

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 PGR2026-00059
Patent 12,569,491 B2

PETITION FOR POST GRANT REVIEW OF
UNITED STATES PATENT NO. 12,569,491 B2

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1001	U.S. Patent No. 12,569,491 to Howerton et al. (“the ‘491 Patent”)
1002	Excerpts from the Prosecution History of the ‘491 Patent (“the Prosecution History”)
1003	Declaration of Maya Lodish, M.D.
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	RESERVED

Exhibit No.	Exhibit Description
1013	Speiser et al., “Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society Clinical Practice Guideline,” <i>J. Clin. Endocrinol. Metab.</i> , 95(9):4133-60 (2010) (“Speiser 2010”).
1014	Turcu A.F. & Auchus R.J., “The Next 150 Years of Congenital Adrenal Hyperplasia,” <i>J. Steroid. Biochem. Mol. Biol.</i> , 153:63-71 (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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1021	RESERVED
1022	RESERVED
1023	European Pat. No. 3 784 233 to Alexis Howerton, et al.
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 Crinicerfont 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	RESERVED
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, Crinicerfont (2026).
1034	Director Review Decision in PGR2021-00088, Paper 66

Exhibit No.	Exhibit Description
1035	Director Review Decision in PGR2022-00025, Paper 64
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	U.S. Pat. No. 11,304,950 to Alexis Howerton, et al. (the “’950 Patent”).
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”).

Exhibit No.	Exhibit Description
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”).
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	U.S. Pat. No. 11,304,950 Request for Certificate of Correction mailed March 12, 2025, and Certificate of Correction issued on June 17, 2025.
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”).

Exhibit No.	Exhibit Description
1056	U.S. Provisional App. No. 62/822,815 (the “’815 provisional”).
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
1063	RESERVED
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).
1065	RESERVED
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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).

Exhibit No.	Exhibit Description
1069	Claahsen-van der Grinten et al., “Gonadal dysfunction in congenital adrenal hyperplasia,” <i>Eur. J. Endocrinol.</i> , 184(3):R85-R97 (2021).
1070	Reisch et al., “Testicular Adrenal Rest Tumors Develop Independently of Long-Term Disease Control: A Longitudinal Analysis of 50 Adult Men With Congenital Adrenal Hyperplasia due to Classic 21-Hydroxylase Deficiency,” <i>J. Clin. Endocrinol. Metab.</i> , 98(11):E1820-E1826 (Nov. 2013).
1071	Mendes-dos-Santos et al., “Prevalence of Testicular Adrenal Rest Tumor and Factors Associated with Its Development in Congenital Adrenal Hyperplasia,” <i>Horm. Res. Paed.</i> , 90:161-168 (2018).
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	NCT00539136, “A Study to Examine the Absorption of GSK561679 in Healthy Male Volunteers,” ClinicalTrials.gov., (GlaxoSmithKline) (“GSK Study”).
1076	Wilson, JD, “Prospects for Research for Disorders of the Endocrine System,” <i>JAMA</i> , 285(5):624-627 (2001) (“Wilson 2001”).
1077	U.S. Pat. App. No. 17/081,694 (“the ’694 Application”), Notice of Allowance and Reasons for Allowance (Feb. 1, 2022).
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
1080	Claahsen-van der Grinten et al., “Testicular Adrenal Rest Tumours in Congenital Adrenal Hyperplasia,” <i>Best Prac. & Res. Clin. Endocrinol. & Metab.</i> 23(2):209-220 (Apr. 2009) (“Claahsen-van der Grinten 2009”).

Exhibit No.	Exhibit Description
1081	O'Shea et al., "Food for thought: formulating away the food effect – a PEARRL review," <i>J. Pharmacy and Pharmacology</i> , 71:510-535 (2019).
1082	Tellew et al., "Discovery of NBI-77860/GSK561679, a potent corticotropin-releasing factor (CRF1) receptor antagonist with improved pharmacokinetic properties," <i>Bioorganic & Medicinal Chem. Ltrs.</i> , 20(24):7259-7264 (Dec. 2010).
1083	Chen et al., "Synthesis and SAR of 2-Aryloxy-4-alkoxy-pyridines as Potent Orally Active Corticotropin-Releasing Factor 1 Receptor Antagonists," <i>J. Med. Chem.</i> 51:1377-1384 (2008).
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)
1086	Declaration of June Ann Munford (May 22, 2026)
1087	RESERVED
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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).

Exhibit No.	Exhibit Description
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., “Crinecerfont, 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
1101	PGR2025-00032, Paper 8
1102	RESERVED
1103	Declaration of Ramesh Tharuvai, Ph.D.

Neurocrine Biosciences, Inc. (“Petitioner” or “Neurocrine”) petitions for Post-Grant Review of claims 1-19 of U.S. Patent 12,569,491 (EX1001, “the ’491 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 ’491 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 ’491 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. 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 '491 patent exemplifies Spruce's abuse of the patent system and the overbroad reach of Spruce's patents.

Each claim of the '491 patent encompasses methods for treating an endocrine disorder associated with CRF1 receptor activity—namely, testicular adrenal rest tumors (TARTs) or ovarian adrenal rest tumors (OARTs). EX1001, 98:46-102:36. TARTs and OARTs are known complications of CAH. EX1006, ¶44; EX1038, e69; EX1003, ¶34. The '491 patent claims administering one of ten listed CRF1 receptor antagonists to treat TARTs or OARTs. But the written description of the '491 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 its related disorders. EX1006, ¶5. Unsurprisingly, the '491 patent contains no written description of using these compounds to treat TARTs or OARTs. The named inventors of the '491 patent never performed that work and never possessed those compounds for use in the claimed methods.

The '491 patent also fails to provide the technical guidance necessary for a POSA to make and use all ten claimed CRF1 receptor antagonists for treating TARTs and OARTs. Instead, the specification rests on the unsupported assertion that all ten claimed compounds can treat TARTs or OARTs based solely on a

single data point involving one TART in one patient administered just one of the claimed compounds (Compound 1). EX1001, 96:17-20; Figs. 10A-10B. But in the provisional application to which the '491 patent claims priority—U.S. Provisional Application 62/663,951—applicants ***admitted*** that the ***same data*** could not be linked to CRF1 receptor antagonist treatment, stating: “it is not known whether Compound 1 can successfully treat TART.” EX1055, ¶¶286-287, 296; EX1003, ¶¶56, 115. The '491 patent omits that admission. *Compare* EX1055, ¶¶286-287, *with* EX1001, 95:18-26.

Not only do the claims of the '491 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. Other prior art likewise teaches that the overproduction of the hormone ACTH in CAH male patients can lead to the

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

production of TARTs. EX1067.³ The '491 patent merely repackages those teachings without contributing to scientific progress or patient care in this field.

The '491 patent should not have issued, and the Examiner erred in allowing its overly broad claims. But the '491 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 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.

³ Yu et al., "Clinical manifestations of testicular adrenal rest tumor in males with congenital adrenal hyperplasia," *Ann. Ped. Endocrinol. Metab.*, 20:155-161 (2015) ("Yu").

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 '491 patent continues that pattern of abuse. Allowing the '491 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]; EX1003, ¶29. Grigoriadis (EX1006) is prior art to Spruce's patents.

In early 2016, Neurocrine also published the results of the first Phase Ib 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. EX1048.⁴

Neurocrine's work on crinecerfont, in particular, delivered a breakthrough therapy for patients with CAH. On December 13, 2024, the FDA approved two

⁴ 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").

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 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.⁵

In PGR2025-00032, Neurocrine challenged claims of Spruce's U.S. Patent 12,115,166. EX1100, 1. In response, Spruce filed a statutory disclaimer

⁵ Spruce's requests for Director Review were denied. EX1031-EX1032; EX1034-EX1035.

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.

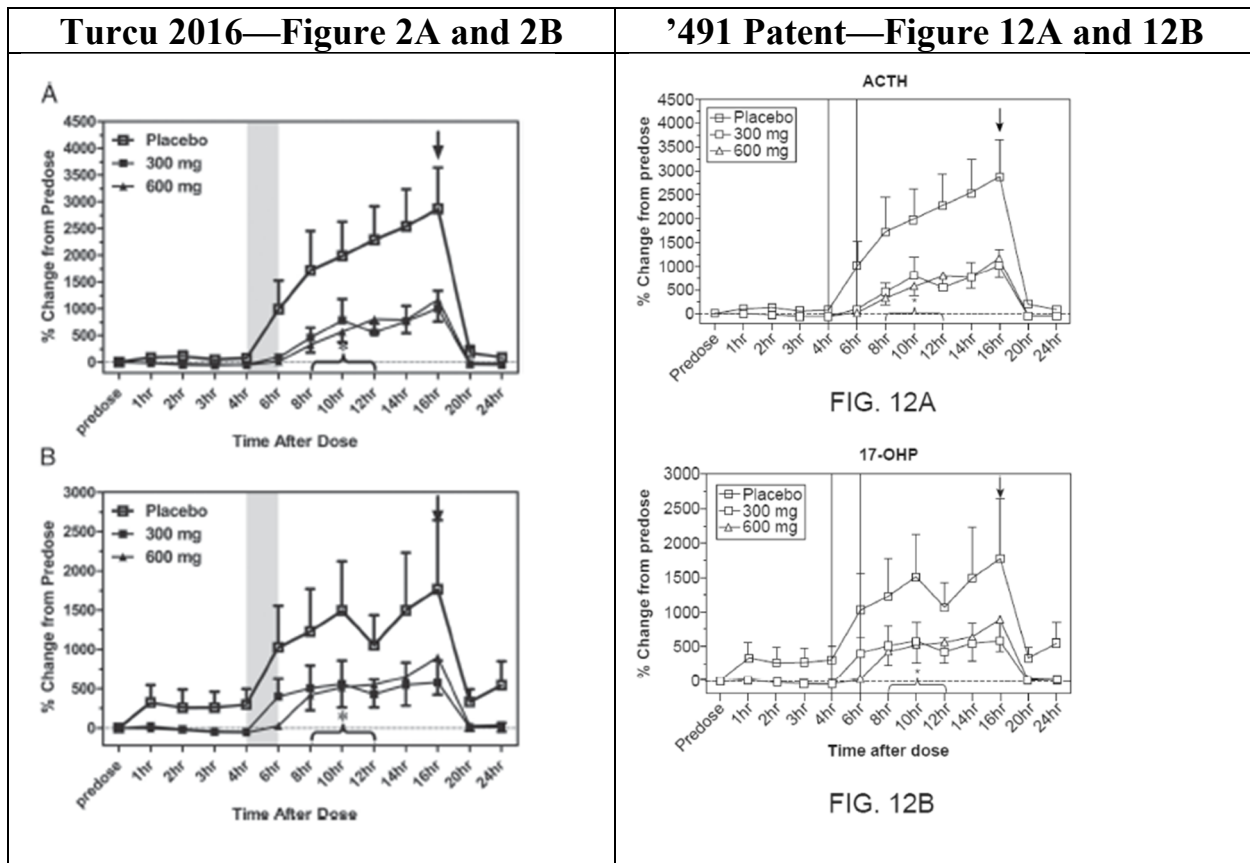
C. The ’491 Patent and Its Prosecution History Illustrate Spruce’s Pattern of Pursuing Overly Broad Claims That Copy the Work of Others

Spruce filed U.S. Application 19/043,275 (“the ’275 application”),⁶ which resulted in the ’491 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, ¶71. Spruce filed for and was granted Track One prioritized examination for the ’275 application. EX1002, 13, 147-148. Despite having the benefit of the Board’s reasoned analysis about the limits of its disclosures, Spruce—for the first time in

⁶ The ’275 application claims priority through a series of continuation applications to April 27, 2018. EX1001, codes [63], [60].

the '275 application—attempted to claim Neurocrine's crinecerfont dosed twice daily and in the fed state, as instructed in the CRENESSITY label. *Id.*, 141-143. It did so even though the named inventors neither possessed nor enabled that subject matter.

Spruce went beyond the CRENESSITY label by directly copying Neurocrine's own published data from Turcu 2016. To justify the use of Compound 1 (tildacerfont) for treating TARTs, the '491 patent invokes "a previous proof-of-concept study using a similar small-molecule CRF1 receptor antagonist." EX1001, 90:30-35. The '491 patent states that this "similar" CRF1 receptor antagonist "produced dose-dependent 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:

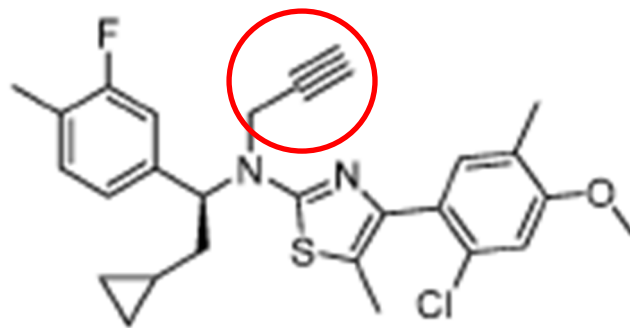


Compare EX1008, 1176, Figures 2A-B, with EX1001, Figures 12A-B; EX1003, ¶¶53-54 (citing EX1072, 13).

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 '491 patent stated that Figures 12A and 12B provided a graphical representation of ACTH and 17-OHP hormone levels after treatment with Compound 1. EX1002, 37 (¶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, 313 (¶48), 413-414 (¶326) (citing Neurocrine's Grigoriadis publication).

The deficiencies of the '491 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, 35 (¶27), 93 (¶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" (–CH₂–C≡C) and is not crinecerfont. EX1003, ¶¶63, 72-73. 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 '491 patent. *Compare* EX1001, 100:20-25, *with id.*, 82:40-50.

The '491 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 '491 patent possessed or enabled a method for treating TARTs or OARTs using each of the 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 the '491 patent), PGR2026-00060 (challenging U.S. Patent 12,569,490), and PGR2026-00061 (challenging U.S. Patent 12,576,084). 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 here, OARTs and menstrual irregularity in PGR2026-00060, and “changing a metabolic parameter” in a subject with TARTs or OARTs in PGR2026-00061. 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 PGR2026-00061 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 '491 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 '491 patent on March 10, 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 '491 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, 3-19	103	Obviousness over Grigoriadis, Yu, Howerton, GSK Study

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

C. The '491 Patent Is Eligible for PGR

The '491 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 '491 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, ¶80. 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). For purposes of this proceeding only, Neurocrine submits that no claim terms need construction. EX1003, ¶¶81-82. The Board determined in the previous PGRs that no claim construction was necessary to resolve the dispute over written description. EX1005, 26; EX1007, 25.

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 “TART” *or* “OART” and each of the ten CRF1 receptor antagonists here—the specification must convey that the named 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.”).⁷ The written description of the ’491 patent fails to meet this requirement.

First, the written description of the ’491 patent fails to show possession of a method for treating OARTs at all. Second, the written description fails to demonstrate possession of treating TARTs with any of the claimed CRF1 receptor antagonists. Third, the written description fails to show possession of seven of the ten claimed CRF1 receptor antagonists—including Neurocrine’s crinecerfont and verucerfont—for treating TARTs or OARTs. Fourth, the written description fails

⁷ Here and throughout, emphasis added unless otherwise stated.

to show possession of crinecerfont at all. For each of these reasons, the specification falls far short of demonstrating possession of the full scope of treating TARTs or OARTs with the full scope of the claimed CRF1 receptor antagonists, rendering all claims of the '491 patent unpatentable under §112(a). EX1003, ¶¶96-97.

A. All Claims of the '491 Patent Lack Written Description Because the Specification Fails to Show Possession of a Method for Treating OARTs

The preamble of claim 1 recites a method for treating an endocrine disorder, and the body of the claim recites that the endocrine disorder is TARTs *or* OARTs. EX1001, 98:47-48, 100:65-67. No dependent claim narrows the method to treating TARTs only. *Id.*, 101:1-102:36. When a claim recites alternatives using the disjunctive “or,” as here, the Board and the Federal Circuit have held that the written-description requirement demands support for each alternative.

In *Mylan Pharms. Inc. v. Sanofi-Aventis Deutschland GmbH*, IPR2018-01680, for example, the Board held that a claim reciting a piston rod comprising “an internal *or* an external fourth thread” lacked written-description support for the “internal” thread because the priority document “disclose[d] only a piston rod with external threads.” Paper 110, 16-29 (PTAB 2020). The Federal Circuit affirmed, holding that substantial evidence supported the Board’s finding of a lack of written description because the patent disclosure was limited to external threading. *Sanofi-*

Aventis Deutschland GmbH v. Mylan Pharms. Inc., 2021 WL 6137375, at *3 (Fed. Cir. Dec. 29, 2021). Similarly, in *Merck Sharp & Dohme Corp. v. Microspherix LLC*, 814 F. App'x 575, 580 (Fed. Cir. 2020) (nonprecedential), the Federal Circuit found that a patent was not entitled to the filing date of its provisional application where the claim at issue recited three alternatives separated by “or,” but the provisional lacked disclosure of one of those three alternatives. These cases reflect the core purpose of the written-description requirement: “to ensure that the scope of the right to exclude...does not overreach the scope of the inventor’s contribution to the field of art as described in the patent specification.” *Reiffin v. Microsoft Corp.*, 214 F.3d 1342, 1345–46 (Fed. Cir. 2000).

Here, the written description of the '491 patent provides no substantive disclosure—and no indication to a POSA—that the named inventors possessed a method for treating OARTs. EX1003 ¶¶98-102. 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, the treatment of OARTs. *Nuvo Pharms. (Ir.) Designated Activity Co. v. Dr. Reddy’s Lab’ys Inc.*, 923 F.3d 1368, 1380 (Fed. Cir. 2019). All claims therefore fail the written-description requirement of §112(a).

The written description of the '491 patent contains no examples, no experimental data, no clinical observations, and no other indicia related to the treatment of OARTs. EX1003, ¶¶98-100. Instead, the *only* references to OARTs in the specification are conclusory statements that merely restate the claim language, without providing any specific technical guidance or data showing that the named inventors actually possessed a method for treating 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.*, 24:7-9 (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.*, 50:47-49 (“In one embodiment, provided herein are methods for treating or preventing ovarian adrenal rest tumors (OART)....”); *id.*, 50:59-60 (same); *id.*, 51:41-42 (same); *id.*, 55:33-36 (same); *id.*, 79:21-23 (same).

As Dr. Lodish explains, a POSA would not have understood the named inventors of the '491 patent to have actually invented a method for treating OARTs based on these bare disclosures. EX1003, ¶98. 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 '491 patent that OARTs were exceedingly rare, with only a handful of cases reported in the literature. EX1003, ¶¶39, 101. 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, a POSA would have understood that OARTs were very rare as of the priority date, more difficult to diagnose than TARTs, and more difficult to treat. EX1003, ¶101. Given this unpredictability in the art, a POSA would have expected substantially more detail—such as experimental data or clinical evidence—to demonstrate that the named inventors were, in fact, in possession of a method of treating OARTs. *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, 101.

But rather than provide the necessary details about the treatment of OARTs, the '491 patent inserts only ambiguity. 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, 102. This error underscores that the inclusion of OARTs in the '491 patent was an afterthought, not the product of actual possession.

At bottom, the written description of the '491 patent must show that the named inventors “possessed the claimed methods by sufficiently disclosing” a method for treating 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 treating OARTs. 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).

And even if the '491 patent adequately describes a method for treating TARTs (it does not), an argument that treating OARTs would have been an obvious variant of treating TARTs does not satisfy written description. *Novartis Pharms. Corp. v. Accord Healthcare, Inc.*, 38 F.4th 1013, 1016 (Fed. Cir. 2022) (“It is not enough that a claimed invention is an obvious variant of that which is disclosed in the specification.” (cleaned up)); *Ariad*, 598 F.3d at 1352 (“a description that merely renders the invention obvious does not satisfy the [written description] requirement”). The Board can find ***all claims*** unpatentable under §112(a) on this basis alone because every claim of the '491 patent encompasses a method for treating OARTs.

B. All Claims Also Lack Adequate Written Description Because the '491 Patent's Alleged Treatment of a Single TART in a Single Patient Cannot Support the Full Scope of the Claimed Treatment Methods

As explained above, all claims (1-19) of the '491 patent fail the written-description requirement because the named inventors lacked possession of a method for treating OARTs. *Supra*, §VI.A. Claims 1-19 also fail the written-description requirement because the specification fails to reasonably convey that they had possession of a method for treating TARTs with Compound 1 (tildacerfont), let alone every claimed CRF1 receptor antagonist. *Juno Therapeutics*, 10 F.4th at 1337; *Ariad*, 598 F.3d at 1351; EX1003, ¶¶103-116.

This is an additional, independent basis on which the Board can find *all claims* of the '491 patent unpatentable.

As discussed above, when a claim recites a method of treating a disease with a pharmaceutical compound—such as a CRF1 receptor antagonist here—the specification must describe the method in sufficient detail that a POSA would have recognized that the pharmaceutical compound would have been efficacious in the treatment of the disease. *Biogen Int'l GmbH v. Mylan Pharms. Inc.*, 18 F.4th 1333, 1343 (Fed. Cir. 2021); *Nuvo*, 923 F.3d at 1384 (holding that, when an inventor expressly claims that a pharmaceutical compound achieves a certain therapeutic result, then that result “must be supported by adequate disclosure in the specification”).

Here, the '491 patent's only purported evidence of treating a TART is from a single 25-year-old male patient with classic CAH. EX1003, ¶¶103-105. The '491 patent mentions this patient only twice. In the Brief Description of the Drawings, the '491 patent states that Figures 10A-10B provide “[i]mages of a patient with TART pre-treatment with a CRF1 antagonist (Compound 1) (A) and 6-weeks post-treatment with a CRF1 antagonist (Compound 1) (B).” EX1001, 10:20-23. In Example 3, the '491 patent states that “FIGS. 10A-10B show approximately 25% shrinkage in TART in a 25 year old male with classic congenital adrenal hyperplasia following 6 weeks treatment with a CRF1 receptor

antagonist.” *Id.*, 96:17-20. These two disclosures fall far short of conveying possession of the full scope of the claims.

From the outset, the written description provides no dosing regimen or treatment protocol describing how Compound 1 (tildacerfont) was administered to the patient. Although Figure 4 of the ’491 patent purports to show lowered ACTH levels in 8 out of 10 CAH patients⁸ treated with Compound 1 (tildacerfont), the written description does not state or suggest that the 25-year-old male patient with a TART is among that cohort. EX1001; EX1003, ¶¶105-106.

Nor does the written description provide any statistical or comparative analysis showing that the purported shrinkage of the patient’s TART was attributable to Compound 1 (tildacerfont) versus a concomitant glucocorticoid. Specifically, a POSA would have understood that, as a patient with classic CAH, the 25-year-old male received glucocorticoids in addition to Compound 1 (tildacerfont). EX1003, ¶106; *id.*, 22-23 (citing EX1013, EX1014, EX1017; EX1026; EX1047). Glucocorticoids were already known to affect TARTs, as evidenced by Yu (EX1067, table 3) and the ’491 patent itself (EX1001, 90:20-22). Without any analysis disentangling the effect of Compound 1 (tildacerfont) from the effect of glucocorticoids, a POSA would not have understood which therapy (if

⁸ These patients are labeled 003-001, 004-001, 004-004, 005-001, 005-002, 005-003, 006-003, 006-004, 007-001, and 007-002. EX1001, Fig. 4.

any) caused the alleged TART shrinkage. That omission undermines any inference that Figures 10A-10B demonstrate the efficacy of Compound 1 (tildacerfont) in treating TARTs. EX1003, ¶106.

The written description also fails to provide any information about the single patient's ACTH levels, including whether the patient experienced any reduction in ACTH levels after treatment with Compound 1 (tildacerfont). As Dr. Lodish explains, a POSA would have expected this information at a minimum, particularly given that Figure 4 purports to show that some CAH patients treated with Compound 1 (tildacerfont) (at any dose) exhibited *no improvement* in ACTH levels at all, and one patient's ACTH level worsened. EX1001, Fig. 4; EX1003, ¶105. Although the '491 patent hypothesizes that Compound 1 "may be effective in reducing ACTH levels, thereby reducing the size of testicular lesions in TART" (EX1001, 93:56-58), it provides no information about the degree of ACTH reduction necessary to achieve a reduction in TART size (EX1003, ¶105).

The '491 patent also fails to identify any response criteria defining what constituted "treatment" of TART for that patient. EX1001; EX1003, ¶107. For example, the written description does not provide any analysis whatsoever of the two ultrasound images shown in Figures 10A-10B, reproduced below. EX1001. As Dr. Lodish explains, a POSA would not have understood Figures 10A-10B to demonstrate any therapeutic difference in TART size between the purported pre-

treatment (Fig. 10A) and post-treatment (Fig. 10B) images for multiple reasons.

EX1003, ¶¶107-113.

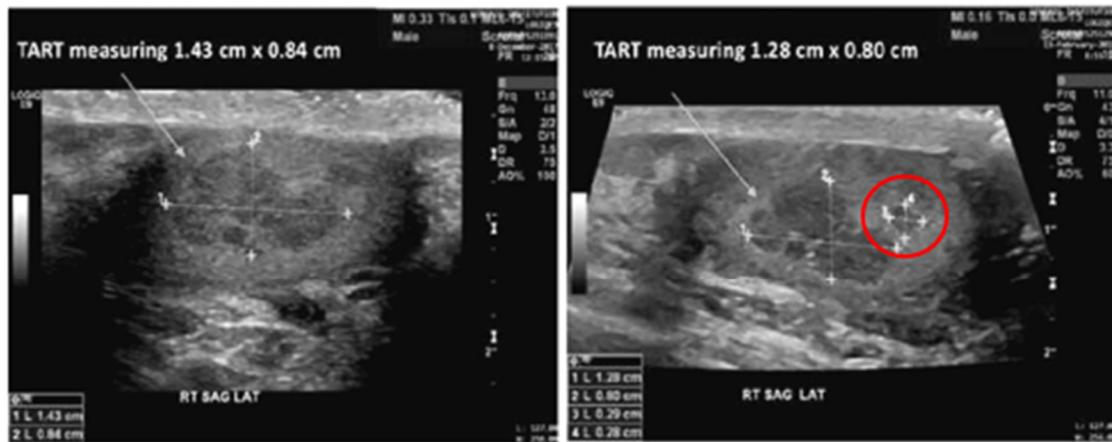


FIG. 10A

FIG. 10B

First, Figure 10A marks and measures a single lesion, whereas Figure 10B appears to mark two lesions, making it unclear whether the second lesion (annotated with a red circle) is part of the first lesion or represents a separate lesion altogether. EX1003, ¶109. A POSA would have considered this ambiguity critical, particularly because the alleged changes in dimensions are only a few millimeters and well within the margin of error due to experimental variability and/or the imaging process itself. EX1003, ¶¶109-110.

The '491 patent alleges that the difference in TART size between Figures 10A and 10B represents “approximately 25% shrinkage,” yet fails to explain how that figure was calculated. EX1003, ¶108. As Dr. Lodish explains, applying the

measurements disclosed yields a reduction in area of only about 15%, not 25%. *Id.* The purported reduction is even smaller, approximately 10.5%, when the change in the longest diameter of the TART is calculated. *Id.*⁹ Either way, the absence of any explanation, coupled with the discrepancy in the reported values, underscores the unreliability of the patent's disclosure. *Id.*

Second, a POSA would have understood that the TART was not scanned or measured in a consistent manner, as the first and second ultrasound images were obtained at different depths (2.5 cm in Figure 10A versus 3.3 cm in Figure 10B). EX1003, ¶110. Because TARTs present as nodular, often lobulated masses, measurements obtained at different depths capture different imaging planes of the lesion, resulting in apparent differences in the measured length and width. *Id.* As Dr. Lodish explains, these differences do not necessarily reflect overall TART shrinkage but result from measurements taken in different imaging planes. *Id.*

Third, Figure 10 depicts only one testicle, even though TARTs are typically bilateral tumors (present in both testicles). EX1003, ¶112 (citing EX1001, 25:9-10; EX1080, 211). Without any information about the second testicle, a POSA could not reasonably conclude that Compound 1 (tildacerfont) had any effect on TART size in the single patient. EX1003, ¶112.

⁹ As Dr. Lodish explains, one standard approach to measuring changes in tumor size is to assess reductions in the tumor's longest diameter. EX1003, ¶108.

Given the state of the art as of the earliest priority date, a POSA would not have accepted that Compound 1 (tildacerfont) treats TARTs based on the results from the single patient. EX1003, ¶116. While not prior art, that conclusion was confirmed when, in 2024—before the application leading to the '491 patent was even filed—Spruce announced that tildacerfont failed in Phase 2b clinical trials for CAH patients because it did not improve underlying hormone levels or meet the primary endpoint of glucocorticoid reduction relative to placebo. EX1044, 1 (stating that “CAHmelia-203” study did not meet primary efficacy endpoint); EX1045, 1 (stating that “CAHmelia-204” study did not meet primary endpoint). A secondary outcome measure in one Phase 2b clinical trial called “CAHmelia-203” (also known as “SPR001-203”) was tildacerfont’s effectiveness in reducing TARTs in male CAH subjects. EX1097, 1. In June 2024, Spruce admitted that the clinical trial “did not meet its primary *and secondary endpoints*,” and therefore terminated the study. EX1097, 1. From this evidence, a POSA would not have expected that *Compound 1 (tildacerfont)* could treat TARTs. *Nuvo*, 923 F.3d at 1384 (invalidating claims where a POSA would not have expected the claimed pharmaceutical compound to achieve the claimed therapeutic result).

Even assuming some reduction in the size of a single TART in this single patient, the written description provides no information about whether that reduction was clinically or statistically significant—particularly given the absence

of a control and the short treatment period (only six weeks). EX1003, ¶114. A POSA would not have extrapolated the results from the one patient to conclude that Compound 1 (tildacerfont) is effective to treat TARTs. *Id.* Indeed, Spruce itself **admitted** that this data could not be definitively linked to CRF1 receptor antagonist treatment in the provisional application to which the '491 patent claims priority—U.S. Provisional Application 62/663,951. That provisional application states that “***it is not known*** whether Compound 1 can successfully treat TART.” EX1055, ¶¶286-287, 296; EX1003, ¶¶56, 115.

Finally, even crediting the reported data in Figures 10A-10B as adequately showing that ***Compound 1 (tildacerfont)*** could treat TARTs (it does not), the written description of the '491 patent still fails to provide any data or disclosure demonstrating possession of methods of treating TARTs across the ***full scope of the claims***—that is, across the additional nine CRF1 receptor antagonists recited in the challenged claims. As Dr. Lodish explains and as discussed in additional detail immediately below (*infra*, §VI.C.), a POSA would not understand treatment of a single patient with Compound 1 (tildacerfont) adequately conveys possession of a method for treating TARTs with the remaining claimed CRF1 receptor antagonists. EX1003, ¶114.

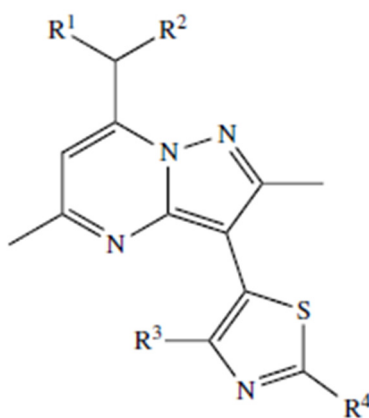
Thus, the '491 patent fails to convey possession of the claimed method of treating TARTs. Claims 1-19 are unpatentable for lack of written description for this additional reason.

C. Claims 1 and 3-19 Fail Because the Written Description Discloses Seven of the Ten Claimed CRF1 Receptor Antagonists Only as “Additional Chemotherapeutic Agent[s]”—Not as Compounds for Treating TARTs or OARTs

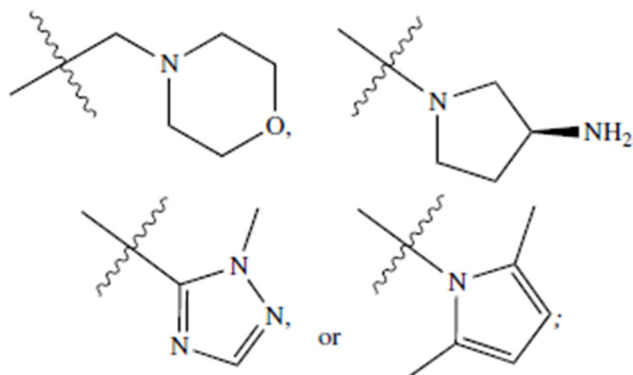
Claims 1 and 4-19 each encompass ten CRF1 receptor antagonists for treating TARTs or OARTs. EX1001, 98:47-100:67, 101:36-102:36. Claim 2 is limited to Compound 1 (tildacerfont) (*id.*, 101:1-19) and claim 3 is limited to Neurocrine's crinecerfont (*id.*, 101:20-35). To satisfy the written-description requirement, the '491 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 '491 patent as compounds for treating TARTs or OARTs (and claim 3's crinecerfont is not disclosed at all). 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, 6:54-56, 6:65-8:52; EX1003, ¶¶117-131. 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 treating TARTs or OARTs

To begin, the '491 patent purports to disclose a method for treating TARTs or OARTs with a CRF1 receptor antagonist having the structural Formula (I):

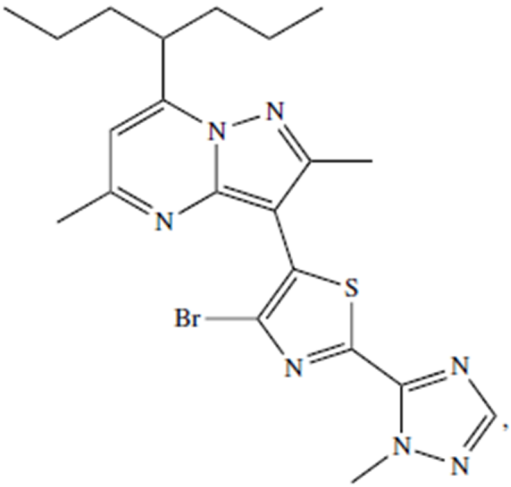


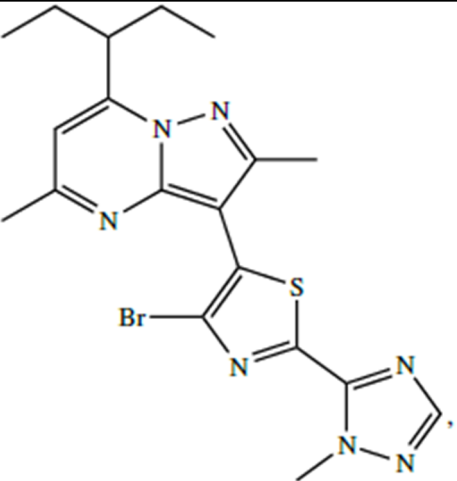
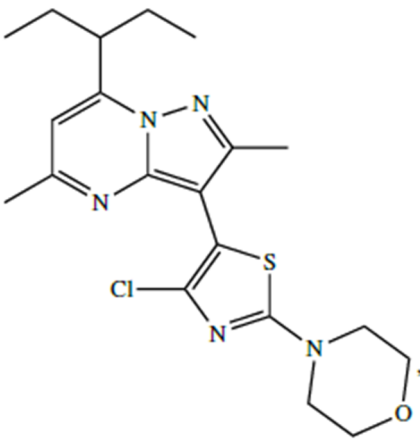
EX1001, 2:13-33; EX1003, ¶¶48-50; 118-119. In its broadest disclosure, the '491 patent provides that R¹ and R² of Formula (I) are independently ethyl or n-propyl; R³ is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy; R⁴ is hydrogen, Br, R^aR^bN-, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, 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 '491 patent as falling within the structure of Formula (I). EX1003, ¶119. These three compounds are disclosed in column 3 of the '491 patent and correspond to the first three compounds recited in claim 1. EX1001, 3:11-67, 98:51-99:30. 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	

Letter Designation	Compound
B	
C	

EX1001, 98:51-99:30 (formatting and letter designations added); EX1003, ¶119 (citing EX1059, EX1091, EX1092).¹⁰ Notably, compound **C** in the table corresponds to “Compound 1” of the ’491 patent, which is tildacerfont. EX1001, 90:42-58, 96:40-45; EX1003, ¶120 (citing EX1059).

¹⁰ 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, ¶¶119, 122.

Every substantive disclosure in the '491 patent is tied to Formula (I) compounds—and, in particular, to Compound 1 (tildacerfont). EX1003, ¶121. In a few instances, the '491 patent mentions treating TARTs or OARTs with CRF1 receptor antagonists generically. EX1001, 2:4-9, 50:54-63. But nowhere does the written description state or suggest that any specific compound falling *outside* the structure of Formula (I) can treat TARTs or OARTs. As one telling comparison, the '491 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, 6:54-8:51; 81:37-83:38; *infra*, §VI.C.2.

The '491 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, 90:25-29. 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, 90:38-41. These statements reinforce that the written description conveys possession of, at most, the CRF1 receptor antagonists of Formula (I) for purportedly treating TARTs—not OARTs, and not even TARTs

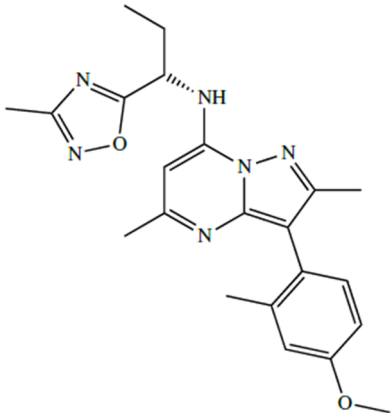
for the seven additional CRF1 receptor antagonists recited in the claims.

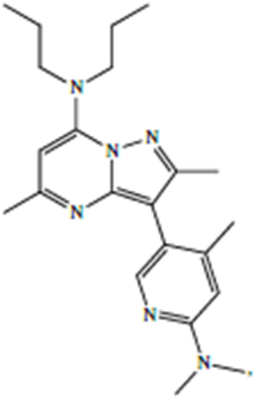
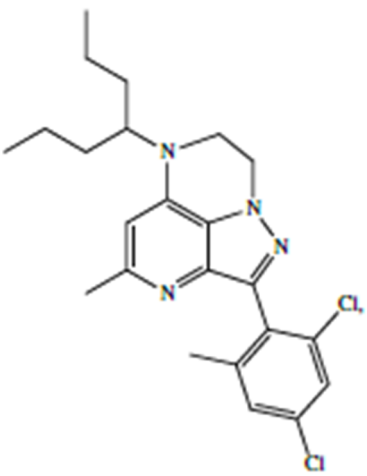
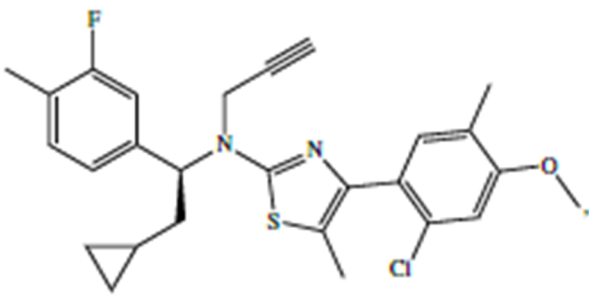
EX1003, ¶121.

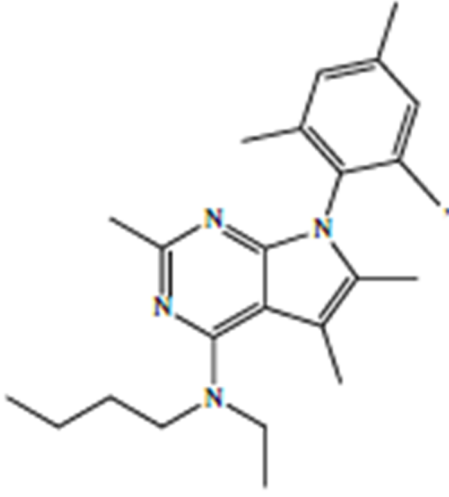
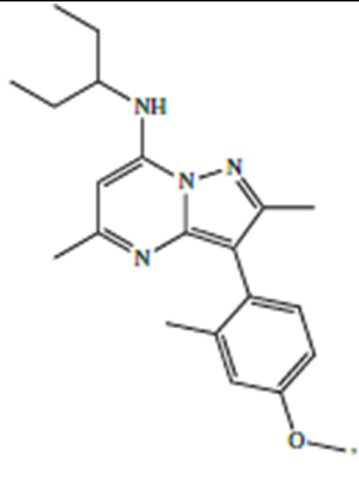
2. The written description discloses the additional seven claimed CRF1 receptor antagonists only as “additional chemotherapeutic agent[s]”

Even though the written description of the '491 patent is limited to CRF1 receptor antagonists of Formula (I) for purportedly treating TARTs or OARTs, claim 1 recites an *additional seven* CRF1 receptor antagonists. EX1003, ¶122.

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

Letter Designation	Compound
D	

Letter Designation	Compound
E	
F	
G	SSR-126374,
H	

Letter Designation	Compound
I	
J	

EX1001, 7:1-8:32 (formatting and letter designations added); EX1003, ¶¶122-123 (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, ¶123 (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 '491 patent as falling within the scope of Formula (I). EX1001. Dr. Lodish confirms that compounds **D-F** and **H-J** are not Formula (I) compounds. EX1003, ¶123. And the '491 patent fails to disclose the structure of the remaining compound **G**, SSR-126374. *Id.*, ¶¶59-67, 123.

The written description of the '491 patent fails to disclose these claimed compounds as CRF1 receptor antagonists for the treatment of TARTs or OARTs. 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, 6:54-8:52, 81:37-83:39 (disclosing additional chemotherapeutic agents), 31:20-37:57 (providing seven-column laundry list of additional agents); EX1003, ¶¶58, 124-125.

The '491 patent states that, “[i]n some embodiments, the method *further comprises* administering to the subject an *additional chemotherapeutic agent*.” EX1001, 6:54-56; *id.*, 81:37-40 (same). The '491 patent then states that, in some embodiments, the “additional chemotherapeutic agent is a glucocorticoid, a mineralocorticoid, an ACAT1 inhibitor, or an anti-androgen.” *Id.*, 6:56-58. The '491 patent states that, “[i]n some embodiments, *the additional chemotherapeutic*

agent is another CRF₁ antagonist.” EX1001, 6:65-66; *id.*, 81:48-49 (same). The ’491 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, 6:66-8:50; *but see id.*, 81:50-83:38 (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, ¶58. The ’491 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, 6:54-8:52, 81:36-83:38; EX1003, ¶125. Nothing in the specification conveys to a POSA that the named inventors were in possession of these “additional chemotherapeutic agent[s]” for purportedly treating TARTs or OARTs themselves. EX1003, ¶¶124-125. That conclusion is reinforced by the fact that the ’491 patent’s disclosure of “twice-daily” dosing where the patient is in the fed state—also recited in claim 1—

appears only in connection with compounds of Formula (I), not the “additional chemotherapeutic agent[s].” EX1001, 59:35-39, 60:50-53, 65:59-68:19, 70:48-73:8.

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 treating TARTs or OARTs 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 *Novozyymes*, 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) (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 ’491 patent is directed to compounds of Formula (I), including Compound 1 (tildacerfont). EX1003, ¶¶121, 126. Every figure, description, dosing strategy,

and example relating to purportedly treating TARTs or OARTs refers exclusively to Compound 1 (tildacerfont). EX1001, 9:55-10:47, Figs. 1-11, 13-17; 89:59-98:22; EX1003, ¶¶121, 126. All the purported data actually generated by the named inventors of the '491 patent is expressly identified as data for Compound 1 (tildacerfont). *Id.* at 89:59-98:22; EX1003, ¶126.¹¹

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, ¶¶127-129. Yet the written description of the '491 patent does not identify what those features are or provide any guidance for identifying other CRF1 receptor antagonists that might share them. EX1003, ¶129. 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, ¶130.

¹¹ 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.

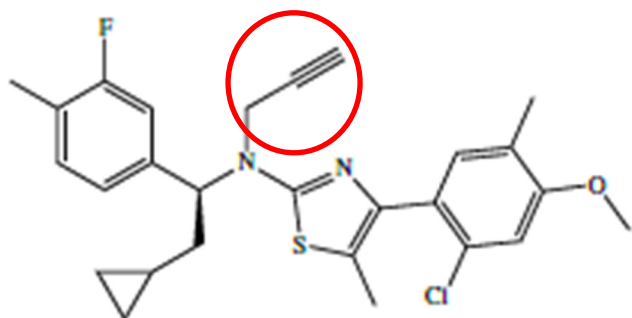
Further, a POSA would not have understood that every CRF1 receptor antagonist recited in claim 1 would work in the claimed method to treat TARTs or OARTs. In the Federal Circuit’s recent opinion in *Teva Pharms. Int’l GmbH v. Eli Lilly & Co.*, 172 F.4th 1367, 1376-77 (Fed. Cir. 2026), the Court found 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 and its related disorders “despite over 30 years of research and hundreds of patents.” EX1029, 1065; EX1008 (Turcu 2016); EX1006 (Grigoriadis U.S. publication). In the 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, ¶128.

For these additional reasons, claims 1 and 3-19 are unpatentable for lack of written description. The ’491 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 treating TARTs or OARTs. EX1003, ¶131.

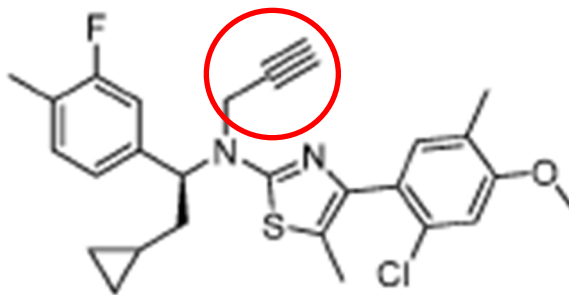
D. Claims 1 and 3-19 Also Fail Because the Written Description Does Not Show Possession of Crinecerfont

In addition to failing to reasonably convey that the named inventors of the '491 patent had possession of Neurocrine's crinecerfont in a method for treating TARTs or OARTs (*supra*, §VI.C.2), the written description also fails to show that they had possession of crinecerfont at all. EX1003, ¶¶132-140.

As explained above, claims 1 and 3-19 encompass Neurocrine's crinecerfont (compound **H**). EX1001, 98:47-100:67, 101:20-102:36. In claim 1 and dependent claim 3, crinecerfont is represented by the following chemical structure:



EX1001, 100:17-26 (claim 1), 101:20-35 (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, ¶132. 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, 35 (¶27), 93 (¶261), 141 (claim 1), 142 (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, ¶133; *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 ’491 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 (EX1002, 149-

178), 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, 310, 396-397 (substitute specification), 418-421 (amended claims). Applicants argued that the amendments “follow a Certificate of Correction (submitted on March 12, 2025, and accepted by the U.S. Patent Office on June 17, 2025) for U.S. Pat. No. 11,304,950” (“the ’950 patent”). EX1002, 422. Notably, in its Request for a Certificate of Correction for the ’950 patent, applicants stated that the structure containing the carbon-carbon quadruple bond reflected a mistake *on part of applicants*. EX1050, 3, 9. But applicants never stated where they had support for correcting the so-called mistake. *Id.*, 9. That’s because they had no support.

The ’950 patent—like the ’491 patent—claims priority to International Application PCT/US2019/029486 (“the PCT application”), the ’815 provisional, and the ’951 provisional. EX1042, codes [63], [60]. None of these applications disclose crinecerfont. EX1003, ¶¶134-135. The PCT application discloses the structure with a carbon-carbon quadruple bond. EX1051, ¶¶27, 261.¹² So does the

¹² 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.

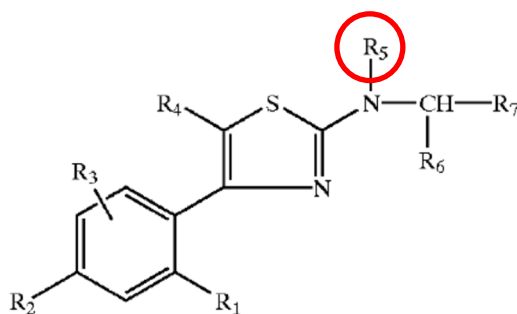
'951 provisional, and in both cases the only disclosure of this compound is as an “additional chemotherapeutic agent.” EX1055, ¶¶231-232; EX1051, ¶¶26-27, 260-261. The '815 provisional discloses tildacerfont only, and no other CRF1 receptor antagonists. EX1056, ¶¶4, 6, 9, 10, 11.

Nowhere in the priority chain or in the application leading to the '491 patent did the named inventors have possession of crinecerfont, as now claimed.

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 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, ¶¶134-135.

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 '491 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, ¶136.

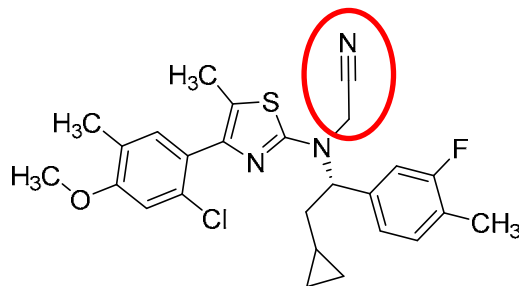
At the time of the alleged invention of the '491 patent, a POSA would have understood that the carbon-carbon quadruple bond structure initially disclosed and claimed was incorrect (it would be impossible) but would not have understood what the intended structure should have been. EX1003, ¶136. A POSA 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, ¶¶137-138. 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:

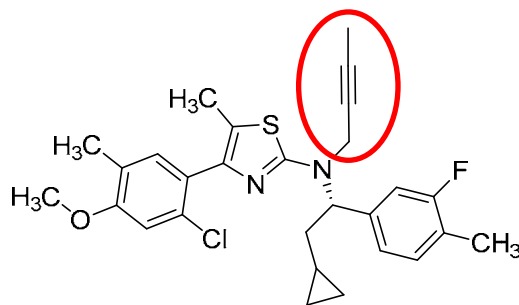
- An aminothiazole derivative having a nitrile moiety (also called a “cyano”) that includes a carbon-nitrogen triple bond—circled in red below:



EX1003, ¶140. In this case, the R₅ substituent is “a cyano (C₁-C₆) alkyl.”

Specifically, R₅ is -CH₂-C≡N. EX1060, 4:46-47; EX1003, ¶140.

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



EX1003, ¶139. 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, ¶139.

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, ¶136.

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 treat TARTs or OARTs with any of the ten claimed CRF1 receptor antagonists without engaging in undue experimentation. EX1003, ¶¶141-157.

As discussed above, the '491 patent discloses only a single arguably relevant data point: one TART in one male patient purportedly treated with Compound 1 (tildacerfont). *Supra*, §VI.B. The '491 patent discloses nothing beyond conclusory statements about OARTs. *Id.*, §VI.A. Even the disclosure about TARTs is sparse. The '491 patent provides no dosing regimen, no treatment protocol, and no response criteria defining what constituted “treatment” of the TART in that case. EX1001. It also includes no statistical or comparative analysis supporting the alleged shrinkage of the patient’s TART, no analysis of the two images in Figures 10A-10B, and no rationale explaining why a POSA would have expected any of the other claimed CRF1 receptor antagonists to produce the same

purported effect in TARTs or OARTs. EX1001. 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 treat TARTs or OARTs. EX1003, ¶¶141-144. *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 treating an endocrine disorder associated with CRF1 activity, and the body of the claim recites that such endocrine disorder is TARTs *or* OARTs. EX1001, 98:47-48, 100:65-67; *supra*, §VI.A. No dependent claim narrows the method to treating only 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 '491 patent must enable a method for treating *both* TARTs and OARTs 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 '491 patent contains no such disclosure. EX1003, ¶¶144-145. Even the claims limited to specific compounds, namely Compound 1 (tildacerfont) and Neurocrine’s crinecerfont—claims 2 and 3, respectively—still require the treatment of OARTs. EX1001, 101:1-35. And the '491 patent discloses nothing about OARTs other than conclusory statements. *Supra*, §VI.A.

Given the breadth of the claims, and the absence of sufficient guidance and working examples in the '491 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 '491 Patent's Lack of Guidance for Using All Claimed CRF1 Receptor Antagonists (Factor 2) and a Single Example Limited to TART and Compound 1 (Tildacerfont) (Factor 3) Weigh Against Enablement

The '491 patent provides a POSA with virtually no guidance about *all ten* claimed CRF1 receptor antagonists and their purported ability to treat *both* TARTs and OARTs. EX1003, ¶¶144-145. The '491 patent discloses only a single TART from a single male 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. 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, ¶¶51-57, 149. The patent provides no examples or data related to the treatment of OARTs. EX1001; EX1003, ¶¶145-146.

The '491 patent provides no guidance for using the “additional chemotherapeutic agent[s]” for treating TARTs or OARTs. The '491 patent does not even identify seven out of the ten claimed CRF1 receptor antagonists as useful for treating TARTs or OARTs. *Supra*, §VI.C.2. Instead, as explained above, the '491 patent describes these compounds only as “additional chemotherapeutic agent[s]” for co-administration with a CRF1 receptor antagonist of Formula (I). EX1001, 6:54-8:51; 81:37-83:38; *supra*, §VI.C.2; EX1003, ¶¶124-125.

At most, the '491 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 '491 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, ¶¶119-120. The entire patent is premised on “promising results” with Compound 1 (tildacerfont) in TARTs—not 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 '491 patent never explains *why* any of the other claimed CRF1 receptor antagonists would also have been expected to treat both TARTs and OARTs. EX1003, ¶¶149-150.

The '491 patent provides no guidance for treating OARTs. As discussed above, a POSA would have known that treating OARTs was highly unpredictable. *Supra*, §VI.A; EX1003, ¶¶39, 146. 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 '491 patent discloses only a single TARTs example. The only disclosures in the '491 patent relating specifically to the treatment of TARTs are Example 1 and Example 3 and they do not enable the breadth of the claims. *Idenix Pharms. LLC v. Gilead Scis. Inc.*, 941 F.3d 1149, 1161 (Fed. Cir. 2019) (“Where, as here, working examples are present but are very narrow, despite the wide breadth of the claims at issue, this factor weighs against enablement.” (cleaned up)). Example 1 describes a *prophetic* Phase 2, open-label study protocol for evaluating the efficacy and safety of Compound 1 (tildacerfont) “specifically in *male* CAH subjects with *TART*.” EX1001, 90:59-91:6. As a prophetic example,

Example 1 contains no clinical data. EX1001, 91:14-30. Example 3 purports to show an “approximately 25% shrinkage” of a single TART in one 25-year-old male after 6 weeks of treatment with Compound 1 (tildacerfont). EX1001, 96:17-20; Figs. 10A-10B. But as Dr. Lodish explains, a POSA would not have understood Figures 10A-10B to show any meaningful difference in TART size. Nor does the record establish that any alleged size difference is attributable to Compound 1 (tildacerfont), rather than concomitant glucocorticoid use. *Supra*, §VI.B; EX1003, ¶¶147-148.

A POSA likewise would not have extrapolated the results from this single patient to conclude that Compound 1 (tildacerfont)—or *any of the other* claimed CRF1 receptor antagonists—would treat TARTs (or OARTs for that matter). EX1003, ¶¶149-151. Spruce itself *admitted* as much in its '951 provisional application (which contains the same results), stating that “*it is not known* whether Compound 1 can successfully treat TART.” EX1055, ¶¶286-287, 296; EX1003, ¶¶56, 115.

In short, the '491 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 treat TARTs or OARTs. EX1003, ¶151. 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 Treat TARTs or OARTs (Factor 1), the Complex Nature of Treating TARTs or OARTs (Factor 4), and the Nascent State and Unpredictability of the Art (Factors 5 and 7) Weigh Against Enablement

The '491 patent's research assignment would require undue experimentation. EX1003, ¶151. The '491 patent focuses almost exclusively on one CRF1 receptor antagonist—Compound 1 (tildacerfont)—yet claims nine additional CRF1 receptor antagonist purportedly capable of treating both TARTs and OARTs. The only way a POSA could determine which of those compounds, if any, could treat TARTs *or OARTs* would be to make and test each one through an iterative, trial-and-error process. EX1003, ¶¶151-152, 157. 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 '491 patent provides no working examples or data for treating OARTs at all, and no working examples or data for treating TARTs with any of the claimed CRF1 receptor antagonists other than Compound 1 (tildacerfont). *Supra*, §VI.B. 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, ¶¶152-153. 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, ¶¶154-155. 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 '491 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, ¶155. The '491 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, ¶155. Furthermore, as Dr. Lodish explains, a POSA would have understood that these structural differences can lead to different biological activity. EX1003, ¶154. 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 '491 patent compares the therapeutic effectiveness of Compound 1 (tildacerfont) to that of the other claimed CRF1 receptor antagonists. EX1003, ¶¶150-154.

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 treat 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.A; EX1003, ¶¶152, 155. The art's unpredictability is further illustrated by 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, ¶130. 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, ¶156. But that expertise cannot overcome the deficiencies described above or the limited state of knowledge in the prior art about the treatment of OARTs. *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 claimed CRF1 receptor antagonists could treat TARTs or OARTs. EX1003, ¶157. 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, 3-19 are unpatentable for obviousness

Claims 1 and 3-19 would have been obvious over Neurocrine's Grigoriadis publication (EX1006), in view of Yu (EX1067), Howerton (EX1074), and the GSK Study (EX1075). EX1003, ¶¶158, 169-173. The mapping below demonstrates that these references teach each and every limitation of claims 1 and 3-19. EX1003, ¶¶174-222.

Grigoriadis discloses the use of several CRF1 receptor antagonists to treat CAH, including crinecerfont and verucerfont. EX1006, ¶¶7, 12, 13. Grigoriadis presents data from a Phase 1 clinical study showing that administration of an effective amount of the CRF1 receptor antagonist verucerfont (NBI-77860) inhibits release of the hormone ACTH in patients with CAH. EX1006, ¶¶7, 40, 91-93. Grigoriadis also identifies the suppression of ACTH as a treatment of CAH-related disorders, including “*testicular adrenal rest tumors* in men.” EX1006, ¶44. Yu also reports a link between TARTs and elevated ACTH levels in male CAH patients and suggests reducing ACTH levels as a therapeutic approach to treating TARTs. EX1067, 158-159. 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 of Yu's discussion of ACTH and TARTs, with a reasonable expectation that CRF1 antagonism by, e.g., administration of verucerfont or crinecerfont would lower ACTH (as shown in Grigoriadis). EX1003, ¶170.

Indeed, Grigoriadis alone discloses nearly all limitations of independent claim 1, except for the specific dosing regimen—"twice per day" and "in the fed state." But it was already known in the prior art to administer a CRF1 receptor antagonist twice per day and in the fed state. Howerton expressly teaches twice-daily dosing of a number of CRF1 receptor antagonists, including Neurocrine's verucerfont (NBI-77860, compound **D**). EX1074, 13:12-17, 2:20-24. And the GSK Study describes a Phase I clinical trial examining the absorption of verucerfont in the fed state and the unfed (or fasted) state, thus teaching administration of a claimed CRF1 receptor antagonist in the fed state. EX1075. A POSA would have been motivated to combine the teachings of Grigoriadis, Howerton, and the GSK Study with a reasonable expectation of success. EX1003, ¶¶169-171.

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 '491 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, ¶¶159-161. 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 patient[s] with CAH.” EX1006, ¶5. Grigoriadis describes such related disorders as, e.g., “testicular adrenal rest tumors in men.” *Id.*, ¶44.

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 1 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. 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 ’491 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.*; EX1003, ¶¶162-165. 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.*

3. Howerton (EX1074)

Howerton published as International Publication WO 2016/065177 A1 on April 28, 2016, more than a year before the earliest possible effective filing date of the '491 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 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; EX1003, ¶¶166-167. 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, ¶166.

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. *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.

4. GSK Study (EX1075)

“GSK Study” is a Phase I study conducted by GlaxoSmithKline publicly available on ClinicalTrials.gov at least as of July 3, 2013. EX1075; EX1086, ¶11 (Declaration of June Ann Munford attesting as to the public availability of the GSK Study at least by July 3, 2013). GSK Study is therefore prior art under 35 U.S.C. §102(a)(1).

The GSK Study describes a Phase I study for determining the pharmacokinetics of verucerfont, then known as GSK561679. EX1075; EX1082; EX1006, ¶84, EX1003, ¶¶45, 168. In this Phase 1 study, healthy male volunteers were to be administered verucerfont in solution under fasted conditions and in tablet form under both fasted and fed conditions. EX1075. The GSK Study sought to measure the Area Under the plasma concentration-time Curve (AUC) for three periods: AUC (0-24h), AUC (0-t), and AUC(0-∞) to examine drug exposure over time. *Id.* The GSK Study also sought to measure other pharmacokinetics

parameters, including λ_Z (drug elimination), $t_{1/2}$ (half-life), t_{lag} (lag time), K_a (absorption rate constant), and the time to absorb the 25, 50 and 90% of the total absorbed dose. *Id.*.

B. Independent Claim 1

1[A] *A method of treating an endocrine disorder associated with corticotropin-releasing factor type-I (CRF1) activity,*

To the extent that the preamble is limiting, Grigoriadis expressly teaches it. EX1006, ¶¶4, 5, 7, 34, 40, 44, 48, 50, 64, FIG. 1; EX1003, ¶¶174-180. Grigoriadis teaches that CAH is a known endocrine disorder associated with CRF1 receptor activity, and that TARTs are a known complication of CAH in male patients. EX1006, ¶44.

Specifically, Grigoriadis explains that corticotropin-releasing factor (CRF) “produce[s] profound alterations in endocrine, nervous, and immune system function.” EX1006, ¶48. CRF binds to CRF1 receptor, “a member of the class B family of G-protein coupled receptors,” causing the release of adrenocorticotrophic hormone (ACTH) from the pituitary gland. *Id.*, ¶¶48, 50. Grigoriadis explains that, in the most common form of CAH, mutations or deletions in the gene encoding the enzyme 21-hydroxylase lead to a decrease in the biosynthesis of cortisol, overproduction of androgens (sex hormones), and excessive ACTH production. *Id.*, ¶¶4, 5, 34, 50; FIG. 1. Grigoriadis explains that cortisol is a

critical negative feedback regulator of ACTH production; the *decrease* in cortisol causes the pituitary gland to *increase* production of ACTH—also contributing to the overproduction of androgens. *Id.*, ¶50.

Grigoriadis teaches that a 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, ¶¶174, 179-180. Thus, Grigoriadis teaches “*an endocrine disorder associated with corticotropin-releasing factor type-I (CRF1) activity*.” EX1003, ¶¶176-178 (citing EX1076, 624-625).

Grigoriadis further teaches a “*method of treating*” an endocrine disorder 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. Grigoriadis further teaches that the goal of CAH treatment is not to simply treat CAH, but also to inhibit related disorders that result from CAH, such as “*testicular*

adrenal rest tumors in men.” EX1006, ¶44. Grigoriadis also teaches that clinicians can evaluate the effectiveness of a CRF1 receptor antagonist with “[s]tandard biomarker assessments used by endocrinologists when monitoring treatment efficacy.” *Id.*, ¶60. These assessments include monitoring plasma levels of A4, the androgen hormone testosterone, cortisol, ACTH, and 17-OHP, a steroid precursor. *Id.*; EX1003, ¶¶174, 180.

1[B] comprising administering to a subject in need thereof a small molecule CRF1 antagonist, or a pharmaceutically acceptable salt thereof,

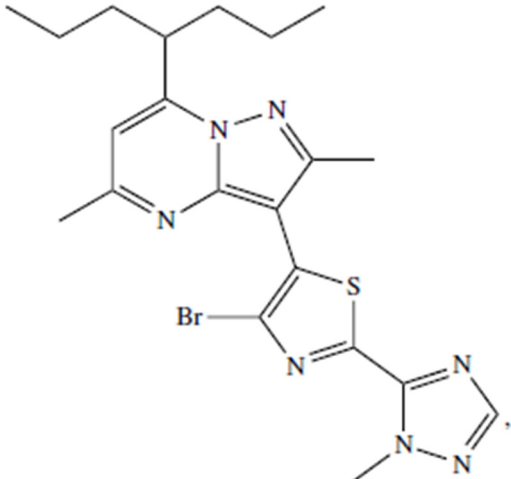
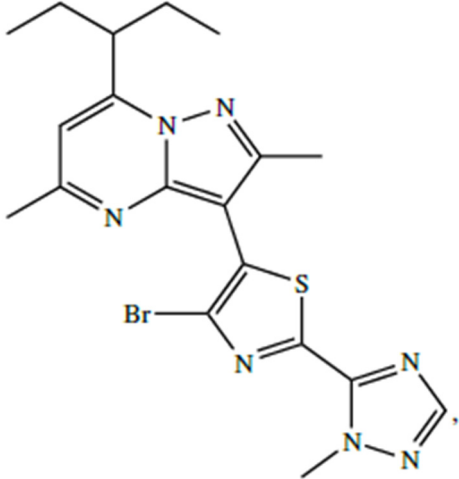
Grigoriadis expressly teaches this limitation. EX1006, ¶¶40, 51, 54, 61, 70, 85, 90-93; EX1003, ¶181. Grigoriadis expressly teaches that “[a]s described herein, CRF₁ receptor antagonists have been found to directly inhibit ACTH release in patients with CAH and thereby allow normalization of androgen 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 antagonist 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

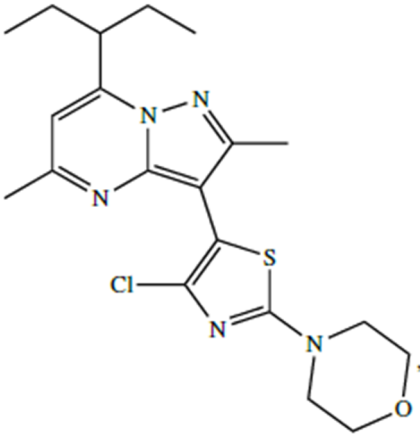
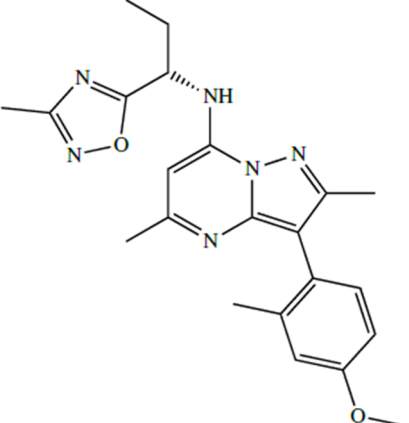
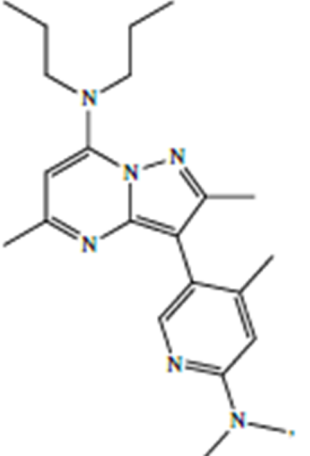
administration of NBI-77860 relative to placebo in these CAH patients.” *Id.*, ¶¶51,

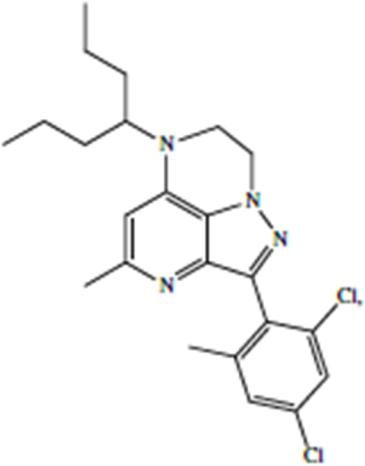
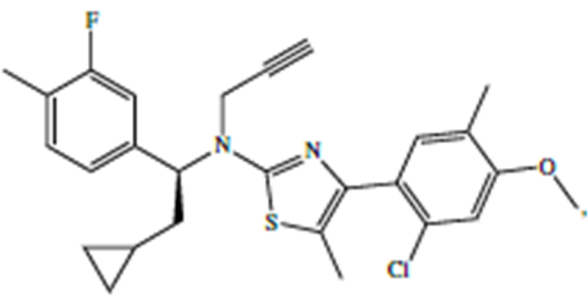
93. As another example, Grigoriadis teaches administering crinecerfont

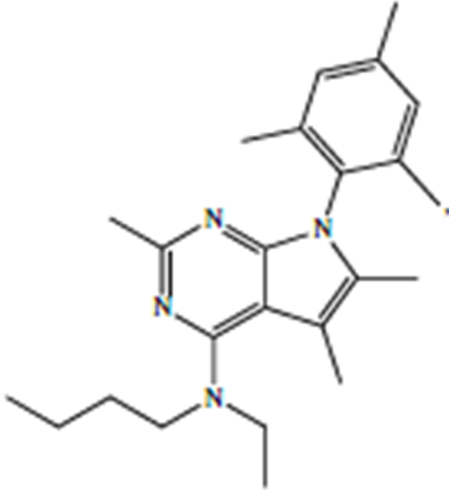
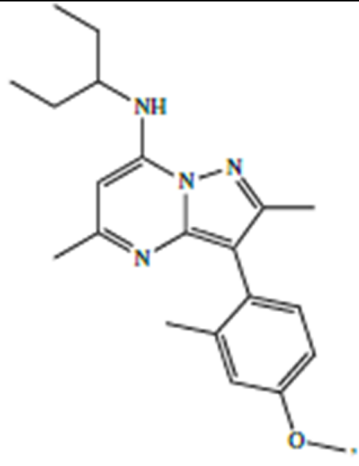
(compound **H**). *Id.*, 54; EX1003, ¶181.

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

Letter Designation	Compound
A	
B	

Letter Designation	Compound
C	
D	
E	

Letter Designation	Compound
F	
G	SSR-126374,
H	

Letter Designation	Compound
I	
J	

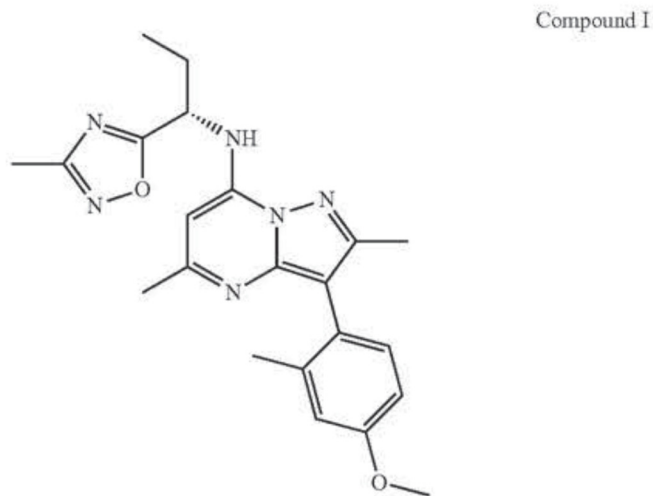
or a pharmaceutically acceptable salt thereof,

EX1001, 98:57-100:67 (formatting and letter designations added); EX1003, ¶¶68-69.

Grigoriadis expressly teaches this limitation. EX1006, ¶¶6, 7, 12, 13, 51, 54, page 6; EX1003, ¶182. To begin, claim 1 recites a genus of ten CRF1 receptor antagonists using the term “or.” EX1001, 100:32. Thus, a single prior-art reference adequately teaches the claimed genus when the reference discloses at

least one species falling within the genus. *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.”). 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:

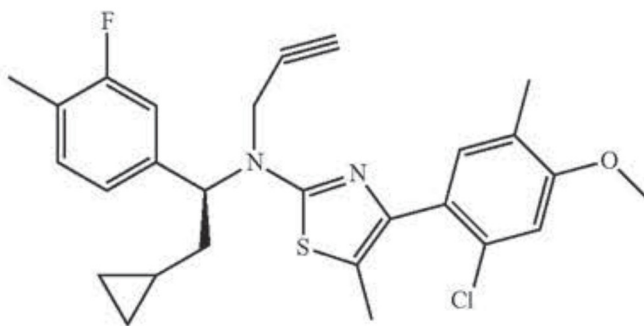


EX1006, ¶¶13, 51. As a POSA would recognize and Dr. Lodish confirms, this CRF1 receptor antagonist—verucerfont—is the same CRF1 receptor antagonist listed in claim 1 (and identified herein as “**D**”). EX1003, ¶182. Thus, Grigoriadis expressly teaches this limitation. *ModernaTX*, 18 F.4th at 1364 (prior 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**”:

SSR-125543



EX1006, ¶¶13, 54, page 6; EX1003, ¶182.

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)).

1[D] wherein the small molecule CRF1 antagonist is administered to the subject twice per day, and wherein the subject is in the fed state,

Neurocrine’s prescribing information for CRENESSITY provides that crinecerfont is administered twice daily and in the fed state. EX1010. Claim 1 of the ’491 patent also recites twice-daily administration in the fed state, 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 or administration of a CRF1 receptor antagonist with food. EX1001, 6:32-41, 60:16-53, 65:59-68:19, 70:58-73:8, 78:54-60. Spruce never claimed these features in combination with crinecerfont until CRENESSITY was approved by the FDA. EX1058; EX1089; EX1003, ¶71. Still, these limitations would have been obvious to a POSA from the teachings of Grigoriadis, as combined with Howerton and the GSK Study. EX1003, ¶¶183-196.

(a) “Twice per day”

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, ¶¶184, 187.

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 the 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, ¶185. Howerton also teaches administering dosages “that range from one to five times per day or more.” EX1074, 25:13–14. And 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, ¶186.

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, ¶187.

Nothing in the ’491 patent teaches or suggests that twice-daily administration produces an unexpected or nonobvious result. EX1001. The ’491 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 ’491 patent refers to once-daily, twice-daily, and thrice-daily dosing synonymously over several columns of repeating boilerplate language. *See id.* at 59:39-60:16, 63:35-65:58, 68:20-70:46 (once-daily), 60:16-53, 65:59-68:19, 70:58-73:8 (twice-daily), 60:53-61:22 (thrice-daily). Taken together, these disclosures show that the named inventors of the ’491 patent never contemplated that administering a CRF1 receptor antagonist twice-daily versus other regimens was an innovative feature of its purported invention. EX1003, ¶187. 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, ¶¶188-189. 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, ¶189.

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, ¶190. 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, ¶¶191-192.

(b) “Fed state” administration

Grigoriadis also does not expressly teach that the subject is in a “fed state.” But, as Dr. Lodish explains, determining whether to administer a drug to a patient in a fed or unfed state is compound-specific, and represents a well-established and routine application of a POSA’s ordinary skill. EX1003, ¶¶43-44 (citing EX1081); 193-196. Grigoriadis supports Dr. Lodish’s testimony by teaching that “[o]ptimal doses may generally be determined using experimental models and/or *clinical trials*.” EX1006, ¶63.

One step in the drug-development process includes a determination of whether or not a drug should be administered with food. EX1003, ¶¶44, 47 (citing EX1018, EX1083), 193. This is determined by pharmacokinetic testing, where the absorption of a drug is measured as Area Under the plasma concentration-time Curve (AUC). The GSK Study supports Dr. Lodish’s testimony. The GSK Study describes a Phase 1 *clinical study* designed to measure the absorption of verucerfont—one of the CRF1 receptor antagonists recited in claim 1—in healthy male volunteers. EX1075, 1; EX1003, ¶45. The volunteers were to be administered verucerfont in solution under fasted conditions and in tablet form under both fasted and fed conditions, and the absorption of verucerfont was measured for three periods: AUC (0-24h), AUC (0-t), and AUC(0-∞). EX1075, 1.

Thus, the GSK study expressly teaches administration of verucerfont (compound **D**) in both the fasted and fed states. EX1003, ¶¶45, 194.

A POSA would have performed a clinical study—like the Phase 1 study described in the GSK Study—to determine whether a CRF1 receptor antagonist should be administered in the fed state. EX1003, ¶¶46, 194. Grigoriadis teaches that optimal doses of CRF1 receptor antagonists may be determined via clinical trials (EX1006, ¶63) and a POSA would have been motivated to look to the GSK Study of verucerfont for a clinical trial study design that determines whether there were any food effects, e.g., better absorption in the fed than in the unfed (fasted) state, and adjust administration accordingly (EX1075, 1). EX1003, ¶¶46, 195. Moreover, a POSA would have had a reasonable expectation of success in determining whether a CRF1 receptor antagonist should have been administered in the fed state because there are a “finite number of identified, predictable solutions”—either the fed state or the unfed (fasted) state. *KSR*, 550 U.S. at 421; EX1003, ¶195.

As with twice-daily administration, nothing in the '491 patent teaches or suggests that administration in the fed state produces an unexpected or nonobvious result. EX1001. The '491 patent states simply that, in some embodiments, the pharmaceutical composition is “administered in the fed state,” whereas in other embodiments, the pharmaceutical composition is “administered in the fasted state.”

EX1001, 6:35-39. This statement is repeated, almost verbatim, two more times in the specification. *Id.*, 78:54-58, 81:4-7. Again, these statements show that the named inventors never contemplated that administering a CRF1 receptor antagonist in the fed state versus a fasted state was an innovative feature of their purported invention, but instead of matter of routine determination of food effects. EX1003, ¶¶46, 196.

In sum, the GSK Study already disclosed administering a CRF1 receptor antagonist in both the fed and fasted states, and it would have been obvious to have picked fed state over the unfed (fasted) state for its claims. *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003). Moreover, the label for CRENESSITY instructs administration of crinecerfont in the fed state, and it is no surprise to Neurocrine that applicants added claims following FDA approval of the CRENESSITY label to recite fed-state dosing. EX1010; EX1089.

1[E] wherein the endocrine disorder associated with CRF1 activity is a testicular adrenal rest tumor (TART) or an ovarian adrenal rest tumor (OART)

Grigoriadis expressly teaches the treatment of TARTs with a CRF1 receptor antagonist, or, at a minimum, renders it obvious in combination with Yu. EX1006, ¶¶5-7, 12, 13 40, 44, 90-93; EX1067, 157-159; EX1003, ¶¶197-201.

As explained above, 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. To do so, Grigoriadis teaches administering an effective amount of a CRF1 receptor antagonist to suppress ACTH release and downstream hormones in patients with CAH. EX1006, ¶¶7, 40, 90-93. Grigoriadis further teaches that the goal of CAH treatment is not simply to treat CAH, but also to inhibit related disorders that result from CAH such as “*testicular adrenal rest tumors* in men.” EX1006, ¶44. A POSA reading Grigoriadis, therefore, would understand that Grigoriadis teaches that the disclosed methods treat CAH *and its related disorders*, including “testicular adrenal rest tumors in men.” EX1006, ¶44; EX1003, ¶197. And because claim 1 recites treating a TART *or* an OART, Grigoriadis need not provide any disclosure about OARTs to satisfy this limitation of claim 1. EX1001, 100:65-67; *ModernaTX*, 18 F.4th at 1363-64; *Brown*, 265 F.3d at 1351.

For additional support, Yu discusses TARTs in CAH patients and reports an association between TARTs size changes and reductions in ACTH levels. EX1067, 159. 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;

- 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.*

From this data, a POSA would have understood that elevated ACTH levels are associated with TARTs and TART size in male CAH patients. EX1003, ¶¶198-199. 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 with a CRF1 receptor antagonist based on the teachings of Grigoriadis and Yu. EX1003, ¶199. Yu discusses elevated ACTH levels as a contributing factor in TARTs. EX1067, 158-159. Grigoriadis teaches that administration of CRF1 receptor antagonists—including crinecerfont (SSR-125543, compound **H**) and verucerfont (NBI-77860, compound **D**)—reduces ACTH levels in CAH patients. EX1006, ¶¶6, 7, 12, 13.

Grigoriadis also emphasizes that effective CAH treatment includes inhibiting related disorders such as “testicular adrenal rest tumors in men.” EX1006, ¶44. In view of these disclosures, a POSA would have been motivated to apply the CRF1 receptor antagonist treatment approaches of Grigoriadis to CAH patients with TARTs. EX1003, ¶199.

A POSA would also have had a reasonable expectation of success in treating TARTs with a CRF1 receptor antagonist such as crinecerfont (SSR-125543, Compound **H**) or NBI-77860 (verucerfont, Compound **D**). EX1003, ¶¶200-201. Claim 1 of the '491 patent imposes no threshold level of treatment. EX1001. And the '491 patent generically states that “‘treating’ and ‘treatment’ refer to *any indicia* of success in the therapy or amelioration of an injury, disease, pathology or condition.” EX1001, 26:60-62. The teachings of the prior art satisfy this low threshold. EX1003, ¶200. Grigoriadis teaches that CRF1 receptor antagonists reduce ACTH levels and downstream hormones in CAH patients. EX1006, ¶¶6, 7, 12, 13, 90-93. Yu reports that CAH patients with TARTs exhibited elevated ACTH levels relative to CAH patients without TARTs and expressly states that reducing ACTH levels may accordingly treat TARTs. EX1067, 158-159. 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 satisfying the claimed subject matter of “treating” TARTs. EX1003, ¶¶200-201.

During prosecution of an intervening continuation ’694 application, Spruce submitted a Declaration from its Vice President, Chris Barnes. EX1061, 19-22. Dr. Barnes asserted that treating TARTs in patients with CAH was unpredictable and uncertain, and, for that reason, a POSA would not have had a reasonable expectation of success in treating TARTs by lowering ACTH levels. EX1061, 20 (¶4), 21-22 (¶19).

As Dr. Lodish explains, however, this declaration does not support Dr. Barnes’ assertion that reducing ACTH levels to treat TARTs would have been unexpected, and the Examiner erred in crediting it. EX1003, ¶¶76-78; 223-228; EX1077, 7-8. *First*, the prior art contradicts Dr. Barnes’s Declaration. Multiple references—including Yu (EX1067), Aycan (EX1068), and Delfino (EX1064)—had already reported the connection between TARTs and elevated ACTH levels. EX1003, ¶224. Clinical studies had already shown that CAH patients with TARTs exhibited elevated ACTH levels. EX1067, 156-159; EX1068, 669; EX1064, 386-387; EX1003, ¶224. Numerous clinicians and researchers had already proposed that lowering ACTH levels in CAH patients could reduce the development, size, or progression of TARTs. EX1067, 158-159; EX1068, 669; EX1064, 386-387; EX1003, ¶¶35-37, 224. Delfino, for example, teaches that TARTs can be

reversible “after adequate replacement therapy to reduce plasma ACTH levels.”

EX1064, 386-387.

Second, the Barnes Declaration mischaracterizes two references—Reisch (EX1070) and Mendes-dos-Santos (EX1071)—leading the Examiner to misunderstand their import. EX1003, ¶225. In the Reasons for Allowance, the Examiner stated that Reisch teaches that “TARTs occur in patients over-treated with glucocorticoids and having suppressed ACTH levels, and no statistical differences were found between glucocorticoid doses in patients with or without TARTs having CAH.” EX1077, 7-8. But Reisch expressly teaches that “TARTs *are* ACTH responsive” and that “*ACTH-suppressive glucocorticoid treatment* with dexamethasone efficiently *reverses TART growth* and restores sperm count and fertility.” EX1070, E1821. Thus, Reisch never challenges the view that ACTH-suppressive therapy can treat TARTs. EX1003, ¶226. Similarly, the Examiner viewed Mendes-dos-Santos as teaching that “no association between TART development and...ACTH levels was found.” EX1077, 7-8. But, just like Reisch, Mendes-dos-Santos did not study the treatment of TARTs. EX1071, 162 (objectives of the study were “to determine TART prevalence 21-hydroxylase deficiency (21-OHD) male patients through testicular ultrasonography and to evaluate factors associated with its development, such as the clinical form of the disease, CYP21A2 genotype, laboratorial disease control, and presence of

puberty”); EX1003, ¶227. And, contrary to the Examiner’s understanding, Mendes-dos-Santos expressly states that TARTs “**are ACTH responsive**” and notes that “[s]tudies have shown that...suppressing ACTH, can lead to tumor **regression** in the short term and even to normal sperm count.” EX1071, 162.

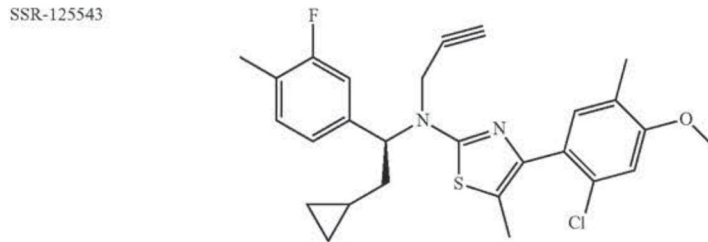
To be sure, the test for obviousness does not require “actual success” in the prior art. *Endo Pharm. Inc. v. Actavis LLC*, 922 F.3d 1365, 1379 (Fed. Cir. 2019) (“As we have repeatedly held, obviousness requires only a reasonable expectation of success, not proof of actual success.”). “[O]nly a reasonable expectation of success, not a guarantee, is needed.” *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1364, 1364 (Fed. Cir. 2007); *Par Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1198 (Fed. Cir. 2014) (“The reasonable expectation of success requirement for obviousness does not necessitate an absolute certainty for success.”). Here, a POSA would have had a **reasonable expectation** that lowering ACTH levels via CRF1 receptor antagonist administration would successfully “treat” TARTs as claimed for the reasons discussed above. EX1003, ¶228.

C. Claims 3-19

1. Claim 3

Claim 3 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, ¶¶13, 54, page 6; EX1003, ¶¶202-203.

Grigoriadis teaches the CRF1 receptor antagonist crinecerfont (SSR-125543, compound **H**):



EX1006, ¶¶13, 54, page 6; EX1003, ¶¶202-203. Grigoriadis teaches administering crinecerfont for the treatment of CAH and its related disorders. EX1006, ¶¶6-7, 12, 13, 64.

2. Claim 4

Claim 4 specifies that the subject has congenital adrenal hyperplasia (CAH). EX1001, 101:36-37. Grigoriadis expressly teaches this limitation. EX1006, ¶¶7, 40; EX1003, ¶¶204-205. 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.

3. Claims 5-7

Claims 5-7 relate to co-administration of a glucocorticoid. Claim 5 recites that “the subject is receiving a glucocorticoid in conjunction with the administering

of the small molecule CRF₁ antagonist.” EX1001, 102:1-3. Claim 6 specifies that the glucocorticoid comprises beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone, or a combination thereof. EX1001, 102:4-8. Claim 7 depends from claim 6 and limits the glucocorticoid to hydrocortisone. EX1001, 102:9-10.

Grigoriadis expressly teaches these limitations. EX1006, ¶70; EX1003, ¶¶206-211. For claim 5, Grigoriadis teaches that, in certain embodiments, the disclosed methods “may further comprise administering a GC [glucocorticoid] at a dose lower than the currently recommended dose of a GC for treating a subject who has CAH.” EX1006, ¶70; EX1003, ¶207. For claim 6, Grigoriadis teaches the co-administration of several species of glucocorticoids, including hydrocortisone, prednisone, prednisolone, dexamethasone, and fludrocortisone. EX1006, ¶70; EX1003, ¶209. For claim 7, Grigoriadis specifically teaches the co-administration of hydrocortisone. EX1006, ¶70; EX1003, ¶211.

4. Claims 8 and 9

Claims 8 and 9 limit the “subject” to “an adolescent” and “at least 18 years old,” respectively. EX1001, 102:11-14. Grigoriadis teaches these limitations. EX1006, ¶¶44, 60, 64, 70, 91; EX1003, ¶¶212-213.

Grigoriadis teaches administration of CRF1 receptor antagonist to block the release of ACTH and that treatment efficacy can be “easily measured in both *children and adults*.” EX1006, ¶60. As Dr. Lodish explains, a POSA would have readily understood that “children” includes an adolescent and “adults” includes a subject who is at least 18 years old. EX1003, ¶213. Grigoriadis also teaches that treatment of CAH occurs throughout “diagnosis in *infancy* through *adulthood*,” and that CRF1 receptor antagonist dosage depends, in part, on the subject’s *age*. EX1006, ¶¶44, 64. Grigoriadis teaches embodiments where the CRF1 receptor antagonist is co-administered with a glucocorticoid, and the dosage of glucocorticoid depends on whether the subject “is a *fully grown* patient” or “a *growing* patient” with CAH. EX1006, ¶70. Thus, claims 8 and 9 recite nothing new or nonobvious. EX1003, ¶213.

Moreover, in Example 6, Grigoriadis teaches the administration of verucerfont (NBI-77860, compound **D**) to CAH patients “ages 19 to 58.” EX1006, ¶91. Grigoriadis’s disclosure of the ages “19 to 58” falls within the claimed range and thus teaches claim 9. *In re Wertheim*, 541 F.2d 257, 267 (CCPA 1976) (“Of course, the disclosure in the prior art of any value within a claimed range is an anticipation of the claimed range.”). Nothing in the ’491 patent teaching or suggesting any meaningful difference in how the alleged invention “operates over the range[]” claimed. *UCB, Inc. v. Actavis Lab ’ys UT, Inc.*, 65 F.4th 679, 687

(Fed. Cir. 2023) (prior art range *prima facie* anticipates “if it describes the claimed range with sufficient specificity such that a reasonable fact finder could conclude that there is no reasonable difference in how the invention operates over the ranges”).

At a minimum, the range “19 to 58” overlaps with “at least 18,” and renders this limitation *prima facie* obvious. *E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1008 (Fed. Cir. 2018) (applying a presumption of obviousness because of overlapping ranges); *Almirall, LLC v. Amneal Pharms. LLC*, 28 F.4th 265, 272 (Fed. Cir. 2022) (same); EX1003, ¶213.

5. Claims 10-14

Claims 10-14 relate to doses. Claim 10 recites that the CRF1 receptor antagonist “is administered at a dose of about 10 mg/day to about 400 mg/day.” EX1001, 102:14-16. Claims 11-13 recite that the CRF1 receptor antagonist “is administered at a dose” of “about 50 mg” (claim 11), “about 100 mg” (claim 12), “about 200 mg” (claim 13). *Id.*, 102:17-22. Claim 14 recites that the CRF1 receptor antagonist “is administered at a dose of about 400 mg.” *Id.*, 102:23-24. Grigoriadis teaches or, at a minimum, suggests these limitations. EX1006, ¶¶63, 88-89, 91-93; EX1003, ¶¶214-216.

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, ¶215. As Dr. Lodish explains, a POSA would understand that those single doses were administered once per day. EX1003, ¶215. 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 10 ("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 11 ("about 50 mg") and claim 14 ("about 400 mg").

While Grigoriadis does not expressly disclose administration of a daily dose of "about 100 mg" (claim 12) or "about 200 mg" (claim 13) 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 ’491 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. EX1001; EX1003, ¶216. 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, ¶216.

6. Claims 15 and 16

Claims 15 and 16 relate to route of administration and dosage forms. Claim 15 provides that the “CRF₁ antagonist is administered orally.” EX1001, 102:25-26. Claim 16 recites that the “CRF₁ antagonist is formulated as a capsule or tablet.” *Id.*, 102:27-28. Grigoriadis teaches these limitations. EX1006, ¶¶65, 74; EX1003, ¶¶217-218. 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

Claims 17-19 specify the timing of administration. The CRF1 receptor antagonist “is administered less than about 6 hours before sleep” (claim 17), “less than about 3 hours before sleep” (claim 18), or “in the evening” (claim 19).

EX1001, 102:29-36. Grigoriadis teaches these limitations. EX1006, ¶66; EX1003, ¶¶219-222.

Grigoriadis discloses “nighttime” administration, administration “prior to sleep (i.e., bedtime administration),” and administration at “10 P.M.” EX1006, ¶66. As Dr. Lodish explains, a POSA would have understood Grigoriadis’s “10 P.M.” administration in particular to encompass administration “in the evening” as recited in claim 19. EX1003, ¶221. Indeed, the ’491 patent repeatedly describes dosing “at about 10 pm at night” (EX1001, 4:58-60, 6:49-53, 79:18-20), which Grigoriadis also expressly discloses (EX1006, ¶66 (teaching “dosing at 10 P.M.”)). EX1003, ¶221. Moreover, claims 17 and 18 recite time ranges having an upper numerical limit (6 or 3 hours before sleep) but no lower limit. A POSA would therefore have understood that these claims encompass administration during the period immediately before a patient goes to sleep. EX1003, ¶222. Grigoriadis’s disclosure of “administration prior to sleep” satisfies these claims for this additional reason. EX1006, ¶66; EX1003, ¶222.

IX. 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.

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

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

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

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

Petitioner is not aware of any disclaimers, reexamination certificates, or petitions for *inter partes* or post-grant review for the '491 patent, nor is Petitioner aware of any pending civil actions involving the '491 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 PGR47291-0011PS1@fr.com.

XI. CONCLUSION

Petitioner respectfully requests that the Board 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 18,691 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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