

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NEUROCRINE BIOSCIENCES, INC.,
Petitioner,

v.

SPRUCE BIOSCIENCES, INC.,
Patent Owner.

PGR2026-00061
Patent 12,576,084

**PETITIONER'S OPPOSITION TO
PATENT OWNER'S DISCRETIONARY DENIAL BRIEF**

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LIST OF EXHIBITS

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1001	U.S. Patent No. 12,576,084 to Howerton et al. (“the ‘084 Patent”)
1002	Excerpts from the Prosecution History of the ‘084 Patent (“the Prosecution History”)
1003	<i>Declaration of Maya Lodish, M.D.</i>
1004	PCT Publication WO/2015/112642 to Grigoriadis et al. (“Grigoriadis PCT”).
1005	Final Written Decision, Paper 64, <i>Neurocrine Biosciences, Inc. v. Spruce Biosciences, Inc.</i> , No. PGR2021-00088 (PTAB Nov. 27, 2024).
1006	U.S. Patent Application Publication No. 2017/0020877 to Grigoriadis et al. (“Grigoriadis”).
1007	Final Written Decision, Paper 62, <i>Neurocrine Biosciences, Inc. v. Spruce Biosciences, Inc.</i> , No. PGR2022-00025 (PTAB Nov. 26, 2024).
1008	Turcu et al., “Single-Dose Study of a Corticotropin-Releasing Factor Receptor-1 Antagonist in Women With 21-Hydroxylase Deficiency,” <i>J. Clin. Endocrinol. Metab.</i> , 101(3):1174-80 (March 2016) (“Turcu 2016”).
1009	RESERVED
1010	CRENESSITY® (crinecerfont) Prescribing Label, U.S. Food and Drug Administration (Dec. 13, 2024).
1011	Neurocrine Biosciences, Inc., Q4 2025 Earnings Release.
1012	PCT Publication WO 2007/105113 to Richard (“Richard”)
1013	Speiser et al., “Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society Clinical Practice Guideline,” <i>J. Clin. Endocrinol. Metab.</i> , 95(9):4133-60 (2010) (“Speiser 2010”).

Exhibit No.	Exhibit Description
1014	Turcu A.F. & Auchus R.J., “The Next 150 Years of Congenital Adrenal Hyperplasia,” <i>J. Steroid. Biochem. Mol. Biol.</i> , 153:63-71 (Sept. 2015) (“Turcu & Auchus 2015”).
1015	El Maouche et al., “Congenital Adrenal Hyperplasia,” <i>Lancet</i> 390:2194-10 (2017) (“El Maouche 2017”).
1016	Merke D.P. & Bornstein S.R., “Congenital Adrenal Hyperplasia,” <i>Lancet</i> , 365:2125-36 (2005) (“Merke & Bornstein 2005”).
1017	Speiser et al., “Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society Clinical Practice Guideline,” <i>J. Clin. Endocrinol. Metab.</i> , 103(11):4043-88 (2018) (“Speiser 2018”).
1018	Fahmy et al., “Structure and Function of Small Non-Peptide CRF Antagonists and their Potential Clinical Use,” <i>Curr. Mol. Pharmacol.</i> , 10(4): 270-281 (2017) (“Fahmy 2017”).
1019	Griebel et al., “4-(2-Chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]5-methyl-N-(2-propynyl)-1,3-thiazol-2-amine Hydrochloride (SSR125543A), a Potent and Selective Corticotrophin-Releasing Factor1 Receptor Antagonist. II. Characterization in Rodent Models of Stress-Related Disorders,” <i>J. Pharmacol. Exp. Ther.</i> , 301(1):333-45 (2002) (“Griebel 2002”).
1020	Gully et al., “4-(2-Chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]5-methyl-N-(2-propynyl)-1,3-thiazol-2-amine Hydrochloride (SSR125543A): A Potent and Selective Corticotrophin-Releasing Factor1 Receptor Antagonist. I. Biochemical and Pharmacological Characterization,” <i>J. Pharmacol. Exp. Ther.</i> , 301(1):322-32 (2002) (“Gully 2002”).
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1023	European Pat. No. 3 784 233 to Alexis Howerton, et al.

Exhibit No.	Exhibit Description
1024	Merke D.P. & Auchus R.J., “Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency,” <i>N. Engl. J. Med.</i> 383(13):1248-61 (2020) (“Merke & Auchus 2020”).
1025	Turcu A.F. & Auchus R.J., “Novel Treatment Strategies in Congenital Adrenal Hyperplasia,” <i>Curr. Opin. Endocrinol. Diabetes Obes.</i> , 23(3):225-32 (June 2016) (“Turcu & Auchus 2016”).
1026	Webb E.A. & Krone N., “Current and Novel Approaches to Children and Young People with Congenital Adrenal Hyperplasia and Adrenal Insufficiency,” <i>Best Pract. Res. Clin. Endocrinol. Metab.</i> , 29:449-68 (2015) (“Webb & Krone 2015”).
1027	“Neurocrine Biosciences to Present New Data Analyses for Crinecerfont in Adults with Classical Congenital Adrenal Hyperplasia at ENDO 2021,” Neurocrine Biosciences (March 20, 2021) (“Neurocrine March 20, 2021, Press Release”).
1028	Decision of the European Patent Office, Opposition Division, revoking EP 3 784 233 (Dec. 12, 2025).
1029	Williams, “Corticotropin-Releasing Factor 1 Receptor Antagonists: A Patent Review,” <i>Expert Opin. Ther. Pat.</i> , 23(8):1057-68 (2013) (“Williams 2013”).
1030	Zorrilla E.P. & Koob G.F., “Progress in Corticotropin-Releasing Factor-1 Antagonist Development,” <i>Drug Discovery Today</i> , 15(9/10):371-83 (2010) (“Zorrilla & Koob 2010”).
1031	Director Review Request in PGR2021-00088, Paper 65
1032	Director Review Request in PGR2022-00025, Paper 63
1033	National Center for Biotechnology Information, PubChem Compound Summary for CID 5282340, Crinecerfont (2026).
1034	Director Review Decision in PGR2021-00088, Paper 66
1035	Director Review Decision in PGR2022-00025, Paper 64
1036	U.S. Patent No. 10,849,908 to Alexis Howerton, et al. (“the ’908 patent”).

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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”).
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1043	“Spruce Biosciences Achieves Proof of Concept in Phase 2 Study of Tildacerfont in Congenital Adrenal Hyperplasia,” Spruce Biosciences (Mar. 25, 2019) (“Spruce Mar. 25, 2019, Press Release”).
1044	“Spruce Biosciences Announces Topline Results from CAHmelia-203 in Adult Classic CAH and CAHptain-205 in Pediatric Classic CAH,” Spruce Biosciences (March 13, 2024) (“Spruce March 13, 2024, Press Release”).
1045	“Spruce Biosciences Announces Topline Results from CAHmelia-204 in Adult CAH and CAHptain-205 in Adult and Pediatric CAH,” Spruce Biosciences (December 10, 2024) (“Spruce December 10, 2024, Press Release”).

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

Exhibit No.	Exhibit Description
1057	“Neurocrine Biosciences Announces U.S. FDA Accepts New Drug Applications and Grants Priority Review for Crinecerfont for Pediatric and Adult Patients with CAH,” Neurocrine Biosciences (July 1, 2024) (“Neurocrine July 1, 2024, Press Release”).
1058	“Neurocrine Biosciences Announces FDA Approval of CRENESSITY® (crinecerfont), a First-in-Class Treatment for Children and Adults With Classic Congenital Adrenal Hyperplasia,” Neurocrine Biosciences (Dec. 13, 2024) (“Dec. 13, 2024, Neurocrine Press Release”).
1059	National Center for Biotechnology Information, PubChem Compound Summary for CID 134694266, Tildacerfont (2026).
1060	U.S. Pat. No. 6,586,456 to Fontaine, et al. (the “’456 patent”).
1061	U.S. Patent Appl. No. 17/081,694, Office Action Response with Declaration of Chris N. Barnes (Dec. 13, 2021).
1062	RESERVED
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1064	Delfino et al., “Testicular Adrenal Rest Tumors in Patients With Congenital Adrenal Hyperplasia: Prevalence and Sonographic, Hormonal, and Seminal Characteristics,” <i>J. Ultrasound Med.</i> , 31:383-88 (2012).
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1067	Yu et al., “Clinical manifestations of testicular adrenal rest tumor in males with congenital adrenal hyperplasia,” <i>Ann. Ped. Endocrinol. Metab.</i> , 20:155-161 (2015).
1068	Aycan et al., “Prevalence and long-term follow-up outcomes of testicular adrenal rest tumours in children and adolescent males with congenital adrenal hyperplasia,” <i>Clin. Endocrinol.</i> , 78, 667-72 (2013).
1069	Claahsen-van der Grinten et al., “Gonadal dysfunction in congenital adrenal hyperplasia,” <i>Eur. J. Endocrinol.</i> , 184(3):R85-R97 (2021).

Exhibit No.	Exhibit Description
1070	RESERVED
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1072	Spruce Biosciences Clinical Study Report, SPR001-202 Protocol, https://cdn.clinicaltrials.gov/large-docs/42/NCT03687242/Prot_000.pdf (2025).
1073	RESERVED
1074	International Publication No. WO 2016/065177 A1 to Howerton et al. (“Howerton”).
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1078	Smeets et al., “Molecular Characterization of Testicular Adrenal Rest Tumors in Congenital Adrenal Hyperplasia: Lesions With Both Adrenocortical and Leydig Cell Features,” <i>J. Clin. Endocrinol. Metab.</i> , 100(3):E524-E530 (Mar. 2015).
1079	RESERVED
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1081	RESERVED
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1083	RESERVED
1084	Preliminary amendment filed in U.S. Patent Application 18/941,832 (05 February 2026).
1085	Claim amendments filed in U.S. Patent Application 18/438,060 (03 April 2026)
1086	RESERVED
1087	RESERVED

Exhibit No.	Exhibit Description
1088	Deussing & Chen, “The Corticotropin-Releasing Factor Family: Physiology of the Stress Response,” <i>Physiol. Rev.</i> , 98:2225-2286 (2018).
1089	FDA News Release, “FDA Approves New Treatment for Congenital Adrenal Hyperplasia” (December 13, 2024)
1090	National Center for Biotechnology Information, PubChem Compound Summary for CID 11596613, Verucerfont (2026).
1091	National Center for Biotechnology Information, PubChem Compound Summary for CID 24758885, 3-[4-Bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl]-2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5-a]pyrimidine] (2026).
1092	National Center for Biotechnology Information, PubChem Compound Summary for CID 24898976, 3-(4-Bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine (2026).
1093	National Center for Biotechnology Information, PubChem Compound Summary for CID 9821250, NBI-30775 (2026).
1094	National Center for Biotechnology Information, PubChem Compound Summary for CID 9888194, NBI-34041 (2026).
1095	National Center for Biotechnology Information, PubChem Compound Summary for CID 9884878, DMP-904 (2026).
1096	National Center for Biotechnology Information, PubChem Compound Summary for CID 177990, Antalarmin (2026).
1097	NCT04457336, “A Ph2b to Evaluate Clinical Efficacy and Safety of Tildacerfont in Adult CAH,” <i>ClinicalTrials.gov.</i> , (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

Exhibit No.	Exhibit Description
1103	Declaration of Ramesh Tharuvai, Ph.D.
1104	Sacks et al., “Guidelines and Recommendations for Laboratory Analysis in the Diagnosis and Management of Diabetes Mellitus,” <i>Diabetes Care</i> 46(10):e151-e199 (2023)
1105	Fujimoto, “The importance of insulin resistance in the pathogenesis of type 2 diabetes mellitus,” <i>Am J Med.</i> 108(6a):9S-14S (2000)
1106	Abdul-Ghani et al., “Contributions of beta-cell dysfunction and insulin resistance to the pathogenesis of impaired glucose tolerance and impaired fasting glucose,” <i>Diabetes Care</i> 29(5):1130-9 (2006).
1107	Merkatz, “Inclusion of Women in Clinical Trials: A Historical Overview of Scientific, Ethical, and Legal Issues,” <i>JOGNN Clinical Issues</i> , 27(1):78-84 (1997)
1108	Moller DE, Flier JS. Insulin Resistance — Mechanisms, Syndromes, and Implications. <i>N Engl J Med.</i> 1991;325(13):938-948P
1109	Panel Change Order in PGR2021-00088, Paper 22
1110	USPTO PTAB Boardside Chat: Updates to Interim Director Review and Related Processes (August 17, 2023)
1111	Request for Comments on Director Review, Precedential Opinion Panel Review, and Internal Circulation and Review of Patent Trial and Appeal Board Decisions, 87 Fed. Reg. 43249 (July 20, 2022)

I. INTRODUCTION

Spruce’s request for discretionary denial attempts to recast this PGR as harassment. Paper 6 (“Br.”), 1. It is not. This PGR concerns whether the Office should decline review despite material evidence that the Office failed to meaningfully address two prior FWDs involving similar claims, did not issue a single written-description or enablement rejection, overlooked the prior art’s express disclosure of inhibiting testicular adrenal rest tumors, and accepted an amendment that improperly introduced new matter. Under the Office’s discretionary-denial framework, the answer is no, the Office should not decline review.

Petitioner Neurocrine is an American innovator. Neurocrine has spent more than thirty years studying CRF₁ receptor antagonists for therapeutic uses, and developed CRENESSITY® (crinecerfont) for treating congenital adrenal hyperplasia (CAH) and its related disorders. Pet. 1-2. CRENESSITY is a breakthrough drug that is the first FDA-approved therapy for treating CAH in seventy years. *Id.* CRENESSITY is manufactured, packaged, and distributed in the United States. *Id.*, 2 (citing EX1010, 16; EX1058; EX1089; EX1103, 2). Spruce pursued a different CRF₁ receptor antagonist, tildacerfont, to treat CAH but abandoned that program after tildacerfont failed in clinical trials. *Id.* (citing EX1044, 2; EX1045, 1; EX1097, 1).

What Spruce did not abandon, however, were its efforts to patent Neurocrine’s

work. Just two months after the Board held all claims of two Spruce patents unpatentable for lack of written-description in previous PGRs, and less than two months after approval of CRENESSITY in the United States, Spruce filed a Track One application that issued as the '084 patent. Pet. 11-12. There, Spruce claimed methods that encompass Neurocrine's crinecerfont, for changing a metabolic parameter in a subject with a testicular adrenal rest tumor (TART) or an ovarian adrenal rest tumor (OART). *Id.* Neurocrine's challenge to the claims of the '084 patent—and defense of its own compounds—is not harassment. It is one of the reasons PGR exists: “The Office institutes review to reconsider its own decision and correct a possible error in the original patent grant....” *Magnolia Med. Techs., Inc. v. Kurin, Inc.*, IPR2026-00097, Paper 17, 6 (May 14, 2026) (precedential) (“*Magnolia*”).

The Board's prior FWDs provide important context. The Board held Spruce's claims to methods for treating CAH with an entire genus of CRF₁ receptor antagonists unpatentable because the patents described only “a single CRF₁ receptor antagonist, Compound 1 (i.e., tildacerfont).” EX1005, 43; EX1007, 41. The Board held that the patents did not reasonably convey possession of the full scope of the challenged claims—including Neurocrine's crinecerfont and verucerfont. Pet. 9-10 (citing EX1005, 4-45, 55-57). Although the challenged claims here are narrower, they raise the same fundamental concern about overbreadth. Pet. 2-3.

The specification of the '084 patent continues to focus on tildacerfont and discloses a generic Formula (I) that encompasses tildacerfont, but not Neurocrine's compounds. Pet. 33-37. Yet the claims recite methods for treating a subject having TART or an OART—disorders associated with CAH—using ten listed CRF₁ receptor antagonists, including Neurocrine's crinecerfont and verucerfont. *Id.*, 3. As explained in the Petition, seven of those ten compounds, including crinecerfont and verucerfont, are described only as “additional chemotherapeutic agent[s]” to be co-administered with a Formula (I) compound. *Id.*, 37-43. The '084 patent also provides no support for treating OARTs other than boilerplate, and, for TARTs, relies on only a single data point from a single patient treated with tildacerfont. *Id.*, 44-46.

Notwithstanding this lack of disclosure, the '084 patent issued without any written-description or enablement rejections, and without any discussion of the Board's prior FWDs. EX1002, 155-156, 415-416. The Office also allowed the claims over Grigoriadis, Neurocrine's prior-art patent publication, on the ground that “Grigoriadis doesn't teach or suggest administering the CRF₁ receptor antagonists for treating a subject having testicular or ovarian adrenal rest tumors, as claimed.” *Id.*, 415-416. But Grigoriadis expressly identifies inhibiting “**testicular adrenal rest tumors** in men” as a goal of the CAH treatment it teaches. Pet. 68-69 (quoting EX1006, ¶44)¹. The Office also accepted an amendment that rewrote an impossible

¹ Emphasis added throughout unless otherwise noted.

chemical structure into Neurocrine’s crinecerfont, introducing new matter into the application. *Id.*, 26-32.

Each of these errors is independently material, and together, they show why this proceeding is not about harassment, and that the Director should decline to exercise discretion to deny institution.

II. THE DIRECTOR SHOULD INSTITUTE TO CORRECT THE OFFICE’S MATERIAL ERRORS

Where a petitioner presents evidence of material error, post-grant review is a proper use of Office resources. *Padagis US LLC v. Neurelis, Inc.*, IPR2025-00464, Paper 12, 2 (July 16, 2025) (informative). Here, the Office committed at least three independent material errors, any one of which warrants institution.

A. The Office Materially Erred in Allowing the Claims Over the Prior Art Grigoriadis

The Examiner expressly allowed the claims over Grigoriadis, stating in the Reasons for Allowance that, although Grigoriadis taught treating CAH by administering a CRF₁ receptor antagonist, it did not teach or suggest “administering the CRF₁ receptor antagonists for treating a subject having *testicular* or ovarian adrenal rest tumors, as claimed.” EX1002, 415-416. That conclusion was material error. Grigoriadis expressly teaches, or at minimum renders obvious, the treatment of TARTs with a CRF₁ receptor antagonist.

As explained in the Petition, Grigoriadis teaches that one goal of CAH

treatment is suppression of the hormone ACTH “to inhibit *testicular adrenal rest tumors* in men.” Pet. 68-69 (quoting EX1006, ¶44). Grigoriadis teaches that administering an effective amount of a CRF₁ receptor antagonist, such as crinecerfont or verucerfont, to CAH patients suppresses ACTH release. EX1006, ¶¶7, 13, 40, 54, 90-93. Grigoriadis thus expressly links CRF₁ receptor antagonist therapy to inhibition of TARTs, and a POSA would have understood Grigoriadis’s treatment methods are directed not only to treating CAH generally, but also to treating CAH-related disorders resulting from ACTH excess, including TARTs. Pet. 68-69; EX1003, ¶¶182-188. As further explained in the Petition, the prior art confirms that understanding. Pet. 72-73 (citing EX1067, 157-159).

Spruce argues that institution would be wasteful because Grigoriadis was previously before the Examiner during prosecution of the ’084 patent and its parent, and that Neurocrine merely disagrees with the Examiner’s analysis. Br. 13-14, 18-19. Not so. The fact that Grigoriadis was before the Examiner does not end the §325(d) inquiry. *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 (Feb. 13, 2020) (precedential). Even though Grigoriadis was before the Examiner under the first part of the *Advanced Bionics* framework, the Examiner materially erred under the second part by concluding that Grigoriadis does not teach treatment of TARTs. Pet. 68-69; EX1006, ¶44. And no reasonable examiner, upon considering ¶44 of Grigoriadis, could conclude

otherwise. *Ecto World, LLC v. RAI Strategic Holdings, Inc.*, IPR2024-01280, Paper 13, 5-6 (May 19, 2025) (precedential §A). Indeed, the Examiner expressly stated that Grigoriadis does not teach treatment of TARTs (EX1002, 415-416), yet ¶44 expressly identifies inhibition of TARTs as a treatment goal achieved through ACTH suppression (EX1006, ¶44). A reference that discloses the very limitation the Examiner identified as absent presents the type of material error that warrants review under § 325(d). *FreightCar Am., Inc. v. Nat’l Steel Car Ltd.*, IPR2025-01046, Paper 20, 3 (Oct. 10, 2025).

Spruce next argues that Grigoriadis’s disclosure concerns only glucocorticoids rather than CRF₁ receptor antagonists. Br. 14. That is also wrong. Grigoriadis’s stated objective is to “improve the health, well-being, quality of life” and “***manage related disorders*** in patient[s] with CAH.” EX1006, ¶¶5-7. Grigoriadis teaches suppressing ACTH through the administration of CRF₁ receptor antagonists, including crinecerfont and verucerfont. *Id.*, ¶¶40, 90-93. And Grigoriadis identifies the inhibition of TARTs as a treatment objective achieved through ACTH suppression. *Id.*, ¶44.

Finally, to the extent the Examiner believed that Grigoriadis had to teach inhibition of ***both*** OARTs and TARTs to satisfy the claim limitation, that too was material error. Claim 1 requires treating a subject having “a testicular adrenal rest tumor (TART) ***or*** an ovarian adrenal rest tumor (OART).” EX1001, 99:3-4.

Grigoriadis need not teach both to satisfy that limitation. Pet. 71 (citing *ModernaTX, Inc. v. Arbutus Biopharma Corp.*, 18 F.4th 1352, 1363-64 (Fed. Cir. 2021)).

B. The Office Materially Erred in Allowing the Challenged Claims Without Addressing the Prior FWDs and the §112 Defects Raised by the Challenged Claims

As explained in the Petition, the Office never issued a written-description or enablement rejection during prosecution. That omission is particularly significant given the Board's prior FWDs in PGR2021-00088 and PGR2022-00025. In those FWDs, the Board held that the challenged claims recited a broad genus of CRF₁ receptor antagonists, but the specification described only a single species, Compound 1 (tildacerfont). EX1005, 42-61; EX1007, 40-58. The Board held that “[g]iven the large number of CRF₁ receptor antagonists with varying structures and effectiveness,” the disclosure of a single species “fails, on its face,” to satisfy the written-description requirement. EX1005, 44; EX1007, 42 (citing *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1350 (Fed. Cir. 2010) (*en banc*)).

The '084 patent focuses on the same single species, Compound 1 (tildacerfont), and compounds falling within Formula (I). Pet. 33-37. But the challenged claims go beyond Formula (I); the ten claimed CRF₁ receptor antagonists include seven compounds appearing in the specification only as “additional chemotherapeutic agent[s].” *Id.*, 37-44. Despite the prior FWDs and these additional disclosure issues, the '084 patent issued without an enablement or written

description rejection, and without any discussion of the Board’s earlier analysis. *See generally* EX2010. That was material error.

In particular, the ’084 patent identifies only *three* of the ten claimed CRF₁ receptor antagonists as falling within Formula (I). Pet. 33-36. The remaining *seven* compounds, including Neurocrine’s crinecerfont and verucerfont, are described for a different purpose: as “additional chemotherapeutic agent[s]” to be co-administered with a compound of Formula (I). *Id.*, 37-44. The ’084 patent does not state or suggest that these “additional chemotherapeutic agent[s]” can treat TARTs or OARTs. *Id.*, 42. In addition, every claim of the ’084 patent encompasses a method for treating a subject with an OART, but the specification provides no disclosure of treating OARTs with a CRF₁ receptor antagonist. *Id.*, 47-50. The patent provides no examples, data, or protocol for treating OARTs, and incorrectly defines OARTs as developing from “intra-testicular adrenal tissue,” an impossibility in females. *Id.*, 49.

In sum, the record shows no analysis of why the challenged claims satisfy §112 despite two prior FWDs involving written-description defects and the lack of written-description support for treating OARTs. Nor does the record contain any analysis of why compounds disclosed only as “additional chemotherapeutic agent[s]” support the challenged claims. The Office’s failure to address those issues constitutes material error.

C. Spruce’s “Narrowed” Claims Do Not Cure the Defects the Board Identified in the Prior FWDs

Spruce argues that its previous claims were found unpatentable because they “were not limited to small molecule inhibitors but broadly included peptide-based therapeutics.” Br. 6-7. That is wrong. The Board expressly held that Spruce’s claims lacked written description because they covered “***all members*** of the genus of CRF₁ receptor antagonists” including not only “a heterogeneous assembly of different classes of ***small molecule*** CRF₁ receptor antagonists,” but also “***large-molecule (peptide)***” CRF₁ receptor antagonists. EX1005, 56-57. The Board never suggested that Spruce possessed all small molecules. It possessed only one, tildacerfont.

Spruce also argues that it responded to the FWDs by “purposefully narrow[ing]” the claims “to a handful of specific compounds expressly identified in the specification” and therefore written-description is satisfied *a fortiori*. Br. 1-2, 6-7. That too is incorrect. Spruce’s decision to limit the current claims to ten CRF₁ receptor antagonists does not cure the written-description defects that the Board previously found. For example, the ’084 patent still describes—at best—only compounds of Formula (I). Yet the claims also encompass seven additional compounds that the specification identifies only as “additional chemotherapeutic agent[s]”—not as treatments for TARTs or OARTs. Pet. 37-44. The prosecution history does not explain why the “narrowed” claims now satisfy §112 despite the Board’s earlier analysis, nor does it address the ***additional*** written-description and enablement defects raised by the new claims. For example, every claim of the ’084

patent recites treating a subject with an OART, but the specification lacks any support for treating OARTs. Pet. 47-50.

Thus, even assuming the challenged claims are narrower than those addressed in the prior FWDs, they still present the same fundamental §112 defects *and* raise additional §112 concerns not present in the earlier PGRs. Spruce’s assertion that the challenged claims were “narrowed” does not undermine Petitioner’s showing of material error.

D. The Office Materially Erred in Accepting the New-Matter Amendment

The application as filed disclosed a structure containing an impossible carbon-carbon “quadruple bond.” Pet. 26-27. That structure is not crinecerfont, and none of the ’084 patent’s priority documents disclose crinecerfont. *Id.*, 28-29. Nevertheless, Spruce amended the specification and claims to recite crinecerfont, and the Examiner accepted the amendment. *Id.* That was material error because it introduced new matter into the application. As explained in the Petition, correction is permissible only where both the error and the correction would have been apparent to a POSA. *Id.*, 29-30. While a POSA here would have recognized the structure as impossible, he or she would not have necessarily known what was intended because multiple corrections could have resolved the error, including corrections that do not result in crinecerfont. *Id.*, 30-32. The Federal Circuit recently reinforced the strict standard for “correction” of an alleged error, rejecting a patentee’s contention that a

POSA would recognize a subscript in a chemical compound as a typographical error and holding that “a disclosure of one chemical compound...cannot necessarily be a disclosure of another, even one close by structurally.” *Enanta Pharms., Inc. v. Pfizer Inc.*, 178 F.4th 1341, 1347-48 (Fed. Cir. 2026).

E. Spruce’s Remaining Arguments Do Not Undermine Petitioner’s Showing of Material Error

Spruce argues that Neurocrine has offered only “conclusory allegations” of error. Br. 17-18. To the extent Spruce is arguing that material error must be shown in a petition, that is incorrect. The Interim Director Discretionary Process states that “[a] petitioner should raise any discretionary issues in its opposition to a patent owner’s discretionary denial brief, including issues relating to 35 U.S.C. § 325(d),” and that “[t]he petition should not address discretionary issues.” §III.A (available at <https://www.uspto.gov/patents/ptab/interim-director-discretionary-process>).

Neurocrine has followed the Office’s instructions.

Spruce’s cited cases are inapposite. Br. 17-18. *Ex parte Belinne* is an *ex parte* appeal about an appellant’s failure to answer an examiner’s findings, while *TankLogix* involved discretionary denial where the petitioner’s *opposition brief* failed to show material error. *TankLogix, LLC v. SitePro, Inc.*, IPR2025-00761, Paper 10, 2 (Sept. 3, 2025). Thus, *TankLogix* does not stand for PO’s proposition that a petitioner must address §325(d) in the petition or else face discretionary denial.

Finally, Spruce complains that Neurocrine filed excerpts rather than the full

file history. Br. 7-8, 16. But Spruce’s own submission of the complete history confirms the dispositive fact: across the entire prosecution, the Office committed material error by failing to reject the claims under §112 for lack of written description and enablement. *Supra*, §II.B-D.

III. SPRUCE HAS NO SETTLED EXPECTATIONS IN THE ’084 PATENT

A. The ’084 Patent Recently Issued

The ’084 patent issued March 17, 2026. EX1001, code [45]. Neurocrine filed this Petition roughly three months later, well within the nine-month PGR window. Neurocrine’s prompt challenge weighs against discretionary denial. *Intas Pharms. Ltd. v. Atossa Therapeutics, Inc.*, PGR2025-00043, Paper 12, 2-3 (Aug. 29, 2025) (“Early challenges favor robust, predictable patent rights and weigh against discretionary denial”). Petitions for PGR “are favored because they must be filed no later than nine months from the grant of the patent..., are close in time to examination, and occur before expectations in the patent rights are strongly settled.” *LifeVac, LLC v. DCSTAR Inc.*, IPR2025-00454, Paper 11, 2 (July 11, 2025) (precedential).

B. Spruce’s Own Conduct Undercuts Any Settled Expectations

Spruce argues that settled expectations arise from “nearly five years” of proceedings before the Board. Br. 9-12. But rather than creating settled expectations, the prior PGRs put Spruce on notice that it could not claim more than it had

described. Yet just two months after the FWDs, Spruce sought Track One prioritized examination and obtained new claims covering subject matter it did not invent and is not described in its specification, including Neurocrine’s crinecerfont and verucerfont, for treating a subject with a TART or an OART. Pet. 11-12. A patent owner cannot invoke settled expectations when, after the Board issues FWDs identifying patentability defects, the patent owner obtains new claims having similar defects. Under these circumstances, Spruce’s arguments weigh against, rather than for, discretionary denial. *See POSCO Co. v. ArcelorMittal*, IPR2025-00370, Paper 10 (June 25, 2025) (“It is an appropriate use of Office resources...to ensure that a patent applicant or owner does not take action inconsistent with the judgment in a prior Office proceeding.”).

C. Neurocrine’s U.S. Manufacturing Favors Institution, While Spruce’s Claim of Continued Investment Lacks Evidentiary Support

Spruce asserts that it “has continued to invest resources in CAH therapeutics.” Br. 12. But it provides absolutely no explanation or evidence supporting that assertion. The Director should decline to credit Spruce’s assertion. *Tesla, Inc. v. Bulletproof Prop. Mgmt., LLC*, IPR2026-00204, Paper 14, 2-3 (June 15, 2026) (informative). Moreover, the record evidence suggests that Spruce has no ongoing investments in CAH therapeutics (other than filing patent applications covering crinecerfont). As explained in the Petition, Spruce’s tildacerfont failed in clinical

trials and Spruce publicly announced in December 2024 that it had discontinued the program. Pet. 2 (citing EX1044, 2; EX1045, 1; EX1097, 1); EX2006, ¶2 n.1. Neurocrine, by contrast, has presented evidence of ongoing U.S.-based commercialization and manufacturing activity. Neurocrine manufactures, packages, and distributes CRENESSITY in the United States. Pet. 2 (citing EX1010, 16; EX1058; EX1089; EX1103, 2). This consideration weighs against discretionary denial. *Magnolia*, 7-8; U.S. MANUFACTURING MEMORANDUM (Mar. 11, 2026), 2.

D. Other Considerations Weigh Against Discretionary Denial

No court or agency is adjudicating any claim of the '084 patent. Accordingly, there is “no concern of inconsistent outcomes or significant duplication of errors resulting from two proceedings operating in parallel.” *Intas*, 2-3. Institution would also promote efficiency and consistency. Neurocrine filed its three PGR petitions simultaneously against patents that share a common specification and raise overlapping §112 issues. Pet. 14-15. The Board is well positioned to address those common issues efficiently and consistently in a single forum. *Embody, Inc. v. Lifenet Health*, IPR2025-00248, Paper 13, 2-3 (June 26, 2025) (stating that it is an efficient use of Board resources to address related patents).

IV. SPRUCE’S HARASSMENT ARGUMENTS FAIL

A. Neurocrine’s Challenges to Spruce’s Overbroad Patents Do Not Constitute “Harassment”

Spruce characterizes Neurocrine’s efforts to challenge Spruce’s patents as

“harassment.” They are not. The petition here is a straightforward challenge to a patent that was improvidently granted because Spruce did not invent, describe, or enable its claimed subject matter. *Supra*, §II. As discussed above and in the Petition, the Office erred in allowing the claims of the ’084 patent, and Neurocrine promptly sought PGR so that the Office could reconsider that decision. *Id.*; Pet. 5-6. Post-grant review exists for precisely this reason. *Magnolia*, 7.

The other conduct Spruce identifies as harassment is nothing more than Neurocrine attempting to defend itself from Spruce’s overbroad patents. After the Board issued the FWDs, Neurocrine sought to address two additional Spruce patents in the same family that shared the same specification and suffered from the same written-description defects by requesting a covenant not to sue. EX2003, 1. Those two additional patents also claimed methods for using CRF₁ receptor antagonists, i.e., a class covering Neurocrine’s crinecerfont and verucerfont. *Id.* Had Spruce not intended to sue, then a covenant not to sue would have been a non-issue—particularly since Spruce had already announced that it had discontinued its CRF₁ receptor antagonist research program. Pet. 2, 25-26; EX2006, ¶2 n.1.

Rather than resolve the whole dispute, however, Spruce signaled its intent to assert its overbroad patents by requesting Director Review of the two Board FWDs.²

² Acting Director Stewart denied Spruce’s requests. PGR2021-00088, Paper 66; PGR2022-00025, Paper 64.

Pet. 10 n.5; EX2006, ¶4 n.4. Neurocrine thereafter filed a petition for PGR on one of the two additional patents (EX1100, 1) and a declaratory-judgment (DJ) action on the remaining patent (EX2006). Because the latter patent was older than 9 months, a written-description challenge via PGR was unavailable. Spruce did not even attempt to defend the PGR, instead filing a statutory disclaimer of all claims. EX1101, 2. The district court dismissed the DJ action for lack of case or controversy required for DJ jurisdiction. EX2002, 6-10. But that decision was procedural; the court made no findings on the merits of Neurocrine's claims. *Id.*

Contrary to Spruce's arguments (Br. 2-5), the specific statements Neurocrine made during these disputes are not evidence of "harassment." Neurocrine's statement that it would be forced to initiate legal and administrative proceedings (Br. 1, 3) signaled its intent to use the procedures available to it. EX2003, 1; EX2005, 1. Neurocrine did not "taunt" Spruce as being in "desperate need for cash." Br. 1, 4. The purpose of Neurocrine's statements was to provide evidence of a case or controversy in its DJ complaint. Specifically, given Spruce's lack of money and failed development program, Spruce appeared to be planning to use its improperly broad patents to sue Neurocrine. EX2006, ¶¶28, 57.

Finally, Spruce's reference to the European proceedings (Br. 5) undermines, rather than supports, Spruce's narrative. The European Patent Office revoked Spruce's patent, which similar to the patent here, claimed the use of CRF₁ receptor

antagonists for treating or preventing TARTs and OARTs. Pet. 10 (citing EX1023, 63-65; EX1028, 11 ¶8.3). Spruce omits this information from its request. That Neurocrine was forced to seek revocation of Spruce's European patent provides evidence of Spruce's abuse of the patent system, not of harassment by Neurocrine.

B. Spruce's Allegations Do Not Meet the Office's Standard for Discretionary Denial Under *Magnolia*

Spruce's allegations, even if accepted as true (which they are not), do not meet the standards for AIA misuse the Director identified in *Magnolia*. *First*, the Director found misuse where parties repeatedly file multiple petitions challenging the same patent without sound reason. *Id.*, 4. Neurocrine has not filed multiple petitions against the same patent; instead, each petition challenges a different Spruce patent. Pet. 14-15. *Second*, the Director found misuse where parties file subsequent petitions on patents challenged unsuccessfully in district court, at the ITC, or at the Office. *Magnolia*, 4. Again, that is not the case here. The '084 patent is challenged for the first time in this PGR, and within a few months of issuance. Pet. 1, 99. *Third*, the Director found misuse where parties take inconsistent positions between different forums. *Magnolia*, 4. Here, the '084 patent is only before this forum. Pet. 1, 99. Spruce identifies no allegedly inconsistent positions in any case, and none exist.

The other cases Spruce cites are similarly off-point. The petitioner in *OpenSky* was sanctioned for offering to undermine the IPR process and for refusing to cooperate in Director-ordered discovery (IPR2021-01064, Paper 127), while the

petitioner in *Patent Quality Assurance* was sanctioned for misrepresentation and for discovery abuse (IPR2021-01229, Paper 131). *WesternGeco* addressed whether a petitioner was time-barred under §315(b). 889 F.3d 1308, 1316-20 (Fed. Cir. 2018). None of these cases support Spruce’s contention that Neurocrine’s challenges to Spruce’s overbroad patents constitute harassment, as no comparable conduct is alleged here.

The above-mentioned DJ action does not change the analysis. As explained above, the court dismissed on jurisdictional grounds for lack of case or controversy and made no finding on validity. EX2002, 6-10. That is the opposite of *Magnolia*, where the petitioner litigated invalidity to a verdict and then sought a second bite at the Office. *Magnolia*, 9-10.

Finally, Spruce’s argument that Neurocrine “falsely repres[ented] that there was no relevant district-court litigation” (Br. 5) is incorrect. Neurocrine represented that there is no district-court litigation involving the ’084 patent (Pet. 1, 99), which is accurate.

C. Spruce’s Remaining Recycled Arguments Fail

To avoid institution, Spruce devotes several pages to relitigating the prior PGRs. Br. 9-12. Those arguments failed then and are irrelevant now.

Expert substitution. Spruce insinuates that Neurocrine acted nefariously by “replac[ing]” its original expert in the previous PGRs. Br. 11. That is false. The

Board approved Neurocrine’s request to substitute its original expert, Dr. Carey, because he had a stroke and was “medically incapable of testifying at deposition or otherwise participating in the proceeding.” EX1005, 5. In the FWDs, the Board also denied Spruce’s motion to exclude the testimony of Dr. Cutler, Neurocrine’s substitute expert. The Board described Spruce’s argument about prejudice as “nonsensical” and found “the record sufficiently clear as to why Dr. Cutler, *with the Board’s approval*, stepped in for the *medically incapacitated* Dr. Carey.” *Id.*, 14-15.

“Well-known, discrete class.” The Board also rejected Spruce’s legally erroneous argument, repeated here (Br. 9-11), that its patents satisfied the written-description requirement because CRF₁ receptor antagonists are a “well-known and discrete class.” The Board found the opposite, and said so expressly: “On the contrary, far from being a ‘well-known, well-characterized, and discrete class’ the prior art teaches a heterogeneous assembly of different classes of *small molecule* CRF₁ receptor antagonists (Type I, Type II, and ‘atypical’) displaying a very considerable variety of structures, both in terms of the core pharmacophore (e.g., monocyclic, bicyclic, tricyclic, phenolic, cyclohexyl amide, etc.) as well as in the various side groups.” EX1005, 56-57.

Director Review. Finally, Spruce suggests that the former Director of the USPTO acted improperly and that the original panel was changed to secure an

outcome of unpatentability. Br. 10-11. First, Spruce’s “panel stacking” argument makes little sense. The panel-change order was signed by then-Acting Deputy Chief Judge Deshpande because one judge—who was not even the authoring judge—became unavailable. EX1109. Second, the Office has already rejected Spruce’s complaints about the previous Director’s *sua sponte* decisions (which most likely resulted from the Office’s transition from the POP process to Director Review after July 20, 2022 Request for Comments). Pet. 10 (citing EX1031-EX1032; EX1034-EX1035); *see also* EX1110; EX1111.

V. INSTITUTION IS IN THE PUBLIC INTEREST

Institution is in the public interest because the Office materially erred in allowing the claims of the ’084 patent. The Office did not address the significance of the prior FWDs, did not substantively evaluate the challenged claims under §112, and allowed claims directed to Neurocrine’s crinecerfont and verucerfont for treating a subject with a TART or an OART despite the absence of any disclosure in the specification and despite Neurocrine’s earlier disclosure in Grigoriadis. The ’084 patent recently issued and no parallel proceeding exists to resolve those questions. Thus, the public interest favors PGR review rather than discretionary denial.

VI. CONCLUSION

The Director should decline to exercise his discretion to deny institution and should institute review of claims 1-19 of the ’084 patent.

Respectfully submitted,

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CERTIFICATE OF SERVICE

Pursuant to 37 CFR § 42.6(e)(4), the undersigned certifies that on September 23, 2026, a complete and entire copy of this Petitioner's Opposition to Patent Owner's Discretionary Denial Brief and added supporting exhibits were provided via electronic mail on Patent Owner's lead and backup counsel listed below at the following email addresses:

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