s approval. EX1037; EX1036 ¶¶17-18. The Board already concluded Auchus was a proper submission. DI, 27-29.

Spruce’s written-description argument fares no better and is likewise premised on an argument the Board and Director have rejected. Decision, 12-13; DI, 44-45. Spruce’s expert admits the specification does not disclose either a representative number of species or common structural features of species that meet the claimed ACTH and 17-OHP reductions—the relevant written-description standard. Spruce’s characterization of what was known in the prior art is wrong and cannot save its deficient specification. For the same reasons the Supreme Court

articulated in its recent *Amgen* decision, the challenged claims also lack enablement.

Having nothing new to say on the merits, Spruce resorts to personally attacking Neurocrine's replacement expert, Dr. Cutler. These attacks are untrue, disgraceful, and speak volumes about the weakness of Spruce's defenses. The Board should find that challenged claims 1–25 are unpatentable.

II. THE BOARD SHOULD REBUKE SPRUCE'S PERSONAL ATTACKS AGAINST DR. CUTLER

Spruce's attacks on Neurocrine's expert, Dr. Cutler, as "not an independent expert" are untrue and should be disregarded by the Board. POR, 2-5. As explained in his declaration, Dr. Cutler is a leading expert in endocrinology and metabolism disorders. EX1036 ¶¶3-13. Spruce's expert described Dr. Cutler as "a respected endocrinologist" and testified "I have great respect for him." EX1038, 36:11-37:4. Spruce's allegation that Dr. Cutler "has interests in both Neurocrine and the outcome of this proceeding" is false. POR, 3. Dr. Cutler has consulted for Neurocrine's CAH program, as he has with many other companies. EX1036 ¶7; EX1044 ¶¶17-19. He has no financial interest in Neurocrine, this proceeding, or Neurocrine's CAH program. EX1044 ¶19; EX1036 ¶14. That Dr. Cutler knew Neurocrine's Chief Medical Officer from when both worked at Eli Lilly and other

Neurocrine scientists through his consulting work has no bearing on his opinions.

Id.

Spruce's allegation that "Neurocrine spent years cultivating Dr. Cutler to testify in this case" is also false. POR, 4. Dr. Cutler did not decline to serve as an expert in 2020 "given his significant conflicts," *id.*, he declined because he had not previously been an expert witness and preferred to focus on scientific consulting rather than legal consulting. EX1044 ¶¶13-14. When Dr. Carey suffered a serious stroke and was unable to continue as Neurocrine's expert, Dr. Cutler agreed to step in because he felt strongly that the opinions Dr. Carey had provided were correct.

Id. ¶¶15-16.

Most egregiously, Spruce faults Dr. Cutler for not discussing the testimony with Dr. Carey. POR, 4-5. As Spruce was informed in a December 14 email conveying information from Dr. Carey's daughter, this was impossible because as a symptom of his stroke, Dr. Carey suffered from severe expressive aphasia that ***made it impossible for him to communicate clearly***. EX1039. That Spruce attempts to use Dr. Carey's illness to discredit Dr. Cutler, and faults Dr. Cutler for failing to do something Spruce knows is impossible, is disgraceful and should be rebuked by the Board.

Far from a "highly unusual situation" (POR, 5), the Board regularly permits substitution of expert witnesses when the original expert becomes unavailable, and

a substitute expert adopts the testimony of the original expert—as Dr. Cutler did here. *Resmed, Inc. v. New York Univ.*, IPR2022-00994, Paper 32 (PTAB Mar. 30, 2023).

III. CLAIMS 1–25 ARE UNPATENTABLE FOR LACK OF WRITTEN DESCRIPTION (GROUND 4)

The Board should find that claims 1–25 are unpatentable for lack of written-description.¹ Decision, 12-14; adopted DI, 44-45. To show sufficient description of the claimed genus, the specification must disclose either a representative number of species falling within the scope of the genus, or structural features common to the members of the genus so that one of skill in the art can “visualize or recognize” the members of the genus. *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1350 (Fed. Cir. 2010) (en banc). Functionally defined genus claims, like the challenged claims, are inherently vulnerable to written-description

¹ Neurocrine addresses Ground 4 first on reply because Spruce’s POR presents no new evidence relevant to the written-description standard. If the Board finds claims 1–25 unpatentable for lacking written-description, it need not reach the other grounds of the Petition. *See Arthrex, Inc. v. Gelfand*, IPR2023-00014, Paper 45 at 59–60 (PTAB Mar. 11, 2024).

challenges. *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1301 (Fed. Cir. 2014).

As the Director found and the Board adopted on the preliminary record, “the ’908 patent claims methods encompassing a genus of materials achieving stated results [i.e., an at least 10% reduction in ACTH or 17-OHP from baseline], but the specification does not disclose a variety of species that accomplish the results.” Decision, 12; DI, 44-45. The specification indisputably discloses only a single species, tildacerfont (“Compound 1”), that can achieve these results, which it classifies as “the invention.” Decision, 12. The specification also “does not describe structural features common to all species within the genus that accomplish the claimed results” and fails to “distinguish effective from ineffective compounds among those encompassed by the broad genus of compounds so claimed.” Decision, 13-14; DI, 44-45. Spruce’s POR presents no new evidence contrary to these findings, instead mischaracterizing the prior art to argue the specification need not disclose a representative number of species or common structural features. POR, 65-69. As explained below, that is wrong. Nothing in the specification or the prior art indicates that Spruce was in possession of using a class of CRF1 receptor antagonists to achieve the claimed results.

A. The Specification Does Not Show Possession of Using a Class of CRF1 Receptor Antagonists to Treat CAH

The specification does not disclose “class effects” of CRF1 receptor antagonists. POR, 60-61. The portions of the specification Spruce cites say nothing about whether *the class* of CRF1 receptor antagonists can achieve the claimed reductions in ACTH or 17-OHP. EX1044 ¶¶86–88. Rather, these citations relate to the use of tildacerfont (12:27-31), or the differences between CRF receptor subtypes and the role of CRF in hormone regulation (1:14-17,10:47-53,10:54-65,11:48-12:26), or that these antagonists had been studied for other indications (11:57-64). *Id.* None of these disclosures relate to whether the specification discloses a representative number of species or common structural features of CRF1 receptor antagonists that achieve the claimed results. Decision, 12.

There is no dispute that the specification fails to disclose a representative number of species that achieve the claimed reductions in ACTH or 17-OHP. Tildacerfont is not “an exemplary embodiment.” POR, 62. It is the *only* embodiment described for use with the claimed methods, as the Director explained. Decision, 12 (the specification “discloses only one particular species, that may be administered to treat CAH and cause a 10% reduction in ACTH or 17-OHP, as claimed”). Spruce’s expert agrees. EX1038, 29:18-32:19. Like *Ariad*, the “claims

here recite methods of encompassing a genus of materials achieving a stated useful result... But the specification does not disclose a variety of species that accomplish the result.” Decision, 12 (citing *Ariad*, 598 F.3d at 1350).

Going even further than *Ariad*, Spruce’s specification describes the use of tildacerfont as the “*present invention*” or “*present disclosure*.” Pet. 11-15,70-75. This is further “strong evidence” that the scope of written description is limited to the use of tildacerfont. *SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc.*, 242 F.3d 1337, 1343 (Fed. Cir. 2001); *Gentry Gallery Inc. v. Berkline Corp.*, 134 F.3d 1473, 1478-80 (Fed. Cir. 1998); *In re Lew*, 257 F. App’x 281, 285 (Fed. Cir. 2007). Spruce’s attempt to distinguish these cases on their facts (POR, 71-72) is unavailing. Each found a patentee characterizing a feature as the “present invention” or “present disclosure” is strong evidence that the written description is limited to that feature. *Id.* The specification does exactly that, defining Spruce’s invention as using tildacerfont. Pet. 11-15,70-75.

B. The Prior Art Did Not Teach a Class of CRF1 Receptor Antagonists Could Treat CAH, or Reduce ACTH or 17-OHP by At Least 10%

Spruce’s argument that the class of CRF1 receptor antagonists was well-known in the prior art (POR, 64-66) was already rejected by the Board and the Director. The Director found Dr. Carey’s testimony that “over 100 CRF1 receptor antagonists had been characterized or were in clinical development prior to the

filing of the '908 patent” **does not** support claims to a class of CRF1 receptor antagonists that can be used to treat CAH and result in the claimed 10% reduction of ACTH or 17-OHP. Decision, 13; EX1005 ¶¶99. The Board adopted this finding. DI, 44-45. Moreover, Spruce itself has argued different species within the CRF1 receptor antagonist genus do not achieve the same results. Decision, 13; Paper 8, 31-34. Spruce’s argument that there is no “*per se* rule” a claim is invalid if there is only one working example assumes the same faulty premise. POR, 72-75. Thus, Spruce’s reliance on *Ajinomoto*, *In re Herschler*, *Erfindergemeinschaft*, and *Merck* is inapposite. *Id.*

As Dr. Cutler explained, the prior art discussed the possibility that CRF1 receptor antagonists may be useful as a “new approach” to treat CAH, but did not provide evidence that a class of CRF1 receptor antagonists could achieve the claimed reductions in ACTH or 17-OHP. EX1044 ¶¶79–80; EX1021, 130–31. Spruce’s suggestion that *Neurocrine’s prior work*, reported in Grigoriadis, shows **Spruce** was in possession of using the claimed genus to reduce ACTH or 17-OHP levels is non-sensical. POR, 65. If Grigoriadis’ disclosure of species of CRF1 receptor antagonists that reduce ACTH and 17-OHP provides written-description support for Spruce’s claims, then it also anticipates the claims (Ground 1). *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 971 (Fed. Cir. 2001). Either way, the claims are invalid.

Moreover, CRF1 receptor antagonists were previously studied for indications other than CAH, and were *ineffective*. EX1044 ¶¶82–85; EX1030, 377–78 (two CRF1 receptor antagonists failed to show efficacy in treating depression); EX1031, 24–25 (same); EX1040, Table 1 (noting several CRF1 receptor antagonists lacked efficacy). Spruce’s expert admitted a POSA would understand that “antagonists of the CRF1 receptor have not demonstrated clinical utility despite over 30 years of research and hundreds of patents.” EX1029, 1065; EX1038, 131:18-132:14. In view of the prior art, a POSA would not have thought a class of CRF1 receptor antagonists were useful for any indication, much less useful to treat CAH, or to lower ACTH or 17-OHP by the claimed amounts. This is particularly true because the specification discloses only tildacerfont and does not provide any way “to distinguish effective from ineffective compounds among those encompassed by the broad genus so claimed.” Decision, 14 (citing *Idenix Pharms., LLC v. Gilead Sciences Inc.*, 941 F.3d 1149, 1165 (Fed. Cir. 2019)).

C. The Specification Does Not Describe Common Structural Features of CRF1 Receptor Antagonists that Achieve the Claimed Reductions in ACTH or 17-OHP

As the Board and Director found, the specification also “does not describe structural features common to all species within the genus that accomplish the claimed results” of reducing ACTH or 17-OHP by at least 10% from baseline.

Decision, 12-13; DI, 44-45. Spruce concedes this point, instead arguing its deficient specification is saved by what was known in the prior art. POR, 65-69; EX1038, 32:6-19. Not so.

CRF1 receptor antagonists are defined as compounds that inhibit CRF1 receptors, not by a particular structure or structures. EX1044 ¶¶89-92. As Dr. Cutler explained, compounds that interact with the CRF1 receptor can have widely diverse structural features. *Id.* The broad structural features observed in some (but not all) CRF1 receptor antagonists would not tell a POSA whether any compounds in this class could accomplish the claimed results of reducing ACTH or 17-OHP by at least 10% from baseline. *Id.* Spruce’s own publication describes tildacerfont, the only species disclosed in the specification, as having “unique structural features” compared to other CRF1 receptor antagonists. EX1041, 4667; EX1038, 52:19-53:14.

The prior art doesn’t identify common structural features of antagonists that achieve the claimed ACTH or 17-OHP reductions. EX1029 (POR, 67–69) does not mention CAH. The generalized structure Spruce asserts is a “typical CRF1 receptor antagonist” is described in EX1029 as one subclass of CRF1 receptor antagonists—i.e., not reflective of the entire class. EX1029, 2, Fig. 2; EX1038, 122:8–123:16. It does not disclose that any antagonists falling within Figure 2’s generalized structure could lower ACTH or 17-OHP but refers to these compounds

as having “less-than-optimal physicochemical properties.” *Id.*, 2. EX1029 also reports other CRF1 receptor antagonist subclasses that do not have the same structural features as Figure 2. EX1044 ¶¶95–99; EX1029, Figs. 1(compounds 1, 4), 6,11. At deposition, Spruce’s expert admitted she is not a chemist and did not know whether other CRF1 receptor antagonists disclosed in EX1029 were encompassed by Figure 2. EX1038, 125:5-126:7,129:17-130:10. She also admitted other CRF1 receptor antagonists in EX1029 are different than Figure 2’s structure. EX1038, 130:13-131:16.

Similarly, EX1018 does not describe structural features of CRF1 receptor antagonists that could reduce ACTH or 17-OHP from baseline. EX1044 ¶¶100–02. It merely provides a general structure that encompasses a large number of compounds, without providing any information on what features are important for CAH treatment or ACTH or 17-OHP reduction. *Id.*; EX1018, 3, Fig. 1. EX1018 also discloses antagonists falling outside the structure of Figure 1, with no way to distinguish compounds that are effective to reduce ACTH or 17-OHP. EX1018, 7-8, Figs. 11-12; EX1044 ¶100-02; EX1038, 132:17-134:20. U.S. Patent 8,030,304 identifies a laundry list of 24 potential indications for CRF1 receptor antagonists, and does not identify any structural features of antagonists useful to treat CAH or achieve the claimed reductions in ACTH or 17-OHP. EX1012, 2:10-62.

Neither the specification nor the prior art disclose a representative number of species, or common structural features of CRF1 receptor antagonists that achieve the claimed results. Thus, the claims are unpatentable. *Ariad*, 598 F.3d at 1350.

IV. CLAIM CONSTRUCTION RELEVANT TO ANTICIPATION AND OBVIOUSNESS GROUNDS

A. Spruce Has Not Disputed Neurocrine’s Proposed Construction of “A Human”/ “The Human”

Spruce doesn’t dispute that “a human” or “the human” in the challenged claims refers to an individual patient. POR, 19-27. As Spruce’s expert admitted, the claims’ plain language recites administering to “a human” a CRF1 receptor antagonist, wherein an ACTH or 17-OHP level in “the human” is reduced by at least 10% from baseline. EX1001, 48:5-12,48:37-42; EX1038, 23:10-21; EX1005 ¶44. Neurocrine’s construction also aligns with the specification, which as Spruce’s expert admitted presents change in ACTH and 17-OHP levels in individual patients and shows some, but not all, patients achieved the claimed reductions. EX1001, Figs. 2-3; EX1038, 20:8-22:2.

While not addressing this construction head on, Spruce argues against inherent anticipation because “some, but not all” patients achieved the claimed reductions in ACTH or 17-OHP. *See* POR, 18,42-43. That is inconsistent with the plain language of the claims and the specification. If the claims require “all

humans” to achieve the claimed reductions, Spruce’s data doesn’t support the claims. EX1001, Figs. 2-3; EX1038, 20:8-22:2. The Board should adopt Neurocrine’s proposal that the claims require the recited ACTH or 17-OHP reductions in “a human”—a single patient, not all patients.

B. The Board’s Construction of “Baseline” Includes Comparisons From Placebo

Spruce spends eight pages of its POR arguing against Neurocrine’s proposed construction of “from baseline” without acknowledging that the Board construed this term. POR, 19-26. The Board, after considering these same arguments in Spruce’s preliminary response, construed the phrase “reduced by at least 10% from baseline” 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.” DI, 8-11. Spruce’s expert did not even consider the Board’s construction in forming her opinions. EX1038, 24:11-17.

Ground 1 includes two separate bases for finding the claims unpatentable: Grigoriadis’ disclosure of crinecerfont, and Grigoriadis’ disclosure of verucerfont (NBI-77860). Both meet the Board’s construction of “from baseline.” The administration of crinecerfont, as disclosed in Grigoriadis, inherently results in the claimed ACTH or 17-OHP reductions compared to measurements made prior to,

and/or at the beginning of, administration of the drug. This is demonstrated by Auchus, which reported at least 10% reductions in ACTH and 17-OHP after 14 days of receiving crinecerfont compared to a patient's ACTH and 17-OHP levels 7 days before the study began. EX1037, 3, Fig. 1-3, Table 1; EX1005 ¶¶56; Pet. 30-37. The Board found, and Spruce's expert agrees, that Auchus' comparison of ACTH and 17-OHP levels on Day 14 and 7 days before the study is a comparison "from baseline." DI, 30; EX1038, 79:13-83:17.

Spruce's argument that a placebo measurement isn't a "baseline" relates only to Grigoriadis' disclosure of verucerfont. Pet. 37-44, 48-51; EX1005 ¶¶63-68; EX1044 ¶¶66-67. Grigoriadis Example 6 reports an at least 10% reduction in ACTH and 17-OHP in a subject after receiving verucerfont, compared to the subject's levels after receiving placebo. EX1006, ¶93, Figs. 5-6. This is a reduction "from baseline" because the placebo is a measurement "made prior to, and/or at the beginning of, administration of the drug"—placebo is not a drug. EX1005 ¶¶37-39, 43, 68; EX1044 ¶¶66-70.

As Dr. Cutler explained, determining the drug effect in relation to prior placebo administration is scientifically acceptable, and can be used to control for a placebo effect. *Id.* ¶¶67-69. Spruce's argument that a placebo baseline can elevate stress hormones is a non-sequitur. POR, 22-26. Placebo can elevate or reduce hormones in a given patient, and Neurocrine's data show verucerfont

administration achieved reductions in ACTH and 17-OHP regardless of any placebo effect. EX1044 ¶70. Dr. Cutler did not admit “placebo was a ‘treatment’ intervention.” POR, 22. He testified about one study in which a placebo treatment was compared to a non-placebo baseline; he also testified that a placebo baseline is appropriate. EX2011,83:6–84:11; EX2013; EX1044 ¶67-69. Spruce’s expert has used a placebo baseline in her own research. EX1042; EX1038, 106:8-111:10,114:9-115:5.

C. Neurocrine’s Construction of “4 Hours Prior to Sleeping” Should Be Adopted

A POSA would understand this term to mean administration prior to the circadian release of ACTH, because the antagonist is typically given 3-4 hours before ACTH is released at 1-2am—i.e., administration around 10-11pm or “bedtime.” Pet. 58; EX1005 ¶¶91-92. Neurocrine’s proposal should be adopted.

V. GRIGORIADIS’ DISCLOSURES ANTICIPATE CLAIMS 1-4,7-9,11-14,17-19, AND 20-24 (Ground 1)

The Board should find that Grigoriadis anticipates the ’908 patent claims. DI, 38. “[A] prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference.” *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). Grigoriadis anticipates the claims through its

disclosure of two CRF1 receptor antagonists to treat CAH: 1) crinecerfont, the administration of which results in the claimed reductions in ACTH and 17-OHP, as shown by Auchus; and 2) verucerfont, which also meets the claimed ACTH and 17-OHP reductions as shown in Grigoriadis.

A. Grigoriadis' Disclosure of Crinecerfont Inherently Anticipate Claims 1 and 11

Spruce doesn't dispute the Board's initial finding that Grigoriadis teaches the administration of a therapeutically-effective amount of crinecerfont to CAH patients. DI, 24-25; Decision, 7-8; EX1006 ¶¶7,54; EX1005 ¶¶ 21,53,54,66. The only remaining limitations recite reducing a human's ACTH (claim 1) or 17-OHP (claim 11) levels by at least 10% from the human's baseline, which as Auchus shows, inevitably flows from and is the natural result of administering crinecerfont to treat CAH. *See In re Montgomery*, 677 F.3d 1375, 1381 (Fed. Cir. 2012) (a result is inherent if "it inevitably flows from the prior art disclosure.").

Auchus shows that administration of crinecerfont to a CAH patient, as disclosed in Grigoriadis, reduces ACTH or 17-OHP by at least 10% from baseline in "a human." That is all the claims require, and all that is required to prove inherent anticipation. *Bristol-Myers Squibb Co. v. Ben Venue Lab 'ys, Inc.*, 246 F.3d 1368, 1378 (Fed. Cir. 2001). As explained above, there is no dispute the

ACTH and 17-OHP reductions in Auchus are reductions “from baseline.” Section IV.B.

1. Unrecited claim elements are irrelevant to anticipation.

Spruce’s assertion that “the petition’s inherency theory depends on employing the Grigoriadis dosing protocol” (POR, 29) attempts to inject additional requirements into the claims. That is legally wrong, as the Board and Director found. DI, 29-30, Decision, 10. Auchus is not required to replicate the clinical study of Grigoriadis Example 6. DI, 29. The relevant question is whether a POSA practicing the method of Grigoriadis—administering crinecerfont—would inherently achieve the claimed results. *Id.* The Board answered in the affirmative. Pet. 30-37,46-48; DI, 23-30. Spruce cites no case for its assertion that “to succeed, Petitioner must demonstrate a method found in Grigoriadis that inherently satisfies the claimed method” (POR, 30) because it is not required. *See MEHL/Biophile Int’l Corp. v. Milgraum*, 192 F.3d 1362, 1366 (Fed. Cir. 1999) (holding unclaimed differences between anticipatory reference and claims “irrelevant to the anticipation analysis”); *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1326-30 (Fed. Cir. 2020) (holding importing limitations from specification for inherent anticipation analysis improper).

Spruce presents a laundry list of alleged differences between Grigoriadis and Auchus, none of which are recited in the claims. POR, 33-41. Dosing with or

without food is not a requirement of the claims. EX1044 ¶¶46-50. Dosing length or dose timing are also not claim limitations. *Id.* ¶¶48-49. Patient characteristics, e.g., women or men of certain ages, are not claim limitations. *Id.* ¶51. There are no formulation requirements in the '908 patent claims. *Id.* ¶48. And claims 1 and 11 do not recite certain dose amounts. *Id.* Spruce's expert agrees. EX1038, 25:8–26:5, 27:6–28:22. These unclaimed differences are “irrelevant to the anticipation analysis.” *MEHL/Biophile*, 192 F.3d at 1366.

The case law Spruce cites does not support its attempt to inject additional limitations into the claims. POR, 31. *Galderma* found no inherent anticipation because the reference didn't disclose the same composition claimed in the patents-in-suit and practicing the reference's general disclosure didn't necessarily achieve the claimed efficacy limitations. *Galderma Lab 'ys, L.P. v. Teva Pharms. USA, Inc.*, 799 F. App'x 838, 844-46 (Fed. Cir. 2020). *Valeant* found no anticipation because the prior art disclosure for making a compound was different than the claimed compound. *Valeant Int'l (Barbados) SRL v. Watson Pharms., Inc.*, No. 10-20526-CIV, 2011 WL 6792653, at *14 (S.D. Fla. Nov. 8, 2011), *aff'd* 534 F. App'x 999 (Fed. Cir. 2013). *Glaxo* found no inherent anticipation because the claimed polymorphic form didn't invariably result from practicing the prior art; various chemists following the prior art protocol achieved differing results. *Glaxo, Inc. v. Novopharm Ltd.*, 830 F. Supp. 871, 874–77 (E.D.N.C. 1993), *aff'd*, 52 F.3d

1043 (Fed. Cir. 1995). Here, the claims require only using a CRF1 receptor antagonist to treat CAH in a human (as disclosed in Grigoriadis), that “necessarily” or “invariably” result in a reduction of ACTH or 17-OHP by 10% from baseline (as shown in Auchus). *Galderma*, 799 F. App’x at 845; *Glaxo*, 830 F. Supp. at 877. Grigoriadis anticipates claims 1 and 11 because the claimed reductions are the “natural result” flowing from the Grigoriadis method. *Valeant*, 2011 WL 6792653, at *5.

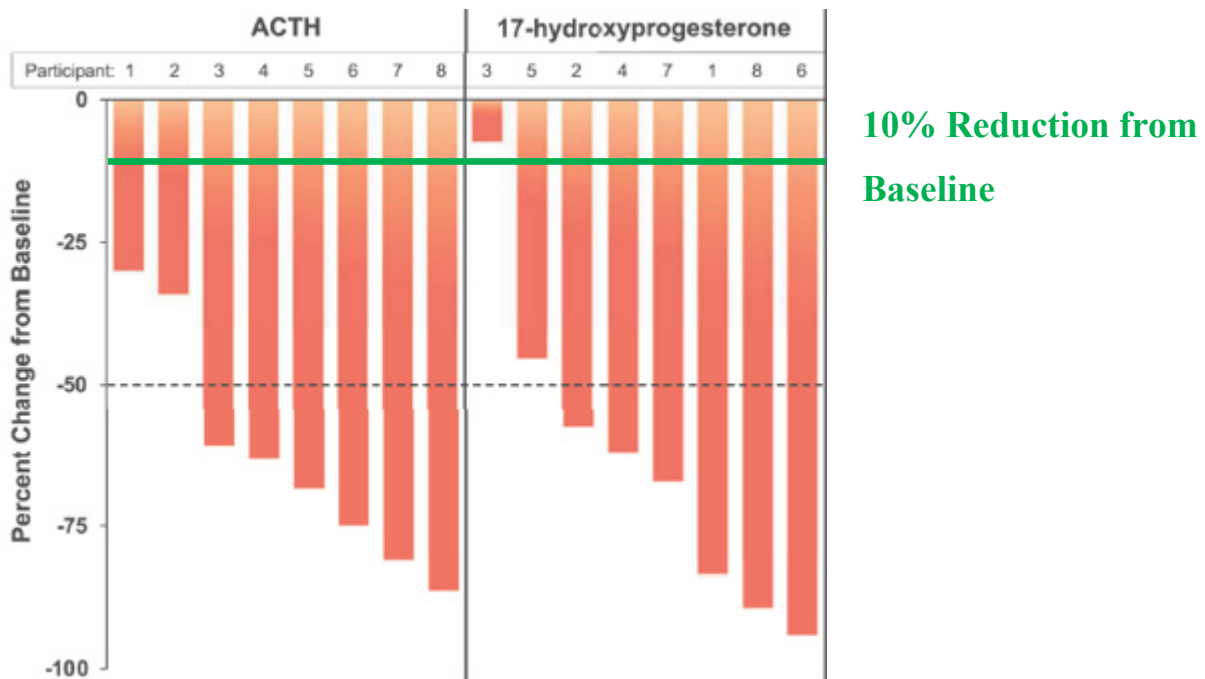
2. Auchus demonstrates the 10% reduction in ACTH and 17-OHP from baseline inevitably flows from the disclosure in Grigoriadis.

Spruce’s argument that Auchus doesn’t show the claimed ACTH and 17-OHP reductions naturally flow from administering crinecerfont assumes *every* patient needs to achieve the claimed reductions. POR, 41–46. That is contrary to the claims, which only require “a human” to achieve the claimed ACTH and 17-OHP reductions, not every human. Auchus demonstrates inherent anticipation because at least one patient, and indeed many patients, achieved the claimed response. *See In re Montgomery*, 677 F.3d at 1384; DI, 23-31.

Spruce’s reliance on non-precedential Board opinions (POR, 42) are distinguishable, and do not undermine the Board’s preliminary analysis or the precedential Federal Circuit authority holding inherent anticipation by “a human”

requires only one human to achieve the claimed effect. DI, 30; *In re Montgomery*, 677 F.3d at 1384. In *Apotex*, the Board denied institution on inherent anticipation grounds where the challenged claims recited dosing requirements that were not disclosed in the prior art. *Apotex Inc. v. Regeneron Pharms., Inc.*, No. IPR2022-01524, 2023 WL 2588222, at *15 (PTAB Mar. 10, 2023). In *Gilead*, the Board found the prior art did not disclose the claimed treatment compound or the claimed efficacy limitations. *Gilead Scis., Inc. v. United States*, No. IPR2019-01456, 2020 WL 582217, at *16–17 (PTAB Feb. 5, 2020). Here, Grigoriadis discloses all the limitations of the challenged claims. DI, 23-31.

Spruce’s assertion that Auchus does not show “any true change in hormone levels” is also wrong. POR, 46–47; EX1044 ¶¶31-43. That Auchus “was not powered to demonstrate statistical significance of a treatment effect or between-cohort difference” is irrelevant because the claims do not require statistical significance. Moreover, a POSA would understand Auchus’ ACTH and 17-OHP reductions from baseline for Cohort 4 are statistically significant and could perform a simple t-test to confirm. EX1044 ¶¶44–45. Each of the patients in Cohort 4 achieved over 10% reduction in ACTH from baseline, and 7/8 patients achieved over 10% reduction in 17-OHP. Consistent with Auchus, Neurocrine’s Phase III trial reported crinecerfont administration substantially reduced 17-OHP in CAH patients. EX1043, 5, Fig.1; EX1044 ¶42; EX1038, 95:18-106:5.



Ex. 1037, Fig. 4; EX1044 ¶¶35–37, 44–45.

B. Grigoriadis’ Disclosure of Verucerfont Anticipates Claims 1 and 11

Grigoriadis anticipates claims 1 and 11 by disclosing the use of verucerfont to reduce ACTH and 17-OHP levels by at least 10% from baseline. Pet 49-51; EX1006 ¶¶90-93, Figs. 5-6. As discussed above, ACTH and 17-OHP reductions compared to placebo are reductions “from baseline” under the Board’s construction. Section IV.B.

1. Variability among patients does not undermine Grigoriadis’ disclosure of the claimed ACTH and 17-OHP reductions.

Spruce’s argument that verucerfont data in Grigoriadis Example 6 is “flawed” and “error-filled” incorrectly conflates variability between patients with whether “a human” achieved the claimed ACTH and 17-OHP reductions. POR, 48-

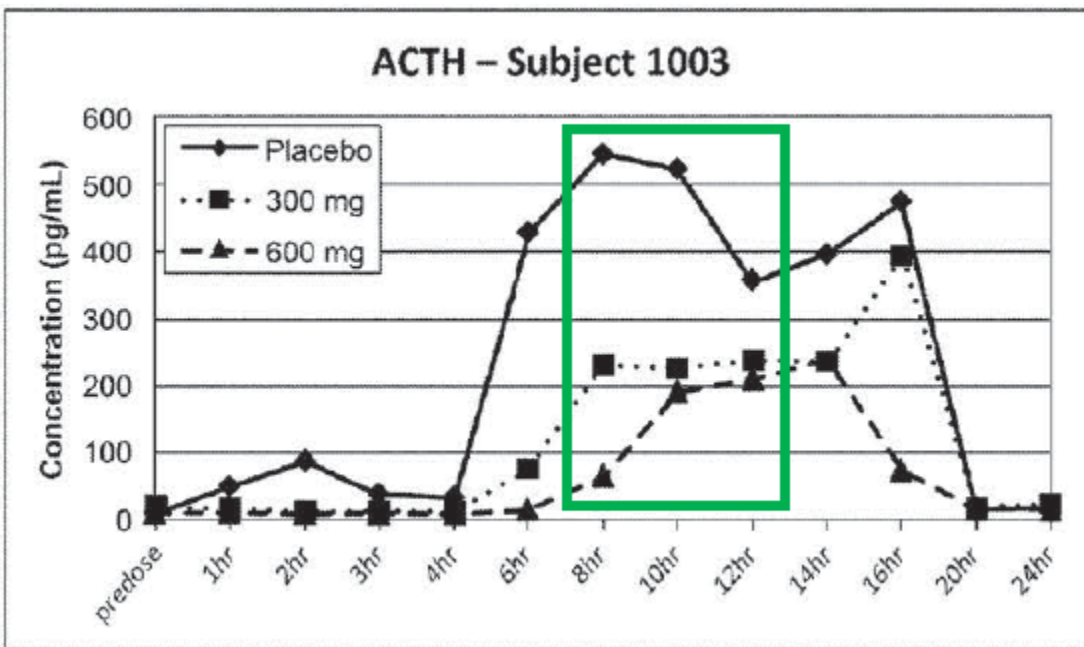
54. Figure 5 shows mean percent change from baseline across eight patients after verucerfont administration. EX1044 ¶¶54–55; EX1006, Fig. 5, ¶92. Spruce’s addition of error bars to this mean data only shows variability *between* patients. *Id.* As its expert admitted, Spruce’s clinical data showed similar variability between patients, yet Spruce characterized the data as showing “notable reductions” in ACTH and 17-OHP. EX1038, 59:2–62:13; EX1041, 4671, Fig. 4.

Variability between patients is irrelevant to whether “a human” achieves at least a 10% ACTH or 17-OHP reduction from baseline, and the data indicate most patients achieved the claimed reductions. EX1044 ¶¶55–67. For example, at the 6-hour, post-dose time point there was an approximately 500% change in mean ACTH levels and over 500% change in mean 17-OHP levels between the verucerfont and placebo treatment groups. Ex. 1005 ¶¶65-66; Ex. 1006, Fig. 5, ¶93. Fifty percent of the eight patients achieved at least a 50% decrease in ACTH and 17-OHP during the peak morning period. *Id.*

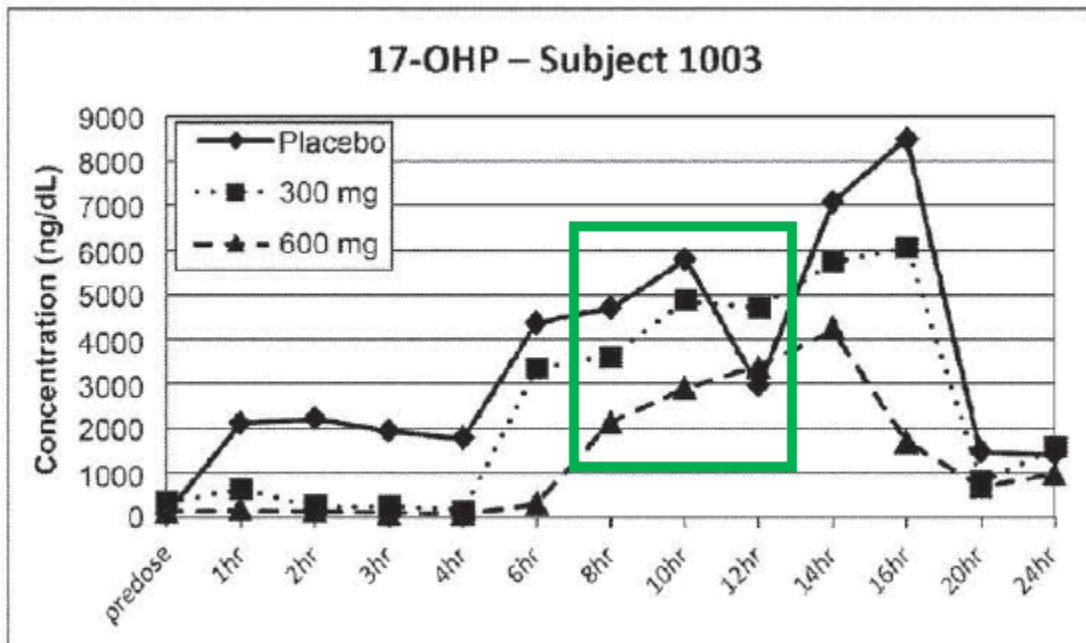
What Spruce refers to as “systemic error” in the verucerfont data (POR, 49-54) simply reflect small, clinically-insignificant 17-OHP differences in the placebo group pre-dose and between 10pm-2am (Figures 5-6 hours 1-4), a time of minimal adrenal hormone secretion. EX1044 ¶¶56–57. These small differences are apparent only because Figures 5-6 present the data as percent change from baseline, which exaggerate these differences compared to the larger, clinically-significant changes

in the peak morning period, the time of highest adrenal production (Figures 5-6 hours 8-12). *Id.*

ACTH data for Subject 1003 showed both doses of verucerfont lowered ACTH in this patient by over 10% compared to the placebo measurement, particularly during the peak morning period as highlighted by the green box below.



Ex. 1006, Fig. 6, ¶ 93; EX1044 ¶¶62–63. 17-OHP values were also reduced by at least 10% in this patient at two of the three peak morning period time points, particularly for the 600 mg verucerfont dose.



Id. A POSA would understand these data disclose a 10% reduction in ACTH and 17-OHP from baseline for at least “a human” which is all the claims require. *Id.*

¶¶62–63. Patient 1011006 achieved greater than 10% reductions in ACTH at mean morning window timepoints, and 17-OHP at all morning window timepoints for both verucerfont doses. EX1044 ¶¶64; EX1008, Table 1. Fluctuation of the placebo treatment between hours 10-14 (POR, 53) does not indicate error. A POSA would understand that adrenal hormones like ACTH and 17-OHP are pulsatile, and fluctuate naturally by subject and throughout the day. *Id.* ¶¶65.

2. Grigoriadis’ verucerfont study was appropriately designed to demonstrate the claimed reductions.

Spruce’s suggestion that Grigoriadis’ verucerfont study was poorly designed (POR, 51-52) is belied by the fact that this same study was published in a peer-

reviewed, respected endocrinology journal. EX1008; EX1038, 48:18-49:8.

Outside of this dispute, scientists in the field found this study and its data and conclusions reliable. *Id.* Contrary to its attacks on these data here, in its own publication Spruce admitted Neurocrine’s verucerfont study showed “17-OHP was reduced by up to 27% and ACTH by up to 43%.” EX1041, 4677; EX1038, 74:7-75:22,77:14-78:4.

Spruce’s criticisms of the study design are irrelevant. The claims do not require a particular protocol for administering CRF1 receptor antagonists, nor a specific way to measure the results. *MEHL/Biophile*, 192 F.3d at 1366. Similarly, Grigoriadis’ enrollment of all-female patients was reasonable, and the claims do not require achieving the claimed ACTH or 17-OHP reductions in a particular gender. *Id.*; EX1044 ¶73.

C. Grigoriadis Anticipates Claims 2–4, 7–9, 12–14, 17–19, and 21–24

Spruce makes no additional arguments regarding dependent claims 2–4, 7–9, 12–14, 17–19 and 23 beyond its arguments for claims 1 and 11. POR, 27-58. As the Petition explains, Grigoriadis anticipates these claims. Pet. 51-57; EX1005 ¶¶69-90.

Spruce’s argument regarding claims 21-22 that Grigoriadis does not disclose 14 consecutive days of repeated dosing misstates Neurocrine’s position. POR, 57. The administration of crinecerfont as disclosed in Grigoriadis inherently results in

maintaining the claimed reductions in ACTH and 17-OHP post 24 hours. Pet. 56–57; EX1005 ¶85; EX1044 ¶¶75-76. It would also be obvious to a POSA that the claimed reductions would be maintained post 24 hours with repeated dosing. Pet. 64-66; EX1005 ¶86-88. Claims 21–22 are unpatentable as anticipated and/or obvious.

Spruce’s only argument regarding claim 24 hinges on its erroneous construction of “administered 4 hours prior to sleeping.” POR, 57–58. As explained in Section IV.C, Neurocrine’s proposed construction is correct, thus claim 24 is unpatentable.

VI. GRIGORIADIS’ DISCLOSURE RENDERS CLAIMS 4, 10, 14, 20-22 AND 25 OBVIOUS (GROUND 2)

Spruce makes no additional arguments regarding obviousness of these claims beyond its incorrect arguments for Ground 1. POR, 58-59. As the Petition explains, Grigoriadis renders these claims obvious. Pet. 59-68; EX1005 ¶¶72–74,83–84,86–88,93–97.

VII. THE COMBINATION OF GRIGORIADIS AND ROMANO RENDERS CLAIMS 5, 6, 15, AND 16 OBVIOUS (Ground 3)

Spruce makes no additional arguments regarding obviousness of claims 5–6 and 15–16 beyond its incorrect arguments for Ground 1. POR, 59. As the Petition

explains, the combination of Grigoriadis and Romano renders these claims obvious. Pet. 68-70; EX1005 ¶¶75–79.

VIII. CLAIMS 1–25 ARE UNPATENTABLE FOR LACK OF ENABLEMENT (GROUND 5)

Neurocrine explained that broad claims must be fully enabled, and the challenged claims were not. Pet. 75-76. After the Petition was filed, the Supreme Court confirmed exactly this. *Amgen Inc. v. Sanofi*, 598 U.S. 594, 610 (2023).

Spruce’s claims—like the claims in *Amgen*—cover “an entire class of things defined by their function.” *Id.* 613. The specification—like the patent in *Amgen*—provides nothing more than “research assignments” for identifying CRF1 receptor antagonists for use in the claimed method. *Id.* 614. A trial-and-error method for identifying compounds within the claimed class—i.e., a “roadmap”—is not sufficient for enablement. *Id.* 613. In the absence of the identification of “a quality common to every functional embodiment,” the specification provides only a hunting license, not enablement. *Id.* at 614.

Here, the specification provides even less of a roadmap than in *Amgen*. It identifies a single species, tildacerfont. Just like in *Amgen*, the specification fails to “identif[y] a quality common to every functional embodiment” that would enable a POSA to make and use the full scope of the claims. This lack of disclosure is particularly acute because the record shows other CRF1 receptor antagonists lack

clinical utility (Decision, 13; EX1044 ¶¶82–85), and Spruce distinguished tildacerfont over other CRF1 receptor antagonists during prosecution as exhibiting unexpected results, Pet. 76.

Spruce’s argument that the Petition’s enablement ground fails because it does not analyze the *Wands* factors is wrong. POR, 77. *Amgen* does not discuss the *Wands* factors. Moreover, the Federal Circuit made clear that the *Wands* factors “are illustrative, not mandatory.” *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991). The Board should follow the Supreme Court’s analysis and find claims 1–25 unpatentable for lacking enablement.

Respectfully submitted,

Dated: June 20, 2024

/ Robert Oakes/
Robert Oakes, Reg. No. 62,189

Attorneys for Petitioner

CERTIFICATION UNDER 37 CFR § 42.24(d)

Under the provisions of 37 CFR § 42.24(d), the undersigned hereby certifies that the word count for the foregoing Petitioners' Reply to Patent Owner's Response totals 5,597, which is less than the 5,600 allowed under 37 CFR § 42.24.

Respectfully submitted,

Dated: June 20, 2024

/ Robert Oakes/
Robert Oakes, Reg. No. 62,189

Attorneys for Petitioner

CERTIFICATE OF SERVICE

Pursuant to 37 CFR §§ 42.6(e)(1) and 42.6(e)(4)(iii), the undersigned certifies that on June 20, 2024, a complete and entire copy of this Petitioner's Reply to Patent Owner's Response and accompanying exhibits were provided by email to the Patent Owner by serving the email correspondence addresses of record as follows:

Michael T. Rosato
Michael J. Hostetler
Jad A. Mills
WILSON SONSINI GOODRICH & ROSATI
mrosato@wsgr.com
mhostetler@wsgr.com
jmills@wsgr.com

/Anastasia Renard/
Anastasia Renard
Fish & Richardson P.C.
60 S. Sixth Street, Suite 3200
Minneapolis, MN 55402
renard@fr.com