

THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NEUROCRINE BIOSCIENCES, INC.,
Petitioner,

v.

SPRUCE BIOSCIENCES, INC.,
Patent Owner.

Case PGR2026-00061
Patent 12,576,084 B2

PETITION FOR POST GRANT REVIEW OF
UNITED STATES PATENT NO. 12,576,084 B2

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1001	U.S. Patent No. 12,576,084 to Howerton et al. (“the ‘084 Patent”)
1002	Excerpts from the Prosecution History of the ‘084 Patent (“the Prosecution History”)
1003	<i>Declaration of Maya Lodish, M.D.</i>
1004	PCT Publication WO/2015/112642 to Grigoriadis et al. (“Grigoriadis PCT”).
1005	Final Written Decision, Paper 64, <i>Neurocrine Biosciences, Inc. v. Spruce Biosciences, Inc.</i> , No. PGR2021-00088 (PTAB Nov. 27, 2024).
1006	U.S. Patent Application Publication No. 2017/0020877 to Grigoriadis et al. (“Grigoriadis”).
1007	Final Written Decision, Paper 62, <i>Neurocrine Biosciences, Inc. v. Spruce Biosciences, Inc.</i> , No. PGR2022-00025 (PTAB Nov. 26, 2024).
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):1174-80 (March 2016) (“Turcu 2016”).
1009	RESERVED
1010	CRENESSITY® (crinecerfont) Prescribing Label, U.S. Food and Drug Administration (Dec. 13, 2024).
1011	Neurocrine Biosciences, Inc., Q4 2025 Earnings Release.
1012	PCT Publication WO 2007/105113 to Richard (“Richard”)
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):4133-60 (2010) (“Speiser 2010”).

Exhibit No.	Exhibit Description
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 (Sept. 2015) (“Turcu & Auchus 2015”).
1015	El Maouche et al., “Congenital Adrenal Hyperplasia,” <i>Lancet</i> 390:2194-10 (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):4043-88 (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):333-45 (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):322-32 (2002) (“Gully 2002”).
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1022	RESERVED
1023	European Pat. No. 3 784 233 to Alexis Howerton, et al.

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1024	Merke D.P. & Auchus R.J., “Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency,” <i>N. Engl. J. Med.</i> 383(13):1248-61 (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):225-32 (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> , 29:449-68 (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 (March 20, 2021) (“Neurocrine March 20, 2021, Press Release”).
1028	Decision of the European Patent Office, Opposition Division, revoking EP 3 784 233 (Dec. 12, 2025).
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):371-83 (2010) (“Zorrilla & Koob 2010”).
1031	Director Review Request in PGR2021-00088, Paper 65
1032	Director Review Request in PGR2022-00025, Paper 63
1033	National Center for Biotechnology Information, PubChem Compound Summary for CID 5282340, Crinecerfont (2026).
1034	Director Review Decision in PGR2021-00088, Paper 66
1035	Director Review Decision in PGR2022-00025, Paper 64

Exhibit No.	Exhibit Description
1036	U.S. Patent No. 10,849,908 to Alexis Howerton, et al. (“the ’908 patent”).
1037	U.S. Patent No. 11,007,201 B2 to Alexis Howerton, et al. (“the ’201 patent”).
1038	Zaarour et al., “Bilateral Ovary Adrenal Rest Tumor in a Congenital Adrenal Hyperplasia Following Adrenalectomy,” <i>Endo. Prac.</i> , 20:4 (Apr. 2014).
1039	Sarafoglou et al., “Interpretation of Steroid Biomarkers in 21-Hydroxylase Deficiency and Their Use in Disease Management,” <i>J. Clin. Endocrinol. Metabol.</i> 108:2154-75 (March 2023) (“Sarafoglou 2023”).
1040	Chen et al., “Ovarian Adrenal Rest Tumors Undetected by Imaging Studies and Identified at Surgery in Three Females with Congenital Adrenal Hyperplasia Unresponsive to Increased Hormone Therapy Dosage,” <i>Endocr. Pathol.</i> , 28:146-151 (2017).
1041	Sarafoglou et al., “Tildacerfont in Adults With Classic Congenital Adrenal Hyperplasia: Results from Two Phase 2 Studies,” <i>J. Clin. Endocrinol. Metabol.</i> 106(11):e4666-79 (2021) (“Sarafoglou 2021”).
1042	RESERVED
1043	“Spruce Biosciences Achieves Proof of Concept in Phase 2 Study of Tildacerfont in Congenital Adrenal Hyperplasia,” Spruce Biosciences (Mar. 25, 2019) (“Spruce Mar. 25, 2019, Press Release”).
1044	“Spruce Biosciences Announces Topline Results from CAHmelia-203 in Adult Classic CAH and CAHptain-205 in Pediatric Classic CAH,” Spruce Biosciences (March 13, 2024) (“Spruce March 13, 2024, Press Release”).
1045	“Spruce Biosciences Announces Topline Results from CAHmelia-204 in Adult CAH and CAHptain-205 in Adult and Pediatric CAH,” Spruce Biosciences (December 10, 2024) (“Spruce December 10, 2024, Press Release”).

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1046	Turcu A.F. & Auchus R.J, “Adrenal Steroidogenesis and Congenital Adrenal Hyperplasia,” <i>Endocrinol. Metabol. Clin. N. Am.</i> , 44:275-96 (2015) (“Turcu & Auchus 2015a”).
1047	Mallappa A. & Merke D.P., “Management challenges and therapeutic advances in congenital adrenal hyperplasia,” <i>Nature Reviews Endocrinol.</i> , 18:337-52 (June 2022) (“Mallappa & Merke”).
1048	Auchus et al., “Crinecerfont Lowers Elevated Hormone Markers in Adults With 21-Hydroxylase Deficiency Congenital Adrenal Hyperplasia,” <i>J. Clin. Endocrinol. Metabol.</i> , 107(3):801-12 (2022) (“Auchus 2022”).
1049	Claahsen-van der Grinten et al., “Congenital Adrenal Hyperplasia—Current Insights in Pathophysiology, Diagnostics, and Management,” <i>Endocrine Reviews</i> , 43(1):91-159 (2022) (“Claahsen-van der Grinten”).
1050	RESERVED
1051	International Application PCT/US2019/029486 to Spruce Biosciences, Inc. (“the PCT application”).
1052	Auchus et al., “Phase 3 Trial of Crinecerfont in Adult Congenital Adrenal Hyperplasia,” <i>N. Engl. J. Med.</i> , 391(6):504-14 (June 2024) (“Auchus 2024”).
1053	Sarafoglou et al., “Phase 3 Trial of Crinecerfont in Pediatric Congenital Adrenal Hyperplasia,” <i>N. Engl. J. Med.</i> , 391(6):493-503 (June 2024) (“Sarafoglou et al. 2024”).
1054	RESERVED
1055	U.S. Provisional App. No. 62/663,951 (the “951 provisional”).
1056	U.S. Provisional App. No. 62/822,815 (the “815 provisional”).

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1057	“Neurocrine Biosciences Announces U.S. FDA Accepts New Drug Applications and Grants Priority Review for Crinecerfont for Pediatric and Adult Patients with CAH,” Neurocrine Biosciences (July 1, 2024) (“Neurocrine July 1, 2024, Press Release”).
1058	“Neurocrine Biosciences Announces FDA Approval of CRENESSITY® (crinecerfont), a First-in-Class Treatment for Children and Adults With Classic Congenital Adrenal Hyperplasia,” Neurocrine Biosciences (Dec. 13, 2024) (“Dec. 13, 2024, Neurocrine Press Release”).
1059	National Center for Biotechnology Information, PubChem Compound Summary for CID 134694266, Tildacerfont (2026).
1060	U.S. Pat. No. 6,586,456 to Fontaine, et al. (the “’456 patent”).
1061	U.S. Patent Appl. No. 17/081,694, Office Action Response with Declaration of Chris N. Barnes (Dec. 13, 2021).
1062	RESERVED
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1064	Delfino et al., “Testicular Adrenal Rest Tumors in Patients With Congenital Adrenal Hyperplasia: Prevalence and Sonographic, Hormonal, and Seminal Characteristics,” <i>J. Ultrasound Med.</i> , 31:383-88 (2012).
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1067	Yu et al., “Clinical manifestations of testicular adrenal rest tumor in males with congenital adrenal hyperplasia,” <i>Ann. Ped. Endocrinol. Metab.</i> , 20:155-161 (2015).
1068	Aycan et al., “Prevalence and long-term follow-up outcomes of testicular adrenal rest tumours in children and adolescent males with congenital adrenal hyperplasia,” <i>Clin. Endocrinol.</i> , 78, 667-72 (2013).

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1069	Claahsen-van der Grinten et al., “Gonadal dysfunction in congenital adrenal hyperplasia,” <i>Eur. J. Endocrinol.</i> , 184(3):R85-R97 (2021).
1070	RESERVED
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1072	Spruce Biosciences Clinical Study Report, SPR001-202 Protocol, https://cdn.clinicaltrials.gov/large-docs/42/NCT03687242/Prot_000.pdf (2025).
1073	RESERVED
1074	International Publication No. WO 2016/065177 A1 to Howerton et al. (“Howerton”).
1075	RESERVED
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1078	Smeets et al., “Molecular Characterization of Testicular Adrenal Rest Tumors in Congenital Adrenal Hyperplasia: Lesions With Both Adrenocortical and Leydig Cell Features,” <i>J. Clin. Endocrinol. Metab.</i> , 100(3):E524-E530 (Mar. 2015).
1079	RESERVED
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1081	RESERVED
1082	RESERVED
1083	RESERVED
1084	Preliminary amendment filed in U.S. Patent Application 18/941,832 (05 February 2026).
1085	Claim amendments filed in U.S. Patent Application 18/438,060 (03 April 2026)

Exhibit No.	Exhibit Description
1086	RESERVED
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1088	Deussing & Chen, “The Corticotropin-Releasing Factor Family: Physiology of the Stress Response,” <i>Physiol. Rev.</i> , 98:2225-2286 (2018).
1089	FDA News Release, “FDA Approves New Treatment for Congenital Adrenal Hyperplasia” (December 13, 2024)
1090	National Center for Biotechnology Information, PubChem Compound Summary for CID 11596613, Verucerfont (2026).
1091	National Center for Biotechnology Information, PubChem Compound Summary for CID 24758885, 3-[4-Bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl]-2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5-a]pyrimidine] (2026).
1092	National Center for Biotechnology Information, PubChem Compound Summary for CID 24898976, 3-(4-Bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine (2026).
1093	National Center for Biotechnology Information, PubChem Compound Summary for CID 9821250, NBI-30775 (2026).
1094	National Center for Biotechnology Information, PubChem Compound Summary for CID 9888194, NBI-34041 (2026).
1095	National Center for Biotechnology Information, PubChem Compound Summary for CID 9884878, DMP-904 (2026).
1096	National Center for Biotechnology Information, PubChem Compound Summary for CID 177990, Antalarmin (2026).
1097	NCT04457336, “A Ph2b to Evaluate Clinical Efficacy and Safety of Tildacerfont in Adult CAH,” ClinicalTrials.gov., (Spruce Biosciences).
1098	Newfield et al., “Crinacerfont, a CRF1 Receptor Antagonist, Lowers Adrenal Androgens in Adolescents With Congenital Adrenal Hyperplasia,” <i>J. Clin. Endocrinol. Metab.</i> 108(11):2871–78 (2023)
1099	RESERVED
1100	PGR2025-00032, Paper 2

Exhibit No.	Exhibit Description
1101	PGR2025-00032, Paper 8
1102	RESERVED
1103	Declaration of Ramesh Tharuvai, Ph.D.
1104	Sacks et al., “Guidelines and Recommendations for Laboratory Analysis in the Diagnosis and Management of Diabetes Mellitus,” <i>Diabetes Care</i> 46(10):e151-e199 (2023)
1105	Fujimoto, “The importance of insulin resistance in the pathogenesis of type 2 diabetes mellitus,” <i>Am J Med.</i> 108(6a):9S-14S (2000)
1106	Abdul-Ghani et al., “Contributions of beta-cell dysfunction and insulin resistance to the pathogenesis of impaired glucose tolerance and impaired fasting glucose,” <i>Diabetes Care</i> 29(5):1130-9 (2006).
1107	Merkatz, “Inclusion of Women in Clinical Trials: A Historical Overview of Scientific, Ethical, and Legal Issues,” <i>JOGNN Clinical Issues</i> , 27(1):78-84 (1997)
1108	Moller DE, Flier JS. Insulin Resistance — Mechanisms, Syndromes, and Implications. <i>N Engl J Med.</i> 1991;325(13):938-948P

Neurocrine Biosciences, Inc. (“Petitioner” or “Neurocrine”) petitions for Post-Grant Review (“PGR”) of claims 1-19 of U.S. Patent No. 12,576,084 (EX1001, “the ’084 patent”) assigned to Spruce Biosciences, Inc. (“Patent Owner” or “Spruce”). There is not now, nor has there been, any district court litigation between the parties involving the ’084 patent.

I. INTRODUCTION

Petitioner Neurocrine, based in San Diego, California, is an industry leader in developing treatments for rare diseases. Neurocrine has studied CRF1 receptor antagonists—the subject matter of the ’084 patent—for over 30 years. It was the first to study and publish on the successful use of a CRF1 receptor antagonist for treating congenital adrenal hyperplasia (CAH). EX1008.¹ CAH is a rare genetic disorder characterized by overproduction of hormones adrenocorticotrophic hormone (“ACTH”), 17-hydroxyprogesterone (“17-OHP”), and androstenedione (“A4”), and insufficient production of the hormone cortisol. EX1003, ¶¶16-24. Infants with classic CAH are typically diagnosed at birth and require lifelong treatment to survive. *Id.*, ¶¶17, 24; EX1016, 2130-2132.

¹ Turcu et al., “Single-Dose Study of a Corticotropin-Releasing Factor Receptor-1 Antagonist in Women With 21-Hydroxylase Deficiency,” *J. Clin. Endocrinol. Metab.*, 101(3):1174-80 (March 2016) (“Turcu 2016”).

Through substantial research and investment, Neurocrine developed the CRF1 receptor antagonist crinecerfont—the active ingredient in its FDA-approved drug CRENESSITY®—for the treatment of CAH. EX1027, 2; EX1057.

CRENESSITY, which is manufactured, packaged, and distributed in the United States, dramatically improves lives. EX1010, 16; EX1058; EX1089; EX1103, 2.

It is the first CAH treatment approved by the FDA in *70 years* and the first successful approved therapeutic use of *any* CRF1 receptor antagonist for *any* disease “despite over 30 years of research and hundreds of patents.” EX1029, 1065; EX1058, 1. Recognizing its significance, the FDA granted CRENESSITY “Fast Track,” “Breakthrough Therapy,” “Priority Review,” “Rare Pediatric Disease,” and “Orphan Drug” designations as a first-in-class therapy addressing a long-felt and unmet medical need for CAH patients. EX1057; EX1058; EX1089, 2.

Patent Owner Spruce, by contrast, was not formed until 2014. It studied a different CRF1 receptor antagonist, Compound 1 (tildacerfont), for the treatment of CAH. But tildacerfont failed to meet both primary and secondary endpoints in clinical trials, and Spruce announced in 2024 that it is no longer pursuing tildacerfont for the treatment of CAH. EX1044, 2; EX1045, 1; EX1097, 1; EX1003, ¶33 (citing EX1043). Even so, Spruce continues to apply for and obtain patents aimed at covering therapeutic uses for CRF1 receptor antagonists that it

neither invented nor enabled. EX1084; EX1085. The '084 patent exemplifies Spruce's abuse of the patent system and the overbroad reach of Spruce's patents.

Each claim of the '084 patent recites methods for “changing a metabolic parameter”—i.e., fasting glucose, HbA1c levels, insulin sensitivity, lipid profile, or a combination thereof—in a subject having a testicular adrenal rest tumor (TART) or ovarian adrenal rest tumor (OART). EX1001, 99:1-102:50. TARTs and OARTs are known complications of CAH. EX1006, ¶44; EX1038, e69; EX1003, ¶34. The '084 patent claims “changing a metabolic parameter” in a subject having a TART or an OART by administering one of ten listed CRF1 receptor antagonists. EX1001, 99:1-102:50. But the written description of the '084 patent is directed to only a single CRF1 receptor antagonist: Compound 1 (tildacerfont). And many of the other claimed CRF1 receptor antagonists—notably crinecerfont and verucerfont—are taken directly from *Neurocrine's earlier published prior art* describing the use of these compounds for treating CAH and related disorders. EX1006, ¶5. Unsurprisingly, the '084 patent contains no written description of using these compounds to change a metabolic parameter in a subject with TARTs or OARTs. The named inventors of the '084 patent never performed that work and never possessed those compounds for use in the claimed methods.

The '084 patent also fails to provide the technical guidance necessary for a POSA to make and use all ten claimed CRF1 receptor antagonists for changing a

metabolic parameter in a subject with TARTs or OARTs. Instead, the specification contains only two disclosures that arguably relate to changing a metabolic parameter, and neither supports the full scope of the claims. In the first disclosure, the '084 patent states that “metabolic symptoms” may be improved by administering an *astressin*. EX1001, 43:67-44:5. Astressin, however, is a peptide—not a small molecule like the claimed CRF1 receptor antagonists. EX1003, ¶¶48-49. The specification’s only other disclosure of metabolic parameters appears in a *prophetic* example, where changes in metabolism are listed as a secondary endpoint for a Phase 2 study. EX1001, 91:60-64. But even that example is limited to administration of Compound 1 (tildacerfont) and provides no data or technical guidance about how any metabolic parameter would change in response to any compound, let alone each of the ten claimed compounds. EX1001, 91:60-67.

Separate from its failure to describe and enable changes in metabolic parameters, the specification also fails to provide any guidance on subjects having TARTs or OARTs. Indeed, the '084 patent specification provides no data at all on OARTs. And the only disclosure related to TARTs consists of a single data point involving one TART in one patient administered just one of the claimed compounds (Compound 1) that likewise fails to support the full scope of claims. EX1001, 96:39-42; Figs. 10A-10B.

Not only do the claims of the '084 patent lack adequate written description and enablement, but their expansive scope also renders them obvious in light of the prior art, including Neurocrine's own pioneering publication, Grigoriadis.

EX1006.² Grigoriadis discloses several of the claimed CRF1 receptor antagonists, including crinecerfont and verucerfont, as well as the link between treating CAH and TARTs. EX1006, ¶¶13, 44. Richard, initially assigned to Sanofi-Aventis and later assigned to Neurocrine, discloses the use of CRF1 receptor antagonists to treat metabolic syndrome, and reports that crinecerfont (called "Compound A" in Richard) improved insulin sensitivity and reduced fasting glucose—i.e., changed a metabolic parameter. EX1012, 17:35-18:10. The '084 patent merely repackages these teachings without contributing to scientific progress or patient care in this field.

The '084 patent should not have issued, and the Examiner erred in allowing its overly broad claims. But the '084 patent does not represent an isolated occurrence, as Spruce's attempts to abuse the patent system by claiming the work of others are pervasive. First, Spruce obtained patents covering the use of *any* CRF1 receptor antagonist, including Neurocrine's crinecerfont and verucerfont, to treat CAH. The Board correctly found that those patents did not provide adequate

² U.S. Patent Application Publication No. 2017/0020877 ("Grigoriadis").

written description for that broad genus and held all challenged claims unpatentable following full trials in PGR2021-00088 and PGR2022-00025. EX1005, 42-61; EX1007, 40-58. A mere two months after the Board's final-written decisions, however, Spruce then pivoted to an even more brazen strategy: filing patent applications and obtaining new patents explicitly claiming crinecerfont and verucerfont for treating CAH-related disorders, despite the named inventors never having worked on those compounds and despite the absence of adequate written-description and enablement.

Patent rights should reward genuine innovation by those who generate concrete scientific evidence and advance the state of the art. Neurocrine has done exactly that with its decades-long work on verucerfont and crinecerfont, and its development of CRENESSITY. Spruce, by contrast, abuses the patent system by continuously seeking claims that exceed what its named inventors described and enabled. The '084 patent continues that pattern of abuse. Allowing the '084 patent to stand would undermine the integrity of the patent system by conferring exclusive rights broader than the underlying disclosure supports. Institution is thus in the public interest, and given that there is no district-court litigation, post-grant review is the most efficient mechanism in which to address this improvidently granted patent. The Director should grant institution.

A. Neurocrine Has Long Been the Industry Leader in the Research and Development of CRF1 Receptor Antagonists for the Treatment of CAH

Neurocrine launched a clinical program studying CRF1 receptor antagonists to treat CAH in 2012 and was the first company to investigate this therapeutic approach. EX1004; EX1008. A CRF1 receptor antagonist is a compound that selectively binds to the corticotropin-releasing factor type 1 (CRF1) receptor to regulate release of the hormone ACTH from the pituitary gland. EX1003, ¶¶25-26 (citing EX1019, 333; EX1020, 322). Neurocrine first disclosed the utility of CRF1 receptor antagonists, including verucerfont (NBI-77860) and crinecerfont (SSR-125543), as a CAH treatment in PCT Application PCT/US2015/012315 to Grigoriadis, which published in 2015 (WO 2015/112642 A1). EX1004. Neurocrine's PCT application entered the U.S. national stage and published in January 2017 as U.S. Patent Application Publication 2017/0020877. EX1006, code [54]; *see also* EX1003, ¶29. Grigoriadis (EX1006) is prior art to Spruce's patents.

In early 2016, Neurocrine also published the results of the first Phase 1b clinical trial of a CRF1 receptor antagonist, verucerfont (NBI-77860), for the treatment of CAH patients, in Turcu 2016. EX1008; EX1003, ¶28 (citing EX1015, 2205; EX1014, 8; EX1025, 6; EX1049, 123). Turcu 2016 reported that administration of verucerfont resulted in meaningful reductions of several

hormones overproduced in CAH patients—ACTH, 17-OHP, and A4. EX1008, 1179-80, Table 3; EX1003, ¶¶27-28, 30. In the early 2020s, Neurocrine then reported the results of the first Phase 2 clinical trial for crinecerfont (SSR-125543) in Auchus, which proved highly effective in treating CAH in both men and women with CAH. EX1048.³

Neurocrine’s work on crinecerfont, in particular, delivered a breakthrough therapy for patients with CAH. On December 13, 2024, the FDA approved two formulations of CRENESSITY—capsule and oral solution—for use in adult and pediatric CAH patients. EX1058; EX1003, ¶32. That same day, the FDA-approved prescribing label for CRENESSITY became public. EX1089; EX1010. The label instructs patients to take CRENESSITY twice daily with a meal. EX1010, 1.

As the first—and only—FDA-approved CRF1 receptor antagonist therapy for CAH, CRENESSITY meets a long-felt and unmet medical need to reduce high-dose glucocorticoid (steroid) treatment for management of classic CAH, which produces serious complications from long-term use. Both adults and children with classic CAH have shown meaningful and durable improvements in clinical

³ Auchus et al., “Crinecerfont Lowers Elevated Hormone Markers in Adults With 21-Hydroxylase Deficiency Congenital Adrenal Hyperplasia,” *J. Clin. Endocrinol. Metab.*, 107(3):801-812 (2022) (first published online Oct. 15, 2021) (“Auchus”).

outcomes after treatment with CRENESSITY. EX1048; EX1098. Demonstrating that CRENESSITY is a medical breakthrough, the prestigious *New England Journal of Medicine* published the results of Neurocrine’s two Phase 3 clinical trials, in adult and pediatric patients, in June 2024. EX1052; EX1053; EX1003, ¶31. Since its launch, CRENESSITY has been a success, generating approximately \$301 million in net sales and more than 2,000 new patient enrollments in its first year on the market. EX1011, 1.

B. Spruce’s Overbroad Patents to Treatment of CAH and Related Disorders Have Repeatedly Failed at the Board and in Europe

Neurocrine successfully challenged Spruce’s patents in PGR2021-00088 and PGR2022-00025. EX1005, 2; EX1007, 2. The Board issued two final written-decisions holding all challenged claims unpatentable for lack of written description. EX1005, 42-61; EX1007, 40-58. Those patents claimed the use of an entire genus of CRF1 receptor antagonists to treat CAH and reduce the hormones ACTH, 17-OHP, and/or A4. EX1036, 48:6-12; EX1037, 47:51-48:5. But the Board found that the patents’ shared specification described only a single CRF1 receptor antagonist, tildacerfont, and did not reasonably convey possession of the full scope of the claimed genus—including claims to Neurocrine’s verucerfont and crinecerfont. *See, e.g.*, EX1005, 4-45, 55-57. In reaching that conclusion, the Board rejected Spruce’s argument that the claimed genus of CRF1 receptor

antagonists represented a “well-known, well-characterized, and discrete class” of compounds. *Id.*, 55-57. Spruce did not appeal the Board’s decisions to the Federal Circuit.⁴

In PGR2025-00032, Neurocrine challenged claims of Spruce’s U.S. Patent 12,115,166. EX1100, 1. In response, Spruce filed a statutory disclaimer disclaiming all claims, and the Board denied institution in light of that statutory disclaimer. EX1101, 2.

In Europe, Spruce obtained claims reciting the use of any CRF1 receptor antagonist—encompassing Neurocrine’s verucerfont and crinecerfont—for treating or preventing TARTs or OARTs. EX1023, 63-65. The European Patent Office’s Opposition Division revoked that patent. EX1028, 11 (¶8.3). Spruce did not appeal that decision, just as it did not appeal the Board’s decisions on its U.S. patents.

⁴ Spruce’s requests for Director Review were denied. EX1031-EX1032; EX1034-EX1035.

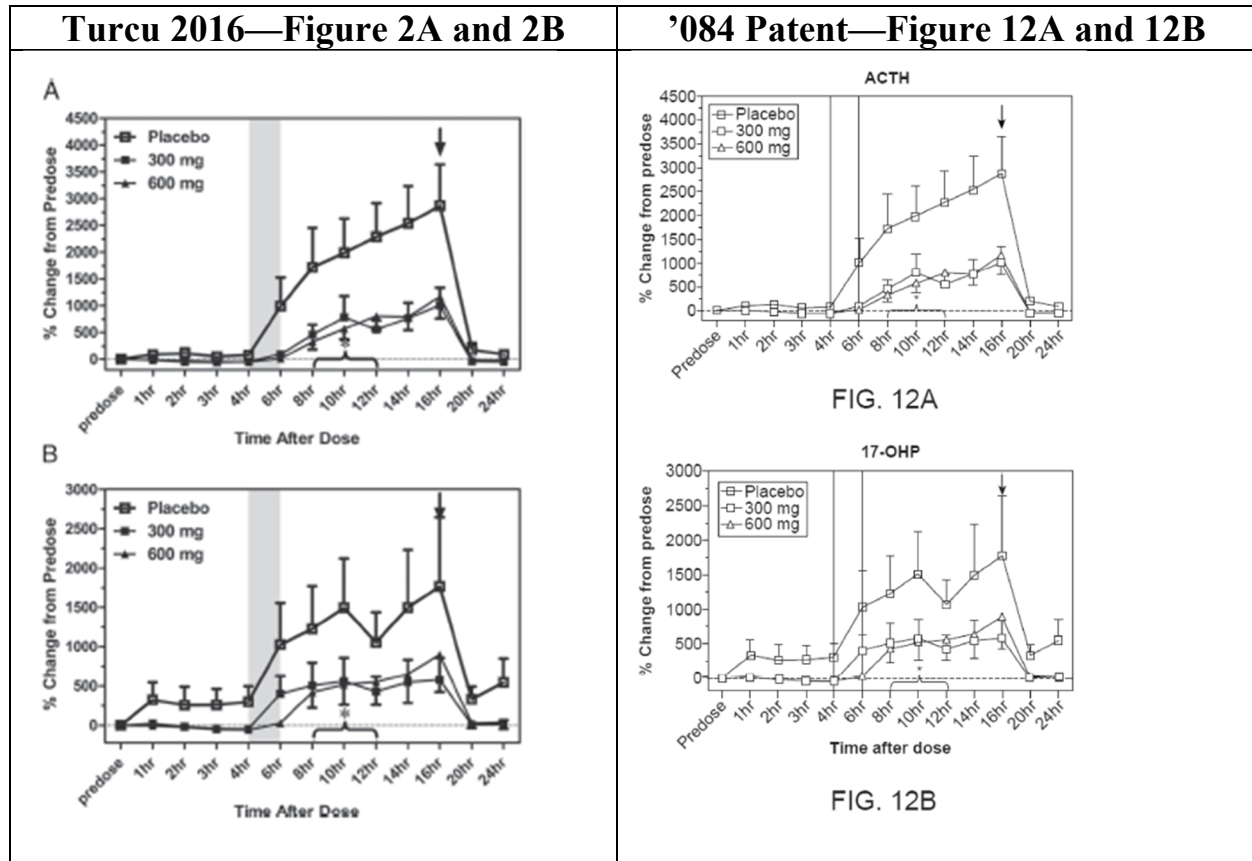
C. The '084 Patent and Its Prosecution History Illustrate Spruce's Pattern of Pursuing Overly Broad Claims That Copy the Work of Others

Spruce filed U.S. Application 19/043,303 (“the '303 application”),⁵ which resulted in the '084 patent, on January 31, 2025. EX1001, code [22]. This was just two months after the Board issued its final written decisions in PGR2021-00088 and PGR2022-00025 and seven weeks after the FDA approved the CRENESSITY label. EX1005, 1; EX1007, 1; EX1089, 1; EX1003, ¶75. Spruce filed for and was granted Track One prioritized examination for the '303 application. EX1002, 27, 151-152. Despite having the benefit of the Board's reasoned analysis about the limits of its disclosures, Spruce attempted to claim Neurocrine's verucerfont and crinecerfont for changing a metabolic parameter in a subject with a TART or an OART. *Id.*, 143-144. It did so even though the named inventors neither invented nor possessed that subject matter.

Spruce went even further by directly copying Neurocrine's own published data from Turcu 2016. To justify the use of Compound 1 (tildacerfont) for treating TARTs, the '084 patent invokes “a previous proof-of-concept study using a similar small-molecule CRF1 receptor antagonist.” EX1001, 95:40-44. The '084 patent states that this “similar” CRF1 receptor antagonist “produced dose-dependent

⁵ The '303 application claims priority through a series of continuation applications to April 27, 2018. EX1001, codes [63], [60].

reductions in ACTH and 17-hydroxyprogesterone (17-OHP) in subjects with CAH” and cites to Figures 12A and 12B. *Id.* But Figures 12A and 12B were copied directly from Neurocrine’s *verucerfont* data published in Turcu 2016, as the side-by-side comparison below illustrates:

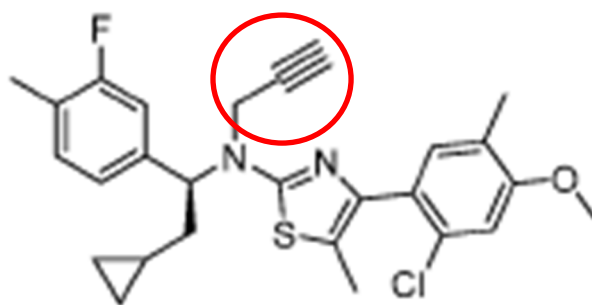


Compare EX1008, 1176, Figures 2A-B, with EX1001, Figures 12A-B; EX1003, ¶¶56-57 (citing EX1072, 13).

To make matters worse, applicants initially presented Figures 12A and 12B as depicting Spruce’s *own Compound 1 (tildacerfont)* data. The original specification of the '084 patent stated that Figures 12A and 12B provided a

graphical representation of ACTH and 17-OHP hormone levels after treatment with Compound 1. EX1002, 39, (¶48). Only after the Examiner had already issued an Office Action did applicants remove the reference to Compound 1 from the description of Figures 12A and 12B, and attribute the reported improvement in ACTH and 17-OHP levels in CAH patients instead to Neurocrine. EX1002, 295 (¶48), page 110, (¶326) (citing Neurocrine's Grigoriadis publication).

The deficiencies of the '084 patent do not end there. The original specification also contains no written-description support for Neurocrine's crinecerfont, further underscoring that the named inventors performed no actual work on that compound. Instead, the original specification disclosed a compound having the following chemical structure:



EX1002, 36-37 (¶27), 123 (¶261). As Neurocrine's expert Dr. Lodish explains, that structure contains a three carbon side chain (circled in red above) with an impossible carbon-carbon "quadruple" bond ($-\text{CH}_2-\text{C}\equiv\text{C}$) and is not crinecerfont. EX1003, ¶¶66, 76-77. Applicants later amended the claims to recite the structure

of Neurocrine’s crinecerfont, but the compound with the original quadruple carbon bond structure remains elsewhere in the ’084 patent. *Compare* EX1001, 7:55-65, *with id.* at 82:40-50.

The ’084 patent reflects a clear pattern of conduct: it claims ownership of CRF1 receptor antagonists—including Neurocrine’s compounds—for treating CAH and related disorders while providing disclosures that fall far short of supporting its overbroad claims. A POSA would not have recognized that the named inventors of the ’084 patent possessed or enabled a method for changing a metabolic parameter in a subject with TARTs or OARTs using each of ten claimed CRF1 receptor antagonists, especially Neurocrine’s verucerfont and crinecerfont.

II. OVERVIEW OF CO-PENDING PGRs

Neurocrine files three Petitions for PGR today: PGR2026-00059 (challenging U.S. Patent No. 12,569,491), PGR2026-00060 (challenging U.S. Patent No. 12,569,490), and PGR2026-00061 (challenging the ’084 patent). All three patents share the same written description and all three suffer from the same problem of claim overbreadth. Addressing all three patents in a coordinated manner promotes efficiency, avoids duplicative proceedings, and enables consistent resolution of shared §112 and §103 patentability issues.

All three patents claim the same ten CRF1 receptor antagonists for treating a CAH-related disorder with minor variations in the claimed disorder: TARTs or

OARTs in PGR2026-00059, OARTs and menstrual irregularity in PGR2026-00060, and “changing a metabolic parameter” in a subject with TARTs or OARTs here. But like the claims found unpatentable in the previous PGRs, the claims in these newly issued patents encompass CRF1 receptor antagonists that the named inventors failed to describe and enable. Accordingly, all three Petitions challenge all claims for lack of written description and enablement.

The present Petition and that in PGR2026-00059 also challenge as obvious all claims covering Neurocrine’s compounds for treating TARTs and for changing a metabolic parameter in a subject with TARTs. As explained above, Neurocrine’s own Grigoriadis publication teaches the use of CRF1 receptor antagonists (including crinecerfont and verucerfont) for treating CAH and its related disorder TARTs. EX1006, ¶¶13, 44. By contrast, the Petition in PGR2026-00060 does not include an obviousness ground because the challenged patent there does not claim a method for treating TARTs.

III. REQUIREMENTS FOR PGR

A. Grounds for Standing

Pursuant to 37 C.F.R. §42.204(a), Neurocrine certifies that the ’084 patent is available for PGR and that Neurocrine is not barred or estopped from requesting PGR challenging claims 1-19 on the below-identified grounds of unpatentability.

This Petition is being filed within nine months of the issuance of the '084 patent on March 17, 2026.

B. Identification of Challenge

Pursuant to 37 C.F.R. §42.204(b), Neurocrine requests PGR of claims 1-19 on the grounds set forth below and requests that the Board cancel all claims of the '084 patent.

Ground	Claims Challenged	35 U.S.C. §	Reference(s)/Basis
1	1-19	112(a)	Lack of Written Description
2	1-19	112(a)	Lack of Enablement
3	1, 3-5, 8-13, 15-19	103	Obviousness over Grigoriadis, Yu, Richard
4	6-7	103	Obviousness over Grigoriadis, Yu, Richard, Delfino
5	14	103	Obviousness over Grigoriadis, Yu, Richard, Howerton

The Declaration of Maya Lodish, M.D. (EX1003) supports the grounds of unpatentability set forth in this Petition.

C. The '084 Patent Is Eligible for PGR

The '084 patent claims priority through a series of continuation applications to provisional Application 62/822,815 (“the '815 provisional”) filed on March 23, 2019, and provisional Application 62/663,951 (“the '951 provisional”), filed on

April 27, 2018. EX1001, code [60]. Accordingly, the '084 patent is an AIA “first-to-file” patent filed on or after March 16, 2013.

IV. LEVEL OF ORDINARY SKILL

A POSA would have possessed 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. EX1003, ¶84. A POSA would also have at least three years of experience researching endocrine disorders, including TARTs, OARTs, or other adrenal disorders. *Id.* A POSA may have also worked as part of a multi-disciplinary team and drawn upon not only his or her own skills, but also consulted with others on the team having specialized skills to solve a problem, including analytical chemistry, pharmaceutical design, development, and formulation, clinical trials, and diagnostic medical sonography. *Id.* Dr. Lodish is well qualified to opine from the perspective of a POSA in this case. EX1003, ¶¶1-13.

V. CLAIM CONSTRUCTION

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; *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-14 (Fed. Cir. 2005) (en banc). Claim

terms are construed only as needed to resolve a controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).

Baseline. In the previous PGRs, the Board, at oral argument, construed the term “baseline” to mean “a series of samples taken from an untreated patient with CAH, prior to treatment at intervals that are time-matched to the sampling intervals to be taken from the patient treated with either a CRF1 receptor antagonist or placebo.” EX1005, 25-26; EX1007, 24-25; EX1003, ¶87. Although the Board provided the parties with additional briefing on this claim construction, the Board ultimately determined in the previous PGRs that no claim construction was necessary to resolve the dispute over written description. EX1005, 26; EX1007, 25. Here, the term “baseline” appears only in dependent claim 19, which recites a reduction in the plasma concentration of certain biomarkers, including 17-OHP, ACTH, and A4, compared to “baseline.” *See* EX1001, 102:49-50 (“The method of claim 17, wherein the plasma concentration of the biomarker is at least 10% from baseline.”). Neurocrine agrees with the Board’s construction and applies it here for claim 19. *Infra*, §VIII.C.7.

Otherwise, and for purposes of this proceeding only, Neurocrine submits that no other claim terms need construction. EX1003, ¶¶85-86.

VI. GROUND 1: Claims 1-19 are unpatentable for lack of written description

“[T]he written description requirement applies to all claims and requires that the specification objectively demonstrate that the applicant actually invented—was in possession of—the claimed subject matter.” *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1349 (Fed. Cir. 2010) (en banc). For claims that recite various elements listed in the alternative—such as a method of changing a metabolic parameter in a subject with “TART” *or* “OART” and each of the ten CRF1 receptor antagonists here—the specification must convey that the inventors had possession of *each* of those alternative elements. *Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, 10 F.4th 1330, 1337 (Fed. Cir. 2021) (“written description must lead a person of ordinary skill in the art to understand that the inventors possessed the *entire scope* of the claimed invention”).⁶ The written description of the ’084 patent fails to meet this requirement.

First, the written description of the ’084 patent fails to demonstrate possession of a method for changing any metabolic parameter with any of the claimed CRF1 receptor antagonists. Second, the written description fails to demonstrate possession of Neurocrine’s crinecerfont at all. Third, the written description fails to show possession of seven of the ten claimed CRF1 receptor

⁶ Here and throughout, emphasis added unless otherwise stated.

antagonists—including Neurocrine’s crinecerfont and verucerfont—for changing a metabolic parameter. Fourth, the written description fails to demonstrate that the named inventors possessed methods for changing a metabolic parameter in a subject with OARTs specifically. For each of these reasons, the specification falls far short of demonstrating possession of the full scope of changing a metabolic parameter in a subject with TARTs or OARTs with the full scope of the claimed CRF1 receptor antagonists, rendering claims of the ’084 patent unpatentable under §112(a). EX1003, ¶¶101-102.

A. All Claims of the ’084 Patent Lack Written Description Because the Specification Fails to Show Possession of a Method for Changing a Metabolic Parameter

The claims of the ’084 patent recite a method for “changing a metabolic parameter” of a subject having a TART or an OART by administering one of ten “small molecule” CRF1 receptor antagonists. EX1001, 99:2-101:22. Claim 1 recites that the “metabolic parameter” comprises “fasting glucose, HbA1c level, insulin sensitivity, or a lipid profile, or a combination thereof.” *Id.*, 101:20-22. The specification references metabolic parameters in only two places, and neither disclosure reasonably conveys to a POSA that the named inventors had possession of a method for changing a metabolic parameter using any of the claimed CRF1 receptor antagonists. All the claims therefore fail the written description requirement of §112(a). EX1003, ¶¶103-109.

1. The '084 patent's disclosure of astressin does not provide adequate written-description support for the claims

In the first disclosure, the specification states:

In one aspect described herein, there is a method of improving metabolic symptoms in a subject in need thereof, comprising administering an *astressin* or a variant having at least about 70% identity thereto; or a pharmaceutically acceptable salt or solvate thereof.

EX1001, 43:67-44:5. This disclosure does not provide adequate written-description support for the claims because it is directed to a fundamentally different compound—astressin—than the claimed CRF1 receptor antagonists. EX1003, ¶¶71, 103-106.

The '084 patent itself highlights the difference between astressin and the claimed CRF1 receptor antagonists. Astressin is a large molecule *peptide* that the specification describes as “a *nonselective* corticotropin releasing hormone [CRH] antagonist that reduces the synthesis of ACTH and cortisol.” EX1001, 43:40-43, By contrast, the claimed compounds are *selective, small molecule* antagonists of the CRF1 receptor subtype. EX1001, 1:30-35 (describing claimed Compound 1 as a “selective” CRF1 receptor antagonist), 6:66-8:33 (describing “additional chemotherapeutic agent[s]” as CRF1 receptor antagonists), 90:32-34 (describing Compound 1 as “a high-affinity and selective small-molecule antagonist” of CRF1 receptor). A POSA would not have viewed the claimed CRF1 receptor antagonists

as interchangeable with astressin because, as Dr. Lodish explains, a nonselective CRH antagonist like astressin acts broadly across CRH receptor subtypes (e.g., CRF1 and CRF2), whereas a selective CRF1 receptor antagonist targets only one (i.e., CRF1). EX1003, ¶¶48-49, 105 (citing EX1030, 373).

Specifically, the CRF1 and CRF2 receptors have different tissue distributions and mediate different physiological responses. Astressin blocks both receptor subtypes and therefore may affect unintended targets and produce biological effects different from those of a compound that selectively targets only CRF1. Accordingly, a POSA would not have understood the '084 patent's disclosure of astressin as demonstrating possession of a method of changing a metabolic parameter with the claimed small-molecule, selective CRF1 receptor antagonists. EX1003, ¶¶105-106 (citing EX1088, 2233-2235).

The written description also fails to bridge the gap between astressin and the small-molecule CRF1 receptor antagonists recited in the claims. The '084 patent does not explain whether or how a selective CRF1 receptor antagonist could change a metabolic parameter. It does not identify any link between selective CRF1 antagonism and changing a metabolic parameter. It does not present any experimental evidence or any data—preclinical or clinical—suggesting that a small-molecule CRF1 receptor antagonist would be effective for changing a metabolic parameter. And it does not even hypothesize that such compounds

could change a metabolic parameter. EX1003, ¶106. The disclosure of improving metabolic symptoms with astressin stands alone, untethered to the claimed compounds.

This is precisely the kind of disconnect that defeats written description. In *Centocor Ortho Biotech, Inc. v. Abbott Laboratories*, 636 F.3d 1341 (Fed. Cir. 2011), the Federal Circuit invalidated claims directed to fully human antibodies where the specification disclosed only mouse and chimeric antibodies for the same therapeutic target. The court held that the specification “at best describes a plan for making” the claimed antibodies and conveyed nothing more than “a mere wish or plan” for the claimed invention. *Id.* at 1348-49. The same analysis compels the same result here. This disclosure relates to metabolic improvement with astressin, a nonselective, large-molecule CRH peptide antagonist—not any of the claimed selective, small-molecule CRF1 receptor antagonists. EX1001, 43:62-67. As in *Centocor*, where disclosing mouse antibodies did not convey possession of the claimed fully human antibodies, disclosing the use of astressin for improving metabolic symptoms does not convey possession of a structurally and pharmacologically distinct class of compounds (i.e., CRF1 receptor antagonists) for changing a metabolic parameter. EX1003, ¶¶106.

2. Example 1 of the '084 patent does not provide adequate written-description support for the claims

The '084 patent's only other disclosure of "metabolic parameters" appears in Example 1. Example 1 describes a *prophetic* Phase 2, open-label study protocol for evaluating the efficacy and safety of Compound 1 (tildacerfont) in male CAH subjects with TARTs. EX1001, 90:8-93:67. As relevant here, the protocol lists "[c]hanges in metabolic parameters" as one of several theoretical secondary endpoints. *Id.*, 91:60-64. The metabolic parameters identified—fasting glucose, HbA1c, insulin sensitivity, and lipid profile—track those recited in claim 1. *Id.*

Example 1 does not provide adequate written description because it is a prophetic example that does no more than *propose* measuring metabolic changes in a future clinical trial. It reports no data (or even expected data) for any metabolic parameter in any subject. And nothing in the '084 patent indicates to a POSA what outcome the proposed study would—or was expected to—produce. EX1003, ¶107.

Although prophetic examples can in some circumstances satisfy the written-description requirement, they cannot do so where the disclosure "is not so much an example as it is a mere mention of a desired outcome." *Ariad*, 598 F.3d at 1357. That is precisely the case here. Example 1 merely identifies a hoped-for endpoint of a Phase 2 study: observing changes in metabolic parameters. It does not

demonstrate that the named inventors actually possessed a method of changing the metabolic parameters recited in the claims. *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1567 (Fed. Cir. 1997) (a “mere wish or plan” to obtain a claimed invention does not satisfy the written description requirement).

The only alleged patient data generated by the named inventors of the '084 patent comes from Figures 10A and 10B, ultrasound images that purportedly show shrinkage of a TART in a single 25-year-old male CAH patient after six weeks of treatment with Compound 1 (tildacerfont). EX1001, 96:17-20. But, as with Example 1, Figures 10A and 10B do not provide any disclosure or data (actual or expected) about any change in the “metabolic parameters” recited in the claims. Tumor shrinkage shown on ultrasound is a morphological observation—not a change in a metabolic parameter. EX1003, ¶¶108-109 (citing EX1104). And a POSA would not necessarily equate a purported reduction in TART size with changes in fasting glucose, HbA1c levels, insulin sensitivity, or lipid profile, or any combination of metabolic parameters required by the claims. EX1003, ¶109 (citing EX1107). Thus, these ultrasound images do not cure the written description’s complete failure to disclose actual or expected metabolic data. *Id.*, ¶¶43-45.

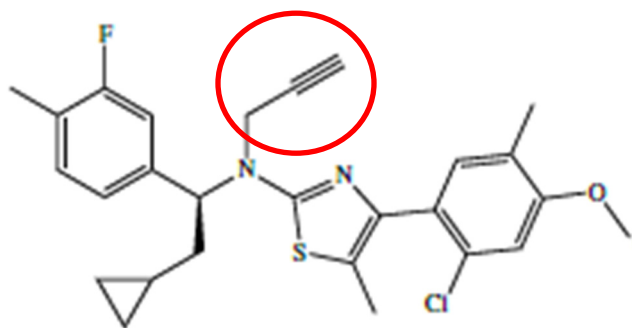
Finally, although not prior art, Spruce publicly announced that Compound 1 (tildacerfont) failed to meet its primary and *secondary endpoints* in its two most

recent clinical trials. EX1044; EX1045; EX1097, 1. And the Example 1 protocol lists “[c]hanges in metabolic parameters” as one of several theoretical secondary endpoints. EX1001, 91:60-64. Therefore, a POSA would understand that these clinical outcomes confirm that the named inventors never had possession of a method for changing a metabolic parameter with Compound 1 (tildacerfont), much less any of the other CRF1 receptor antagonists recited in the claims. *Nuvo Pharms. (Ir.) Designated Activity Co. v. Dr. Reddy’s Lab’ys Inc.*, 923 F.3d 1368, 1384 (Fed. Cir. 2019) (invalidating claims where POSA would not have expected claimed pharmaceutical compound to achieve claimed therapeutic result). For these reasons, claims 1-19 are unpatentable for lack of written description.

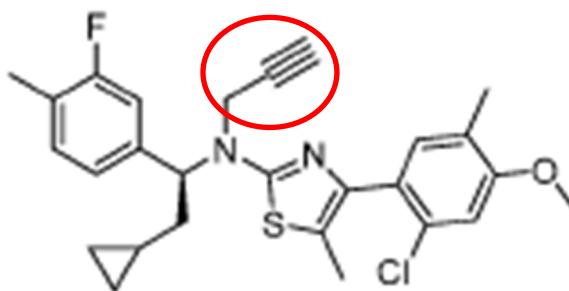
B. Claims 1 and 3-19 Fail Because the Written Description Does Not Show Possession of Crinecerfont

In addition to failing to reasonably convey that the named inventors of the ’084 patent had possession of a method for “changing a metabolic parameter” (*supra*, §VI.A.), the written description also fails to show that they had possession of crinecerfont at all. EX1003, ¶¶110-118.

As explained above, claims 1 and 3-19 encompass Neurocrine’s crinecerfont (compound **H**). EX1001, 99:1-101:22, 101:50-102:50. In claim 1 and dependent claim 3, crinecerfont is represented by the following chemical structure:



EX1001, 100:40-50 (claim 1), 101:50-102:12 (claim 3). Crinecerfont has a propynyl moiety (circled in red above), which is a three-carbon side chain that contains a carbon-carbon triple bond ($-\text{CH}_2-\text{C}\equiv\text{CH}$). EX1003, ¶110. But in the written description and claims as originally filed, the named inventors did not disclose crinecerfont, and instead disclosed a compound having the following chemical structure:



EX1002, 36-37 (¶27), 123 (¶261), 143 (claim 1), 144 (claim 3). As explained above, this structure contains a three-carbon side chain (circled in red above) with an impossible carbon-carbon quadruple bond ($-\text{CH}_2-\text{C}\equiv\text{C}$). As Dr. Lodish

explains, this structure is not crinecerfont, and cannot exist. EX1003, ¶111; *supra*, §I.C.

“Satisfaction of the description requirement [e]nsures that a claim subsequent to the filing date of the application was sufficiently disclosed at the time of filing so that the *prima facie* date of invention can fairly be held to be the filing date of the application.” *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1562 (Fed. Cir. 1991) (cleaned up). Here, because the named inventors of the ’084 patent did not have possession of crinecerfont as now claimed in the original specification, all claims reciting crinecerfont (compound **H**) (claims 1 and 3-19) fail the written-description requirement as containing new matter. *Ariad*, 598 F.3d at 1348.

The Examiner erred in allowing the amendments to the specification and claims. After the Examiner issued a first, non-final Office Action objecting to claims 1 and 3 (EX1002, 153-163), applicants filed a Response with amendments to the claims and a substitute specification changing the disclosed structure (with the carbon-carbon quadruple bond) to crinecerfont. EX1002, 292, 378 (substitute specification), 403-404 (amended claims). Applicants argued that support for the amendments “can be found in the as-filed application.” *Id.*, 399. But applicants never stated where they had support in the “as-filed application” for correcting the so-called mistake. *Id.* That’s because they had no support.

Nowhere in the priority chain or in the application leading to the '084 patent did the named inventors have possession of crinecerfont, as now claimed. The '084 patent claims priority to International Application PCT/US2019/029486 (“the PCT application”), the '815 provisional, and the '951 provisional. EX1001, codes [63], [60]. None of these applications disclose crinecerfont. EX1003, ¶¶112-113. The PCT application discloses the structure with a carbon-carbon quadruple bond. EX1051, ¶¶27, 261.⁷ So does the '951 provisional, and in both cases the only disclosure of this compound is as an “additional chemotherapeutic agent.” EX1055, ¶¶231-232; EX1051, ¶¶26-27, 260-261. The '815 provisional discloses tildacerfont only, and no other CRF1 receptor antagonists. EX1056, ¶¶4, 6, 9, 10, 11.

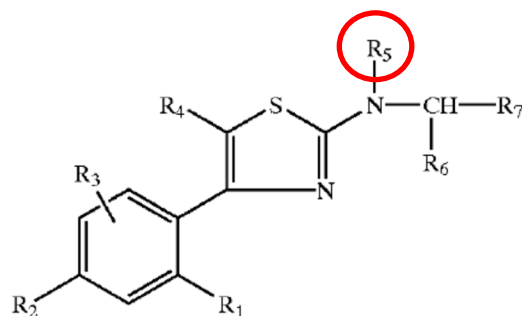
Accordingly, the recitation of crinecerfont (compound **H**) in claims 1 and 3-19 constitutes new matter and these claims are unpatentable for lack of written description. 35 U.S.C. §132(a); MPEP §2163.06 (a claim amendment adding new matter should be rejected under 35 U.S.C. §112(a) for lack of written description); *Ariad*, 598 F.3d at 1352 (“For example, a propyl or butyl compound may be made

⁷ Notably, the only claim in the PCT application reciting the compound at issue—claim 61—defines it as “an additional chemotherapeutic agent” (claim 60) that is “further...administer[ed]” to the subject in need (claim 56). EX1051, 118-119. This framing further demonstrates that the named inventors never contemplated these “additional chemotherapeutic agent[s]” as compounds for treating TARTs or OARTs, let alone changing metabolic parameters in those patients.

by a process analogous to a disclosed methyl compound, but, in the absence of a statement that the inventor invented propyl and butyl compounds, such compounds have not been described and are not entitled to a patent.”); EX1003, ¶¶112-113.

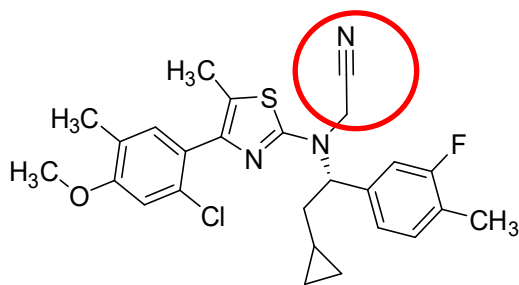
The Board should reject any argument that the amendments constituted an obvious correction of an obvious error. *In re Oda*, 443 F.2d 1200, 1205-06 (CCPA 1971). As Dr. Lodish explains, a POSA would not have recognized that the ’084 patent’s original structure must have been corrected in the way applicants did to attempt to claim crinecerfont, even if the original structure’s quadruple carbon bond was an obvious error. EX1003, ¶114.

At the time of the alleged invention of the ’084 patent, a POSA would have understood that the carbon-carbon quadruple bond structure initially disclosed and claimed was incorrect (it would be impossible), but a POSA would not have understood what the intended structure should have been. EX1003, ¶114. A POSA would have understood that this structure could have been corrected in several ways, including in ways that would not result in crinecerfont. For example, a POSA attempting to understand the quadruple carbon bond structure would have looked to prior-art U.S. Patent 6,586,456 (“the ’456 patent”), a Sanofi patent licensed by Neurocrine, which discloses several aminothiazole derivatives as CRF receptor antagonists having the following formula (I):



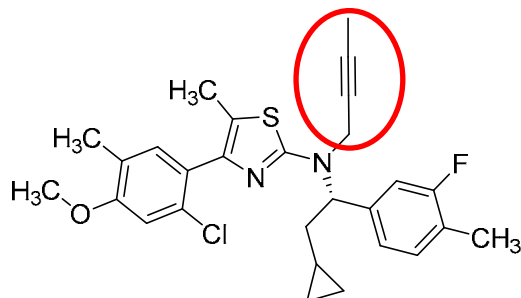
EX1060, 4:5-14; EX1003, ¶¶115-116. The '456 patent teaches that the side chain at issue, R₅ (circled in red above), “represents an alkenyl of 3 to 6 carbon atoms; an alkynyl of 3 to 6 carbon atoms; a cyano(C₁-C₆)alkyl; [or] a (C₁-C₄)alkoxy.” *Id.*, 4:45-47. A POSA would have understood that multiple alternative R₅ substituents could have served as a “correction” to the originally disclosed quadruple carbon bond structure, including but not limited to:

- An aminothiazole derivative having a nitrile moiety (also called a “cyano”) that includes a carbon-nitrogen triple bond—circled in red below:



EX1003, ¶118. In this case, the R₅ substituent is “a cyano (C₁-C₆) alkyl.” Specifically, R₅ is -CH₂-C≡N. EX1060, 4:46-47; EX1003, ¶118.

- An aminothiazole derivative having a butynyl moiety (an alkynyl group of four carbon atoms) circled in red below:



EX1003, ¶117. In this case, the R₅ substituent is an “alkynyl of 3 to 6 carbon atoms.” Specifically, R₅ is –CH₂–C≡C–CH₃. EX1060, 4:45-46; EX1003, ¶117.

Given these multiple plausible alternatives, a POSA would not have recognized that the only appropriate correction to the disclosed structure—with its carbon-carbon quadruple bond—was crinecerfont. The amendment applicants made during prosecution was not an obvious correction and therefore constitutes impermissible new matter. EX1003, ¶114.

C. Claims 1 and 3-19 Also Fail Because the Written Description Discloses Seven of the Ten Claimed CRF1 Receptor Antagonists as “Additional Chemotherapeutic Agent[s]”—Not as Compounds for Changing a Metabolic Parameter

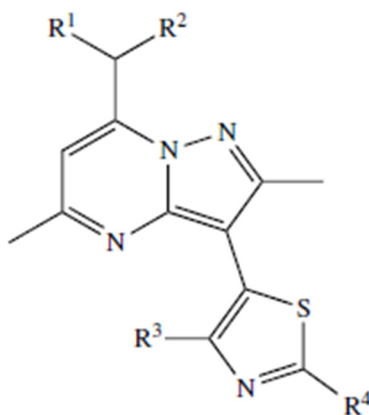
Claims 1 and 4-19 encompass ten CRF1 receptor antagonists for changing a metabolic parameter in a subject with a TART or an OART. EX1001, 99:2-101:22, 102:14-102:50. Claim 2 is limited to Compound 1 (tildacerfont) (*id.*, 101:24-49) and claim 3 is limited to Neurocrine’s crinecerfont (*id.*, 101:50-

102:13). To satisfy the written-description requirement, the '084 patent “must lead a person of ordinary skill in the art to understand that the inventors possessed the *entire scope* of the claimed invention.” *Juno Therapeutics*, 10 F.4th at 1337. The written description fails to do so here because seven of the ten claimed CRF1 receptor antagonists are not, in fact, disclosed in the '084 patent as compounds for changing a metabolic parameter (and claim 3's crinecerfont is not disclosed at all, as explained above). At most, they appear in the written description *only* as “an additional chemotherapeutic agent” to be co-administered with a compound of Formula (I). EX1001, 6:56-58, 6:66-8:33; EX1003, ¶¶119-133. Thus, all claims *not* limited to tildacerfont (claims 1 and 3-19) lack adequate written description for this additional reason.

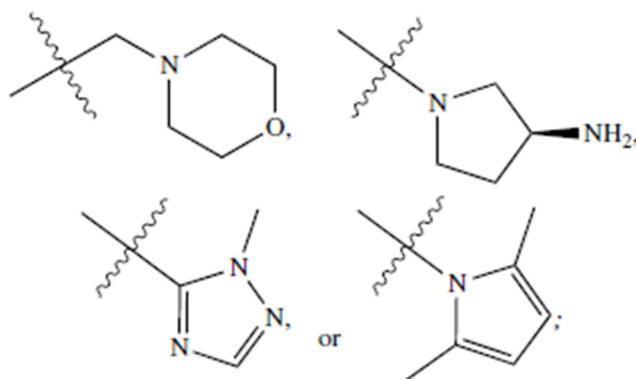
1. The written description purports to disclose compounds of Formula (I) for changing a metabolic parameter in a subject with TARTs or OARTs

To begin, the '084 patent purports to disclose a method of treating an adrenal tumor (i.e., TARTs or OARTs⁸) with a CRF1 receptor antagonist having the structural Formula (I):

⁸ A method for treating TARTs or OARTs is claimed in U.S. Patent No. 12,569,491 and challenged in PGR2026-00059.



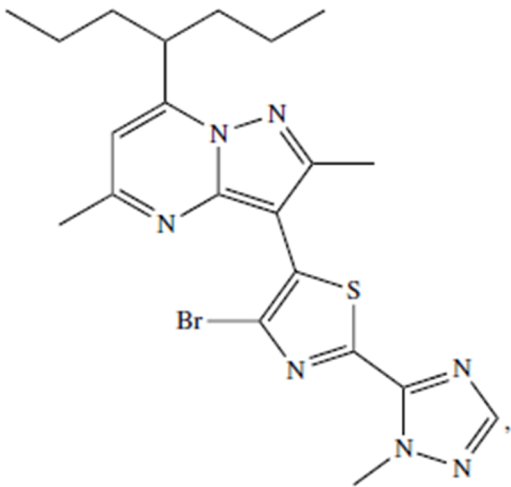
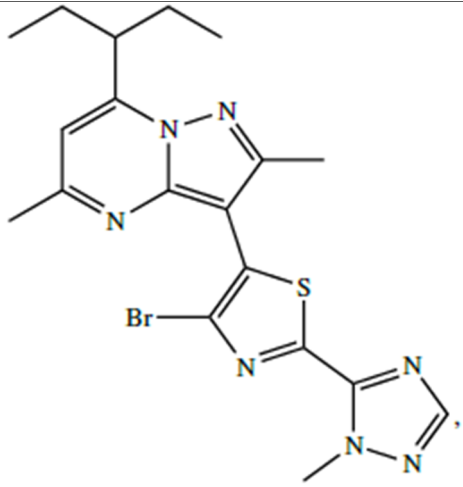
EX1001, 2:13-33; EX1003, ¶¶51-53; 120-121. In its broadest disclosure, the '084 patent provides that R¹ and R² of Formula (I) are independently ethyl or n-propyl; R³ is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy; R⁴ is hydrogen, Br, R^aR^bN-, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,

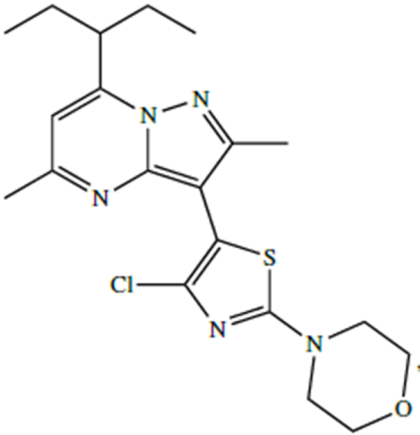


and R^a and R^b are independently hydrogen, C₁-C₃alkyl, H₂NCH₂CH₂-, (CH₃)₃COC(O)NHCH₂CH₂-, or CH₃CH₂CH₂NHCH₂CH₂-. EX1001, 2:34-55.

Only *three* of the ten CRF1 receptor antagonists recited in claim 1 are identified in the '084 patent as falling within the structure of Formula (I). EX1003,

¶121. These three compounds are disclosed in column 3 of the '084 patent and correspond to the first three compounds recited in claim 1. EX1001, 3:10-67, 99:10-50. These three Formula (I) compounds are reproduced here in a table with formatting and letter designations added for ease of identification:

Letter Designation	Compound
A	
B	

Letter Designation	Compound
C	

EX1001, 99:10-50 (formatting and letter designations added); EX1003, ¶121 (citing EX1059, EX1091, EX1092).⁹ Notably, compound **C** in the table corresponds to “Compound 1” of the ’084 patent, which is tildacerfont. EX1001, 90:46-62, 96:64-97:2; EX1003, ¶122 (citing EX1059).

Every substantive disclosure in the ’084 patent is tied to Formula (I) compounds—and, in particular, to Compound 1 (tildacerfont). EX1003, ¶123. In a few instances, the ’084 patent mentions CRF1 receptor antagonists generically. EX1001, 2:4-9, 50:53-63. But nowhere does the written description state or suggest that any specific compound falling *outside* the structure of Formula (I) can treat adrenal tumors, much less “chang[e] a metabolic parameter” as claimed. As

⁹ For clarity and ease of reference, Petitioner adds letters **A** through **J** to identify each CRF1 receptor antagonist listed in claim 1 and refers to these letters throughout. Dr. Lodish uses the same convention for efficiency and ease of reference. EX1003, ¶¶121, 124.

one telling comparison, the '084 patent recites Formula (I) *four hundred and twelve times*, while the other claimed compounds appear *only twice*—and, as described below, only as “additional chemotherapeutic agent[s]” to be co-administered with a compound of Formula (I). EX1001, 6:65-8:33, 81:43-83:17; *infra*, §VI.C.2.

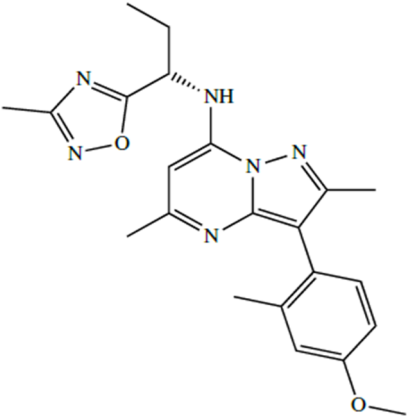
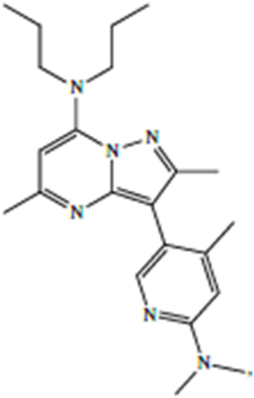
The '084 patent also states that Compound 1 (tildacerfont) “may be effective in blocking ACTH synthesis,” and—based on that asserted mechanism—states that suppression of the hormone ACTH would “thereby reduc[e] the size of testicular lesions in TART.” EX1001, 90:29-34. It states that “promising results” with Compound 1 (tildacerfont) in pre-clinical and Phase 1 clinical studies in healthy volunteers “provide a rationale for *investigating the use of Compound 1* in the treatment of TART, in combination with replacement glucocorticoids and mineralocorticoids.” EX1001, 90:42-45. These statements reinforce that the written description conveys possession of, at most, the CRF1 receptor antagonists of Formula (I), not the seven additional CRF1 receptor antagonists recited in the claims. EX1003, ¶123.

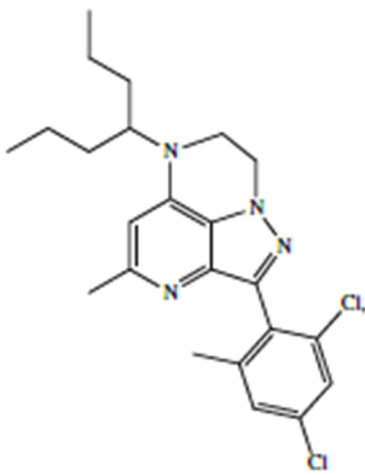
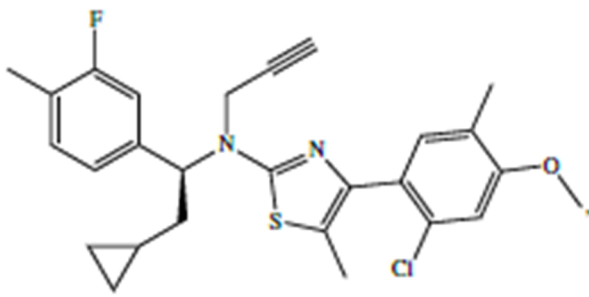
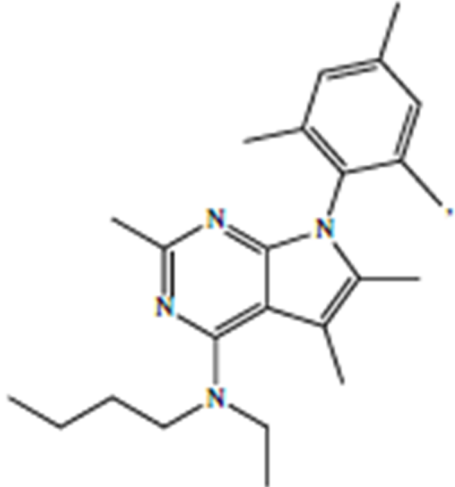
2. The written description discloses the additional seven CRF1 receptor antagonists only as “additional chemotherapeutic agent[s]”

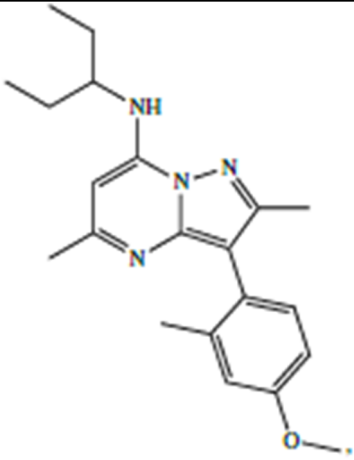
Even though the written description of the '084 patent is limited to CRF1 receptor antagonists of *Formula (I)* for purportedly treating adrenal tumors,

claim 1 recites an *additional seven* CRF1 receptor antagonists. EX1003, ¶124.

These claimed CRF1 receptor antagonists are reproduced here with formatting and letter designations **D-J** for ease of identification:

Letter Designation	Compound
D	
E	

Letter Designation	Compound
F	
G	SSR-126374,
H	
I	

Letter Designation	Compound
J	

See EX1001, 7:1-8:30 (formatting and letter designations added); EX1003, ¶¶124-125 (citing EX1033, EX1090, EX1093-1096). As Dr. Lodish explains, several of these “additional” CRF1 receptor antagonists are CRF1 receptor antagonists developed by Neurocrine for the treatment of CAH. Compound **D** is Neurocrine’s NBI-77860 (verucerfont). EX1003, ¶125 (citing EX1090). Compound **E** is Neurocrine’s NBI-30775. *Id.* (citing EX1093). Compound **F** is Neurocrine’s NBI-34041. *Id.* (citing EX1094). Compound **H** is Neurocrine’s crinecerfont, SSR-125543. *Id.* (citing EX1033). Importantly, *none* of these seven claimed compounds **D-J** are identified in the ’084 patent as falling within the scope of Formula (I). See generally EX1001. Dr. Lodish confirms that compounds **D-F** and **H-J** are not Formula (I) compounds. EX1003, ¶125 (citing EX1095; EX1096). And the ’084 patent fails to disclose the structure of the remaining compound **G**, SSR-126374. *Id.*, ¶¶62-70, 125.

The written description of the '084 patent fails to disclose these claimed compounds as CRF1 receptor antagonists for “changing a metabolic parameter” in a subject with TARTs or OARTs, as claimed, or—for that matter—for treating any adrenal tumor at all. Instead, compounds **D-G** and **I-J** and the carbon-carbon quadruple bond compound (later amended during prosecution to depict crinecerfont, compound **H**) appear only in a laundry list of additional chemotherapeutic, biologic, and immunotherapeutic agents that can be *co-administered* with the compounds of Formula (I). EX1001, 6:65-8:33, 81:43-83:17 (disclosing additional chemotherapeutic agents), 31:22-37:59 (providing seven-column laundry list of potential additional agents); EX1003, ¶¶61, 126-127.

The '084 patent states that, “[i]n some embodiments, the method *further comprises* administering to the subject an *additional chemotherapeutic agent*.” EX1001, 6:55-57; *id.*, 81:33-35 (same). The '084 patent then states that, in some embodiments, the “additional chemotherapeutic agent is a glucocorticoid, a mineralocorticoid, an ACAT1 inhibitor, or an anti-androgen.” *Id.*, 6:58-60. The '084 patent states that, “[i]n some embodiments, *the additional chemotherapeutic agent is another* CRF₁ antagonist.” EX1001, 6:66-67; *id.*, 81:44-45 (same). The '084 patent *then lists* the six additional CRF1 receptor antagonists recited in claim 1 (compounds **D-G** and **I-J**) and the compound later amended in one portion of the

specification to be Neurocrine’s crinecerfont (compound **H**). EX1001, 6:65-8:33; *but see id.*, 81:43-83:17 (disclosing compound that is not crinecerfont).

A POSA would recognize from the written description that these claimed compounds—none identified as Formula (I) compounds—are disclosed *only* as optional co-therapies, i.e., “an additional chemotherapeutic agent,” to be administered as chemotherapeutic agents in combination with a compound of Formula (I). EX1001, 29:42-47 (describing co-administration of an “anti-cancer agent, chemotherapeutic, or treatment for a neurodegenerative disease”); EX1003, ¶61. The ’084 patent’s written description treats these claimed compounds no differently than the other listed “additional chemotherapeutic agent[s]” (i.e., glucocorticoids, mineralocorticoids, ACAT1 inhibitors, and anti-androgens) that may also be co-administered with a compound of Formula (I). EX1001, 6:65-8:33, 81:43-83:17; EX1003, ¶127. Nothing in the specification conveys to a POSA that the named inventors were in possession of these “additional chemotherapeutic agent[s]” for purportedly changing a metabolic parameter in a subject with a TART or an OART, as claimed. EX1003, ¶¶126-127.

In this way, Spruce has violated the written-description requirement by expanding the scope of the claims to encompass subject matter that it did not invent. Spruce attempts to pick-and-choose disparate embodiments in the specification to create an undisclosed invention: a method for changing a metabolic

parameter in a subject with a TART or an OART with any of the ten claimed CRF1 receptor antagonists recited in claim 1. But the Federal Circuit has repeatedly rejected attempts to assemble written description support by combining features from separate embodiments.

In *Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1341 (Fed. Cir. 2013), for example, the claims were directed to “BSG alpha-amylase variants” having three specifically claimed features. Although the specification literally disclosed each of these claimed features, it “never presented them together in any particular embodiment.” *Id.* The patentee nonetheless argued that a POSA would have understood the specification to have disclosed the claimed features and, accordingly, a POSA “would have had no difficulty in deriving the claimed invention from [that] disclosure.” *Id.* at 1345. The Federal Circuit rejected that argument, emphasizing that a patentee cannot cobble together features from different parts of the specification to support claimed subject matter that was never actually invented. *Id.* at 1346 (“Taking the claims as a whole rather than as the sum of their individual limitations, nothing in the 2000 application indicates that Novozymes then possessed what it now claims.”).

Here, as in *Novozymes*, Spruce’s attempt to mix and match embodiments—Formula (I) compounds with the “additional chemotherapeutic agent[s]”—cannot manufacture written description support for the claims as granted. *See also Flash-*

Control, LLC v. Intel Corp., 2021 WL 2944592, at *4 (Fed. Cir. July 14, 2021) (nonprecedential) (“A patent owner cannot show written description support by picking and choosing claim elements from different embodiments that are never linked together in the specification.”). And again, written description is not satisfied even if it would have been obvious to substitute one of the claimed CRF1 receptor antagonists of Formula (I) (i.e., compounds **A-C**) with one of the remaining seven claimed CRF1 receptor antagonists (compounds **D-J**). “[A] description that merely renders the invention obvious does not satisfy the [written description] requirement.” *Ariad*, 598 F.3d at 1352.

3. The disclosure of Compound 1 (tildacerfont) does not provide adequate written description for every CRF1 receptor antagonist recited in claim 1

Finally, a POSA would recognize that the written description of the '084 patent is directed to compounds of Formula (I), including Compound 1 (tildacerfont). EX1003, ¶¶123, 128. Every figure, description, dosing strategy, and example relating to purportedly treating an adrenal tumor refers exclusively to Compound 1 (tildacerfont). EX1001, Figs. 1-11, 13-17, 9:55-10:48, 89:63-98:67; EX1003, ¶¶123, 128. All the purported data actually generated by the named

inventors of the '084 patent is expressly identified as data for Compound 1 (tildacerfont). *Id.* at 89:63-98:67; EX1003, ¶128.¹⁰

These disclosures cannot be extrapolated to provide written description support for all ten CRF1 receptor antagonists recited in claim 1 because Spruce itself stated in scientific papers that Compound 1 (tildacerfont) possesses “unique structural features.” EX1041, 4667; EX1003, ¶¶129-131. Yet the written description of the '084 patent does not identify what those features are or provide any guidance for identifying other CRF1 receptor antagonists that might share them. EX1003, ¶131. The clinical histories of tildacerfont and crinecerfont underscore their functional divergence: Compound 1 (tildacerfont) failed in clinical development, whereas Neurocrine’s crinecerfont was a clinical success and ultimately received FDA breakthrough designation as a CAH treatment. EX1044; EX1045; EX1058; EX1089; EX1097; EX1003, ¶132.

Further, a POSA would not have understood that every CRF1 receptor antagonist recited in claim 1 would work in the claimed method to change a metabolic parameter in a subject with a TART or an OART. In the Federal Circuit’s recent opinion in *Teva Pharms. Int’l GmbH v. Eli Lilly & Co.*, 172 F.4th

¹⁰ As described above, Figures 12A and 12B, related to changes in ACTH and 17-OHP levels in patients with CAH, were copied from *Neurocrine’s* prior art Turcu 2016 publication and reflect *Neurocrine’s* work on verucerfont—not Spruce’s work on tildacerfont. *Supra*, §I.C.

1367, 1376-77 (Fed. Cir. 2026), the Court found adequate written description where “critically, a skilled artisan would have understood from the specification that all” claimed antibodies would work in the claimed treatment method. That is not true here. Until Neurocrine’s groundbreaking work, a POSA would have known that **no** CRF1 receptor antagonist had demonstrated **any** clinical utility for CAH or its related disorders “despite over 30 years of research and hundreds of patents.” EX1029, 1065; *see also* EX1008 (Turcu 2016); EX1006 (Grigoriadis U.S. publication). In previous PGRs, the Board recognized that, even though “a very considerable structural diversity of molecules” could “act as CRF1 receptor antagonists,” as of the priority date “very few studies existed demonstrating that CRF1 receptor antagonists are effective in the treatment of CAH.” EX1005, 55-56; EX1003, ¶130.

For these additional reasons, claims 1 and 3-19 are unpatentable for lack of written description. The '084 patent’s disclosure of Formula (I) and its purported data on Compound 1 (tildacerfont) cannot support claims directed to the other claimed CRF1 receptor antagonists for changing a metabolic parameter in a subject with a TART or an OART. EX1003, ¶133.

**D. All Claims Also Lack Adequate Written Description
Because the Specification Provides No Guidance on OARTs**

As discussed above, the '084 patent contains no data demonstrating that any of the claimed CRF1 receptor antagonists change any metabolic parameter in any subject. That lack of disclosure is compounded here because the written description of the '084 patent likewise provides no substantive disclosure—and no indication to a POSA—that the named inventors possessed a method for changing a metabolic parameter specifically in a subject with OARTs. The Federal Circuit has invalidated claims for lack of written description where “the record evidence demonstrates that a person of ordinary skill in the art would not have known or understood that the” claimed subject matter was effective for achieving a claimed therapeutic result—here, changing a metabolic parameter in a subject with a TART or an OART. *Nuvo*, 923 at 1380. All claims therefore fail the written-description requirement of §112(a). EX1003 ¶¶134-138.

More fundamentally, the '084 patent does not reasonably convey that the named inventors possessed a method for treating a subject with an OART at all, much less changing that subject's metabolic parameters. The written description of the '084 patent provides no examples, no experimental data, no clinical observations, and no other indicia related to changing a metabolic parameter in a subject with OARTs. EX1003, ¶¶135-136. And, as discussed above, the

specification mentions metabolic parameters in only two places—and critically, neither disclosure is specific to a subject with OARTs. *Supra*, §VI.A. The *astressin* disclosure does not identify any patient population at all, and Example 1 describes only a proposed trial design in subjects with a **TART**, not those with an OART. The written description thus fails to connect metabolic parameters to a subject with an OART in any way. EX1003, ¶¶135-136.

As Dr. Lodish explains, a POSA would not have understood the named inventors of the '084 patent to have actually invented a method of changing a metabolic parameter in a subject with an OART based on these bare disclosures. EX1003, ¶134. OARTs are characterized by the presence of extra-adrenal tissue in the ovaries of females with CAH. EX1038, e70; EX1069, R91; EX1003, ¶38. A POSA would have known as of the earliest priority date of the '084 patent that OARTs were exceedingly rare, with only a handful of cases reported in the literature. EX1003, ¶¶39, 137. Zaarour, for example, taught in 2014 that “only 11 cases of OART have been described in the English-language literature” and that this scarcity “mak[es] it difficult to choose an optimal treatment approach for affected patients.” EX1038, e70; *id.*, e72 (concluding that “[t]he optimal treatment of the ovaries in cases of OART remains unclear”). Chen taught in 2017 that OARTs were “very rare,” that “[c]linical studies of this condition have not been performed,” and that “only a few cases have been published.” EX1040, 146. Chen

also taught that “OARTs are seldom revealed with standard imaging techniques, *making their diagnosis and subsequent treatment difficult.*” *Id.*, 147; EX1003, ¶40.

Given these teachings and the unpredictability in the art, a POSA would have expected substantially more detail—such as experimental data or clinical evidence—to demonstrate that the inventors were, in fact, in possession of a method of changing a metabolic parameter in subject with an OART. *Ariad*, 598 F.3d at 1351 (stating that “[t]he level of detail required to satisfy the written description requirement” necessarily “varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology”); *Hologic, Inc. v. Smith & Nephew, Inc.*, 884 F.3d 1357, 1361 (Fed. Cir. 2018) (stating that a lower level of detail is required to satisfy written description where the field of the invention is a predictable art); EX1003, ¶¶41, 137.

But rather than provide the necessary details about changing a metabolic parameter in a subject with OARTs, the ’084 patent says virtually nothing about changing a metabolic parameter and inserts only ambiguity as to OARTs. It defines OARTs incorrectly, stating that both TARTs and OARTs “may develop from ectopic remnants of *intra-testicular adrenal tissue.*” EX1001, 25:4-8. But as Dr. Lodish explains, a POSA would immediately recognize that OARTs—tumors of the *ovaries*—cannot derive from *intra-testicular* adrenal tissue, because females

do not have testicular tissues. EX1003, ¶¶42, 138. This error underscores that the inclusion of OARTs in the '084 patent was an afterthought, not the product of actual possession.

At bottom, the written description of the '084 patent must show that the named inventors “possessed the claimed methods by sufficiently disclosing” a method for changing a metabolic parameter in a subject with OARTs, so as to “satisfy the inventor’s obligation to disclose the technologic knowledge upon which the patent is based, and to demonstrate that the patentee was in possession of the invention that is claimed.” *Ariad*, 598 F.3d at 1355. Here, however, the written description offers nothing more than a “mere wish or plan” for doing so. This does not satisfy the written description requirement. *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1566 (Fed. Cir. 1997).

The Board can find ***all claims*** unpatentable under §112(a) on this basis alone because every claim of the '084 patent encompasses a method of changing a metabolic parameter in a subject with an OART.

VII. GROUND 2: Claims 1-19 are unpatentable for lack of enablement

Section 112(a) also requires that the specification enable the full scope of the claimed invention. 35 U.S.C. § 112(a). “The more one claims, the more one must enable.” *Amgen Inc. v. Sanofi*, 598 U.S. 594, 610 (2023). Here, claims 1-19 lack enablement because the specification fails to teach a POSA how to change one or

more of the specifically claimed metabolic parameters in a subject with a TART or an OART with any of the ten claimed CRF1 receptor antagonists without engaging in undue experimentation. EX1003, ¶¶139-158.

As discussed above, the '084 patent contains no disclosure showing a change in any metabolic parameter in any subject. *Supra*, §VI.A. The written description's only arguably relevant data point—one TART in one male patient purportedly treated with Compound 1 (tildacerfont)—reflects a morphological observation, not a change in a metabolic parameter. *Id.* The only references to metabolic parameters are the aspirational astressin disclosure and the prophetic Example 1 secondary endpoint list—neither of which produced any data. *Supra*, §§VI.A-B. The '084 patent discloses nothing beyond conclusory statements about OARTs. *Id.*, §VI.D. Even the disclosure about TARTs is sparse. A POSA would therefore be left to engage in trial-and-error testing to determine which, if any, of the claimed CRF1 receptor antagonists could change a metabolic parameter in a subject with TARTs or OARTs—and indeed, whether any of them could do so at all. EX1003, ¶¶139-142. *Amgen* makes clear that such iterative experimentation is insufficient to satisfy the enablement requirement. 598 U.S. at 610.

An analysis of the *Wands* factors shows that, even allowing for some reasonable degree of experimentation, a POSA here is left with the same trial-and-error approach that the Supreme Court rejected in *Amgen*. The *Wands* factors

include “(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.” *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988); *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991) (stating that the *Wands* factors “are illustrative, not mandatory”). A review of the evidence about each of these eight factors demonstrates that the specification does not teach a POSA how to make and/or use the full scope of the claimed invention without undue experimentation.

A. Claim Scope Weighs Against Enablement (Factor 8)

As explained above, the preamble of claim 1 recites a method for changing a metabolic parameter in a subject with TARTs or OARTs, where the metabolic parameter is fasting glucose, HbA1c level, insulin sensitivity, or a lipid profile, or a combination thereof. EX1001, 98:47-48, 100:65-67; *supra*, §VI.A. No dependent claim narrows the method to changing a metabolic parameter in only a subject having TARTs. EX1001, 101:1-102:36. Claims 1 and 4-19 each also encompass ten different CRF1 receptor antagonists. *Id.*, 98:47-100:67, 101:36-102:36.

Accordingly, the '084 patent must enable a method for changing a metabolic parameter in **both** TARTs and OARTs subjects using **each** of the listed CRF1

receptor antagonists. *In re Fouché*, 439 F.2d 1237, 1242 (C.C.P.A. 1971) (“an applicant must use some technique of providing teaching of how to use which is commensurate with the breadth of protection sought by the claim, unless such knowledge is already available to persons skilled in the art”). The claims are thus broad in three independent dimensions: (1) ten diverse CRF1 receptor antagonists, (2) two distinct patient populations (males with TARTs or females with OARTs), and (3) multiple metabolic parameters (fasting glucose, HbA1c level, insulin sensitivity, or a lipid profile, or a combination thereof). The specification must enable this full scope—but it does not. EX1003, ¶¶142-145. Even the claims limited to specific compounds, namely Compound 1 (tildacerfont) and Neurocrine’s crinecerfont—claims 2 and 3, respectively—still require changing a metabolic parameter in a patient with OARTs, which is not disclosed. EX1001, 101:1-35.

OARTs provides a clear example regarding lack of enablement. EX1003, ¶143. The specification’s *only* references to OARTs are conclusory statements asserting treatment without any disclosure about *changing a metabolic parameter* in a subject with OARTs. EX1001, 2:4-6 (“One aspect provided herein is a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)...”); *id.*, 2:13-15 (same); *id.*, 4:62-64 (same); *id.*, 24:7-11 (identifying TARTs and OARTs as a disease); *id.*, 24:26-29 (identifying

TARTs and OARTs as a cancer); *id.*, 38:62-63 (same); *id.*, 39:30-36 (identifying TARTs and OARTs as a CRF1-associated disease); *id.*, 39:45-52 (same); *id.*, 50:45-48 (“In one embodiment, provided herein are methods for treating or preventing ovarian adrenal rest tumors (OART)...”); *id.*, 50:59-60 (same); *id.*, 51:39-42 (same); *id.*, 55:31-37 (same); *id.*, 79:21-23 (same). Given the breadth of the claims, and the absence of sufficient guidance and working examples in the ’084 patent, this factor weighs against enablement. *MagSil Corp. v. Hitachi Glob. Storage Techs., Inc.*, 687 F.3d 1377, 1381 (Fed. Cir. 2012) (stating that the enablement “doctrine prevents both inadequate disclosure of an invention and overbroad claiming that might otherwise attempt to cover more than was actually invented”); *Alcon Rsch., Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1368 (Fed. Cir. 2012) (in the context of claims covering both enabled and non-enabled material, stating that “[c]ourts do not rewrite the claims to narrow them for the patentee to cover only the valid portion”).

B. The ’084 Patent’s Lack of Guidance for Using All Claimed CRF1 Receptor Antagonists (Factor 2) and Lack of Examples Showing a Change in a Metabolic Parameter (Factor 3) Weigh Against Enablement

The ’084 patent provides a POSA with virtually no guidance about *all ten* claimed CRF1 receptor antagonists and their purported ability to change a metabolic parameter in a subject with TARTs or OARTs. EX1003, ¶¶142-145.

The '084 patent discloses only a single TART from a single patient purportedly administered a single CRF1 receptor antagonist—Compound 1 (tildacerfont). EX1001, 90:42-58, 96:40-45; EX1003, ¶¶147-149. Every example with applicants' data in the specification relates to Compound 1 (tildacerfont) alone. *See* EX1001, 90:4-93:52 (Example 1), 93:53-95:50 (Example 2), 95:51-96:37 (Example 3), 96:38-98:11 (Example 4); EX1003, ¶¶53-60, 147. The patent provides no examples or data related to the treatment of OARTs. *See generally*, EX1001; EX1003, ¶¶143-145, 149.

The '084 patent provides no guidance for using the “additional chemotherapeutic agent[s]” for changing a metabolic parameter in a subject with TARTs or OARTs. The '084 patent does not even identify seven out of the ten claimed CRF1 receptor antagonists as compounds of Formula (I). *Supra*, §VI.C.2. Instead, as explained above, the '084 patent describes these compounds only as “additional chemotherapeutic agent[s]” for co-administration with a CRF1 receptor antagonist of Formula (I). EX1001, 6:65-8:33, 81:43-83:17; *supra*, §VI.C.2; EX1003, ¶70.

At most, the '084 patent purports to disclose a method for treating TARTs (not OARTs) with a CRF1 receptor antagonist having the structural Formula (I). EX1001, 2:13-33. But the '084 patent identifies only ***three*** of the ten CRF1 receptor antagonists recited in the claims as falling within the scope of Formula (I),

including Compound 1 (tildacerfont, compound **C**). EX1003, ¶¶121-122. The entire patent is premised on “promising results” with Compound 1 (tildacerfont) in TARTs—not OARTs and not changing a metabolic parameter in a subject with OARTs—stating that pre-clinical and Phase 1 clinical studies in healthy volunteers “provide a rationale for *investigating the use of Compound 1* in the treatment of *TART*, in combination with replacement glucocorticoids and mineralocorticoids.” EX1001, 90:38-41. In addition, the ’084 patent never explains *why* any of the other claimed CRF1 receptor antagonists would have been expected to change a metabolic parameter in a subject with TARTs, and gives no guidance on using all ten compounds for changing a metabolic parameter in a subject with OARTs. EX1003, ¶¶152-154.

The ’084 patent provides no guidance about OARTs. As discussed above, a POSA would have known that treating OARTs was highly unpredictable. *Supra*, §VI.B; EX1003, ¶¶39, 144, 149. Zaarour reported that “only 11 cases of OART have been described in the English-language literature” making “it difficult to choose an optimal treatment approach for affected patients.” EX1038, e70; *id.*, e72 (concluding that “[t]he optimal treatment of the ovaries in cases of OART remains unclear”). Chen likewise taught that OARTs were “very rare,” that “[c]linical studies of this condition have not been performed,” and that “only a few cases have been published.” EX1040, 146. Chen further explained that “OARTs

are seldom revealed with standard imaging techniques, *making their diagnosis and subsequent treatment difficult.*” *Id.*, 147; EX1003, ¶40.

The '084 patent discloses no working examples related to changing a metabolic parameter. The only disclosures in the '084 patent relating to metabolic parameters are the astressin passage (which relates to a different compound altogether, *supra*, §VI.A.1) and prophetic Example 1 (which was never conducted and produced no data, *supra* §VI.A.2). EX1001, 43:67-44:5 (astressin), 91:14-30 (Example 1). Neither of these disclosures enable the full scope of the claims because “[w]here, as here, working examples are present but are very narrow, despite the wide breadth of the claims at issue, this factor weighs against enablement.” *Idenix Pharms. LLC v. Gilead Scis. Inc.*, 941 F.3d 1149, 1161 (Fed. Cir. 2019) (cleaned up). The situation is even starker here than in *Idenix*: the '084 patent contains no working examples at all for the claimed method of changing a metabolic parameter in a subject with OARTs. Moreover, as Dr. Lodish explains, treating an OART may not necessarily result in a change in a metabolic parameter, and vice versa. EX1003, ¶146.

In short, the '084 patent provides nothing more than a research assignment: a trial-and-error effort to test ten different CRF1 receptor antagonists to see whether any might change at least one of the claimed metabolic parameters in a subject with TARTs or OARTs. EX1003, ¶¶145, 149. As the Supreme Court made clear,

“[t]hat is not enablement.” *Amgen*, 598 U.S. at 614. These factors weigh against enablement.

C. The Undue Amount of Experimentation Necessary to Identify Which Claimed CRF1 Receptor Antagonists Could Change a Metabolic Parameter in a Subject with TARTs or OARTs (Factor 1), the Complex Nature of Treating TARTs or OARTs Subjects (Factor 4), and the Nascent State and Unpredictability of the Art (Factors 5 and 7) Weigh Against Enablement

The '084 patent's research assignment would require undue experimentation. EX1003, ¶154. The '084 patent focuses almost exclusively on one CRF1 receptor antagonist—Compound 1 (tildacerfont)—yet claims nine additional CRF1 receptor antagonists purportedly capable of changing a metabolic parameter in a subject with TARTs or OARTs. The only way a POSA could determine which of those compounds, if any, could change a metabolic parameter in a subject with TARTs *or OARTs* would be to make and test each one through an iterative, trial-and-error process. EX1003, ¶¶152, 154, 158. This is insufficient, as the Federal Circuit has made clear that all embodiments claimed must be enabled by the specification. *Trs. of Bos. Univ. v. Everlight Elecs. Co.*, 896 F.3d 1357, 1364 (Fed. Cir. 2018) (rejecting patentee's argument that enablement of five out of the six claimed permutations was sufficient because “[o]ur precedents make clear that the specification must enable the full scope of the claimed invention”).

As explained above, the '084 patent provides no evidence, working examples, or data for changing a metabolic parameter in any subject with any of the claimed CRF1 receptor antagonists, and no working examples or data related to OARTs at all. *Supra*, §VI.D. As to humans, a POSA would be forced to conduct years of costly testing of the claimed CRF1 receptor antagonists across the extremely small population of subjects with OARTs. EX1003, ¶¶150-152. That is the definition of undue experimentation. *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1325 (Fed. Cir. 2005) (as to claims covering a method of treating a disease, stating that enablement requires “that the inventor enable an invention rather than merely proposing an unproved hypothesis”).

Background knowledge in the art cannot fill in the gaps here. EX1003, ¶¶155-156. First, as to TARTs, Spruce itself took the opposite position about background knowledge during prosecution of U.S. Application 17/081,694, a parent application to which the '084 patent claims priority. EX1001, code [63]. In that application, Spruce submitted a declaration from its then Vice President, Chris Barnes, stating that the treatment of TARTs in patients with CAH was “uncertain[] and unpredictabl[e].” EX1061, 19-20 (¶2). Dr. Barnes also stated that it was “not clear whether reduced ACTH levels can lead to reduced TART growth.” *Id.*, 21-22 (¶9).

Second, as Dr. Lodish explains and Spruce has admitted, Compound 1 (tildacerfont) and many of the other claimed CRF1 receptor antagonists do not share the same structural features. Spruce's own prior-art publication describes Compound 1 (tildacerfont) as being a "second-generation CRF1 antagonist" having "unique structural features" compared to other CRF1 receptor antagonists. EX1041, 4667; EX1003, ¶156. The '084 patent does not describe these "unique structural features," nor does it teach the POSA which other claimed CRF1 receptor antagonists might share these features. EX1003, ¶156. Furthermore, as Dr. Lodish explains, a POSA would have understood that these structural differences can lead to different biological activity. EX1003, ¶155 (citing EX1018). The Board previously found that "the structure-function relationship between CRF₁ receptor and CRF₁ receptor [antagonist]s was still largely unknown and unpredictable." EX1005, 59. Nothing in the '084 patent compares the therapeutic effectiveness of Compound 1 (tildacerfont) to that of the other claimed CRF1 receptor antagonists. EX1003, ¶152.

Even if Compound 1 (tildacerfont) shares some common structural features with the other claimed CRF1 receptor antagonists, a POSA still would not know whether any of those other CRF1 receptor antagonists could change a metabolic parameter in subject with OARTs without impermissible trial-and-error testing. That uncertainty is amplified by the extreme scarcity of OARTs cases and the high

degree of unpredictability as to OARTs. *Supra*, §VI.D; EX1003, ¶¶144, 149. The art's unpredictability is further illustrated by the divergent clinical outcomes: Spruce's Compound 1 (tildacerfont) failed in clinical development whereas Neurocrine's crinecerfont achieved clinical success and breakthrough FDA approval. EX1044; EX1045; EX1058; EX1089; EX1097; EX1003, ¶132. These factors weigh against enablement.

D. The Relatively High Level of Skill Does Not Support Enablement (Factor 6)

The relatively high skill of those in the art does not rescue the claims. As is typical in the pharmaceutical arts, a POSA would have possessed substantial education and experience. EX1003, ¶157. But that expertise cannot overcome the deficiencies described above or the limited state of knowledge in the prior art about OARTs or the effect of CRF1 receptor antagonists on metabolic parameters. *Id.* The Federal Circuit reached the same conclusion in *Idenix*, holding that even a highly skilled artisan could not bridge the enablement gap where the patent “d[id] not provide enough meaningful guidance or working examples, across the full scope of the claim, to allow a POSA to determine which” compounds could perform the claimed function of treating hepatitis C without undue experimentation. 941 F.3d at 1162. The Board should reach the same result here.

In the end, a POSA would have to engage in trial-and-error testing to determine which CRF1 receptor antagonists could change a metabolic parameter in a subject with a TART or an OART. Such “random trial-and-error discovery” is not enablement. *Amgen*, 598 U.S. at 615. This factor does not support enablement, and at most, is neutral.

E. Summary

Factors 1-5 and 7-8 weigh against enablement while factor 6 is, at most, neutral. Thus, taken together, the *Wands* factors weigh against enablement. The Board should determine that claims 1-19 lack enablement.

VIII. GROUND 3: Claims 1, 3-5, 8-13, and 15-19 are unpatentable for obviousness

Claims 1, 3-5, 8-13, and 15-19 would have been obvious over Neurocrine’s Grigoriadis publication (EX1006), in view of Richard (EX1012) and Yu (EX1067). EX1003, ¶¶159, 175-179. The mapping below demonstrates that these references teach each and every limitation of claims 1, 3-5, 8-13, and 15-19. *Id.*, ¶¶180-217. As further explained below, a POSA would have been motivated to combine the teachings of these references, with a reasonable expectation of success. Specifically, a POSA would have been motivated to apply the CRF1 receptor antagonist therapies of Grigoriadis as an approach for treating TARTs in male CAH patients based on Grigoriadis alone, or at least in view Yu, with a

reasonable expectation that CRF1 antagonism would treat CAH and its related disorders by lowering ACTH levels (as shown in Grigoriadis). In addition, a POSA would have reasonably expected from the teachings of Richard that administering the CRF1 receptor antagonist crinecerfont to lower ACTH would also result in a change in a metabolic parameter of the patient, such as insulin resistance and glucose intolerance. EX1003, ¶¶175-179.

A. Prior Art

The following prior-art references show that all claim limitations are found in the prior art per 37 C.F.R. §42.204(b)(4).

1. Grigoriadis (EX1006)

Grigoriadis published as U.S. Patent Publication 2017/0020877 on January 26, 2017, more than a year before the earliest possible effective filing date of the '084 patent (April 27, 2018). EX1006, codes [10], [43]. Grigoriadis therefore qualifies as prior art under 35 U.S.C. §§102(a)(1) and (a)(2).

Grigoriadis discloses treating CAH and its related disorders with a number of CRF1 receptor antagonists, including NBI-77860 (verucerfont) and SSR-125543 (crinecerfont). EX1006, ¶¶51, 54; EX1003, ¶¶160-163. Grigoriadis teaches that a goal of the disclosed invention is to provide a treatment regimen that “improve[s] the health, well-being, quality of life” and “manage[s] related disorders in

patients[s] with CAH.” EX1006, ¶5. Grigoriadis describes such related disorders as, e.g., “testicular adrenal rest tumors in men.” *Id.*, ¶44.

Grigoriadis explains that conventional treatment for CAH relied on administration of supraphysiologic doses of glucocorticoids. EX1006, ¶¶45-47. But such treatment is associated with several negative side effects, including elevated risk for cardiovascular disease, obesity, hypertension, insulin resistance, glucose intolerance, and decreased bone mineral density. *Id.*, ¶¶46-47. Grigoriadis teaches that use of a CRF1 receptor antagonist enables administration of lower, more physiologic doses of hydrocortisone in CAH patients, thereby reducing these treatment-associated side effects. *See id.*, ¶40 (“administration of a CRF1 receptor antagonist permits use of lower, more physiologic doses of hydrocortisone in subjects with CAH and thus reduces treatment-associated side effects”).

Grigoriadis further teaches various doses for pharmaceutical CRF1 receptor antagonist compositions “for treating CAH or a related disease or disorder,” including doses ranging from 50-1000 mg. *Id.*, ¶¶63-64. Example 6 of Grigoriadis describes a Phase I clinical study in which NBI-77860 (verucerfont) was administered to 8 adult female patients with CAH, concurrently with the patients’ usual glucocorticoid (steroidal) treatment. *Id.*, ¶¶90-91. Each patient received single doses of placebo, 300 mg NBI-77860, and 600 mg NBI-77860, each during separate treatment periods. *Id.*, ¶91, Fig. 4. The study provided for a 21-day drug-

free interval (washout period) between each treatment period. *Id.* Grigoriadis discloses 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.” *Id.*, 91. Grigoriadis reports that “[c]onsistent and clinically meaningful reductions from predose levels of both 17-OHP and ACTH were observed” following the administration of NBI-77860 (verucerfont) in these CAH patients. *Id.*, 93; Figs. 5-6. Grigoriadis also reports that 50% of the CAH patients achieved an at least 50% reduction in 17-OHP and ACTH after receiving NBI-77860 (verucerfont) compared to placebo. *Id.*, 93.

2. Richard (EX1012)

Richard published as International Publication WO 2007/105113 A2 on September 20, 2007, more than a year before the earliest possible effective filing date of the '084 patent (April 27, 2018). EX1012, codes [10], [43]. Richard therefore qualifies as prior art under 35 U.S.C. §102(a)(1).

Richard describes CRF1 receptor antagonists of its formula (I), including compound A, which is crinecerfont, and its use in “preventatively or curatively treating metabolic syndrome and/or obesity and/or dyslipoproteinemia in mammals.” EX1012, 1:5-2:8, 2:30-33, 13:35-14:2, 14:28-31; EX1003, ¶¶164-165. Richard examined the effect of compound A on metabolic parameters including

fasting glucose, insulin sensitivity, and plasma triglycerides in a rat model of obesity. EX1012, 14:9-31, 16:13-24, 17:35-18:10; EX1003, ¶166. The rats are “characterized by a massive obesity that develops early after birth,” are “hyperlipidemic, hyperinsulinemic, glucose intolerant, and insulin resistant.” These rats also have very high levels of corticosterone due to an overstimulated hypothalamo-pituitary-adrenal (HPA) axis. EX1012, 14:18-26. Crinecerfont prevented “the fasting-induced increase in corticosterone levels in obese rats,” reduced circulating glucose levels “to values similar to those of lean and untreated food-deprived obese rats,” “improved insulin sensitivity,” “reduced circulating triglyceride levels in lean rats,” and prevented “fasting-induced reduction of triglycerides in obese rats.” EX1012, 18:2-18, Figs. 3a-3g; EX1003, ¶166.

3. Yu (EX1067)

Yu, titled “Clinical Manifestations of testicular adrenal rest tumors in males with congenital adrenal hyperplasia,” published in the *Annals of Pediatric Endocrinology & Metabolism* in 2015—more than a year before the earliest possible effective filing date of the ’084 patent (April 27, 2018). EX1067, 155. Yu therefore qualifies as prior art under 35 U.S.C. §102(a)(1).

Yu reports a study designed “to investigate the prevalence of TARTs in male patients with CAH” and “to identify contributing factors to TART.” *Id.*; see also EX1003, ¶¶167-170. Yu detected TARTs in 61.5% of the evaluated CAH patients

(8 out of 13). EX1067, 157. Yu also found that CAH patients with TARTs exhibited a statistically significant ($P < 0.05$) elevation in serum ACTH levels compared to those without TARTs. *Id.*, 157-158. The median value in CAH patients with TARTs was 144.6 pg/mL (above Yu's 70 pg/mL threshold for "uncontrolled" disease), but only 36.5 pg/mL in CAH patients without TARTs (below Yu's 70 pg/mL threshold). *Id.* Yu observed "no clear differences in other laboratory values" between the two groups of CAH patients. *Id.*

Yu also found that CAH patients whose tumor size decreased over time "demonstrated significantly decreased ACTH levels compared to the baseline study," whereas the single patient whose tumor size increased "did not show a significant decrease in serum ACTH level." *Id.*

Citing earlier publications, Yu notes that previous studies had identified ACTH "the most frequently suggested causative and growth promoting factor in TARTs." *Id.*, 159. Yu concludes that the present study "support[s] the previous hypothesis that exposure to high concentrations of the serum ACTH level can be a major factor in the development of TARTs." *Id.* Yu states that "[t]his hypothesis could be taken in consideration for the treatment of TARTs." *Id.*; *see also* EX1003, ¶¶34-36 (citing EX1068, 669).

B. Independent Claim 1

1[A] A method of changing a metabolic parameter of a subject having a testicular adrenal rest tumor (TART) or an ovarian adrenal rest tumor (OART),

To the extent that the preamble is limiting, the combination of Grigoriadis with Richard and Yu renders it obvious. EX1006, ¶¶5-7, 12, 13, 40, 44, 46, 47, 64, 69; EX1012, 18:2-18, Figs. 3a-3g; EX1067, 157-159; EX1003, ¶¶181-191.

Grigoriadis teaches that CAH is a known endocrine disorder associated with CRF1 receptor activity, and that testicular adrenal rest tumors (TARTs) are a known complication of CAH in male patients. EX1006, ¶44. Grigoriadis teaches that one goal of the invention is to provide a treatment regimen that “improve[s] the health, well-being, quality of life” and “manage[s] related disorders in patients[s] with CAH.” *Id.*, ¶5. Grigoriadis further teaches various doses for pharmaceutical CRF1 receptor antagonist compositions “for treating CAH or a related disease or disorder.” *Id.*, ¶64. A POSA reading Grigoriadis, therefore, would understand that the disclosed methods treat CAH and its related disorders, including “testicular adrenal rest tumors in men.” *Id.*, ¶44; EX1003, ¶¶182, 188. Thus, Grigoriadis teaches administration of a CRF1 receptor antagonist in “*a subject having a testicular adrenal rest tumor (TART).*”

Grigoriadis also teaches that CAH patients have an increased prevalence of negative side effects due to conventional treatment with supraphysiologic doses of

glucocorticoids. EX1006, ¶5, 46, 47, 69; *see also* EX1003, ¶183. Specifically, Grigoriadis teaches that CAH patients “require lifelong management with glucocorticoids and the attendant problems associated with such treatment.” *Id.*, ¶5. Grigoriadis teaches that administration of supraphysiologic glucocorticoids in adults elevates the risk of cardiovascular disease, obesity, hypertension, insulin resistance, glucose intolerance, and decreased bone-mineral density. *Id.*, ¶¶46–47. In children, supraphysiologic glucocorticoids “can impede statural growth”—the increase in height over time. *Id.*, ¶69. Grigoriadis thus teaches that use of a CRF1 receptor antagonist like verucerfont or crinecerfont for treating CAH and its related disorders (e.g., TARTs) enables administration of lower, more physiologic doses of hydrocortisone in CAH patients, thereby reducing these treatment-associated side effects. *Id.*, ¶40. Of these side effects, insulin resistance and glucose intolerance are well-known metabolic parameters. EX1012, 18:2-18; EX1003, ¶¶46-47 (citing EX1105; EX1106). Thus, Grigoriadis teaches or at least suggests that a metabolic parameter in a subject with TARTs will change following administration of verucerfont or crinecerfont with a concomitant decrease in glucocorticoid administration. EX1003, ¶¶184-185.

In addition, Richard expressly teaches “*changing a metabolic parameter*” by administration of a CRF1 receptor antagonist alone. Specifically, Richard teaches that administration of crinecerfont (called “Compound A” in Richard) changes

metabolic parameters including fasting glucose, insulin sensitivity, and a lipid profile in a rat model of obesity. EX1012, 18:2-18, Figs. 3a-3g; EX1003, ¶186. Richard reports that crinecerfont prevented a fasting-induced increase in corticosterone levels, reduced circulating glucose levels, improved insulin sensitivity, reduced circulating triglyceride levels, and prevented fasting-induced reduction of triglycerides in obese rats. EX1012, 18:2-18, Figs. 3a-3g; EX1003, ¶186. As Dr. Lodish explains, these are all metabolic parameters falling within the scope of the claims. EX1003, ¶187.

A POSA seeking to change a metabolic parameter in a patient with TARTs would have had a reason to look to Richard to confirm that crinecerfont could not only treat a TART in a patient with CAH (as Grigoriadis teaches) but also address the related metabolic side effects of, *e.g.*, insulin resistance and glucose intolerance discussed in Grigoriadis. EX1006, ¶¶46–47; EX1003, ¶186. Thus, a POSA would have been motivated to combine the teachings of Grigoriadis and Richard to achieve the claimed invention: changing a metabolic parameter in a subject with a TART by administering a CRF1 receptor antagonist such as crinecerfont (compound **H**) or verucerfont (compound **D**). Their combination reflects “no more than the predictable use of prior art elements according to their established functions.” *KSR*, 550 U.S. at 417; EX1003, ¶186.

And because claim 1 recites administering to a subject having a TART *or* an OART, Grigoriadis need not provide any disclosure about OARTs to satisfy this limitation of claim 1. EX1001, 99:2-3; *see also ModernaTX, Inc. v. Arbutus Biopharma Corp.*, 18 F.4th 1352, 1363-64 (Fed. Cir. 2021); *Brown v. 3M*, 265 F.3d 1349, 1351 (Fed. Cir. 2001) (“When a claim covers several structures or compositions, either generically or as alternatives, the claim is deemed anticipated if any of the structures or compositions within the scope of the claim is known in the prior art.”).

A POSA would also have had a reasonable expectation of success in changing a metabolic parameter in a subject with a TART by administering a CRF1 receptor antagonist such as verucerfont or crinecerfont. First, claim 1 requires no specific direction or amount of change. The teachings of the prior art readily satisfy this low threshold. EX1003, ¶187. Grigoriadis teaches that CRF1 receptor antagonists reduce ACTH levels and that suppression of ACTH serves as a treatment of CAH-related disorders, including TARTs. EX1006, ¶¶6, 7, 12, 13, 44. Richard demonstrates that administration of CRF1 receptor antagonists changes such metabolic parameters as fasting glucose levels, insulin sensitivity, and a lipid profile. EX1012, 18:2-18, Figs. 3a-3g. Taken together, these teachings provide a POSA with a reasonable expectation that administering a CRF1 receptor

antagonist will lower ACTH levels and change fasting glucose, insulin sensitivity, and/or a lipid profile in a patient with a TART. EX1003, ¶187.

Moreover, claim 1 requires only that the administration of the CRF1 receptor antagonist changes one of the recited metabolic parameters, not that it treats a TART or OART. To avoid all doubt, however, Yu discloses treating TARTs by reducing ACTH levels. EX1067, 159. It would have been obvious for a POSA to have administered CRF1 receptor antagonists to a subject with a TART based on the combination of Grigoriadis and Yu. EX1003, ¶¶188-191. Yu reports a study designed “to investigate the prevalence of TARTs in male patients with CAH” and “to identify contributing factors to TART.” *Id.* Yu detected TARTs in 61.5% of the evaluated CAH patients (8 out of 13). *Id.*, 157. Yu found:

- A statistically significant increase in serum ACTH levels in CAH patients with TARTs (144.6 pg/mL) compared to CAH patients without TARTs (36.5 pg/mL) with “no clear differences in other laboratory values” between the two groups of CAH patients. *Id.*, 157-158;
- CAH patients whose tumor size decreased over time “demonstrated significantly decreased ACTH levels compared to the baseline study,” whereas the single patient whose tumor size increased “did not show a significant decrease in serum ACTH level.” *Id.*

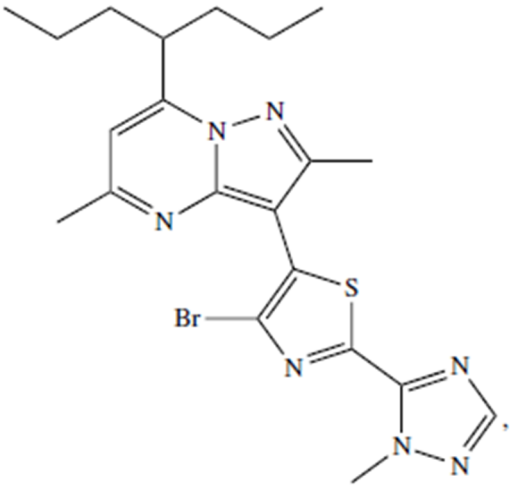
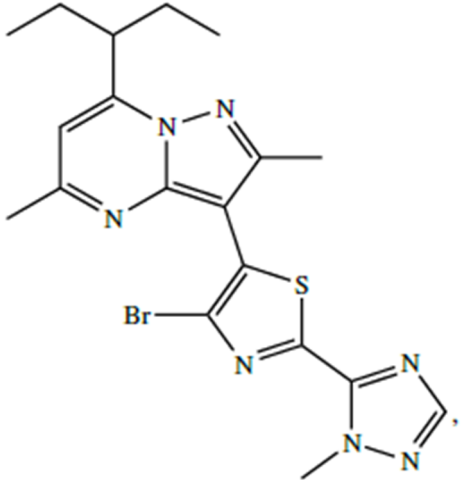
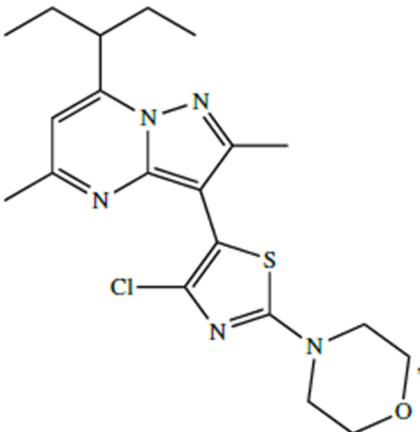
From this data, a POSA would have clearly understood that elevated ACTH levels are associated with TARTs and TART size in male CAH patients. EX1003, ¶189. Indeed, Yu explains that their study validates previous studies that had identified ACTH as “the most frequently suggested causative and growth promoting factor in TARTs.” *Id.*, 159. Yu concludes that their results “support the previous hypothesis that exposure to high concentrations of the serum ACTH level can be a major factor in the development of TARTs.” *Id.* And Yu states that “[t]his hypothesis could be taken in consideration for the treatment of TARTs.” *Id.*

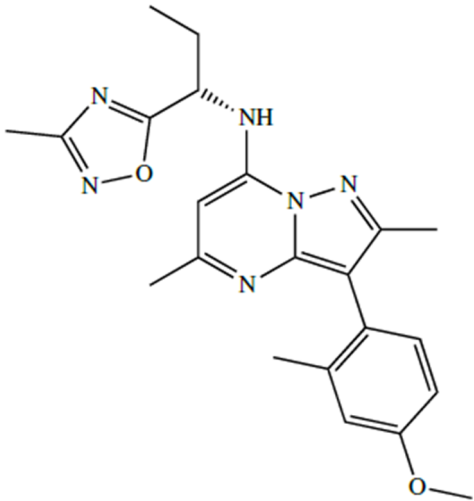
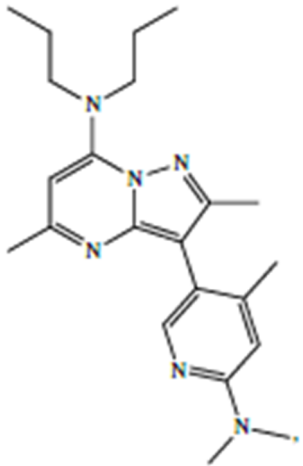
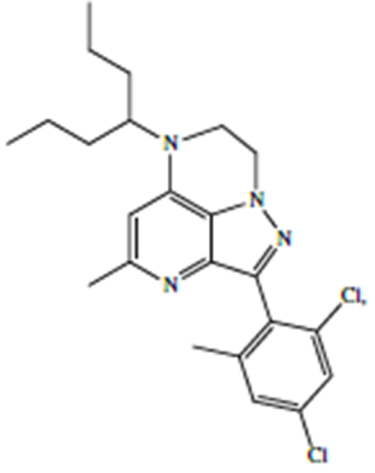
A POSA would have been motivated to treat TARTs by lowering ACTH levels with a CRF1 receptor antagonist based on the teachings of Grigoriadis and Yu. EX1003, ¶189. Yu expressly links TARTs to elevated ACTH levels. EX1067, 158-159. Grigoriadis teaches that administration of CRF1 receptor antagonists reduce ACTH levels. EX1006, ¶¶6, 7, 12, 13. Grigoriadis also emphasizes that CAH treatment can include preventing related disorders such as “testicular adrenal rest tumors in men.” EX1006, ¶44. Taken together, these teachings provide a POSA with a reasonable expectation that administering a CRF1 receptor antagonist would lower ACTH levels in CAH patients with TARTs, thus “treating” TARTs. EX1003, ¶¶190-191.

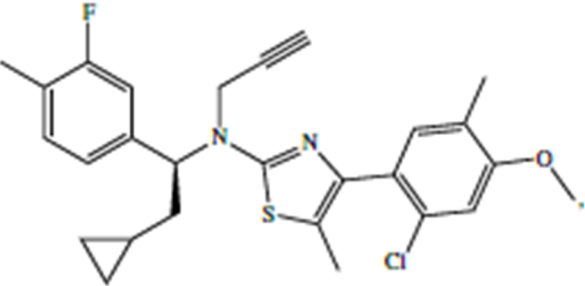
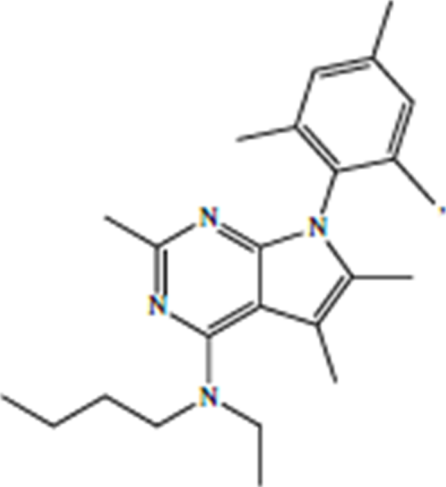
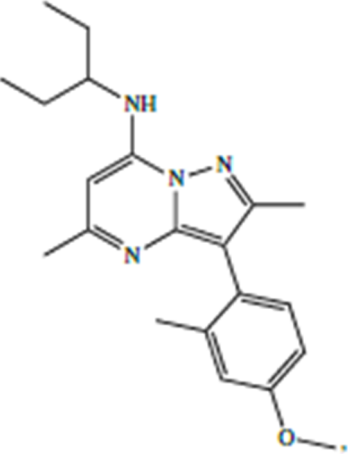
1[B] comprising administering to the subject in need thereof a small molecule corticotropin-releasing factor type-1 (CRF₁) antagonist, or a pharmaceutically acceptable salt thereof,

Grigoriadis expressly teaches this limitation. EX1006, ¶¶40, 51, 54, 61, 70, 85, 90-93; EX1003, ¶192. Grigoriadis expressly teaches that “[a]s described herein, CRF1 receptor antagonists have been found to directly inhibit ACTH release in patients with CAH and thereby allow normalization of androgen production.” EX1006, ¶40. Grigoriadis teaches “administering to a subject in need thereof an effective amount of a CRF1 antagonist” and further teaches pharmaceutical compositions comprising CRF1 receptor antagonists for doing so. *Id.*, ¶¶61, 70. As one example, Grigoriadis teaches administering the “small molecule NBI-77860” CRF1 receptor antagonist (verucerfont, compound **D**). *Id.*, ¶¶85, 90-93. Grigoriadis teaches that NBI-77860 (verucerfont) treats CAH and that “[c]onsistent and clinically meaningful reductions from predose levels of both 17-OHP and ACTH were observed throughout the postdose period following administration of NBI-77860 relative to placebo in these CAH patients.” *Id.*, ¶¶51, 93. As another example, Grigoriadis teaches administering crinecerfont (compound **H**). *Id.*, 54.

1[C] wherein the small molecule CRF 1 antagonist is:

Letter Designation	Compound
A	
B	
C	

Letter Designation	Compound
D	
E	
F	

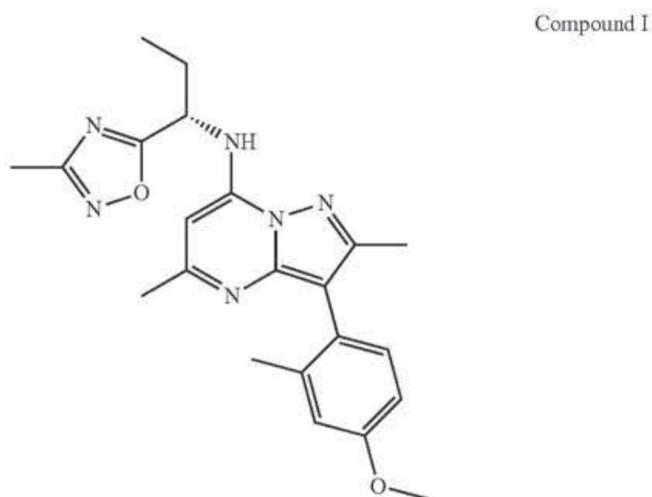
Letter Designation	Compound
G	SSR-126374,
H	
I	
J	

or a pharmaceutically acceptable salt thereof,

EX1001, 99:10-101:17 (formatting and letter designations added); EX1003, ¶¶72-73.

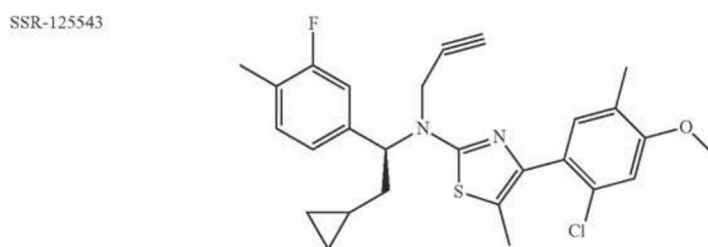
Grigoriadis expressly teaches this limitation. EX1006, ¶¶6, 7, 12, 13, 51, 54, page 6; EX1003, ¶193. To begin, claim 1 recites a genus of ten CRF1 receptor antagonists using the term “or.” EX1001, 100:57. Thus, a single prior-art reference adequately teaches the claimed genus when the reference discloses at least one species falling within the genus. *ModernaTX*, 18 F.4th at 1363-64; *Brown*, 265 F.3d at 1351. Here, Grigoriadis teaches not just one, but several species falling within the scope of the claimed genus.

For example, Grigoriadis teaches that, in one embodiment, the CRF1 receptor antagonist is NBI-77860 (verucerfont), having the following structure:



EX1006, ¶¶13, 51. As a POSA would recognize and Dr. Lodish confirms, this CRF1 receptor antagonist—verucerfont—is the same CRF1 receptor antagonist listed in claim 1 (and identified herein as “**D**”). EX1003, ¶193. Thus, Grigoriadis expressly teaches this limitation. *ModernaTX*, 18 F.4th at 1364 (prior art need show only one species of claimed genus to anticipate); *In re Slayter*, 276 F.2d 408, 411 (CCPA 1960) (“It is well settled that a generic claim cannot be allowed to an applicant if the prior art discloses a species falling within the claimed genus....”).

As another example, Grigoriadis teaches the CRF1 receptor antagonist SSR-125543 (crinecerfont), which corresponds to the claimed compound “**H**”:



EX1006, ¶¶13, 54, page 6; EX1003, ¶193.

Grigoriadis teaches that these CRF1 receptor antagonists are useful for inhibiting ACTH release in patients with CAH. EX1006, ¶¶6-7, 12 (disclosing embodiment where the CRF1 receptor antagonist is NBI-77860 (verucerfont)), 13 (disclosing embodiment where the CRF1 receptor antagonist is SSR-125543 (crinecerfont)). Grigoriadis also teaches that use of these CRF1 receptor antagonists in CAH patients enables administration of lower, more physiologic

doses of hydrocortisone, thereby reducing treatment-associated side effects like insulin resistance and glucose intolerance. *Id.*, ¶40.

1[D] and wherein the metabolic parameter comprises fasting glucose, HbA1c level, insulin sensitivity, or a lipid profile, or a combination thereof.

As discussed above, Grigoriadis teaches that CAH patients have an increased prevalence of insulin resistance and glucose intolerance, and Richard expressly teaches that administration of the CRF1 receptor antagonist crinecerfont changes metabolic parameters including fasting glucose, insulin sensitivity, and a lipid profile in a rat model of obesity. EX1006, ¶46, EX1012, 18:2-18, Figs. 3a-3g; EX1003, ¶¶194-196.

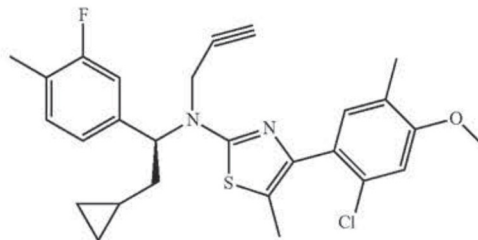
As Dr. Lodish explains, a POSA would understand that both insulin sensitivity and insulin resistance refer to the body's response to insulin. EX1003, ¶195 (citing EX1108, 941). Richard discloses that administration of crinecerfont "improved insulin sensitivity," and thus expressly teaches this metabolic parameter. EX1012, 18:2-18; EX1003, ¶194. A POSA would also understand that glucose intolerance can be measured by the amount of fasting glucose in the plasma. EX1003, ¶196 (citing EX1106, 9S). Richard discloses that administration of crinecerfont reduced fasting glucose and thus expressly teaches this claimed metabolic parameter. EX1012, 18:2-18; EX1003, ¶194.

C. Claims 3-19

1. Claim 3

Claim 3 depends directly from claim 1 and limits the small molecule CRF1 receptor antagonist to crinecerfont or a pharmaceutically acceptable salt thereof. EX1001, 101:20-35. Grigoriadis expressly teaches this limitation. EX1006, ¶¶6-7, 12, 13, 40, 54, page 6; EX1003, ¶¶197-198. Grigoriadis teaches the CRF1 receptor antagonist crinecerfont (SSR-125543, compound **H**):

SSR-125543



EX1006, ¶¶13, 54, page 6; EX1003, ¶198. Grigoriadis teaches that crinecerfont enables the administration of lower, more physiologic doses of hydrocortisone in patients with CAH, thereby reducing treatment-associated side effects like insulin resistance and glucose intolerance. EX1006, ¶¶6-7, 12, 13, 40.

2. Claim 4

Claim 4 depends directly from claim 1 and specifies that the metabolic parameter is insulin sensitivity. EX1001, 102:13-14. Grigoriadis and Richard expressly teach this limitation. EX1006, ¶46; EX1012, 18:2-18, Figs. 3a-3g; EX1003, ¶¶199-200. Grigoriadis teaches that CAH patients have an increased

prevalence of cardiovascular risk factors such as insulin resistance, and Richard expressly teaches that administration of the CRF1 receptor antagonist crinecerfont changes metabolic parameters including insulin sensitivity. EX1006, ¶46; EX1012, 18:2-18, Figs. 3a-3g. As Dr. Lodish explains, a POSA would understand that both insulin resistance and the claimed insulin sensitivity refer to the body's response to insulin, such that a subject with insulin resistance also has impaired sensitivity to insulin. EX1003, ¶200 (citing EX1108, 941).

3. Claim 5

Claim 5 depends directly from claim 1 and specifies that the subject has congenital adrenal hyperplasia (CAH). EX1001, 102:15-16. Grigoriadis expressly teaches this limitation. EX1006, ¶¶7, 40; EX1003, ¶¶201-202. Grigoriadis teaches a method of treating CAH by administering an effective amount of a CRF1 receptor antagonist. EX1006, ¶¶7, 40. Grigoriadis expressly teaches that “[a]s described herein, CRF₁ receptor antagonists have been found to directly inhibit ACTH release in patients with CAH and thereby allow normalization of androgen production.” EX1006, ¶40.

4. Claims 8-12

Claims 8-12 relate to doses. Claim 8 depends directly from claim 1 and recites that the CRF1 receptor antagonist “is administered at a dose of about 10 mg/day to about 400 mg/day.” EX1001, 102:21-23. Claims 9-12 each depend

from claim 8 and recite that the CRF1 receptor antagonist “is administered at a dose” of “about 50 mg” (claim 9), “about 100 mg” (claim 10), “about 200 mg” (claim 11) or “about 400 mg” (claim 12). *Id.*, 102:24-32. Grigoriadis teaches or, at a minimum, suggests these limitations. EX1006, ¶¶63, 88, 89, 91-93; EX1003, ¶¶203-205.

Grigoriadis teaches that a dose of a CRF1 receptor antagonist “is about 50 to 1000 mg.” EX1006, ¶63. In Example 5, Grigoriadis discloses the administration of a single 50 mg dose and a single 400 mg dose of NBI-77860 (verucerfont, compound **D**). EX1006, ¶¶88-89; EX1003, ¶204. As Dr. Lodish explains, a POSA would understand that those single doses were administered once per day. EX1003, ¶204. In Example 6, Grigoriadis discloses the administration of a single 300 mg dose and a single 600 mg dose of NBI-77860 (verucerfont). EX1006, ¶¶91-93. Grigoriadis’s explicit disclosures of 50 mg, 300 mg, and 400 mg doses per day represent individual species teaching the range in claim 8 (“about 10 mg/day to about 400 mg/day”). *Wertheim*, 541 F.2d at 267; *UCB*, 65 F.4th at 687 (“If the prior art discloses a point within the claimed range, the prior art anticipates the claim.”). These explicit disclosures also expressly teach the doses recited in claim 9 (“about 50 mg”) and claim 12 (“about 400 mg”).

While Grigoriadis does not expressly disclose administration of a daily dose of “about 100 mg” (claim 10) or “about 200 mg” (claim 11) of the CRF1 receptor

antagonist, the subject matter of these claims is, at a minimum, *prima facie* obvious over Grigoriadis's dose range of "about 50 to 1000 mg" and/or Grigoriadis's disclosure of individual doses of 50 mg and 300 mg. EX1006, ¶¶63, 88-89, 91-93. "[W]here there is a range disclosed in the prior art, and the claimed invention falls within that range, the burden of production falls upon the patentee to come forward with evidence that (1) the prior art taught away from the claimed invention; (2) there were new and unexpected results relative to the prior art; or (3) there are other pertinent secondary considerations." *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013). Nothing in the '084 patent teaches or suggests that a dose of 100 mg or of 200 mg produces a unique or unexpectedly improved result compared to the "about 50 to 1000 mg" range or the 50 mg or 300 mg single doses taught in Grigoriadis. *See generally* EX1001. Grigoriadis also does not teach away from administering a CRF1 receptor antagonist in the claimed "about 100 mg" or "about 200 mg" doses. To the contrary, Grigoriadis teaches that the use of the minimum effective dose is preferred. EX1006, ¶63; EX1003, ¶205.

5. Claim 13

Claim 13 specifies that the CRF1 receptor antagonist is administered to the subject "once per day." EX1001, 102:23-24. Grigoriadis expressly teaches once-per-day administration. EX1006, ¶¶88-89; EX1003, ¶206. In Example 5,

Grigoriadis discloses the administration of a single 50 mg dose and a single 400 mg dose of NBI-77860 (verucerfont, compound **D**), and in Example 6 Grigoriadis discloses administration of a single 300 mg dose and a single 600 mg dose of verucerfont. EX1006, ¶¶88-89, 91-93; EX1003, ¶206. As Dr. Lodish explains, a POSA would understand that those single doses were administered once per day. EX1003, ¶206.

6. Claims 15 and 16

Claims 15 and 16 relate to route of administration and dosage forms. Claim 15 depends directly from claim 1 and provides that the “CRF₁ antagonist is administered orally.” EX1001, 102:25-26. Claim 16 also depends directly from claim 1 and recites that the “CRF₁ antagonist is formulated as a capsule or tablet.” *Id.*, 102:35-38. Grigoriadis teaches these limitations. EX1006, ¶¶65, 74; EX1003, ¶¶207-208. Grigoriadis teaches that a CRF₁ receptor antagonist “may be administered to a subject in need by any one of several routes that effectively deliver an effective amount of the compound” including “for example, *oral*” administration. EX1006, ¶65. Grigoriadis also teaches that the “oral formulations” may be in the form of “*tablets*, powders, granules, or *capsules*.” EX1006, ¶74.

7. Claims 17-19

Claim 17 depends from claim 1 and specifies that “administering reduces a plasma concentration of a biomarker comprising” 17-OHP, ACTH, or A4, among others. EX1001, 102:39-45. Claim 18, which depends on claim 17, requires that the biomarker “is selected from the group consisting of 17-OHP, ACTH, and A4.” EX1001, 102:46-48. Grigoriadis expressly teaches these limitations. EX1006, ¶¶54, 60, 90-93, Figs. 5-6; EX1003, ¶¶209-217.

Grigoriadis teaches that “[s]tandard biomarker assessments used by endocrinologists when monitoring treatment efficacy may be used for monitoring the effects of” CRF1 receptor antagonists. EX1006, ¶60. Grigoriadis identifies 17-OHP, androstenedione (A4), testosterone, cortisol and ACTH as standard biomarkers and indicates that they are “easily measured in both children and adults giving rapid and meaningful data regarding treatment impact.” *Id.*

In Example 6, Grigoriadis teaches the administration of NBI-77860 (verucerfont) to CAH patients resulted in “consistent and clinically meaningful reductions from predose levels of both 17-OHP and ACTH...following administration of NBI-77860 relative to placebo in these CAH patients.” *Id.*, ¶¶90-93, Fig. 5, Fig. 6. Grigoriadis teaches that 50% of patients had “at least a 50% decrease in 17-OHP and ACTH.” *Id.* Thus, a POSA would have understood

Example 6 shows the reduction of the plasma concentration of the claimed biomarkers. EX1003, ¶¶210-211.

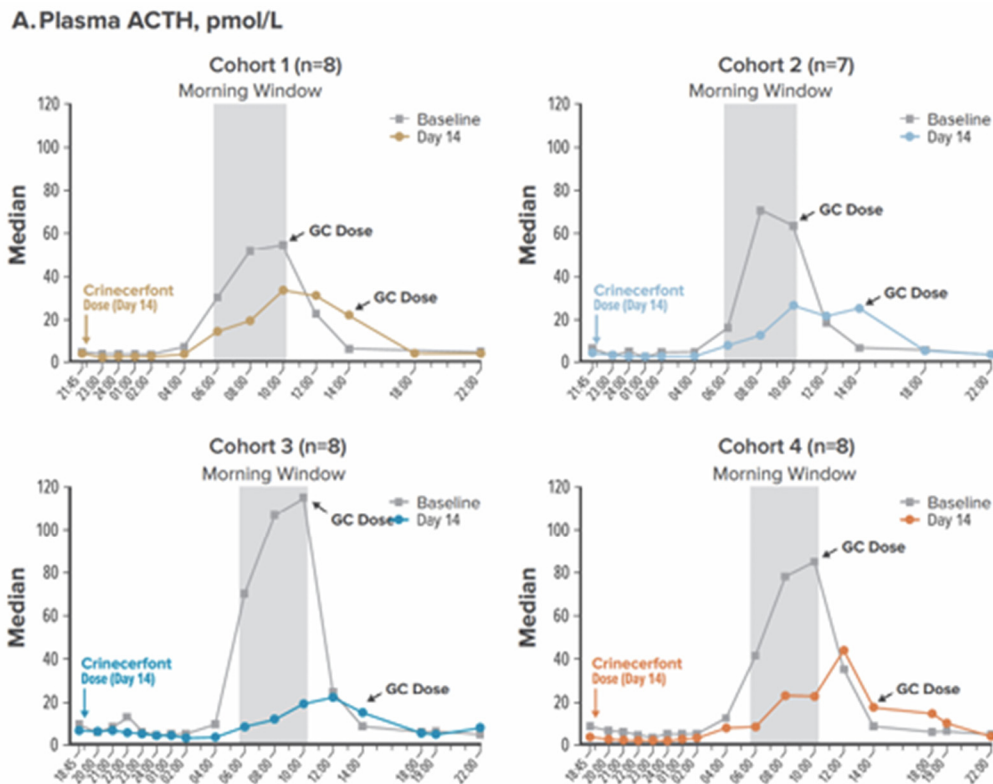
Claim 19, which also depends on claim 17, specifies that the plasma concentration of the biomarker is reduced by at least 10% “from baseline.” EX1001, 102:49-50. As explained above, the Board construed “baseline” to mean “a series of samples taken from an untreated patient with CAH, prior to treatment at intervals that are time-matched to the sampling intervals to be taken from the patient treated with either a CRF1 receptor antagonist or placebo.” *Supra*, §V. Grigoriadis teaches administering crinecerfont to a CAH patient. EX1006, ¶54. And, as Dr. Lodish explains, administration of crinecerfont as taught in Grigoriadis inherently results in at least 10% reduction from baseline in the claimed biomarkers ACTH and 17-OHP. EX1003, ¶212.

Auchus (EX1048) confirms that inherent result. EX1048; EX1003, ¶213. Although Auchus is not prior art, it may properly be relied on to show what is necessarily present in Grigoriadis. *See Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1329 (Fed. Cir. 2020) (“Extrinsic evidence can be used to demonstrate what is necessarily present in a prior art embodiment even if the extrinsic evidence is not itself prior art.” (cleaned up)). Auchus shows that the administration of crinecerfont to a patient with CAH—as taught by Grigoriadis—produced at least a 10% reduction in ACTH and 17-OHP compared to the patient’s

pre-treatment baseline levels. EX1048, Figs. 2, 4. Auchus reports these results in time-matched 24-hour profile data for four patient cohorts (1-4) in Figure 2.

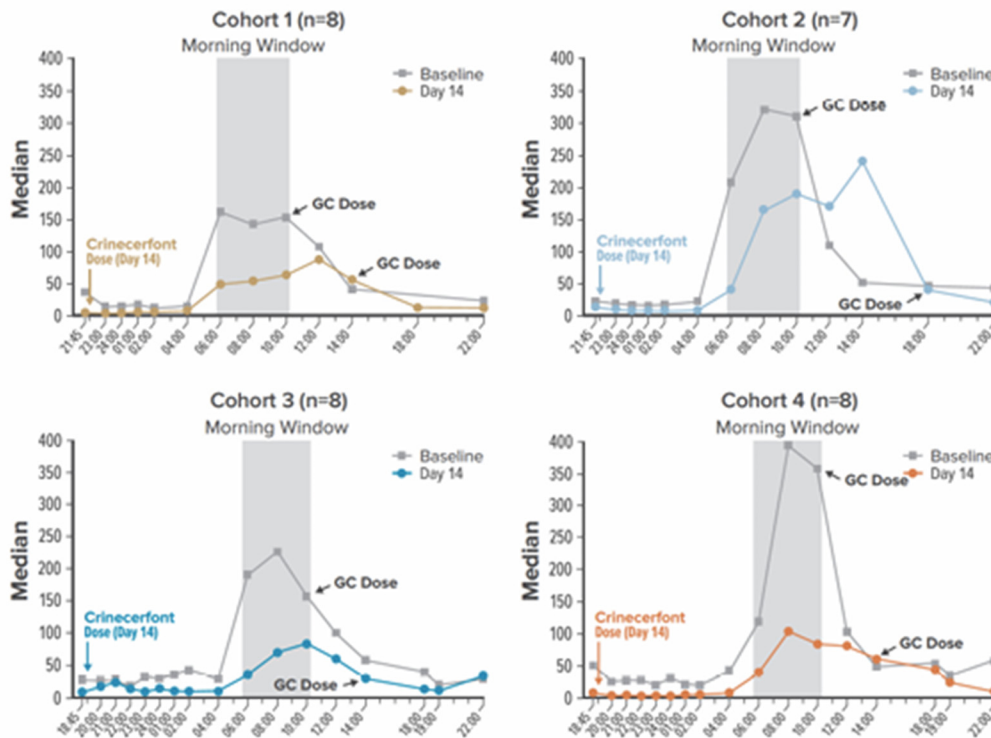
EX1048, Fig. 2.

Figure 2 shows that the median percent reduction in morning-window ACTH and 17-OHP levels in all four patient cohorts exceeded 10% after 14 days of crinecerfont treatment (shown in orange), relative to the patients' baseline (untreated) measurements (shown in gray). EX1048, Fig. 2. Panel A of Figure 2 (excerpted below) shows the decrease in biomarker ACTH.



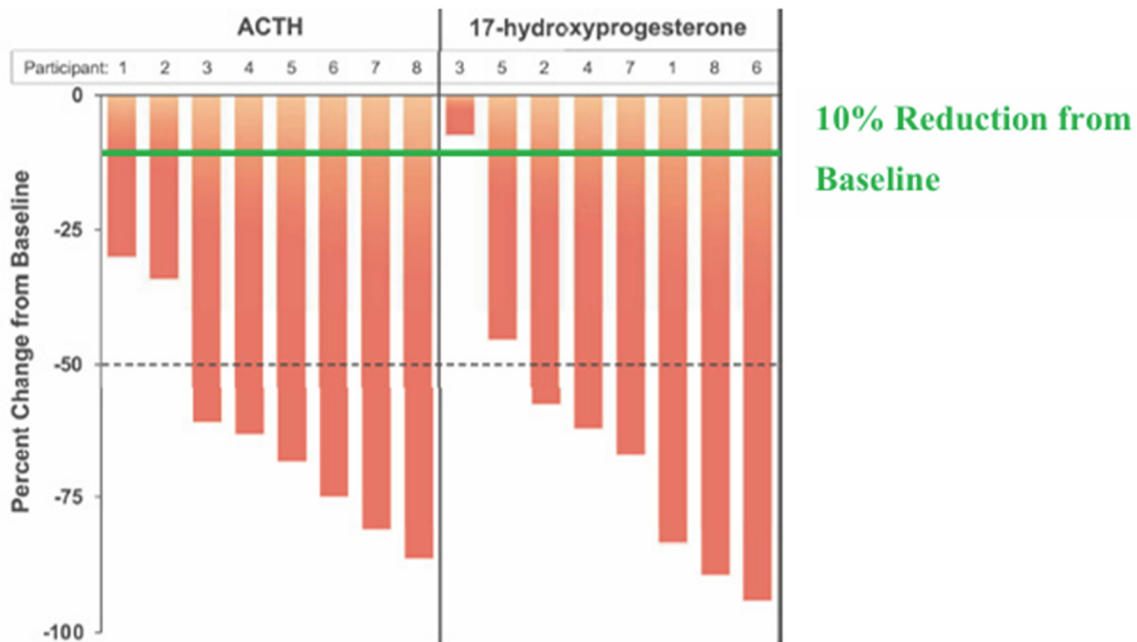
EX1048, FIG. 2, Panel A. Panel B of Figure 2 (excerpted below) shows the decrease in biomarker 17-OHP.

B. Serum 17OHP, nmol/L



EX1048, Panel B; *see also* EX1003, ¶¶214-215.

Figure 4 (reproduced below) likewise shows that every patient in Cohort 4 achieved over 10% reduction in ACTH and 7 of 8 patients achieved over 10% reduction in 17-OHP, as compared to the time-matched “baseline” samples taken before treatment with crinecerfont. EX1048, Fig. 4.



EX1048, Fig. 4 (annotation added); EX1003, ¶216. Thus, Auchus confirms that the administration of crinecerfont taught by Grigoriadis inherently satisfies claim 19. EX1003, ¶217.

IX. GROUND 4: Claims 6 and 7 are unpatentable for obviousness

Claims 6 and 7 each depend directly from claim 1 and recite a reduction in the size (claim 6) or number (claim 7) of a TART or an OART. EX1001, 102:17-20. Delfino expressly teaches these features. EX1064, 385-387; *see also* EX1003, ¶¶171-172. And, as explained below, a POSA would have been motivated to combine the teachings of Grigoriadis, Yu, and Richard with Delfino with a reasonable expectation of success. EX1003, ¶¶218-221.

A. Delfino (EX1064)

Delfino, titled “Testicular Adrenal Rest Tumors in Patients with Congenital Adrenal Hyperplasia,” published in the *Journal of Ultrasound Medicine* in 2012—more than a year before the earliest possible effective filing date of the ’084 patent (April 27, 2018). EX1064, 155. Delfino therefore qualifies as prior art under 35 U.S.C. §102(a)(1) and is relied on here to show that all claim limitations are found in the prior art per 37 C.F.R. §42.204(b)(4).

Delfino describes a longitudinal study to determine the role of ACTH plasma levels in the “induction and persistence of testicular adrenal rest tumors.” EX1064, 383. “High plasma ACTH levels were detected” in all 11 patients with TART, despite long-term therapy.” *Id.* However, preliminary results from the longitudinal study showed that after six months of “modified cortisone acetate therapy,” three patients’ ACTH levels returned to normal, with a “consequent disappearance or reduction in the tumor diameter.” *Id.*, 386. Delfino concluded that “testicular adrenal rest tumors are reversible lesions, as shown by the reduction or disappearance after adequate replacement therapy to reduce plasma ACTH levels.” *Id.*, 386-87.

B. Claims 6 and 7

Claims 6 and 7 each depend directly from claim 1 and recite a reduction in the size (claim 6) or number (claim 7) of a TART or OART. EX1001, 102:17–20.

Grigoriadis does not explicitly describe reduction in the size or number of TARTs, but Delfino expressly does. It would have been obvious to a POSA to administer CRF1 receptor antagonists to reduce the size or number of TARTs, as claimed, based on the combination of Grigoriadis, Yu, Richard, and Delfino. EX1003, ¶¶218-221.

As described above, Grigoriadis, Yu, and Richard provide a clear rationale for using a CRF1 receptor antagonist to lower ACTH in patients with TARTs—and reasonable expectation of success to thereby change a metabolic parameter of a subject having a TART. *Supra*, §VIII.B. A POSA would have looked to Delfino for explicit disclosure of clinical outcomes for such TART patients. EX1003, ¶220. Delfino, like Yu, teaches that TARTs are tied to elevated ACTH levels and that normalizing ACTH levels in TART patients leads to ***disappearance or reduction in the tumor diameter***. EX1064, 383 (confirming the “high prevalence of testicular adrenal rest tumors in patients with CAH and the major role played in its pathogenesis by high plasma ACTH levels”); 386-387 (finding the “reduction or disappearance” of TARTs after reduction of plasma ACTH levels); EX1003, ¶221. Thus, Delfino expressly teaches reduction in the size (i.e., tumor diameter) or number (i.e., disappearance), of TARTs as recited in claims 6 and 7, respectively.

A POSA would also have had a reasonable expectation of success in reducing the size or number of TARTs because Delfino expressly teaches that

normalizing ACTH levels resulted in the reduction in size or disappearance of the TARTs. EX1064, 386-387.

X. GROUND 5: Claim 14 is unpatentable for obviousness

Neurocrine's prescribing information for CRENESSITY provides that crinecerfont is administered twice daily. EX1010, 1, 2. Claim 14 of the '084 patent also specifies "twice per day" dosing, even though the written description discloses these limitations only in connection with the pharmaceutical compounds of Formula (I) and does not describe any surprising results or benefits associated with twice-daily dosing. EX1001, 6:32-41, 60:16-53, 65:59-68:19, 70:58-73:8, 78:54-60. Spruce never claimed this feature in combination with crinecerfont until CRENESSITY was approved by the FDA. EX1058; EX1089; EX1003, ¶¶75. Regardless, this limitation would have been obvious to a POSA from the teachings of Grigoriadis, Richard, and Yu (as described above) combined with Howerton. EX1003, ¶¶222-232.

Howerton expressly teaches twice-daily dosing of a number of CRF1 receptor antagonists, including Neurocrine's NBI-77860 (verucerfont, compound **D**). EX1074, 13:12-17, 2:20-24; EX1003, ¶¶173-174. As explained below, a POSA would have been motivated to combine the teachings of Grigoriadis, Richard, Yu with those of Howerton with a reasonable expectation of success.

A. Howerton (EX1074)

Howerton published as International Publication No. WO 2016/065177 A1 on April 28, 2016, more than a year before the earliest possible effective filing date of the '084 patent (April 27, 2018). EX1074, codes [10], [43]. Howerton therefore qualifies as prior art under 35 U.S.C. §102(a)(1) and no exception under §102(b) applies. Howerton is relied on here to show that all claim limitations are found in the prior art per 37 C.F.R. §42.204(b)(4).

Howerton discloses methods for treating a variety of disorders in a male subject with a pharmaceutically effective amount of a CRF1 receptor antagonist. *Id.*, 2:2-9; *see also* EX1003, ¶¶173-174. In some embodiments, “the disorder manifests hypersecretion of corticotropin-releasing factor (CRF).” EX1074, 12:25–28. In some embodiments, the disorder is stress- or anxiety-related. *Id.*, 12:29-13:11. Howerton provides a list of CRF1 receptor antagonists useful for treating these disorders, including Neurocrine’s NBI-77860 (verucerfont), as well as Spruce’s LY2371712 (tildacerfont). *Id.*, 13:12-17; EX1003, ¶224.

Howerton teaches that administration of CRF1 receptor antagonists to a human “may be carried out using known procedures, at dosages and for periods of time effective to treat a disease or disorder in the patient.” EX1074, 23:16-18. Howerton specifically teaches administering dosages “that range from one to five times per day or more.” *Id.*, 25:13–14; *id.*, 31:2-3 (teaching that the dose may be

administered “for example from 1 to 4 or more times per day”). Howerton further teaches that this range includes all individual numbers within that range. *See id.*, 12:14-22 (“Accordingly, the description of a range should be considered to have specifically disclosed all the possible sub-ranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed sub-ranges...as well as individual numbers within that range.”). Howerton teaches that a “suitable dose” may be administered “in a single dosage or in multiple dosages” per day. *Id.*, 30:32-31:3. As an example of multiple dosages, Howerton teaches that “a dose of 1 mg per day may be administered as two 0.5 mg doses, with about a 12-hour interval between doses.” *Id.*, 31:4-5.

B. Claim 14: “twice per day” administration

Grigoriadis does not expressly teach twice-per-day administration. However, Howerton teaches twice-daily dosage of CRF1 receptor antagonists—including Spruce’s Compound 1 (tildacerfont, compound **C**) and Grigoriadis’s NBI-77860 (verucerfont, compound **D**). EX1074, 2:20-24 (listing several Neurocrine CRF1 receptor antagonists). It would have been obvious to a POSA to administer CRF1 receptor antagonists twice per day as claimed based on the combination of Grigoriadis and Howerton. EX1003, ¶¶223-224.

A POSA seeking appropriate dosage regimens for Grigoriadis's CRF1 receptor antagonists would have looked to Howerton for explicit disclosure of dosing regimens, including twice-daily dosing. *Id.* Howerton teaches that administration of a CRF1 receptor antagonist to a human “may be carried out using known procedures, at dosages and for periods of time effective to treat a disease or disorder in a patient.” EX1074, 23:16-18. Specifically, Howerton teaches that a “suitable dose” of a CRF1 receptor antagonist may be administered “in a single dosage or in multiple dosages” per day. *Id.*, 30:32-31:3. As an example of multiple dosages, Howerton teaches that “a dose of 1 mg *per day* may be administered as *two* 0.5 mg doses, with about a 12-hour interval between doses.” *Id.*, 31:4-5.

Thus, Howerton expressly discloses twice-per-day administration. EX1074, 31:4-5; EX1003, ¶225. Howerton also teaches administering dosages “that range from one to five times per day or more.” EX1074, 25:13–14. Howerton teaches that this range includes all individual numbers within that range—thus, one to five times per day includes once-daily, twice-daily, etc. *Id.*, 12:14-22 (“Accordingly, the description of a range should be considered to have specifically disclosed all the possible sub-ranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to

have specifically disclosed sub-ranges...as well as individual numbers within that range.”); EX1003, ¶226.

A POSA would also have had a reasonable expectation of success with twice-daily dosing because Howerton expressly teaches that dosing. EX1074, 31:4-5. Howerton also teaches a “finite number of identified, predictable solutions”—ranging from once per day to five-times per day. *KSR Int’l Co. v. Teleflex*, 550 U.S. 398, 421 (2007). This is not, therefore, a situation where the prior art gave no direction on how to reach a successful result. *In re: Copaxone Consol. Cases*, 906 F.3d 1013, 1026 (Fed. Cir. 2018). To the contrary, Howerton squarely directs a POSA to evaluate dosing frequency within a finite, routine range, and specifically provides an example of twice-per-day dosing. EX1074, 31:4-5; EX1003, ¶227.

Nothing in Spruce’s ’084 patent teaches or suggests that twice-daily administration produces an unexpected or nonobvious result. *See generally* EX1001. The ’084 patent generally states that the pharmaceutical composition “can be administered on a regimen of one (1) to four (4) times per day, including once, twice, three times, and four times per day.” EX1001, 59:37-39. And the ’084 patent refers to once-daily, twice-daily, and thrice-daily dosing synonymously over several columns of repeating boilerplate language. *See, e.g., id.* at 59:40-60:17, 63:36-65:59, 68:22-70:50 (once-daily), 60:17-54, 65:60-68:21, 70:51-73:11

(twice-daily), 60:54-61:23 (thrice-daily). Taken together, these disclosures show that the named inventors of the '084 patent never contemplated that administering a CRF1 receptor antagonist twice-daily versus other regimens was an innovative feature of its purported invention. EX1003, ¶227. And for good reason, as the Federal Circuit has made clear that “where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295-96 (Fed. Cir. 2012) (cleaned up).

Moreover, Dr. Lodish explains that, in normal individuals, the pituitary gland secretes ACTH in rhythmic pulses throughout the day based on CRF agonism, circadian regulation, and cortisol-mediated negative feedback. EX1003, ¶¶228-229. But in CAH patients, that regulatory system is disrupted: ACTH levels remain chronically elevated and the rhythmic ACTH pulses become both larger and more frequent. EX1003, ¶229.

A POSA aiming to regulate ACTH values over a full 24-hour period, therefore, would have reasonably expected that twice-daily dosing would result in more consistent control of ACTH levels. EX1003, ¶230. And Howerton teaches exactly that: Howerton teaches a POSA that a “suitable dose” may be administered “in multiple dosages” per day and expressly teaches splitting a daily dose of 1 mg per day into two 0.5 mg administrations with a 12-hour interval between them.

EX1074, 30:32-31:5. A POSA would have recognized that splitting a full dose into two equally-spaced out doses would successfully provide more consistent control of ACTH levels. EX1003, ¶¶231-232.

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

Petitioner authorizes the Patent and Trademark Office to charge any fees to Deposit Account No. 06-1050.

XII. 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 '084 patent, nor is Petitioner aware of any pending civil actions involving the '084 patent.

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

Neurocrine provides the following designation of counsel.

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D. Service Information

Please address all correspondence and service to the address listed above.

Neurocrine consents to email service at PGR47291-0010PS1@fr.com.

XIII. CONCLUSION

For the above-described reasons, claims 1-19 are unpatentable under 35 U.S.C. §112(a) for lack of written description and for lack of enablement, and claims 1 and 3-19 are unpatentable under 35 U.S.C. § 103 for obviousness.

Petitioner requests that the Board grant the petition and hold claims 1-19 unpatentable.

Respectfully submitted,

Dated: June 18, 2026

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CERTIFICATION UNDER 37 CFR § 42.24

Under the provisions of 37 CFR § 42.24(d), the undersigned hereby certifies that the word count for the foregoing Petition for Post Grant Review totals 18,439 words, which is less than the 18,700 allowed under 37 CFR § 42.24.

Dated : June 18, 2026

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CERTIFICATE OF SERVICE

Pursuant to 37 CFR §§ 42.6(e)(4)(i) *et seq.* and 42.105(b), the undersigned certifies that on June 18, 2026, a complete and entire copy of this Petition for Post Grant Review and all supporting exhibits were provided by Federal Express, to the Patent Owner, by serving the correspondence address of record as follows:

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