

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent of:      Howerton et al.  
U.S. Patent No.:      12,115,166                      Attorney Docket No. 47291-0007PS1  
Issue Date:              October 15, 2024  
Appl. Serial No.:      18/307,718  
Filing Date:              April 26, 2023  
Title:                      CORTICOTROPIN RELEASING FACTOR RECEPTOR  
                                    ANTAGONISTS

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**PETITION FOR POST GRANT REVIEW OF**  
**UNITED STATES PATENT NO. 12,115,166**

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**LIST OF EXHIBITS**

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| 1003        | Declaration of Maya Lodish, M.D.                                                                                                                                                                                      |
| 1004        | Declaration of David E. Bugay, Ph.D.                                                                                                                                                                                  |
| 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        | Auchus et al., “Crinecerfont Lowers Elevated Hormone Markers in Adults With 21-Hydroxylase Deficiency Congenital Adrenal Hyperplasia,” <i>J. Clin. Endocrinol. Metab.</i> 1-12 (2021) (“Auchus 2021”).                |
| 1010        | Director Decision, Paper 16, <i>Neurocrine Biosciences, Inc. v. Spruce Biosciences, Inc.</i> , No. PGR2021-00088 (Aug. 4, 2023).                                                                                      |

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| 1011        | Director Decisions, Paper 15, <i>Neurocrine Biosciences, Inc. v. Spruce Biosciences, Inc.</i> , No. PGR2022-00025 (Aug. 4, 2023).                                                                                                                                                                                                                                                                               |
| 1012        | U.S. Patent No. 8,030,304 to Chen et al. (“Chen”).                                                                                                                                                                                                                                                                                                                                                              |
| 1013        | Speiser et al., “Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society Clinical Practice Guideline,” <i>J. Clin. Endocrinol. Metab.</i> , 95(9):4133-60 (2010) (“Speiser”).                                                                                                                                                                                             |
| 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> 390:2194-210 (2017) (“El Maouche 2017”).                                                                                                                                                                                                                                                                                                     |
| 1016        | Merke D.P. & Bornstein S.R., “Congenital Adrenal Hyperplasia,” <i>Lancet</i> , 365:2125-36 (2005) (“Merke & Bornstein 2005”).                                                                                                                                                                                                                                                                                   |
| 1017        | Speiser et al., “Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society Clinical Practice Guideline,” <i>J. Clin. Endocrinol. Metab.</i> , 103(11):4043-88 (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): 270-81 (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                                                                                                             |

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|             | Characterization,” <i>J. Pharmacol. Exp. Ther.</i> , 301(1):322-32 (2002) (“Gully 2002”).                                                                                                                                                   |
| 1021        | Merke D.P. & Cutler G.B., “New Ideas for Medical Treatment of Congenital Adrenal Hyperplasia,” <i>Endocrinol. Metab. Clin. North. Am.</i> , 30(1):121-35 (2001) (“Merke & Cutler 2001”).                                                    |
| 1022        | Merke et al., “Future Directions in the Study and Management of Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency,” <i>Ann. Intern. Med.</i> , 136:320-34 (2002) (“Merke 2002”).                                              |
| 1023        | Trapp et al., “Congenital adrenal hyperplasia: an update in children,” <i>Curr. Opin. Endocrinol. Diabetes Obes.</i> , 18(3):166-70 (2011) (“Trapp”).                                                                                       |
| 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        | Nella et al., “A Phase 2 Study of Continuous Subcutaneous Hydrocortisone Infusion in Adults With Congenital Adrenal Hyperplasia,” <i>J. Clin. Endocrinol. Metabol.</i> , 101(12):4690-98 (December 2016) (“Nella”)                          |

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| 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        | Kehne J.H. & Cain C.K., “Therapeutic Utility of Non-Peptidic CRF1 Receptor Antagonists in Anxiety, Depression, and Stress-Related Disorders: Evidence from Animal Models,” <i>Pharmacol. Ther.</i> , 128(3):460-87 (2010). (“Kehne & Cain 2010”).                            |
| 1032        | Deore et al., “The Stages of Drug Discovery and Development Process,” <i>Asian J. Pharm. R. &amp; D.</i> , 7(6):62-67 (2019) (“Deore”).                                                                                                                                      |
| 1033        | National Center for Biotechnology Information (2025), PubChem Compound Summary for CID 5282340, Crinecerfont. Retrieved February 4, 2025, from <a href="https://pubchem.ncbi.nlm.nih.gov/compound/Crinecerfont">https://pubchem.ncbi.nlm.nih.gov/compound/Crinecerfont</a> . |
| 1034        | Reserved                                                                                                                                                                                                                                                                     |
| 1035        | U.S. Provisional Application Serial No. 62/545,406.                                                                                                                                                                                                                          |
| 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        | Yamaguchi et al., “Approval success rates of drug candidates based on target, action, modality, application, and their combinations,” <i>Clin. Transl. Sci.</i> 14:1113-22 (2021) (“Yamaguchi”).                                                                             |
| 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        | Reserved                                                                                                                                                                                                                                                                     |

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| 1041        | Sarafoglou et al., “Tildacerfont in Adults With Classic Congenital Adrenal Hyperplasia: Results from Two Phase 2 Studies,” <i>J. Clin. Endocrinol. Metabol.</i> 106(11):e4666-79 (2021) (“Sarafoglou 2021”).        |
| 1042        | Reserved                                                                                                                                                                                                            |
| 1043        | “Spruce Biosciences Achieves Proof of Concept in Phase 2 Study in Tildacerfont in Congenital Adrenal Hyperplasia,” Spruce Biosciences (March 25, 2019) (“Spruce March 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”).      |
| 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., “Crinicerfont 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 Review</i> , 43(1):91-159 (2022) (“Claahsen-van der Grinten”).     |
| 1050        | “Guidance for Industry, Q1A(R2) Stability Testing of New Drug Substances and Products,” U.S. Department of Health and Human Services, Food and Drug Administration (November 2003).                                 |

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| 1051        | “Guidance for Industry, Q1E Evaluation of Stability Data,” U.S. Department of Health and Human Services, Food and Drug Administration (June 2004).                                                                                                                       |
| 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        | Product Quality Review: CRENESSITY™ (Crinecerfont), Center for Drug Evaluation and Research, Food & Drug Administration (Nov. 4, 2022) (“FDA Product Quality Review”).                                                                                                   |
| 1055        | Reserved                                                                                                                                                                                                                                                                 |
| 1056        | Reserved                                                                                                                                                                                                                                                                 |
| 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 (2025), PubChem Compound Summary for CID 134694266, Tildacerfont. Retrieved February 4, 2025, from <a href="https://pubchem.ncbi.nlm.nih.gov/compound/134694266">https://pubchem.ncbi.nlm.nih.gov/compound/134694266</a> . |
| 1060        | Reserved                                                                                                                                                                                                                                                                 |
| 1061        | Petition for Post Grant Review of U.S. Patent No. 10,849,908, Paper 2, <i>Neurocrine Biosciences, Inc. v. Spruce Biosciences, Inc.</i> , No. PGR2021-00088 (May 28, 2021).                                                                                               |
| 1062        | Petitioner’s Reply to Patent Owner’s Response, Paper 32, <i>Neurocrine Biosciences, Inc. v. Spruce Biosciences, Inc.</i> , No. PGR2021-00088 (June 20, 2024).                                                                                                            |

| Exhibit No. | Exhibit Description                                                                                                                                                                               |
|-------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1063        | Petition for Post Grant Review of U.S. Patent No. 11,007,201, Paper 2, <i>Neurocrine Biosciences, Inc. v. Spruce Biosciences, Inc.</i> , No. PGR2022-00025 (Feb. 18, 2022).                       |
| 1064        | Petitioner's Reply to Patent Owner's Response, Paper 30, <i>Neurocrine Biosciences, Inc. v. Spruce Biosciences, Inc.</i> , No. PGR2022-00025 (June 20, 2024).                                     |
| 1065        | Sertkaya et al., "Key cost drivers of pharmaceutical trials in the United States," <i>Clin. Trials</i> , 13(2):117-26 (2016).                                                                     |
| 1066        | Spierling S.R. & Zorrilla E.P., "Don't stress about CRF: Assessing the translational failures of CRF <sub>1</sub> antagonists," <i>Psychopharmacology (Berl.)</i> , 234(9-10):1467-81 (May 2017). |

Neurocrine Biosciences, Inc. (“Petitioner” or “Neurocrine”) petitions for Post Grant Review (“PGR”) under 35 U.S.C. §§ 321-326 and 37 C.F.R. § 42 of claims 1-10 and 12-21 (the “Challenged Claims”) of U.S. Patent No. 12,115,166 (the “’166 patent,” EX1001) assigned to Spruce Biosciences, Inc. (“Patent Owner” or “Spruce”).

## **I. INTRODUCTION**

The ’166 patent is Spruce’s latest attempt to lay claim to work it did not do in an effort to cover the groundbreaking work of its competitor, Neurocrine. The ’166 patent issued on October 15, 2024, approximately six weeks before the Board issued Final Written Decisions determining all claims of two other Spruce patents in this family—U.S. Patent Nos. 10,849,908 (“the ’908 patent”) and 11,007,201 (“the ’201 patent”)—unpatentable for lack of written description. The ’166 patent shares the same defective specification as those patents and, like Spruce’s other patents, impermissibly claims a sweeping genus of CRF1 receptor antagonists for treating congenital adrenal hyperplasia (“CAH”). Spruce’s third shot at patent overreach must also fail for violating the requirements of 35 U.S.C. § 112(a).

While Neurocrine and Spruce each studied CRF1 receptor antagonists for the treatment of CAH, Neurocrine led the way. *See* EX1003, ¶¶23-31.

Neurocrine’s pioneering work on CRF1 receptor antagonists spans over 30 years. Neurocrine launched a clinical program studying CRF1 receptor antagonists to

treat CAH in 2012 and was the first company to investigate CRF1 receptor antagonists for the treatment of CAH. By January 2016, Neurocrine had completed and published the first clinical study of a CRF1 receptor antagonist to treat CAH. EX1008. Neurocrine went on to develop a second CRF1 receptor antagonist, crinecerfont, which was highly effective in treating CAH in clinical studies. EX1054; EX1009. In 2016, Neurocrine filed an Investigational New Drug application seeking authorization from the FDA to study crinecerfont in humans with CAH. In January 2017, Neurocrine's published patent application disclosed the utility of crinecerfont as a CAH treatment. EX1006, [0054]. Spruce, by contrast, was not formed until 2014—two decades after Neurocrine first began work on CRF1 receptor antagonists, and two years after Neurocrine launched its CAH clinical program. Spruce did not report results of its first clinical study until March 2019. EX1043.

Neurocrine's work on crinecerfont for treating CAH is groundbreaking. Crinecerfont is the first new CAH treatment to be approved by the FDA in 70 years, and is the first and only CRF1 receptor antagonist approved as a CAH therapy. The FDA granted Neurocrine "Fast Track," "Breakthrough Therapy," "Priority Review," and "Orphan Drug" designations for crinecerfont as a first-in-class therapy that meets a long-felt and unmet medical need to reduce glucocorticoid dosing in CAH patients. EX1057. The FDA approved two

formulations of crinecerfont (capsule and oral solution) for treating CAH in December 2024, and both are now available to patients under the trade name CRENESSITY™. EX1058. In stark contrast, the only compound disclosed in Spruce's patents, tildacerfont, has been an abject failure. Tildacerfont failed to meet its primary efficacy endpoint in its last two clinical trials, and Spruce has announced it is no longer pursuing tildacerfont as a CAH treatment. EX1044; EX1045.

Having lost on the science, Spruce's '166 patent represents its latest attempt to capture Neurocrine's innovation by improperly expanding its patent claims to a scope it neither described nor enabled. Unsurprisingly, the entire disclosure of the '166 patent relates to tildacerfont, the only CRF1 receptor antagonist Spruce studied. The Challenged Claims, however, recite the use of *an entire genus of CRF1 receptor antagonists* to treat CAH and achieve specific clinical results. The specification does not disclose a representative number of species within the scope of that genus—it discloses only one, tildacerfont. The specification likewise fails to disclose common structural features of the claimed genus. Thus, the Challenged Claims are unpatentable under §112(a) for lack of written description.

As noted above, the Board already addressed this exact issue in Neurocrine's challenges to Spruce's other patents in this family: PGR2021-00088 (determining all claims of the '908 patent unpatentable) and PGR2022-00025 (determining all

claims of the '201 patent unpatentable). Like the '166 patent, both of those patents broadly claimed the use of an entire genus of CRF1 receptor antagonists to treat CAH, but, like the '166 patent here, only disclosed a single species, tildacerfont. Both patents share the same specification as the '166 patent. In its Final Written Decisions, the Board determined that all claims of Spruce's patents were unpatentable under §112(a) for lack of written description. EX1005, 42-59; EX1007, 40-57. Given that the '166 patent has the same disclosure as Spruce's other patents, the Board should also find the Challenged Claims of the '166 patent unpatentable for lack of written description.

Spruce's overbroad genus claims are also unpatentable under §112(a) for lack of enablement because the '166 patent's disclosure does not enable a person of ordinary skill in the art ("POSA") to make and use the full scope of the claims without undue experimentation. The Challenged Claims recite an entire genus of CRF1 receptor antagonists by their function—treating CAH and achieving specific clinical results—but the specification does not provide a sufficiently predictable way for a POSA to identify CRF1 receptor antagonists useful for the claimed methods. The POSA is, instead, left with a trial-and-error approach for determining which CRF1 receptor antagonists fall within the scope of the broad claims. Trial-and-error is insufficient to satisfy the enablement requirement for the reasons the Supreme Court articulated in *Amgen Inc. v. Sanofi*, 598 U.S. 594, 610 (2023).

Disclosure of a single failed species (tildacerfont) does not show possession of the use of an entire class of CRF1 receptor antagonists to treat CAH. Trial-and-error is not enablement. Neurocrine respectfully requests that the Board institute this PGR and cancel the Challenged Claims as unpatentable.

## **II. REQUIREMENTS FOR PGR**

### **A. Grounds for Standing**

Pursuant to 37 C.F.R. §42.204(a), Neurocrine certifies that the '166 patent is available for PGR and that Neurocrine is not barred or estopped from requesting PGR challenging claims 1-10 and 12-21 on the below-identified grounds of unpatentability. This Petition is being filed within nine months of the issuance of the '166 patent on October 15, 2024.

### **B. Identification of Challenge**

Pursuant to 37 C.F.R. §42.204(b), Neurocrine requests PGR of the Challenged Claims on the grounds set forth below, and requests that the Board cancel each of the Challenged Claims.

| Ground | Claims Challenged | 35 U.S.C. § | Reference(s)/Basis          |
|--------|-------------------|-------------|-----------------------------|
| 1      | 1-10, 12-21       | 112(a)      | Lack of Written Description |
| 2      | 1-10, 12-21       | 112(a)      | Lack of Enablement          |

**C. The '166 Patent Is Eligible for PGR**

The '166 Patent claims an earliest-possible filing date of August 14, 2017. EX1001, code [60]. Accordingly, the '166 patent is an AIA “first-to-file” patent filed on or after March 16, 2013.

**III. THE BOARD PREVIOUSLY DETERMINED THAT THE SAME SPECIFICATION DOES NOT SUPPORT CLAIMS RECITING A GENUS OF CRF1 RECEPTOR ANTAGONISTS**

Neurocrine previously challenged two other Spruce patents in PGR proceedings: PGR2021-00088 (challenging all claims of the '908 patent) and PGR2022-00025 (challenging all claims of the '201 patent). Both the '908 and '201 patents are in the same family as the '166 patent. And, except for cross-reference information, all three patents share the same specification.

Like the Challenged Claims, the '908 and '201 patent claims recite the use of an entire class of CRF1 receptor antagonists to treat a CAH patient and achieve specific clinical effects (e.g., reduction in adrenal hormones). EX1036, 48:5-49:15; EX1037, 47:50-48:51. Neurocrine asserted that all claims of both patents were invalid for lacking written description, because the disclosure does not show that Spruce possessed an entire class of CRF1 receptor antagonists to treat CAH. EX1061, 70-75; EX1062, 4-12; EX1063, 75-79; EX1064, 4-11.

In detailed Final Written Decisions, the Board held that all claims of the '908 and '201 patents were unpatentable for lack of written description support.

EX1005, 42-59; EX1007, 40-57. The Board noted the undisputed fact that the shared specification discloses only a single CRF1 receptor antagonist, Compound 1 (tildacerfont). *See, e.g.*, EX1005, 43. The Board found that “[g]iven the large number of CRF1 receptor antagonists with varying structures and effectiveness,” the disclosure of a single species, Compound 1, “fails on its face to meet *Ariad*’s requirement that the Specification disclose ‘a representative number of species falling within the scope of genus or structural features common to the members of the genus so that one of skill in the art can ‘visualize or recognize’ the members of the genus.” *Id.*, 44-45 (citing *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1350 (Fed. Cir. 2010) (en banc). The Board also found that the prior art of record “indicate a very considerable structural diversity of molecules that can act as CRF1 receptor antagonists” and rejected Spruce’s characterization of these antagonists as a “well-known, well-characterized, and discrete class.” *Id.*, 55-57.

The Board concluded that a skilled artisan “would not have recognized, either from the express disclosures of the [] Specification or from the knowledge of the prior art, the ‘structure, formula, chemical name, physical properties, or other properties, of species falling within the genus’ of claimed CRF1 receptor antagonists” and held all claims unpatentable. *Id.*, 59. These findings were consistent with former Director Vidal’s decisions in PGR2021-00088 and

PGR2022-00025. EX1010, 10-14; EX1011, 3.<sup>1</sup>

Because the Board held all claims of the '908 and '201 patents unpatentable for lack of written description, the Board did not reach Neurocrine's other grounds of unpatentability based on lack of enablement, anticipation, and obviousness. EX1005, 59; EX1007, 57.

#### **IV. THE '166 PATENT**

##### **A. The '166 Patent Disclosure**

The '166 patent discloses the use of a single CRF1 receptor antagonist, 3-4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-a) pyrimidine or "Compound 1," for treating CAH. This compound is also known as tildacerfont.<sup>2</sup> Spruce developed tildacerfont as a treatment for CAH. However, tildacerfont failed to meet its primary efficacy endpoint in two Phase II(b) clinical trials, and in December 2024, Spruce announced that it is no longer pursuing tildacerfont as a CAH treatment. EX1044;

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<sup>1</sup> Spruce has requested Director Review of the Final Written Decisions. PGR2021-00088, Paper 65; PGR2022-00025, Paper 63. Those requests are pending. Neurocrine believes Spruce's requests are meritless, and has requested an opportunity to respond to address the new arguments and numerous misstatements in Spruce's requests.

<sup>2</sup> The '166 patent discloses two chemical names that can be referred to as "Compound 1." EX1001, 14:40–67. These two chemical names are alternative names for the same compound, tildacerfont. *See* EX1059, 4, 6; EX1003, ¶33.

EX1045.

The '166 patent repeatedly characterizes the “present invention” or “present disclosure” as Compound 1, i.e., tildacerfont. For example, the Abstract states:

*The present invention* provides novel pharmaceutical compositions comprising **[3]-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-a) pyrimidine** and methods of using the same for the treatment of Congenital adrenal hyperplasia (CAH).

EX1001, Abstract (emphasis added). The Summary of the Invention states:

*The present invention* provides novel pharmaceutical compositions comprising **3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-a) pyrimidine** and methods using such pharmaceutical compositions for treating congenital adrenal hyperplasia (CAH).

In one aspect, *the present disclosure* provides a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering a pharmaceutical composition comprising **Compound 1 . . . .**

*Id.*, 1:40-48 (emphasis added).

The methods described in the specification are likewise limited to the use of Compound 1, or salts or solvates of Compound 1:

Disclosed herein is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering a pharmaceutical composition **comprising Compound 1, or a pharmaceutically acceptable salt or solvate thereof.**

*Id.*, 26:50-55 (emphasis added).

Nowhere does the '166 patent describe or disclose the use of any compound other than Compound 1 (tildacerfont) to treat CAH or any other condition. The only stability data provided for an CRF1 receptor antagonist is for Compound 1. EX1001, 25:20-29, 34:58-36:57. The only disclosure of reducing the amount of glucocorticoid needed in a patient is in reference to administering Compound 1, not any other CRF1 receptor antagonist. *Id.*, 32:22-29.

The same is true as to the specification's disclosure of clinical data. Examples 3-8 of the '166 patent describe clinical studies related to Compound 1. Example 3 discloses the results of two Phase I clinical studies evaluating Compound 1 in healthy adults, and reports pharmacokinetic data from subjects after administration of Compound 1. *Id.*, 36:58-42:32. Example 4 describes a 6-week Phase II clinical study of Compound I in adults with classic CAH. *Id.*, 42:36-44:67. The '166 patent reports that the subjects in the Phase II study demonstrated reduction in ACTH, 17-OHP, and A4 levels after six weeks of receiving Compound 1. *Id.*, 44:42-67; Figs. 2-4. Examples 5-8 describe prophetic clinical study protocols (all using only tildacerfont) but do not disclose any data. *Id.*, 45:1-48:61.

The '166 patent does not contain any description or data for any compound besides Compound 1 (tildacerfont). EX1003, ¶¶32-38.

## **B. The '166 Patent Claims**

In contrast to the specification, the '166 patent claims are not limited to the use of Compound 1 to treat CAH, but instead recite the use of a much broader genus of CRF<sub>1</sub> receptor antagonists for treating CAH. Specifically, claim 1, the only independent claim, recites a method for treating CAH as follows:

1. A method for treating congenital adrenal hyperplasia (CAH) in a human, comprising:

administering to said human a therapeutically-effective amount of a CRF<sub>1</sub> receptor antagonist or a pharmaceutically acceptable salt thereof,

wherein said human has received or has been previously determined to receive a first dose of a glucocorticoid, and

administering to said human a second dose of a glucocorticoid, wherein said second dose of glucocorticoid is reduced compared to said first dose of glucocorticoid,

wherein an androstenedione (A4) level in said human is reduced from baseline, or

wherein an adrenocorticotrophic hormone (ACTH) level in said human is reduced from baseline, or

wherein a 17-hydroxyprogesterone (17-OHP) level in said human is reduced from baseline,

wherein said CRF<sub>1</sub> receptor antagonist or a pharmaceutically acceptable salt thereof is administered at a dose between about 50 mg/day and about 200 mg/day, and wherein said CRF<sub>1</sub> receptor antagonist is stable for storage for a minimum of six months.

EX1001, 48:63-49:19.

None of the dependent Challenged Claims narrow the scope of the genus of CRF1 receptor antagonists recited in claim 1 despite reciting additional limitations.<sup>3</sup> Dependent claims 2-6 require specific reductions in A4, ACTH, or 17-OHP levels, and dependent claims 7-9 require those reductions be maintained for a specific amount of time. EX1001, 49:20-46. Dependent claims 10 and 12-15 specify the glucocorticoid and how it should be administered. *Id.*, 49:47-50:34. Dependent claims 16-20 specify dosing requirements, and dependent claim 21 recites stability parameters for the CRF<sub>1</sub> receptor antagonist. *Id.*, 50:35-48.

### **C. The '166 Patent Prosecution History**

The '166 patent was filed on April 26, 2023, as U.S. Patent Application No. 18/307,718 (“the '718 application”), with 21 claims. *See* EX1002, 1-3. The '718 application claimed priority through a series of continuation/divisional applications to provisional Application No. 62/545,406 (“the '406 provisional”), which was filed on August 14, 2017. The claims of the '406 provisional were limited to the administration of Compound 1 or a pharmaceutically acceptable salt or solvate thereof. *See* EX1035, 50-59.

As noted above, the '166 patent shares the same disclosure as the '908 patent and the '201 patent. The '201 patent is a continuation of the application that

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<sup>3</sup> Neurocrine is not challenging claim 11, which is limited to Compound 1. EX1001, 50:3-22.

issued as the '908 patent. EX1037, code [63]. The '166 patent is a continuation of an application that claims priority through several applications to the '908 patent. EX1001, code [60].

During prosecution, the Examiner issued only one Office Action, making a non-final rejection of claims 1-21 as obvious over Neurocrine's published patent Application No. 2017/0020877 ("Grigoriadis"; EX1006) in combination with other prior-art references.<sup>4</sup> EX1002, 2474-82. The Examiner also provisionally rejected the claims for non-statutory double patenting over a co-pending application, in view of Grigoriadis and other prior art. *Id.*, 2482-86; EX1003, ¶¶39-40. The Examiner did not make any other rejections.

Thereafter, the Examiner conducted an interview with Applicant's representatives. EX1002, 2510-11. The Examiner wrote in the Interview Summary that "Applicant proposed claim amendments, and discussed unexpected results, to distinguish the instant claim 16 from the prior art." *Id.*, 2511. The Examiner "advised the Applicant to provide evidence of the criticality of the claim 16 dose range, and to amend claim 1" to avoid "the closest prior art, Grigoriadis et al (of

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<sup>4</sup> These references included Speiser et al., *J. Clin. Endocrinol. Metabol.*, 2010, 95(9), 4133-4169 (EX1013), Trapp et al., *Curr. Opin. Endocrinol. Diabetes Obes.*, 2011, June, 18(3), 166-170 (EX1023), Nella et al., *J. Clin. Endocrinol. Metabol.*, December 2016, 101(12), 4690-4698 (EX1028), and U.S. Patent No. 8,030,304 B2 to Chen, (EX1012).

record).” *Id.*, 2511.

Applicant then submitted a Response to Non-Final Office Action amending claim 1 to recite a dosage range and stability: “wherein said CRF1 receptor antagonist or a pharmaceutically acceptable salt thereof is administered at a dose between about 50 mg/day and about 200 mg/day, and wherein the CRF1 receptor antagonist is stable for storage for a minimum of six months.” *Id.*, 2500-08.

Applicant argued that these amendments overcame the Examiner’s obviousness rejection because Grigoriadis “does not teach that the CRF1 receptor antagonist is stable in storage for a minimum of six months as the dosages described.” *Id.*, 2501-02. Applicant also argued that “the dosage provided in claim 1 has an unexpected benefit of being more stable for shelf-storage, which [the prior art] do not teach, suggest, or render obvious such claim elements.” *Id.* Applicant also submitted a terminal disclaimer to overcome the non-statutory double patenting rejection. *Id.*, 2490-92.

In response, the Examiner issued a Notice of Allowance. *Id.*, 2528. The Examiner did not make any statement on the record about the reasons for allowance. *Id.*

After paying the issue fee, Applicant twice submitted petitions to withdraw the application from issuance pending review of two information disclosure statements. *Id.*, 2563-64, 2706-07. The information disclosure statements listed,

*inter alia*, the Petitions in PGR2021-00088 and PGR2022-00025 and the Decisions Granting Institution in PGR2022-00025 and PGR2021-00088. *Id.*, 2538, 3106.

Applicant did not submit any other information from the previous PGRs. *Id.*

The Examiner initialed the information disclosures statements but provided no comment on any of the post-issue fee references. *Id.*, 2538, 3106. The Examiner issued a final Notice of Allowance with an Examiner's Amendment (changing the word "subject" in claim 1 to "human") on August 7, 2024. *Id.*, 3090-96.

The '166 patent issued on October 15, 2024, approximately six weeks before the Board issued its Final Written Decisions in PGR2021-00088 and PGR2022-00025, finding all claims of the '908 and '201 patents unpatentable under §112(a) for lack of written description, respectively. EX1005; EX1007.

## **V. 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, ¶43; *see also id.*, ¶¶15-31; EX1004, ¶¶23-25. A POSA would also have at least three years of experience conducting research concerning endocrine disorders, including CAH 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 and pharmaceutical formulation.

*Id.*

## **VI. 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; *see also Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-14 (Fed. Cir. 2005) (en banc). Claim terms are construed only to the extent necessary to resolve a controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999). For purposes of this proceeding only, Neurocrine submits that no claim terms of the Challenged Claims need construction. EX1003, ¶¶44-46; EX1004, ¶19. The Board determined in the previous PGRs that no claim construction was necessary to resolve the dispute over written description. EX1005, 26; EX1007, 25.

## **VII. DETAILED EXPLANATION OF GROUNDS**

As detailed below, each Challenged Claim is unpatentable under §112(a) at least for lacking written description support, and for lacking enablement.

Accordingly, the Board should cancel each Challenged Claim of the ’166 patent.

### **A. Ground 1: Claims 1-10, 12-21 are unpatentable for lack of written description**

All the Challenged Claims are unpatentable for lack of written description. EX1003, ¶¶47-51, 56-75; EX1004, ¶¶20-22, 26-36, 47-53. The test for written

description support is “whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date” based on an “objective inquiry into the four corners of the specification.” *Ariad*, 598 F.3d at 1351. The written description requirement is satisfied when the specification “set[s] forth enough detail to allow a person of ordinary skill in the art to understand what is claimed and to recognize that the inventor invented what is claimed.” *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 928 (Fed. Cir. 2004). The written description requirement ensures that a patent’s claims “do[] 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 (Fed. Cir. 2000).

“The 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.” *Ariad*, 598 F.3d at 1351 (citing *Capon v. Eshhar*, 418 F.3d 1349, 1357-58 (Fed. Cir. 2005)). Factors used to evaluate the sufficiency of a disclosure include: 1) “the existing knowledge in the particular field”; 2) “the extent and content of the prior art”; 3) “the maturity of the science or technology”; and 4) “the predictability of the aspect at issue.” *Id.* A “mere wish or plan” for obtaining the claimed subject matter does not satisfy the written description requirement. *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119

F.3d 1559, 1566 (Fed. Cir. 1997).

The Challenged Claims do not have the requisite written description support. Instead, the Challenged Claims are directed to a wide-ranging and functionally defined genus. The claimed genus captures any CRF1 receptor antagonist that treats CAH and achieves the clinical effects of reducing glucocorticoid dosing and reducing A4, ACTH, or 17-OHP levels from baseline. EX1001, 48:63-49:19. To show sufficient written description of a genus, the specification must disclose either a representative number of species falling within the scope of the genus, or structural features common to the members of the genus so that one of skill in the art can “visualize or recognize” the members of the genus. *Ariad*, 598 F.3d at 1350. Spruce can show neither because the specification describes only a single non-representative species—tildacerfont. Sweeping and functionally defined genus claims rooted in a deficient specification, like the Challenged Claims, are inherently vulnerable to written-description challenges. *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1301 (Fed. Cir. 2014).

**1. The '166 Patent Specification Does Not Disclose a Representative Number of Species or Common Structural Features of the Claimed Genus**

All the Challenged Claims recite administering, to a human with CAH, a therapeutically effective amount of a “CRF1 receptor antagonist or pharmaceutically acceptable salt thereof.” EX1001, 48:63-50:48. The specification

indisputably discloses only a single CRF1 receptor antagonist, Compound 1 (tildacerfont). See EX1003, ¶¶57-59; EX1005, 43; EX1010, 12. The Challenged Claims are not limited to the '166 patent's disclosure, Compound 1 (tildacerfont), but instead encompass "essentially all members of the genus of CRF1 receptor antagonists" that treat CAH and achieve the claimed clinical results—reducing glucocorticoid dosing and reducing an A4, ACTH, or 17-OHP level from baseline.<sup>5</sup> EX1005, 43-44 (citing *Ariad*, 598 F.3d at 1341, and noting that the genus claims encompassed the use of all substances that achieved the desired result).

As Neurocrine's expert, Dr. Maya Lodish, explains and as the Board found in the previous PGRs, the genus of CRF1 receptor antagonists encompasses a large and indeterminate number of compounds with varying structures and effectiveness. EX1003, ¶¶41-42, 60-72; EX1018, 270-271; EX1029, 1065; EX1005, 55-57. The specification's disclosure of a single CRF1 receptor antagonist, Compound 1 (tildacerfont), "fails, on its face, to meet *Ariad*'s requirement that the Specification disclose 'a representative number of species falling within the scope of the genus or structural features common to the members of the genus'" so that a POSA can "visualize or recognize the members of the genus." EX1005, 44-45; EX1010, 13-

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<sup>5</sup> As the Board previously found, the shared specification "provides ample description of Compound 1." EX1005, 43. Neurocrine is not challenging dependent claim 11, which is limited to Compound 1. EX1001, 50:3-22.

14 (quoting *Ariad*, 598 F.3d at 1350).

This is especially true because Spruce has admitted that Compound 1 (tildacerfont) has “unique structural features,” yet the specification does not describe what these features are, or how to identify other CRF1 receptor antagonists that share these features. EX1041, 4667; EX1003, ¶58; EX1005, 58 (finding that “Patent Owner’s own publication noted that the single species disclosed in the ’908 Specification as having ‘unique structural features’ compared to other CRF<sub>1</sub> receptor antagonists.”). Indicative of the variability of the CRF1 receptor antagonists’ structures and clinical outcomes, Spruce’s Compound 1 (tildacerfont) failed in the clinic whereas Neurocrine’s crinecerfont went on to clinical success and breakthrough approval by the FDA. EX1058. Thus, the Challenged Claims are unpatentable for lacking written description support. *Id.*

**2. The ’166 Patent Disclosure Does Not Convey to a POSA that the Inventor Possessed the Claimed Subject Matter**

The ’166 patent disclosure also fails to meet *Ariad*’s requirement that a POSA be able to recognize from the specification the “structure, formula, chemical name, physical properties, or other properties of species falling within the claimed genus.” *Ariad*, 598 F.3d at 1350 (citing *Capon*, 418 F.3d at 1357-58). In the previous PGRs, Spruce conceded that the specification (the same one as here) discloses only Compound 1 (tildacerfont), but argued that the prior art, specifically

the Williams (EX1029) and Fahmy (EX1018) references, allowed a POSA to recognize the claimed genus. EX1005, 46. The Board disagreed in the previous PGRs, *id.*, 58-59, and should do the same here. Neither the specification nor the prior art discloses a relationship between the structure of the claimed genus and its claimed function (i.e., reducing glucocorticoid dosing and reducing an A4, ACTH, or 17-OHP level from baseline). *Ariad*, 598 F.3d at 1350 (citing *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 323 F.3d 956, 964 (Fed. Cir. 2002)).

Williams is a review article of CRF1 receptor antagonists from 2013. EX1029. Williams' disclosure highlights the considerable structural diversity of molecules that can act as CRF1 receptor antagonists. For example, while Williams identifies a structure it refers to as a "typical" CRF1 receptor antagonist, the reference also describes a number of classes and subclasses of CRF1 receptor antagonists that do not fall within that structure. EX1029, 1060-63, Figs. 1, 6, 11; EX1003, ¶¶62-67. These include monocyclic CRF1 receptor antagonists, which have a monocyclic heterocycle (instead of the bicyclic heterocycle that Williams describes as "typical"), and atypical CRF1 antagonists, which "do not appear to overlap in similar chemical space to the traditional compounds." *Id.* As the Board previously found, Williams indicates "a very considerable structural diversity of molecules that can act as CRF1 receptor antagonists." EX1005, 55.

Williams provides no information on whether any CRF1 receptor antagonist structure can achieve the function of treating CAH, reducing glucocorticoid dosing, and reducing A4, ACTH or 17-OHP levels from baseline. EX1003, ¶¶64-65; EX1029. In fact, Williams does not mention CAH at all. *Id.* Williams discloses that the majority of clinical studies examining CRF1 receptor antagonists studied stress-related conditions such as anxiety, depression, substance abuse, post-traumatic stress disorder, and stress-induced relapse in craving responses to food, nicotine, and alcohol. EX1029, 1058-59; EX1003, ¶¶64-65; EX1005, 55. These studies provide no information on a structure/functional relationship of CRF1 receptor antagonists that could treat CAH.

Moreover, none of the antagonists studied worked. Williams reports that the “typical” CRF1 receptor antagonist subclass “ha[s] been associated with less than optimal physicochemical properties and it was assumed that these were a major contributor to CRF1 antagonist struggles in the clinic.” EX1029, 1058; EX1003, ¶63. Williams goes on to describe a number of optimization efforts that were aimed at improving the physicochemical properties of CRF1 antagonists. EX1029, 1058-60; EX1003, ¶63. But Williams nonetheless concludes that “antagonists of the CRF1 receptor have not demonstrated clinical utility despite over 30 years of research and hundreds of patents.” EX1029, 1065; EX1003, ¶65. In sum, Williams provides a POSA no evidence of any relationship between CRF1 receptor

antagonist structure and the function of treating CAH. *Ariad*, 598 F.3d at 1350.

Fahmy (EX1018) does not permit a POSA to recognize the claimed genus either. Like Williams, Fahmy provides a POSA with no information regarding CRF1 receptor antagonist structure and the claimed functions. Rather, Fahmy discloses a broad structure described as a “basic CRF1 receptor antagonist pharmacophore” that encompasses a large and indeterminate number of chemical structures. EX1018, 272, Fig 1; EX1003, ¶¶68. Fahmy describes multiple classes of CRF1 receptor antagonists—monocyclic, bicyclic, and tricyclic—some of which fall within the Fahmy’s “basic pharmacophore” and some of which do not. EX1018, 272-74, Figs. 2-5; EX1003, ¶¶68-72; *see also* EX1005, 48-51. Fahmy also describes subclasses of each of the monocyclic, bicyclic, and tricyclic CRF1 receptor antagonists, all of which have different chemical structures. *Id.*

Fahmy likewise provides no information on the structural features of CRF1 receptor antagonists that can achieve the claimed functions of treating CAH, much less doing so in a way that reduces glucocorticoid dosing and reduces A4, ACTH, or 17-OHP levels from baseline. Fahmy’s clinical focus is on “aliments associated with stress such as depression, anxiety, and stress-induced relapse in drug addiction.” EX1018, abstract. The article concludes that “a new class of antidepressants and anti-anxiety agents” may emerge from the study of CRF1 receptor antagonists. *Id.*, 277; EX1005, 51. Fahmy makes only a single mention of

CAH, stating that one CRF1 antagonist was under investigation as a possible treatment for the disease. EX1018, 276; EX1003, ¶72. Nothing in Fahmy, however, would inform a POSA whether a particular CRF1 receptor antagonist could treat CAH in a human, reduce glucocorticoid dosing, and reduce an A4, ACTH, or 17-OHP level, let alone the structural features of such antagonists that could achieve these clinical effects. EX1003, ¶72.

As Dr. Lodish explains, the prior art as a whole taught that it was highly unpredictable whether any CRF1 receptor antagonist would be therapeutically-effective in a human for any indication, much less to treat CAH. EX1003, ¶¶62-75. Dr. Lodish's opinion is consistent with the Board's previous findings that the teachings of the prior art demonstrate "a very considerable structural diversity of molecules that can act as CRF1 receptor antagonists" (EX1005, 55), but that "very few studies existed that CRF1 receptor antagonists are effective for the treatment of CAH, as recited in the challenged claims" (*id.*, 56).

As in the previous PGRs, here: (1) the specification discloses only a single species of the claimed genus; (2) Spruce's own publication describes that single species as having "unique structural features"; (3) there was little to no knowledge in the prior art regarding CRF1 receptor antagonists achieving the claimed therapeutic effects; (4) the use of CRF1 receptor antagonists to treat CAH, or any clinical application, was unpredictable; and (5) the structure-function relationship

for CRF1 receptor antagonists was largely unknown and unpredictable. EX1005, 58-59. A POSA would not have recognized, either from the specification or the prior art, the “structure, formula, chemical name, physical properties, or other properties of species” falling within the claimed genus of CRF1 receptor antagonists. *Id.*, 59; *see also Ariad*, 598 F.3d at 1350. The Board should find the Challenged Claims unpatentable for failing to meet the written description requirement of §112(a).<sup>6</sup>

### **3. There is No Written Description Support for the Challenged Claims’ Stability Limitation**

The Challenged Claims are even more deficient than the claims the Board found unpatentable in PGR2021-00088 and PGR2022-00025, because there is also no written description support for the requirement that all members of the recited genus of CRF1 receptor antagonists be “stable for storage for a minimum of six months.” EX1001, 48:63-50:48. As Neurocrine’s expert, Dr. David Bugay, explains, the only stability information disclosed in the specification relates to Compound 1 (tildacerfont). EX1004, ¶¶30-53.

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<sup>6</sup> While the Petition sets forth an additional ground for unpatentability, if the Board finds the Challenged Claims unpatentable for lacking written description, it need not reach the other ground. *See Arthrex, Inc. v. Gelfand*, IPR2023-00014, Paper 45, 59-60 (PTAB Mar. 11, 2024); *Boston Sci. Scimed, Inc. v. Cook Grp. Inc.*, 809 F.App’x 984, 990 (Fed. Cir. 2020).

As an initial matter, the specification describes stability only in reference to

Compound 1:

Stable *as used herein* refers to pharmaceutical compositions *having about 95% or greater of the initial Compound 1 amount* and about 5% w/w or less total impurities or related substances at the end of a given storage period. The percentage of impurities is calculated from the amount of impurities *relative to the amount of Compound 1*.

EX1001, 25:20-28 (emphases added). It makes little sense that the Challenged Claims recite a sweeping genus of CRF1 receptor antagonists that are “stable” for at least 6 months but the specification describes that stability requirement only in terms of Compound 1 (tildacerfont). The inconsistency in the specification’s explanation of “stable” and the scope of the Challenged Claims further highlights Spruce’s attempt to claim more than it invented.

As Dr. Bugay explains, the only stability data disclosed in the ’166 patent relates to capsules containing Compound 1 (tildacerfont). EX1001, 34:57-36:57; EX1004, ¶53. The specification concludes only that “supportive data demonstrate that *the pharmaceutical composition*”—i.e., Compound 1—is stable for a minimum of 6 months. *Id.*, 36:45-48. There is no disclosure of whether any other CRF1 receptor antagonist in the claimed genus would be stable for storage for 6 months or more. EX1004, ¶¶47, 51.

The defectiveness of the stability disclosures in the specification is exacerbated by the fact that the Challenged Claims are unlimited as to dosage

form. Beyond the capsules of Compound 1 (tildacerfont) tested in Example 2, the specification fails to inform a POSA as to whether other members of the claimed genus of CRF1 receptor antagonists would meet the claimed stability requirements for different dosage forms. EX1004, ¶52. Indeed, Spruce argued to the Examiner that the claimed dosages of Compound 1 tested in Example 2 were special, having “an unexpected benefit of being more stable for shelf storage.” EX1002, 2501.

For the same reasons described above regarding the clinical limitations of the Challenged Claims, the '166 patent specification does not disclose a representative number of species or common structural features of the claimed genus of CRF1 receptor antagonists that would meet the stability limitation, such that a POSA could visualize or recognize members of the genus. *Ariad*, 598 F.3d at 1350. The Challenged Claims lack written description support for this additional reason.

**B. Ground 2: Claims 1-10, 12-21 are unpatentable for lack of enablement**

Section 112(a) also requires that the specification enable the claimed invention. 35 U.S.C. § 112(a). “The more one claims, the more one must enable.” *Amgen*, 598 U.S. at 610. Just as the Supreme Court held in *Amgen*, the Board should determine that the Challenged Claims lack enablement. EX1003, ¶¶52-55, 76-93.

The Challenged Claims—like the claims in *Amgen*—cover “an entire class of things defined by their function.” 598 U.S. at 613. In *Amgen*, the entire class was “every antibody that binds to particular areas of the sweet spot of PCSK9 and blocks PCSK9 from binding to LDL receptors.” *Id.* Here, the entire class is every CRF1 receptor antagonist that treats CAH and achieves specific clinical results (i.e., reducing glucocorticoid dosing and reducing an A4, ACTH, or 17-OHP level from baseline). EX1001, Claim 1; EX1003, ¶¶77-79. Spruce (like the patent owner in *Amgen*) cannot dispute that its claims cover a broad genus of CRF1 receptor antagonists having the claimed functions. *See, e.g.*, EX1005, 43-44 (Board finding that claims reciting “a CRF<sub>1</sub> receptor antagonist or a pharmaceutically acceptable salt thereof” encompass “all members of the genus of CFR<sub>1</sub> receptor antagonists” that perform the claimed function (i.e., reducing ACTH or 17-OHP levels)). But as the Supreme Court explained, this poses Spruce “with a challenge. For if our cases teach anything, it is that the more a party claims, the broader the monopoly it demands, the more it must enable.” *Amgen*, 598 U.S. 613.

Here, the ’166 patent disclosure—like in *Amgen*—does not enable a POSA to make and use the claimed invention. Instead, it provides nothing more than a hunting license for identifying functional CRF1 receptor antagonists by a laborious trial-and-error approach. 598 U.S. at 614. The ’166 patent discloses only Compound 1 (tildacerfont). EX1001, 1:40-43; EX1003, ¶79. It does not identify

what qualities make Compound 1 (tildacerfont) particularly suited to treat CAH, reduce glucocorticoid dosing, and reduce A4, ACTH, or 17-OHP levels, nor does it identify any other CRF1 receptor antagonist out of the broadly claimed genus of CRF1 receptor antagonists that could achieve those functions. EX1003, ¶79. In the absence of “a quality common to every functional embodiment,” as the Court explained, the specification provides mere “random trial-and-error discovery”—not enablement. *Amgen*, 598 U.S. at 614-615. This lack of disclosure is particularly acute here because the record shows that the only disclosed CRF1 receptor antagonist, Compound 1 (tildacerfont), was a clinical failure. EX1003 ¶88; EX1058 (announcing that a phase IIb study of once-daily tildacerfont in adult CAH “did not achieve primary endpoint of glucocorticoid reduction” and that Spruce is “winding down [it]’s investment in tildacerfont for the treatment of CAH”). In contrast, Neurocrine showed a different species in the CRF1 receptor antagonist genus, crinecerfont, was highly effective in clinical trials. EX1052; EX1053.

Although *Amgen* does not discuss the *Wands* factors, Neurocrine presents a discussion of the *Wands* factors below to assist the Board in determining that the Challenged Claims lack enablement. 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); *see also Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991) (stating that the *Wands* factors “are illustrative, not mandatory”).

The *Wands* factors show that, even allowing for some reasonable degree of experimentation, a POSA is left here with the same trial-and-error approach that the Supreme Court rejected in *Amgen*. The Board should follow the Court’s analysis in *Amgen* and conclude that the Challenged Claims are unpatentable for lack of enablement.

**1. The broad scope of the claims weighs against enablement (Factor 8)**

All Challenged Claims encompass every CRF1 receptor antagonist that has the function of treating CAH, reducing glucocorticoid dosing, and reducing levels of A4, ACTH, or 17-OHP from baseline. *See, e.g.*, EX1005, 43-44 (Board finding that claims reciting “a CRF<sub>1</sub> receptor antagonist or a pharmaceutically acceptable salt thereof” encompasses “all members of the genus of CFR<sub>1</sub> receptor antagonists” that perform the claimed function). On its face, claim 1 encompasses a large and indeterminate number of CRF1 receptor antagonists. EX1003, ¶¶77-79; EX1005, 57. The claim recites no structural requirements for the CRF1 receptor

antagonists—only that they function in the way claimed. EX1003, ¶¶77-78.

No other Challenged Claim narrows that broad genus of CRF1 receptor antagonists or recites any “quality common to every functional embodiment” of that genus. *Amgen*, 598 U.S. at 614. The remaining Challenged Claims specify only the amount of hormone reduction (claims 2-6), the timing of hormone reduction (claims 7-9), features related to co-administrating a glucocorticoid (claims 10, 12-15, and 20), CRF1 receptor antagonist administration route and timing (claims 16-19), and the stability of the CRF1 receptor antagonist (claim 21). EX1001, 49:20-50:2, 50:23-48.

The *only* claim that actually recites a CRF1 receptor antagonist purportedly having the functions of treating CAH, reducing glucocorticoid dosing, and reducing A4, ACTH, or 17-OHP levels by its structure—Compound 1 (tildacerfont) (claim 11)—is not challenged in this Petition. This factor weighs against enablement.

**2. The '166 patent's lack of guidance for making and using the claimed genus (Factor 2) and examples limited to Compound 1 (Factor 3) weigh against enablement**

The '166 patent provides a POSA little to no guidance about the broadly claimed genus of CRF1 receptor antagonists. EX1003, ¶¶79-93. For example, the specification provides the POSA with no starting point for selecting compounds to

test for CRF1 receptor antagonist activity. EX1003, ¶80. The specification also provides no guidance as to which CRF1 receptor antagonists (e.g., out of those already known) will treat CAH in a human, reduce glucocorticoid dosing, and reduce A4, ACTH, or 17-OHP levels from baseline. EX1003, ¶¶81-88. The specification discloses only a single CRF1 receptor antagonist—Compound 1 (tildacerfont)—that allegedly performs these functions. EX1001, 1:40-64, 14:40-15:4; EX1003, ¶¶81-84. Every example in the specification relates to Compound 1 (tildacerfont). EX1001, 34:50-48:61; EX1003, ¶¶81-84. Not coincidentally, the '166 patent repeatedly calls Compound 1 “the invention.” EX1001, abstract, 1:40-48, 26:50-55; EX1003, ¶34.

At most, the '166 patent states that “the development of biologically-active small molecules having significant CRY [*sic*] receptor binding activity and which are capable of antagonizing the CRF<sub>1</sub> receptor remains a desirable goal.” EX1001, 12:16-21. The '166 patent also states that CRF1 receptor antagonists have “been the subject of ongoing research and development for the treatment of” a wide range of diseases, including “anxiety, depression, irritable bowel syndrome, post-traumatic stress disorder, and substance abuse.” *Id.*, 12:21-24. But the '166 patent never explains *why* any particular CRF1 receptor antagonists out of the large and indeterminate number of unique chemical structures making up the genus of CRF1 receptor antagonists would treat CAH in a human and achieve the clinical effects

of reducing glucocorticoid dosing and an A4, ACTH, or 17-OHP level from baseline.<sup>7</sup> EX1003, ¶¶90-93; EX1005, 57. And a POSA would be aware of literature reporting that “antagonists of the CRF1 receptor have not demonstrated clinical utility despite 30 years of research and hundreds of patents.” EX1029, 1065.

The '166 patent does not provide a POSA with any quality common to members of the genus (such as size, structure, chemical nature, drug absorption, metabolism, or receptor binding affinity) so that a POSA could make and use CRF1 receptor antagonists other than Compound 1 (tildacerfont). EX1003, ¶¶90-93. The '166 patent does not describe any features common to CRF1 receptor antagonists that could accomplish the claimed clinical results. EX1003, ¶¶87-93. Indeed, the '166 patent does not even describe any structural features common to CRF1 receptor antagonists *per se*. And the '166 patent does not distinguish effective from ineffective CRF1 receptor antagonists. *Id.*

The examples in the '166 patent provide, at most, a means for packaging Compound 1 (tildacerfont) in a hard gelatin capsule (Example 1), testing the stability of those capsules over time (Example 2), and the results from Phase I and

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<sup>7</sup> As explained in Section VII.A above, this is because the named inventors did not have possession of the use of an entire genus of CRF1 receptor antagonists to treat CAH, reduce glucocorticoid dosing, and reduce an A4, ACTH, or 17-OHP level from baseline. *See* Section VII.A, *supra*.

Phase II clinical trials of Compound 1 (tildacerfont) (Examples 3-4). The remaining examples are prophetic examples for studying the effects of Compound 1 (tildacerfont) in advanced clinical studies (Examples 5-8). EX1001, 33:35-48:61. Nothing in these examples provides a POSA with any guidance as to which compounds out of the broadly claimed genus of CRF1 receptor antagonists will treat CAH in a human by reducing glucocorticoid dosing and A4, ACTH, or 17-OHP levels. EX1003, ¶¶81-84.

All the '166 patent does is provide the POSA with a research assignment: a trial-and-error test of potential CRF1 receptor antagonists to see if they work. EX1003, ¶¶78, 80, 93. As the Supreme Court explained, “[t]hat is not enablement.” *Amgen*, 598 U.S. at 614. These factors weigh against enablement.

**3. The undue amount of experimentation necessary to identify CRF1 receptor antagonists that achieve the recited results (Factor 1) and the lack of any structure-function relationship for CRF1 receptor antagonists in the art (Factor 5) weigh against enablement**

The '166 patent's research assignment would require undue experimentation. EX1003, ¶¶80-88. Again, the '166 patent discloses only one CRF1 receptor antagonist—Compound 1 (tildacerfont)—but claims every CRF1 receptor antagonist capable of treating CAH in a human, reducing glucocorticoid dosing, and reducing an A4, ACTH, or 17-OHP level from baseline. The only way

a POSA could determine which compounds not only bind to and antagonize the CRF1 receptor, but also achieve the claimed clinical results in a human, would be to make and test an undue number of compounds through an iterative, trial-and-error process.

As Dr. Lodish testifies, in addition to CRF1 receptor antagonists already known, the claimed genus of CRF1 receptor antagonists potentially encompasses many more candidates. EX1003, ¶¶77-78. These potential CRF1 receptor antagonists include not only small molecule receptor antagonists, but also large molecules such as peptides. EX1018, 272. Indeed, the Board recognized that the scope of the claimed CRF1 receptor antagonist genus represents “a very considerable structural diversity of molecules” that could be “peptidergic or small molecule receptor antagonists.” EX1005, 55-56.

A POSA would be required to synthesize and screen a large and indeterminate number of candidate compounds to determine which are even CRF1 receptor antagonists. EX1003, ¶80. Dr. Bugay further testifies that this trial-and-error approach would take several years and would cost millions of dollars. EX1004, ¶¶26-29. Then—because the challenged claims require a specific clinical outcome (i.e., treatment of CAH in a human, reduction of glucocorticoid dosing, and reduction of an A4, ACTH, or 17-OHP level from baseline)—a POSA would have to conduct years of costly clinical trials to test the candidate compounds in

the few CAH patients that exist. EX1003, ¶¶85-88. That is undue experimentation. *See Wyeth & Cordis Corp. v. Abbott Lab's*, 720 F.3d 1380, 1385 (Fed. Cir. 2013) (finding undue experimentation where a POSA would “need, at a minimum, to engage in a laborious iterative process to determine what candidates fall within the claimed genus”).

Knowledge in the art does not compensate for the failure of disclosure in the '166 patent. As the Board previously found, “the structure-function relationship between CRF<sub>1</sub> receptor and CRF<sub>1</sub> receptors was still largely unknown and unpredictable.” EX1005, 59 (citing EX1029, 1065-66). Indeed, the Board found that compounds that bind to and antagonize the CRF<sub>1</sub> receptor encompass “a wide variety of large and small molecule compounds.” *Id.*, 58-59 (citing EX1018; EX1029).

These include, for example, CRF<sub>1</sub> receptor antagonists comprising (1) monocyclic, (2) bicyclic, or (3) tricyclic nitrogen cores. EX1005, 49 (citing EX1018, 272-74); EX1003, ¶¶62-72. Of these, monocyclic CRF<sub>1</sub> receptor antagonists can be subclassified, based upon the nature of the central ring structure, into (a) pyrazines, (b) pyridines, (c) pyrimidines, and (d) thiazoles. *Id.* (citing EX1018, 272-74); EX1003, ¶69. Bicyclic CRF<sub>1</sub> receptor antagonists can be subclassified into: (a) pyrrolo[2,3-d]pyrimidines, (b) pyrazolo[1,5- $\alpha$ ]1,3,5-triazines, (c) pyrazolo[1,5- $\alpha$ ]pyrimidines, and (d) imidazo[1,2-b]pyridazines. *Id.* at

50 (citing EX1018, 274-76); EX1003, ¶70. And tricyclic CRF1 receptor antagonists can be subclassified into: (a) triazaacenaphthylenes, and (b) tetraazaacenaphthylenes. EX1005, 51 (citing EX1018, 276-77); EX1003, ¶71. CRF1 receptor antagonists can also include compounds that fall outside these structures—with additional rings adjacent to the core nitrogen heterocycle and those with the branched alkyl region supported by additional ring. EX1005, 53-54 (citing EX1029, 1061, Figs. 7, 8).

In addition to “Type I” antagonists, the prior art included “Type II” CRF1 receptor antagonists having “more complicated side chains for biological activity” (EX1005, 54 (quoting EX1029, 1061)), as well as “other, atypical CRF1 receptor antagonists that do not appear to be directly related to the traditional Type I or II CRF1 antagonists” (*id.* (quoting EX1029, 1062)); *see also* EX1003, ¶67. “Type II” CRF1 receptor antagonists can have both monocyclic and bicyclic nitrogen cores, while the “atypical” CRF1 receptor antagonists “include benzimidazole-containing amides, a ‘very unusual phenol,’ amidrazones, and N-phenylphenyl glycines, and a trans-4-aminomethylcyclohexylamine with links to two aryl groups.” EX1005 (quoting EX1029, 1062-63); EX1003, ¶67.

Given these teachings, the Board concluded that the claimed genus of CRF1 receptor antagonists were “far from being a well-known, well-characterized, and discrete class.” EX1005, 56. Instead, the genus represented “a heterogeneous

assembly of different classes of small molecule CRF<sub>1</sub> 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.” *Id.*, 57.

Spruce’s own post-filing date publication describes Compound 1 (tildacerfont)—the only CRF<sub>1</sub> receptor antagonist disclosed in the specification—as being a “second-generation CRF<sub>1</sub> antagonist” having “unique structural features” compared to other CRF<sub>1</sub> receptor antagonists. EX1041, 4667; EX1003, ¶¶90. But nothing in the ’166 patent describes these “unique structural features” or guides the POSA in making and using other CRF<sub>1</sub> receptor antagonists within the broadly claimed genus of compounds that might share these features. EX1003, ¶¶90. These factors weigh against enablement.

**4. The complex nature of treating CAH patients  
(Factor 4) and unpredictability in the art (Factor 7)  
weigh against enablement**

Even if Compound 1 (tildacerfont) shares some common structural features with other CRF<sub>1</sub> receptor antagonists, a POSA would still not know whether any of those other CRF<sub>1</sub> receptor antagonists could treat CAH in a human, reduce glucocorticoid dosing and reduce an A4, ACTH, or 17-OHP level from baseline without impermissible trial-and-error testing, given the high level of unpredictability in the art. EX1003, ¶¶85-89. Indeed, as the Board previously

found, “the effective use of CRF1 receptor antagonists in the treatment of CAH, or indeed in any clinical application, at the time of filing, was far from being mature, and was unpredictable.” EX1005, 59 (citing EX1018, 276; EX1029, 1065).

Specifically, at the time of the ’166 patent, **no** CRF1 receptor antagonist had demonstrated **any** clinical utility “despite over 30 years of research and hundreds of patents.” EX1029, 1065; EX1003, ¶89. CRF1 receptor antagonists had been studied for indications other than CAH and were ineffective. EX1030, 377-78 (two CRF1 receptor antagonists failed to show efficacy in treating depression); EX1031, 24-25 (same); EX1066, Table 1 (noting several CRF1 receptor antagonists lacked efficacy); EX1003, ¶¶73, 89. Given this data, a POSA would not have thought a class of CRF1 receptor antagonists were useful for any indication, much less useful to treat CAH, reduce glucocorticoid dosing, and reduce an A4, ACTH, or 17-OHP level from baseline in view of the prior art. *Id.*, ¶89. This is particularly true because the specification discloses only Compound 1 (tildacerfont) and does not provide any way “to distinguish effective from ineffective compounds among those encompassed by the broad genus so claimed.” *Idenix Pharms., LLC v. Gilead Sciences Inc.*, 941 F.3d 1149, 1165 (Fed. Cir. 2019).

Moreover, as Dr. Lodish explains, a POSA would have expected differences in therapeutic effectiveness among different CRF1 receptor antagonists based on their CRF1 receptor affinity. Grigoriadis, for example, tested 13 different CRF1

receptor antagonists and found a 980-fold difference in the kinetically determined CRF1 receptor affinities. EX1006, ¶78; EX1003, ¶74. Grigoriadis also reported dramatically different half-lives for CRF1 receptor antagonist dissociation (from 2.6 min for NBI 27914 to 430 min for crinecerfont—a 165-fold difference) among the 13 different CRF1 receptor antagonists. EX1006, ¶¶80-83; EX1003, ¶74. Nothing in the '166 patent describes structure that could result in greater receptor affinity nor compares differences in effectiveness between Compound 1 (tildacerfont) and CRF1 receptor antagonists with weaker receptor affinity. EX1003, ¶74.

For these reasons, a POSA could not predict *which* CRF1 receptor antagonists would treat CAH in a human, reduce glucocorticoid dosing, and reduce A4, ACTH, or 17-OHP levels from baseline. These factors weigh against enablement.

**5. The relatively high level of skill is does not support enablement (Factor 6)**

The relatively high skill of those in the art does not save the Challenged Claims. As in most cases involving pharmaceuticals, a POSA would have had a high level of education and experience. EX1003, ¶43. But the POSA's high level of education and experience does not compensate for the fact that—as the Board found in the previous PGRs—“there was *very little* knowledge” in the prior art

about the ability of CRF1 receptor antagonists to reduce hormone levels. EX1005, 58 (citing EX1018; EX1029). Indeed, faced with the same question in *Idenix*, the Federal Circuit held that a high level of skill in the art did not compensate for the fact that the patent at issue “d[id] not provide enough meaningful guidance or working examples, across the full scope of the claim, to allow a POSA to determine which” species out of a broadly claimed genus of compounds could perform the claimed function of treating hepatitis C without undue experimentation. 941 F.3d at 1162. The Board should find the same here.

In the end, a POSA would have to engage in trial-and-error testing to identify CRF1 receptor antagonists having the claimed function. And, as the Supreme Court explained, 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.

## **6. 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 the Challenged Claims lack enablement.

## **VIII. NO BASIS EXISTS FOR DISCRETIONARY DENIAL**

### **A. §324(a)**

This is the first petition challenging the claims of the '166 patent, and there is no co-pending litigation between the parties involving the '166 patent. Thus, discretionary denial under 35 U.S.C. §324(a) is not warranted. *See Gen. Plastic Industrial Co. v. Canon Kabushiki Kaisha*, IPR2016-01357, Paper 19 at 8-10 (PTAB Sept. 6, 2017) (precedential) (setting forth factors for discretionary denial of follow-on petitions); *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 at 5-6 (PTAB Mar. 20, 2020) (precedential) (setting forth factors for discretionary denial of petitions involving co-pending litigation).

### **B. §325(d)**

Discretionary denial under 35 U.S.C. §325(d) is also not warranted because the Examiner did not have the benefit of the Board's Final Written Decisions determining all claims of the '908 and '201 patents unpatentable for lack of written description. The '166 patent shares the same written description as the '908 and '201 patents and claims the same broad genus of CRF1 receptor antagonists that the Board determined was not adequately described by the common specification. Given the same claimed subject matter, the issuance of the claims of the '166 patent constitutes material error.

The Office applies a two-part framework for discretionary denial under §325(d). *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 8 (PTAB Feb. 13, 2020) (precedential). In the first part of the framework, the Board asks whether the same or substantially the same art or arguments were presented to the Office. *Id.*, 8. If either condition of the first part of the framework is satisfied, then then Board asks whether the petitioner has demonstrated that the Office erred in a manner material to patentability. *Id.* Here, neither part of the framework is satisfied.

First, neither written description nor enablement was raised during prosecution of the '166 patent. The Examiner issued only one non-final rejection of the claims for obviousness and double patenting. EX1002, 2474-87. The Examiner allowed the claims over the prior art after Spruce amended claim 1 to add a dosage range limitation (“wherein said CFR1 receptor antagonist or a pharmaceutically acceptable salt thereof is administered at a dose between about 50 mg/day and about 200 mg/day”) and a stability range limitation (“wherein the CFR1 receptor antagonist is stable for storage for a minimum of six months”). And the Examiner withdrew the double-patenting rejection after Spruce filed a terminal disclaimer. EX1002, 2528.

Nothing in the prosecution history shows that the Examiner rejected the claims under §112(a) or raised any issues at all about the written description or

enablement of the claimed genus of CRF1 receptor antagonists. Nor does the prosecution history show that that Spruce ever addressed written description or enablement. Indeed, Spruce specifically described both amendments to claim 1 as overcoming the prior art. *See* EX1002, 2501 (stating that the prior art “does not teach that the CRF1 receptor antagonist is stable in storage for a minimum of six months at the dosages described”). Nothing in the prosecution history suggests that Spruce made these amendments to narrow the scope of the claimed genus of CRF1 receptor antagonists to the subject matter actually disclosed in the specification—i.e., Compound 1 (tildacerfont). For these reasons, neither the same nor substantially the same arguments were presented to the Office and the *Advanced Bionics* inquiry should end here. *Advanced Bionics*, Paper 6 at 8; *see also, e.g., Motorola Mobility LLC v. Largan Precision Co.*, IPR2022-01170, Paper 11 at 9 (PTAB Jan. 26, 2023) (determining that the first part of the *Advanced Bionics* framework not met when “there were no arguments raised regarding written description support or whether any of the prior applications in the chain constituted prior art” in the prosecution history); *Adello Biologics LLC v. Amgen Inc.*, PGR2019-00001, Paper 13 at 10-11 (PTAB Apr. 19, 2019) (declining to exercise discretion under §315(d) where there was no express discussion of enablement during prosecution and petitioner had met the more-likely-than-not standard of institution).

Second, even if the same arguments were before the Office (they weren't), the Examiner erred in a manner material to patentability in allowing the claims because they lack written description and enablement under §112(a) for the reasons discussed above. *Supra* §§ VII.A-B. Although the Examiner initialed an IDS disclosing the Petitions and Decisions Granting Institution in the previous PGRs, Spruce disclosed all but one of those documents after the claims had already been allowed *twice*. Compare EX1002, 2513 (disclosing the Institution Decision in PGR2021-00088 pre-allowance) with EX1002, 2924 (disclosing the Petitions and Institution Decision in PGR2022-00025 after the second allowance). The Examiner, in any event, did not reopen prosecution to reject the claims.

Further, the Examiner did not have the benefit of the Board's Final Written Decisions in the previous PGRs determining claims reciting a broad genus of CRF1 receptor antagonists unpatentable for lack of written description. Put differently, when the issue of written description *was* squarely presented to the Office in the previous PGRs, the Board determined that the broad scope of the claims was not adequately described. EX1005, 42-59; EX1007, 40-57. It would be unjust for Spruce to maintain broad claims to every member of the genus of CRF1 receptor antagonists in the '166 patent in view of the Board's previous findings that the common specification only discloses Compound 1 (tildacerfont) and the art is unpredictable. *Id.* For these reasons, the Board should not exercise its discretion

to deny institution under §325(d).

**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 '166 Patent, nor is Petitioner aware of any pending civil actions involving the '166 patent.

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

Neurocrine provides the following designation of counsel.

| Lead Counsel                                                                                                                                                                                                                                            | Backup counsel                                                                                                                                                                                                                                                        |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
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**D. Service Information**

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

Neurocrine consents to email service at [PGR47291-0007PS1@fr.com](mailto:PGR47291-0007PS1@fr.com).

## **XI. CONCLUSION**

For the above-described reasons, claims 1-10 and 12-21 are unpatentable under 35 U.S.C. §112(a) for lack of written description and for lack of enablement. Accordingly, Petitioner requests that the Board grant the petition and hold claims 1-10 and 12-21 unpatentable.

Respectfully submitted,

Dated: February 10, 2025

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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 9,586 words, which is less than the 18,700 allowed under 37 CFR § 42.24.

Dated : February 10, 2025

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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 February 10, 2025, 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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