IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NEUROCRINE BIOSCIENCES, INC.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	C.A. No. _____
	)	
SPRUCE BIOSCIENCES, INC.,	)	
	)	
Defendant.	)	

COMPLAINT

Plaintiff, Neurocrine Biosciences, Inc. ("Neurocrine"), by and through its attorneys, brings this action against Spruce Biosciences, Inc. ("Spruce") for declaratory judgment of invalidity for U.S. Patent No. 11,344,557 (the "'557 patent"). Neurocrine alleges as follows:

INTRODUCTION

1. Neurocrine brings this lawsuit to prevent Spruce from capitalizing on Neurocrine's development of the first new therapy in over *70 years* for classic congenital adrenal hyperplasia ("CAH"). CAH is a rare and often deadly genetic disease associated with an excess of androgen, a male sex hormone. For the better part of a century, its standard of care has stagnated. A month ago, Neurocrine's dedication and innovation in classic CAH treatment reached fruition: after issuing "Fast Track," "Breakthrough Therapy," "Priority Review," and "Orphan Drug" designations, FDA approved Neurocrine's first-in-class adjunctive therapy, CRENESSITY™ (crinecerfont). As the first (and only) corticotropin-releasing factor type 1 (CRF_1) receptor antagonist therapy for classic CAH, crinecerfont meets a long-felt and unmet medical need to reduce high-dose glucocorticoid (steroid) treatment for management of classic CAH, which has serious complications from long-term use. This watershed moment in the treatment of classic CAH is the product of Neurocrine's ingenuity, long-term investment, deep

technical expertise, and determination to improve the lives of patients with limited treatment options.

2. Neurocrine's development of crinecerfont as a classic CAH therapy leans on over thirty years of its pioneering work on CRF_1 receptor antagonists—over twenty years of which predated Spruce's existence. In contrast to Neurocrine's commercial release of CRENESSITY™, Spruce's attempt to develop a therapeutically effective CRF_1 receptor antagonist for CAH has been an unquestionable failure. Spruce's entire product pipeline consists of just one compound: tildacerfont, a CRF_1 receptor antagonist. But Spruce's clinical testing of tildacerfont in CAH has been a dead end. Spruce's recent press releases reveal tildacerfont's inability to meet primary endpoints in two Phase 2b trials. Given those failures, Spruce announced on December 10, 2024, that it is "winding down Spruce's investment in tildacerfont for the treatment of CAH."[1]

3. Unable to directly compete with Neurocrine, Spruce is instead interfering with Neurocrine's CAH business with a portfolio of invalid, overbroad patents: U.S. Patent Nos. 10,849,908 (the "'908 patent"); 11,007,201 (the "'201 patent"); 12,115,166 (the "'166 patent"); and the '557 patent (collectively, the "Spruce CAH Patents"). Initially, the claims of the '908 patent, the earliest-filed of the Spruce CAH Patents, were limited to methods of treating CAH using Spruce's tildacerfont. The scope of those early claims mirrored the limited disclosure of the specification: Spruce's tildacerfont is the *sole* basis for the Examples and clinical data. And yet, Spruce improperly expanded its claims to cover the *entire genus* of CRF_1 receptor antagonists to

[1] Spruce Biosciences, "Spruce Biosciences Announces Topline Results from CAHmelia-204 in Adult CAH and CAHptain-205 in Adult and Pediatric CAH" (Dec. 10, 2024, https://investors.sprucebio.com/news-releases/news-release-details/spruce-biosciences-announces-topline-results-cahmelia-204-adult) (Exhibit E).

target Neurocrine's crinecerfont, without including structural limitations or sufficient written description support. All of the Spruce CAH Patents suffer from these same defects.

4. To nullify Spruce's impermissibly overbroad patents, Neurocrine petitioned for Post-Grant Review ("PGR") of Spruce's '908 and '201 patents by the Patent Trial and Appeal Board ("PTAB"). On November 26-27, 2024, the PTAB issued Final Written Decisions ("FWDs"), finding all claims of the '908 and '201 patents invalid for lack of written description.[2] Given Spruce's announcement that it is no longer pursuing tildacerfont for CAH[3]—and the fact that the Spruce CAH Patents are *only* directed to use of CRF_1 receptor antagonists in CAH—Spruce had no legitimate business reason to appeal the FWDs. Nevertheless, Spruce filed for Director Review of the FWDs on December 26, 2024, immediately after Neurocrine's CRENESSITY™ achieved FDA approval and launched on the market.[4]

5. It is clear that Spruce intends to interfere with Neurocrine's commercialization of CRENESSITY™. Since it terminated its CAH program, Spruce has *repeatedly* refused to provide Neurocrine with a covenant not to sue for infringement of the Spruce CAH Patents, or to refrain from challenging the FWDs invalidating the '908 and '201 patents. Instead, Spruce has sought "business discussions" (despite being *out of the business*)—a blatant

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[2] *Neurocrine Biosciences, Inc. v. Spruce Biosciences, Inc.*, PGR2021-00088, Paper 64 at 42-59 (PTAB, Nov. 26, 2024) (Exhibit F); Neurocrine Biosciences, Inc. v. Spruce Biosciences, Inc., PGR2022-00025, Paper 62 at 40-57 (PTAB, Nov. 27, 2024) (Exhibit G).

[3] Spruce Biosciences, "Spruce Biosciences Announces Topline Results from CAHmelia-204 in Adult CAH and CAHptain-205 in Adult and Pediatric CAH" (Dec. 10, 2024, https://investors.sprucebio.com/news-releases/news-release-details/spruce-biosciences-announces-topline-results-cahmelia-204-adult) (Exhibit E).

[4] *Neurocrine Biosciences, Inc. v. Spruce Biosciences, Inc.*, PGR2021-00088, Paper 65 (PTAB, Dec. 26, 2024) (Exhibit H); Neurocrine Biosciences, Inc. v. Spruce Biosciences, Inc., PGR2022-00025, Paper 63 (PTAB, Dec. 26, 2024) (Exhibit I).

attempt to extract money from Neurocrine for Spruce's portfolio of invalid, overbroad patents.[5] Indeed, Spruce's proposed "business discussions" are in the context of Spruce's desperate need for cash: it has publicly announced that it has a one-year runway based on its current cash burn rate.[6]

6. Given Spruce's staunch and repeated refusals to provide assurances, Neurocrine has no choice but to bring this action to remove the cloud of uncertainty Spruce is casting over its commercial release of CRENESSITY™. Because the '557 patent, unlike the '166 patent, is not PGR-eligible, we bring this action in this Court. This lawsuit will confirm that the impermissibly overbroad '557 patent is invalid.

NATURE OF THE ACTION

7. Neurocrine seeks declaratory judgment under the patent laws of the United States, 35 U.S.C. § 1 *et seq*., and the Declaratory Judgment Act, 28 U.S.C. §§ 2201 *et seq*., that the '557 patent is invalid.

PARTIES

8. Neurocrine Biosciences, Inc. is a corporation organized and existing under the laws of the State of Delaware, having a place of business at 12780 El Camino Real, San Diego, CA 92130.

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[5] *See* Letter to Dr. Javier Szwarcberg at Spruce Biosciences (Dec. 10, 2024, Exhibit J); Email from Michael Rosato at Wilson Sonsini Goodrich & Rosati (Dec. 17, 2024, Exhibit K); Letter to Michael Rosato at Wilson Sonsini Goodrich & Rosati (Jan. 6, 2025, Exhibit Y); Email from Michael Rosato at Wilson Sonsini Goodrich & Rosati (Jan. 10, 2025, Exhibit Z).

[6] Spruce Biosciences, "Spruce Biosciences Reports Third Quarter 2024 Financial Results and Provides Corporate Updates" (Nov. 11, 2024, https://investors.sprucebio.com/news-releases/news-release-details/spruce-biosciences-reports-third-quarter-2024-financial-results) (Exhibit N).

9. On information and belief, Spruce Biosciences, Inc. is a corporation organized and existing under the laws of the State of Delaware, having a place of business at 611 Gateway Boulevard Suite 740, South San Francisco, CA 94080.

JURISDICTION AND VENUE

10. This Court has subject matter jurisdiction over these claims for declaratory judgment pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202 based on an actual controversy between the parties arising under the patent laws of the United States, 35 U.S.C. § 1 *et seq*.

11. This Court has personal jurisdiction over Spruce because Spruce is a corporation organized and existing under the laws of Delaware, is qualified to do business in Delaware, and has appointed a registered agent for service of process in Delaware. As such, Spruce has purposefully availed itself of the privileges of conducting business in Delaware and consented to general personal jurisdiction in Delaware.

12. Venue is proper in this District with respect to Spruce, at least because, upon information and belief, Spruce is a corporation organized and existing under the laws of Delaware and therefore resides in Delaware for purposes of venue.

FACTUAL BACKGROUND

A. Neurocrine Was Founded to Address the Need for New Therapies for Patients with Limited Treatment Options

13. Since its founding in 1992, Neurocrine has focused on developing cutting-edge treatments for under-addressed diseases. Rare disease patients, in particular, often have limited treatment options; it is not uncommon for the standard of care to be unchanged for the better part of a century.

14. From its inception, Neurocrine has focused on transforming the treatment paradigm for underserved patients through substantial investment and years of research and

development. Neurocrine's founding scientist duo included Wylie Vale, Ph.D., a scholar at the Salk Institute for Biological Sciences and contributor to Nobel Prize-winning work in endocrinology, and Lawrence Steinman, M.D., a professor of Neurology and Pediatrics at Stanford University School of Medicine with a focus on neuroimmunology. Drs. Vale and Steinman marshalled their combined expertise in neurology and endocrinology to fulfill unmet medical needs for a constellation of diseases, with the goal of delivering novel therapies to patients with limited treatment options.

15. Leveraging its deep scientific and technical expertise, Neurocrine has a proven track record for therapeutic development, including four FDA-approved drugs—INGREZZA®, CRENESSITY™, ORILISSA®, and ORIAHN®. Neurocrine also has a robust pipeline of drug candidates currently in clinical trials, spanning a spectrum of disease states: dyskinetic cerebral palsy, rare pediatric epilepsy, movement disorders, adrenal insufficiency, schizophrenia, major depressive disorder, and other neuropsychiatric conditions.

B. Neurocrine's CRENESSITY™ Is the First New Treatment for Classic Congenital Adrenal Hyperplasia Patients in Over 70 Years

16. Classic CAH is a rare disease that affects about 30,000 people in the U.S. Starting from birth, classic CAH is a debilitating genetic condition in which patients' adrenal glands do not produce sufficient amounts of stress-regulating hormone cortisol. That lack of cortisol leads to increased secretion of a different class of hormones called androgens. This imbalance results in an array of life-long symptoms (*e.g.*, abnormal blood pressure and blood sugar, susceptibility to physical stressors, atypical genitalia, altered growth, and fertility issues), including the ever-present risk of adrenal crisis, a life-threatening condition. Despite the challenge of living with classic CAH, the same treatment options of hormone replacement, surgery, and/or

psychological support have existed for much of the last century—until the recent addition of first-in-class CRENESSITY™ (crinecerfont).

17. Neurocrine's pioneering work on CRF_1 receptor antagonists spans over thirty years. In 1995, Neurocrine scientists identified a naturally-occurring regulator of corticotropin-releasing factor ("CRF") receptors, and showed that interference with the binding of CRF receptors to their ligands modulates CRF receptor activity and downstream signaling. That same year, Neurocrine identified CRF receptors, including CRF_1, as potential drug targets for various endocrine, psychiatric, neurologic, and inflammatory disorders. In 1996, Neurocrine published on one of the first non-peptide synthetic CRF_1 receptor antagonists.

18. For almost two decades, Neurocrine iteratively improved its CRF_1 receptor antagonist drug candidates and explored their utility in new disease states. In 2012, Neurocrine launched a new clinical program for CAH. In 2014, Neurocrine filed two provisional patent applications describing and claiming treatment of CAH with crinecerfont, a CRF_1 receptor antagonist originally developed by Sanofi. In 2016, Neurocrine filed an Investigational New Drug (IND) application seeking authorization from FDA to test crinecerfont in humans.

19. After crinecerfont's promising initial data, Neurocrine performed years of extensive clinical testing of crinecerfont to support regulatory approval, including two Phase 3 trials in CAH patients: CAHtalyst Adult and CAHtalyst Pediatric. Indeed, Neurocrine's CAHtalyst represents the largest-ever clinical trial program of classic CAH. Both studies required extensive, multi-year efforts involving ~100-180 patients each and significant investment of Neurocrine's time and resources. As proof that crinecerfont is a medical breakthrough for a disease with decades of stagnant therapeutic development: the prestigious New England Journal of

Medicine published both Phase 3 trial results back-to-back in June 2024. Both CAHtalyst trials met their primary endpoints without any treatment-related serious adverse events.

20. Crinecerfont is a significant advancement in treatment of classic CAH. The standard of care for classic CAH requires high doses of glucocorticoids through hormone replacement therapy both to replace deficient cortisol and reduce excessive androgens. However, chronic treatment with such high doses of glucocorticoids is linked with serious complications, such as metabolic issues, bone loss, growth impairment, or iatrogenic Cushing's syndrome. Crinecerfont is the *first and only* therapy for classic CAH that allows patients to take *lower* doses of glucocorticoids while still maintaining or improving their androgen levels. In recognition of these benefits, crinecerfont received FDA's "Fast Track," "Breakthrough Therapy," "Priority Review," and "Orphan Drug" designations, which are collectively applied to treatments for serious conditions that show signs of substantial improvement in safety or efficacy over available therapy and fill an unmet medical need.

21. Neurocrine's efforts for over three decades culminated in FDA approval of CRENESSITY™ (crinecerfont) on December 13, 2024—the first new treatment available to classic CAH patients in over 70 years. Neurocrine commercially released CRENESSITY™ on December 20, 2024.

C. Spruce Has Failed to Develop its Only Product Candidate—Tildacerfont, a CRF_1 Receptor Antagonist—for CAH

22. On information and belief, Spruce was initially formed as a limited liability company in Delaware in November 2014 under the name Spruce Biosciences LLC. On information and belief, Spruce Biosciences LLC converted into a Delaware corporation in April 2016 under the name Spruce Biosciences, Inc. At the time of formation of Spruce's

precursor company, Neurocrine had already dedicated two decades to developing CRF_1 receptor antagonists and submitted patent applications for the use of crinecerfont to treat CAH.

23. In contrast to Neurocrine's success with crinecerfont, Spruce's attempts to develop a therapeutic CRF_1 receptor antagonist for CAH have repeatedly fallen short, failing each iteration of clinical testing.

24. Spruce has no approved products and lists only one drug candidate, tildacerfont, in its development pipeline.[7] Spruce licensed tildacerfont from Eli Lilly in May 2016. Spruce admits in SEC filings that the company "currently depend[s] entirely on the success of tildacerfont, which is [its] only product candidate."[8] Spruce further admits that "[i]f we are unable to advance tildacerfont in clinical development, obtain regulatory approval, and ultimately commercialize tildacerfont, or experience significant delays in doing so, our business will be materially harmed."[9]

Product Candidate	Indication	Status	
Tildacerfont	Polycystic Ovary Syndrome	Partnering opportunities available.	P.O.W.E.R. STUDY
	Major Depressive Disorder	Initiation of Phase 2 proof of concept study anticipated in the fourth quarter of 2024.	

25. Tildacerfont is a CRF_1 receptor antagonist, which, on information and belief, Spruce is currently developing *only* for potential use in polycystic ovary syndrome and major depressive disorder, but not CAH (since Spruce's clinical trials for tildacerfont in CAH

[7] Spruce Biosciences, "Pipeline" (accessed Jan. 13, 2025, https://sprucebio.com/pipeline/tildacerfont/) (Exhibit L).

[8] Excerpts of Spruce SEC Form 10-K (Mar. 18, 2024) at 42 (Exhibit M).

[9] *Id.*

patients have repeatedly failed to meet their primary endpoints). On information and belief, Spruce's non-CAH development programs are still in early stages; an underpowered Phase 2 study for polycystic ovary syndrome cannot establish statistical significance as to its primary endpoint, and a Phase 2 study for major depressive disorder (funded and conducted by a collaborator) is not yet underway.

26. In March 2024, Spruce reported that its first Phase 2b study (CAHmelia-203) of tildacerfont, in adult CAH patients with hyperandrogenemia, did not meet its primary endpoint of A4 reduction.

27. In December 2024, Spruce reported that a second Phase 2b study (CAHmelia-204) of tildacerfont, in adult CAH patients with relatively controlled A4, did not meet its primary endpoint of glucocorticoid reduction. On information and belief, because of its repeated failure to show clinical efficacy for tildacerfont in CAH, Spruce discontinued its final Phase 2 study (CAHptain-205). In a December 10, 2024 press release, Spruce announced that it would now be "winding down Spruce's investment in tildacerfont for the treatment of CAH" and focusing on cost-saving measures.[10]

28. On November 11, 2024, Spruce reported that it has only a one-year runway based on its current cash burn rate.[11] On information and belief, and in light of its inability to advance its "only product candidate," Spruce's continued survival cannot depend solely on its

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[10] Spruce Biosciences, "Spruce Biosciences Announces Topline Results from CAHmelia-204 in Adult CAH and CAHptain-205 in Adult and Pediatric CAH" (Dec. 10, 2024, https://investors.sprucebio.com/news-releases/news-release-details/spruce-biosciences-announces-topline-results-cahmelia-204-adult) (Exhibit E).

[11] Spruce Biosciences, "Spruce Biosciences Reports Third Quarter 2024 Financial Results and Provides Corporate Updates" (Nov. 11, 2024, https://investors.sprucebio.com/news-releases/news-release-details/spruce-biosciences-reports-third-quarter-2024-financial-results) (Exhibit N).

remaining, non-CAH development efforts for tildacerfont. Instead, it hopes to use its invalid Spruce CAH Patents, including the ’557 patent at issue in this suit, to improperly extract money from Neurocrine.

D. Spruce Improperly Expanded the Scope of its Patents with Overbroad Claims Bereft of Written Description Support

29. On information and belief, despite its development of only tildacerfont, Spruce has systematically collected an arsenal of patents with claims broadly directed to CRF_1 receptor antagonists without adequate written description support. On information and belief, Spruce obtained these patents to block competition by other CRF_1 receptor antagonists—and, more specifically, to target the first-in-class CRF_1 receptor antagonist, Neurocrine’s crinecerfont.

30. According to the face of the ’908 patent and the electronic records of the U.S. Patent and Trademark Office (“PTO”), the ’908 patent, titled “Corticotropin Releasing Factor Receptor Antagonists,” issued on December 1, 2020. The ’908 patent lists Alexis Howerton, Hal Gerber, and Michael Huang as the purported named inventors. The ’908 patent lists Spruce Biosciences, Inc. as the purported assignee. A true and correct copy of the ’908 patent is attached to the Complaint as Exhibit B.

31. According to the face of the ’201 patent and the electronic records of the PTO, the ’201 patent, titled “Corticotropin Releasing Factor Receptor Antagonists,” issued on May 18, 2021. The ’201 patent lists Alexis Howerton, Hal Gerber, and Michael Huang as the purported named inventors. The ’201 patent lists Spruce Biosciences, Inc. as the purported assignee. A true and correct copy of the ’201 patent is attached to the Complaint as Exhibit C.

32. According to the face of the ’557 patent and the electronic records of the PTO, the ’557 patent, titled “Corticotropin Releasing Factor Receptor Antagonists,” issued on May 31, 2022. The ’557 patent lists Alexis Howerton, Hal Gerber, and Michael Huang as the

purported named inventors. The ’557 patent lists Spruce Biosciences, Inc. as the purported assignee. A true and correct copy of the ’557 patent is attached to the Complaint as Exhibit A.

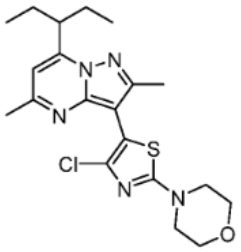
33. According to the face of the ’166 patent and the electronic records of the PTO, the ’166 patent, titled “Corticotropin Releasing Factor Receptor Antagonists,” issued on October 15, 2024. The ’166 patent lists Alexis Howerton, Hal Gerber, and Michael Huang as the purported named inventors. The ’166 patent lists Spruce Biosciences, Inc. as the purported assignee. A true and correct copy of the ’166 patent is attached to the Complaint as Exhibit D.

34. According to the faces of the Spruce CAH Patents, and the electronic records of the PTO, the ’908, ’201, ’557, and ’166 patents share the same specification, belong to the same patent family, and each contain independent claims directed to methods for treating CAH by administering a “CRF_1 receptor antagonist” (or a pharmaceutically acceptable salt thereof). Claim 1 of the ’557 patent is exemplary (Exhibit A at Claim 1):

> **1**. A method for treating congenital adrenal hyperplasia (CAH) in a human comprising administering to the human a therapeutically-effective amount of a CRF_1 receptor antagonist or a pharmaceutically acceptable salt thereof, wherein an adrenocorticotropic hormone (ACTH) level in the human is reduced by at least about 10% from baseline, and wherein a 17-hydroxyprogesterone (17-OHP) level is reduced in the human by at least about 10% from baseline.

35. According to the electronic records of the PTO, U.S. Patent Application No. 16/388,620 for the ’908 patent (the earliest-filed member of this patent family) was originally submitted on April 18, 2019, with claims directed *only* to methods of treating CAH with tildacerfont (or a pharmaceutically acceptable salt or solvate thereof) (*see* Exhibit O at Claim 1):

1. 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, wherein Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day.

36. According to the electronic records of the PTO, Spruce submitted a preliminary amendment that same day—April 18, 2019—cancelling all claims enumerating the tildacerfont structure and instead claiming the *entire genus* of CRF_1 receptor antagonists for treating CAH, but without a single structural limitation in the amended claims (*see* Exhibit P). The other Spruce CAH Patents subsequently issued with similarly broad claims.

37. Starkly contrasting the broad scope of the claims, the specification of the Spruce CAH Patents discloses a *single* CRF_1 receptor antagonist—tildacerfont. Tildacerfont, referred to as "Compound 1," is the *only* compound structure disclosed in the specification. Tildacerfont is also the *only* compound underlying all of the Examples and clinical data in the specification.

38. To overcome the Examiner's rejection during prosecution, Spruce admitted that it did not possess the genus of CRF_1 receptor antagonists. Spruce characterized tildacerfont's clinical activity profile in CAH as an "unexpected result" for administration of a CRF_1 receptor antagonist.[12] Spruce also represented that tildacerfont has a "significant and practical advantage"

[12] '908 File History (Appl. No. 16/388,620), Patent Owner's Supp. Amendment at 6 (June 15, 2020) (Exhibit Q).

over other CRF_1 receptor antagonists for use in CAH.[13] Spruce cannot justify its claims to the entire genus of CRF_1 receptor antagonists on the basis that disclosure of tildacerfont alone is sufficient when it previously argued that tildacerfont is different from *all other* CRF_1 receptor antagonists to get its patent allowed. Proof positive that all CRF_1 receptor antagonists are not the same: Spruce's sole embodiment is a clinical failure for CAH in contrast to Neurocrine's crinecerfont.

39. Nothing in the Spruce CAH Patents describes the entire genus of CRF_1 receptor antagonists and their use for treating CAH. The specification does not disclose a representative number of species falling within the genus of CRF_1 receptor antagonists or structural features common to the members of the genus such that one of skill in the art can visualize or recognize the members of the genus.

40. As such, the Spruce CAH Patents do not convey to a person of skill in the art that the inventors were in possession of the full scope of the claimed subject matter. The overbroad claims of the Spruce CAH Patents, including the '557 patent, are invalid at least for lack of written description.

E. The PTAB has Determined that Spruce's Overbroad Patents are Invalid For Lack of Written Description

41. Neurocrine filed a Petition with the PTAB for PGR of the '908 patent on May 28, 2021 (PGR2021-00088), asserting that the claims of the '908 patent were invalid on multiple grounds, including anticipation and obviousness based on prior art, lack of written description, and lack of enablement. The PTAB instituted PGR on December 1, 2023.

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[13] *Id.* at 7-8.

42. The Board issued a FWD on the PGR of the ’908 patent on November 26, 2024, agreeing with Neurocrine’s assessment that the specification does not provide written description support for claims to treatment of CAH using, without limitation, the genus of CRF_1 receptor antagonists. Specifically, the PTAB noted that: (1) specification disclosures in the Examples and clinical data were limited to tildacerfont, a single species of the claimed genus; (2) Spruce’s own publication noted tildacerfont had “unique structural features” compared to other members of the genus; (3) little was known in the art that could be relied upon to develop a CRF_1 receptor antagonist with therapeutic efficacy; (4) at the time of Spruce’s alleged invention, known species of the genus of CRF_1 receptor antagonists were structurally diverse; (5) effective use of CRF_1 receptor antagonists to treat CAH was unpredictable; and (6) the structure-function relationship between the CRF_1 receptor and any antagonists was “still largely unknown and unpredictable.” *Neurocrine Biosciences, Inc. v. Spruce Biosciences, Inc.*, PGR2021-00088, Paper 64 at 42-59 (PTAB, Nov. 26, 2024) (Exhibit F).

43. In a parallel proceeding, Neurocrine filed a Petition with the PTAB on May 28, 2021, for PGR of the ’201 patent (PGR2022-00025). This PGR followed the same procedural path as the PGR of the ’908 patent, including issuance of a FWD by the PTAB invalidating the ’201 patent claims for the same reasons as the ’908 patent. *Neurocrine Biosciences, Inc. v. Spruce Biosciences, Inc.*, PGR2022-00025, Paper 62 at 40-57 (PTAB, Nov. 27, 2024) (Exhibit G).

44. The FWDs were so decisive that the Board did not even reach the numerous other grounds for invalidity raised in Neurocrine’s Petitions. As the PTAB concluded: “a person of ordinary skill in the art would not have recognized, either from the express disclosures of the [’908/’201] 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." *Neurocrine Biosciences, Inc. v. Spruce Biosciences, Inc.*, PGR2021-00088, Paper 64 at 59 (PTAB, Nov. 26, 2024) (Exhibit F); *Neurocrine Biosciences, Inc. v. Spruce Biosciences, Inc.*, PGR2022-00025, Paper 62 at 57 (PTAB, Nov. 27, 2024) (Exhibit G).

45. Because the '557 and '166 patents share the same defects as the '908 and '201 patents, the PTAB's FWDs apply equally to the '557 and '166 patents, such that all the Spruce CAH Patents are invalid for lack of written description support. The '166 patent remains eligible for PGR, but the '557 patent is not.

46. On December 26, 2024, less than a week after Neurocrine commercially released CRENESSITY™ (crinecerfont), Spruce filed requests for Director Review of the FWDs invalidating the '908 and '201 patents. *Neurocrine Biosciences, Inc. v. Spruce Biosciences, Inc.*, PGR2021-00088, Paper 65 (PTAB, Dec. 26, 2024) (Exhibit H); *Neurocrine Biosciences, Inc. v. Spruce Biosciences, Inc.*, PGR2022-00025, Paper 63 (PTAB, Dec. 26, 2024) (Exhibit I).

F. Spruce's Interference with Neurocrine's CRENESSITY™ and Staunch Refusal to Provide a Covenant Not to Sue Present a Substantial, Real, and Immediate Harm to Neurocrine

47. There is an actual and substantial controversy between Spruce and Neurocrine, parties with adverse legal interests, which creates an immediate and real risk of harm to Neurocrine and its launch of CRENESSITY™.

48. On information and belief, from its inception, Spruce closely tracked Neurocrine's development of crinecerfont, in recognition of crinecerfont as the most advanced CRF_1 receptor antagonist candidate with Spruce's tildacerfont falling far behind. For example, Spruce reported in its earliest 10-Q report that in 2020, Neurocrine had just "completed a two-week Phase 2 clinical trial in adults with classic CAH" and had "initiated a Phase 2 clinical trial

in [children]."[14] In 2022, Spruce followed up on Neurocrine's pediatric classic CAH trial, reporting it "ha[d] completed a . . . 2-week Phase 2 clinical trial in adolescents aged 14 to17 years with classic CAH."[15] The following year, Spruce noted that Neurocrine "ha[d] initiated Phase 3 registrational trials in adult and pediatric classic CAH and reported positive topline results from both studies."[16] And most recently, in November 2024, Spruce reported on Neurocrine's efforts and market timing, noting the FDA had "accepted both NDAs with priority review designations with ***target action dates in December 2024***."[17] On information and belief, Spruce explicitly forecasted the competitive landscape following crinecerfont's approval, where "competitors also may obtain FDA . . . approval for their products more rapidly . . . which could result in our competitors establishing a strong market position before [Spruce is] able to enter the market or make [Spruce's] development more complicated."[18]

49. On information and belief, as Spruce tracked Neurocrine's market-leading progress with crinecerfont, Spruce deliberately acquired a portfolio of overly broad patents for assertion against Neurocrine's crinecerfont. As Spruce repeatedly emphasized in its SEC disclosures upon issuance of several of the Spruce CAH Patents, including the '557 patent, these patents "cover[] ***broad*** claims regarding the use of a ***CRF-1 receptor antagonist*** for the treatment of CAH."[19] Given that Neurocrine has the *first and only* approved CRF-1 receptor antagonist for

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[14] Excerpts of Spruce SEC Form 10-Q (Nov. 18, 2020) at 49 (Exhibit R).

[15] Excerpts of Spruce SEC Form 10-Q (Nov. 10, 2022) at 44 (Exhibit S).

[16] Excerpts of Spruce SEC Form 10-Q (Nov. 13, 2023) at 45 (Exhibit T).

[17] Excerpts of Spruce SEC Form 10-Q (Nov. 12, 2024) at 29 (Exhibit U) (emphasis added).

[18] *Id.* at 29-30.

[19] Spruce SEC Form 8-K (Jan. 6, 2021) at 6 ('908 patent) (Exhibit V); Spruce SEC Form 8-K (Aug. 10, 2021) at 4 ('201 patent) (Exhibit W); Spruce SEC Form 8-K (Aug. 10, 2022) at 5 ('557 patent) (Exhibit X).

the treatment of classic CAH, and had the only such compound in late stage development when Spruce made those statements, it was effectively telling the public, in its SEC disclosures, that its patents cover Neurocrine's products.

50. On information and belief, given the failure of its own CAH program, Spruce intends to recover its loss with tildacerfont by asserting the Spruce CAH Patents, including the '557 patent, to capitalize on Neurocrine's success with crinecerfont. On December 10, 2024, Spruce reported the second clinical failure of tildacerfont for treating CAH and announced the discontinuation of its development of CRF_1 receptor antagonists for CAH, noting that ongoing CAH "clinical trials will be discontinued, and [Spruce] will be winding down [its] investment in tildacerfont for the treatment of CAH."[20] On information and belief, without any marketable CAH product in its pipeline (since tildacerfont is Spruce's sole drug candidate), Spruce is essentially a patent holding company, dependent on enforcement of overly broad patents that it does not practice as a source of income.

51. On December 13, 2024, FDA approved Neurocrine's crinecerfont (*i.e.*, CRENESSITY™) for adult and pediatric classic CAH patients.

52. A week later, on December 20, 2024, Neurocrine commercially released CRENESSITY™ in the United States.

53. Within two weeks of CRENESSITY™'s approval and commercial launch as the only CRF_1 receptor antagonist therapy for classic CAH on the market, Spruce filed for Director Review seeking to restore the '908 and '201 patents. Those patents claim use of any

[20] Spruce Biosciences, "Spruce Biosciences Announces Topline Results from CAHmelia-204 in Adult CAH and CAHptain-205 in Adult and Pediatric CAH" (Dec. 10, 2024, https://investors.sprucebio.com/news-releases/news-release-details/spruce-biosciences-announces-topline-results-cahmelia-204-adult) (Exhibit E).

CRF_1 receptor antagonist, but *only* for treating *CAH*—an indication renounced by Spruce. There is only one reasonable explanation for Spruce's decision to seek Director Review: to position itself to imminently assert or otherwise exploit the Spruce CAH Patents, including the '557 patent, against Neurocrine.

54. Neurocrine faces significant uncertainty given the immediate and real threat of Spruce asserting its self-proclaimed "broad claims" (to CRF_1 receptor antagonists used to treat CAH) against recently-launched CRENESSITY™.

55. Spruce has staunchly refused—on multiple occasions—to provide Neurocrine with certainty as to a CRENESSITY™ market launch without the looming specter of an infringement suit.

56. Neurocrine first contacted Spruce requesting a covenant not to sue on December 10, 2024.[21] In its letter, Neurocrine raised the PTAB's FWDs (and the significant expense associated with its successful challenge of the '908 and '201 patents), as well as Spruce's targeting of Neurocrine with a portfolio of invalid patents, including the '557 patent. Neurocrine requested from Spruce, by December 18, 2024, a covenant not to sue Neurocrine with claims directed to CRF_1 receptor antagonists, such as crinecerfont, and a commitment not to challenge the PTAB's FWDs regarding the '908 and '201 patents.

57. Spruce did not provide the requested assurances.[22] Instead, counsel for Spruce reverted with a request for a "business discussion," despite that it had completely left the "business." Upon information and belief, Spruce's request was an improper attempt to extract money from Neurocrine with its portfolio of overly broad patents, including the '557 patent.

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[21] *See* Letter to Dr. Javier Szwarcberg at Spruce Biosciences (Dec. 10, 2024, Exhibit J).

[22] *See* Email from Michael Rosato at Wilson Sonsini Goodrich & Rosati (Dec. 17, 2024, Exhibit K).

Indeed, given Spruce's abandonment of its CAH business and its desperate need for cash (with a one-year runway based on its current cash burn rate), Spruce's proposed "business discussion" is an immediate and real threat to enforce its invalid patents unless Neurocrine pays ransom. Neurocrine responded that it was not interested in engaging in such coerced "business discussions" but was waiting for Spruce's covenant not to sue.[23]

58. Spruce did not provide the requested covenant not to sue—on patents that do not cover *any* product in its development pipeline. Instead, Spruce filed for Director Review of the FWDs invalidating the '908 and '201 patents.

59. On January 6, 2025, Neurocrine contacted Spruce yet again,[24] stressing Spruce's complete withdrawal from the CAH business and filing for Director Review of the PTAB's FWDs. Neurocrine emphasized that there was no legitimate business discussion to be had, because Spruce was improperly attempting to extract money from Neurocrine with plainly invalid patents. Neurocrine repeated its requests for written assurances by January 8, 2025. Spruce did not respond until January 10, 2025, again seeking a "business discussion" without providing the requested covenant not to sue.[25] On January 11, 2025, Neurocrine made clear that only written assurances would suffice and proceeded to file this action.[26]

60. Spruce has engaged in a course of conduct that shows a preparedness and a willingness to enforce its patent rights. A definite and concrete patent dispute exists between

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[23] *See* Email to Michael Rosato at Wilson Sonsini Goodrich & Rosati (Dec. 19, 2024, Exhibit K).

[24] *See* Letter to Michael Rosato at Wilson Sonsini Goodrich & Rosati (Jan. 6, 2025, Exhibit Y).

[25] *See* Email from Michael Rosato at Wilson Sonsini Goodrich & Rosati (Jan. 10, 2025, Exhibit Z).

[26] *See* Email to Michael Rosato at Wilson Sonsini Goodrich & Rosati (Jan. 11, 2025, Exhibit Z).

Spruce and Neurocrine on the former's "broad claims regarding the use of a CRF-1 receptor antagonist for the treatment of CAH," statements clearly directed towards Neurocrine, with its first-in-class drug meeting that description. Spruce's repeated refusal to give a covenant not to sue on those "broad claims"—in the immediate aftermath of Neurocrine's CRENESSITY™ launch and alongside its challenge of PTAB's invalidity determinations for patents it has no intention of practicing—make Spruce's intentions clear: to imminently enforce its patents against CRENESSITY™. Such an action would cause real, substantial harm to Neurocrine, including derailment of its recent CRENESSITY™ product launch.

61. Neurocrine has no choice but to file this lawsuit to remove the cloud of uncertainty Spruce has cast over Neurocrine's launch of CRENESSITY™. Neurocrine is in the untenable position of either abandoning CRENESSITY™ or running the risk of being sued for infringement, which is precisely the type of situation that the Declaratory Judgment Act was intended to remedy.

62. An actual, substantial, and justiciable controversy, within the meaning of 28 U.S.C. §§ 2201 and 2202, exists between Neurocrine and Spruce.

63. Neurocrine seeks a judicial determination and declaration that the '557 patent is invalid.

COUNT I - DECLARATORY JUDGMENT OF INVALIDITY OF U.S. PATENT NO. 11,344,557

64. Neurocrine repeats and incorporates paragraphs 1-63 as if fully set forth herein.

65. A real, immediate, and justiciable controversy exists between Neurocrine and Spruce regarding, *inter alia*, the invalidity of the '557 patent.

66. The claims of the ’557 patent are invalid for failure to comply with the statutory prerequisites of Title 35 of the United States Code, including without limitation, one or more of §§ 101, 102, 103, 112, improper inventorship, the doctrine of obviousness-type double-patenting, and/or any other judicially created or non-statutory requirements for patentability of patents, and/or in view of the defenses recognized in 35 U.S.C. § 282.

67. By way of further example and without limiting the grounds of invalidity that will be asserted in this action, each claim of the ’557 patent is invalid for failure to satisfy the written description requirement of 35 U.S.C. § 112. The claims of the ’557 patent are directed generally to methods of treating CAH using any species in the entire genus of CRF_1 receptor antagonists. But the ’557 patent fails to provide sufficient written description, such as a representative number of species falling within the genus of CRF_1 receptor antagonists 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. The specification therefore fails to demonstrate to a person of skill in the art that the inventors of the ’557 patent were in possession of the full scope of the claimed subject matter.

68. Neurocrine seeks a declaratory judgment from this Court that each claim of the ’557 patent is invalid for failure to satisfy one or more of the conditions for patentability in Title 35 of the United States Code and/or for any judicially-created and/or non-statutory bases for invalidity.

REQUEST FOR RELIEF

WHEREFORE, Plaintiff respectfully requests that the Court enter a Judgment and Order in its favor and against Spruce as follows:

(a) Declaring that the claims of the '557 patent are invalid;

(b) Declaring that this case is exceptional under 35 U.S.C. § 285;

(c) Awarding Neurocrine its attorneys' fees, together with costs and disbursements; and

(d) Awarding such other and further relief as the Court deems just and proper.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP

/s/ Rodger D. Smith II

Rodger D. Smith II (#3778)
Megan E. Dellinger (#5739)
1201 North Market Street
P.O. Box 1347
Wilmington, DE 19899
(302) 658-9200
rsmith@morrisnichols.com
mdellinger@morrisnichols.com

Attorneys for Plaintiff

OF COUNSEL:

Michael A. Morin
David P. Frazier
LATHAM & WATKINS LLP
555 Eleventh Street, NW, Suite 1000
Washington, DC 20004
(202) 637-2200

Arlene L. Chow
LATHAM & WATKINS LLP
1271 Avenue of the Americas
New York, NY 10020
(212) 906-1200

Yi Sun
LATHAM & WATKINS LLP
12670 High Bluff Drive
San Diego, CA 92130
(858) 523-5400

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