

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NEUROCRINE BIOSCIENCES, INC.,
Petitioner,

v.

SPRUCE BIOSCIENCES, INC.,
Patent Owner.

Case No. PGR2026-00059
Patent 12,569,491

**PATENT OWNER'S PRELIMINARY RESPONSE
PURSUANT TO 37 C.F.R. § 42.107**

TABLE OF CONTENTS

	<u>Pages</u>
I. INTRODUCTION	1
II. OVERVIEW OF '491 PATENT	3
III. THE PETITION FAILS TO ESTABLISH IT IS MORE LIKELY THAN NOT THAT ANY CHALLENGED CLAIM IS UNPATENTABLE.....	4
A. Ground 1: Petitioner's Written Description Challenge Is Incurably Deficient and Legally Erroneous	5
1. Petitioner Erroneously Ignores The <i>Ipsis Verbis</i> Support Of The Original Claims	5
2. Petitioner Fails to Explain Why Literal Support in the Specification Is Insufficient.....	12
3. A (Corrected) Typographical Error is Not Worth Exhausting Board Resources.....	17
B. Ground 2: Petitioner Fails to Demonstrate Lack of Enablement	19
1. Petitioner's Own Publications Undermine Its Enablement Challenge	21
2. Narrow Scope of Claims Defeats Petitioner's Enablement Challenge.....	24
a. Petitioner's Arguments Are Misplaced In View of a Narrow Scope of Explicitly Disclosed Compounds.....	25
b. Petitioner's Relied-Upon Caselaw is Inapt	28
c. Petitioner's Demand For Clinical Proof of Each Compound Is Not The Standard.....	29
C. Ground 3: Petitioner Fails to Demonstrate Obviousness	31
IV. CONCLUSION.....	33
V. APPENDIX.....	35

I. INTRODUCTION

Spruce Biosciences, Inc. (“Spruce”) is a small American company dedicated to advancing targeted, first-in-class therapies that address serious, underserved conditions. Its work includes targeted therapies for rare conditions like OARTs and TARTs—the kinds of conditions larger competitors often pass over.

Petitioner Neurocrine Biosciences, Inc. (“Neurocrine”) is a public company with a long history of using litigation for purposes of harassment. Since 2024, Petitioner has demanded “unconditional” access to Spruce’s intellectual property portfolio “without charge” under threat of continued patent challenges. EX2003, EX2004, EX2005, EX2006, 4, 10, 20 (threatening to exploit a perceived “desperate need for cash”). A district court in Delaware squarely rejected Petitioner’s “manufactured” dispute, observing that “if this is a war, only Neurocrine is waging it,” and that, “the most [Neurocrine] has pled is that Spruce refused to concede when Neurocrine asked it to do so.” EX2002, 1, 7, 10.

Petitioner’s current PGR challenges continue its history of harassment and amount to a misuse of Office resources. Should this case survive discretionary review (Paper 8), the petition should be denied institution because the challenges are incurably deficient, based on legal error, and fail on the merits.

The challenged claims are limited to a narrow set of 10 specific compounds that are explicitly disclosed in the specification and listed in the claims. The

challenges under 35 U.S.C. §112 (Grounds 1 & 2) are fundamentally deficient and fail in at least three ways. First, the petition argument critically ignores *ipsis verbis* support for the challenged claims, including originally filed claims substantively identical to those challenged here. It is well-established that original claims are considered part of the specification, and the Office has repeatedly deemed petitions in AIA challenges incurably deficient for ignoring such specification content, as Petitioner has done here. Second, the petition argument is premised on legal error in assuming descriptive support requires experimental data (e.g., actual reduction-to-practice) for literally every claimed species. There is no such requirement and Petitioner's arguments discussing different, broad genus claims are misplaced vis-à-vis the narrow set of 10 specifically claimed compounds at issue here. Third, Petitioner's arguments inexcusably ignore its own publications and its arguments elsewhere that are inconsistent with its §112 challenges. The petition argument is contradicted at least by Petitioner's own later published study presenting experimental verification that a claimed CRF₁ receptor antagonist (crinecerfont) successfully prevented growth of TART lesions.

Petitioner's prior art challenge (Ground 3) is an afterthought and based on argument inconsistent with the §112 challenges of Grounds 1 & 2. Furthermore, the same prior art was already considered by the Examiner during prosecution and the petition provides no reason to second-guess the Office's prior consideration of

those references here.

Accordingly, Patent Owner respectfully requests that institution be *denied*.

II. OVERVIEW OF '491 PATENT

The '491 patent is directed to the treatment of variants of the same underlying condition (one version male, one version female) with a discrete group of ten compounds having similar structure and a shared mechanism of action.

The claims concern treatment of adrenal rest tumors that occur in testes (TARTs) and in ovaries (OARTs). Such lesions derive from adrenal tissue interchelated within the organs during embryogenesis; the tissues undergo hyperplasia, producing lesions that may cause pain and infertility. EX1001, 1:39-51. Before the invention, there were no non-steroidal, non-surgical solutions to control, shrink, or reduce these disorders. *Id.*, 1:49-51.

The claimed methods treat the tumors with a discrete group of ten compounds expressly recited by the specification and having a shared mechanism of action. The ten claimed compounds are all explicitly identified as CRF₁ receptor antagonists for treating both TARTs and OARTs in the original application that issued as the '491 patent. *See, e.g.*, Section III.A.1.

The method of treating OARTs and TARTs with the closed group of ten compounds was claimed from the outset. As originally filed, the application's independent claim recited “[a] method of treating an endocrine disorder associated

with a corticotropin-releasing factor type-1 (CRF₁) activity, comprising administering to a subject in need thereof a small molecule CRF₁ antagonist” selected from the same closed group of ten compounds. Its dependent claim recited that “the endocrine disorder associated with CRF₁ activity is a testicular adrenal rest tumor (TART) or an ovarian adrenal rest tumor (OART).” EX2008, 246-47 (claim 4). The treatment of TART and OART with these CRF₁ receptor antagonists was therefore recited in the originally-filed claims, and the same subject matter is repeated throughout the specification. *E.g.*, EX1001, 2:4-8, 50:59-60, 79:21-25.

The Examiner allowed the challenged claims after substantive examination, which included (overcome) rejections of the claimed subject matter over prior art, including references Petitioner presents here. EX2008, 4659-60, 4671-72. In providing reasons for allowance, the Examiner found that “the closest prior art[] Howerton and Grigoriadis teach treatment of congenital adrenal hyperplasia by administering a CRF1 receptor antagonist, however, treating of the subject having an ovarian adrenal rest tumor or a testicular adrenal rest tumor, as required by the claims, is not taught or suggested.” *Id.*, 4671. The Grigoriadis reference cited by the Examiner in the reasons for allowance is the same reference that forms the foundation of Petitioner’s obviousness challenge.

III. THE PETITION FAILS TO ESTABLISH IT IS MORE LIKELY THAN NOT THAT ANY CHALLENGED CLAIM IS UNPATENTABLE

Institution of post-grant review requires a petitioner to “demonstrate that it is

more likely than not that at least 1 of the claims challenged in the petition is unpatentable.” 35 U.S.C. § 324(a); *see also* 37 C.F.R. § 42.208(c). The petitioner bears the unshifting burden to make that showing. 35 U.S.C. § 326(e) (“the petitioner shall have the burden of proving a proposition of unpatentability”); *Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015) (“the burden of persuasion is on the petitioner...and that burden never shifts to the patentee.”). Where, as here, the Petitioner falls short of this statutory threshold, the Office must deny institution.

A. Ground 1: Petitioner’s Written Description Challenge Is Incurably Deficient and Legally Erroneous

1. Petitioner Erroneously Ignores The *Ipsis Verbis* Support Of The Original Claims

Petitioner’s entire written description challenge ignores the patent application’s originally-filed claims, which are substantively identical to the challenged claims. This matters here because the content of the original claims contradicts virtually every written description argument Petitioner advances. The Petition can be denied for at least this reason alone.

The written description inquiry “requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art.” *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). The Federal Circuit has long recognized that originally-filed claims must be

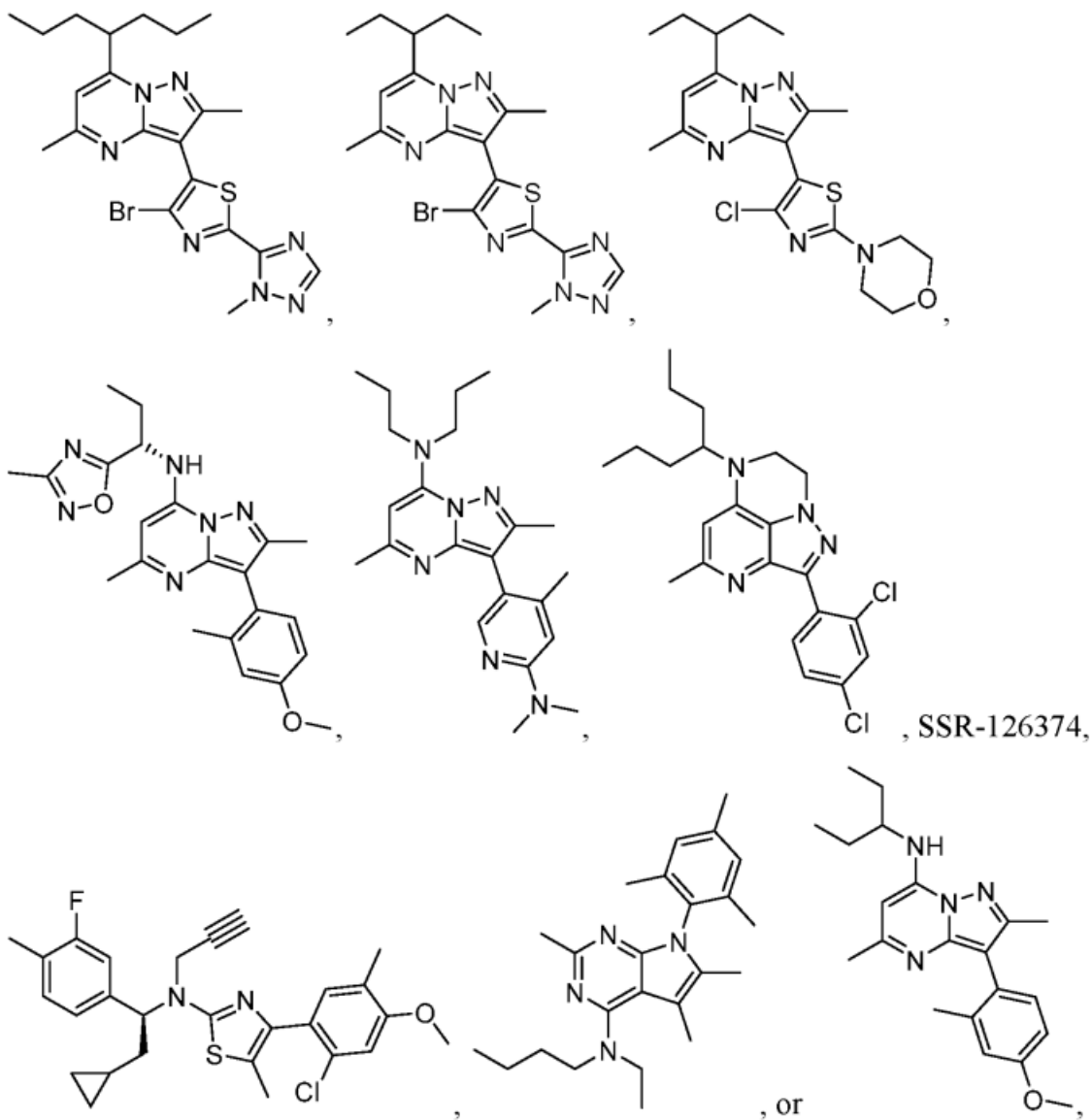
considered in the written description analysis. *See, e.g., Allergan v. MSN Laby's*, 111 F.4th 1358, 1374 (Fed. Cir. 2024) (“Originally filed claims have long been held to be part of the specification to be considered in any § 112 analysis.”); *see also id.* (original claims “would undoubtedly have satisfied the written description requirement of § 112...because it would be directly supported *in haec verba* by the disclosure.”); *In re Gardner*, 480 F.2d 879, 879-80 (CCPA 1973) (“[W]e consider the original claim in itself adequate ‘written description’ of the claimed invention. It was equally a ‘written description’ whether located among the original claims or in the descriptive part of the specification.”).

The PTAB has repeatedly denied petitions for failing to address the original claims. *See, e.g., Neosales Corp LP v. Wendling*, PGR2021-00058, Paper 6 (PTAB, 2021) (“Petitioner fails to establish sufficiently that the claims lack sufficient written description support. In particular, Petitioner does not account adequately, if at all, for whether the original claims in the application that issued as the ’285 patent provide written description support.”); *L’Oréal USA, Inc. v. Liqwd, Inc.*, PGR2018-00024, Paper 12 (PTAB, 2018) (“Petitioner’s [written description] argument fails for at least the reason that it does not account for the original claims of the ’954 patent...”); *Emerson Electric Co. v. Sipco, LLC*, CBM2016-00095, Paper 39 (PTAB, 2018) (“Petitioner fails to explain why the ’842 Original Disclosure, which includes the original claims, would not have reasonably

conveyed to such an artisan that the inventor had possession of the claimed subject matter.”).

The PTAB has further explained that failure of the petition to address the original claims renders the petition incurably deficient. *Emerson Electric Co. v. Sipco, LLC*, CBM2016-00095, Paper 39 (PTAB, 2018) (“In its Petition, Petitioner’s showing proffers no explanation as to why the original claims cannot be part of the ’842 Original Disclosure.... In its Reply, Petitioner advances two new arguments.... Such arguments *should have been introduced in the Petition.*”); see also *Wasica Fin. GmbH v. Cont’l Auto. Sys.*, 853 F.3d 1272, 1286 (Fed. Cir. 2017) (“subsequent arguments” not in the petition “amount to an entirely new theory of *prima facie* obviousness absent from the petition. Shifting arguments in this fashion is foreclosed by statute, our precedent, and Board guidelines.”). That is precisely the incurable error Petitioner committed here.

Here, the originally-filed claims are substantively identical to the challenged claims. The originally-filed claims *explicitly list each of the 10 compounds*, reciting “[a] method of treating an endocrine disorder associated with a corticotropin-releasing factor type-1 (CRF₁) activity, comprising administering to a subject in need thereof a small molecule CRF₁ antagonist...wherein the small molecule CRF₁ antagonist is...”



and “...wherein the endocrine disorder associated with CRF₁ activity is a testicular adrenal rest tumor (TART) or an ovarian adrenal rest tumor (OART).” EX2008, 246-47 (claims 1, 4). This is substantively identical to the challenged claims, which recite the combination of as-filed independent claim 1 and dependent claim 4. Petitioner’s failure to account for the original claims undermines virtually every one of its written description arguments. Pet., 18-52.

Petitioner incorrectly argues (Pet., 33-37) that written description support was limited to compounds of Formula (I). However, Petitioner’s argument ignores the originally filed claims. *ScriptPro LLC v. Innovation Assocs.*, 833 F.3d 1336, 1341 (Fed. Cir. 2016) (“a specification’s ***focus on one particular embodiment...cannot limit the described invention*** where that specification expressly contemplates other embodiments or purposes. This is ***especially true in cases such as this, where the originally filed claims are not limited to the embodiment...that is the focus of the specification.***”).

The petition wrongly states that “the ’491 patent fails to show possession of a method for treating OARTS ***at all.***”¹ Pet., 18. Again, such argument is directly contradicted by the original claims, which provide literal support for treating OARTs. EX2008, 246-47 (claims 1 and 4) (“***A method of treating an endocrine disorder...wherein the endocrine disorder*** associated with CRF₁ activity is a testicular adrenal rest tumor (TART) or ***an ovarian adrenal rest tumor (OART).***”). Moreover, *ipsis verbis* support is not limited to the originally-filed claims, but is repeated throughout the specification. See, e.g., EX1001, 2:4-8 (“One aspect provided herein is a ***method of treating or preventing...ovarian adrenal rest***

¹ Bold-italic emphases added throughout unless noted otherwise.

tumors (OART), comprising administering to a subject in need thereof a corticotropin-releasing factor type-1 (CRF₁) antagonist...”), 24:26-29 (“Exemplary cancers that may be *treated with a compound or method provided herein include adrenal cancer and tumors (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)...*”), 24:7-9 (“The disease may be a malignant or benign tumor (e.g., testicular adrenal rest tumors (TART) or *ovarian adrenal rest tumors (OART)*.”), 38:59-63 (“In some embodiments, a CRF1 associated disease modulator is a compound that *reduces the severity of one or more symptoms of a disease associated with CRF₁ (e.g. an endocrine disorder, a cancer including but not limited to TART or OART)*.”), 39:30-36 (“...a CRF₁ associated disease (e.g., testicular adrenal rest tumors (TART) or *ovarian adrenal rest tumors (OART)*) means that the disease (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)) is caused by (in whole or in part), or a symptom of the disease is caused by (in whole or in part) the substance or substance activity or function.”), 39:44-52 (“For example, an endocrine disorder associated with CRF1 activity or function or a CRF1 associated disease (e.g., an endocrine disorder including but not limited to *TART or OART*), *may be treated with a compound described herein (e.g., CRF1 modulator, CRF1 inhibitor, or CRF1 antagonist)*, in the instance where *increased CRF1 activity or function* (e.g. signaling pathway activity) *causes the disease* (e.g., an endocrine disorder *such as TART or*

OART).”).

The petition incorrectly asserts the specification fails to disclose “treating TARTs with **any** of the claimed CRF1 receptor antagonists.” Pet., 18. Petitioner’s argument is again contradicted by the original claims, which explicitly list **all** 10 claimed compounds and provide literal support for treating TARTs with the claimed CRF₁ receptor antagonists. EX2008, 246-47 (claims 1 and 4) (“***A method of treating an endocrine disorder***... comprising administering to a subject in need thereof a small molecule CRF₁ antagonist...wherein the small molecule CRF₁ antagonist is [***10 listed compounds***]...***wherein the endocrine disorder*** associated with CRF₁ activity is ***a testicular adrenal rest tumor (TART)*** or an ovarian adrenal rest tumor (OART).

”).

Finally, Petitioner erroneously states the specification fails to disclose “***seven of the ten*** claimed CRF1 receptor antagonists—including Neurocrine’s crinecerfont and verucerfont—for treating TARTs or OARTs.” Pet., 18; *see also id.*, 41 (“***Nothing in the specification*** conveys to a POSA that the named inventors were in possession of these ‘additional chemotherapeutic agent[s]’ for purportedly treating TARTS or OARTs themselves.”); EX1003, ¶116 (Dr. Lodish erroneously stating “the disclosure relating to treatment of TARTs is limited to a single, briefly described patient treated with Compound 1”); *id.*, ¶124 (“These seven compounds are not described in the ’491 patent as compounds for treating TARTs or

OARTs.”); ¶125 (“I did not identify *any portion* of the ’491 patent that describes the compounds designated D-J as compounds used to treat TARTs or OARTs themselves.”); ¶126 (“Every figure, description, and example relating to purportedly treating TARTs or OARTs refers exclusively to Compound 1 (tildacerfont).”).

Again, Petitioner’s argument is directly contradicted by the original claims which explicitly disclose treating TARTs or OARTs with each of the 10 claimed CRF₁ receptor antagonists. EX2008, 246-47 (claims 1 and 4) (“A method of treating an endocrine disorder...comprising administering to a subject in need thereof a small molecule CRF₁ antagonist...wherein the small molecule CRF₁ antagonist is [10 listed compounds]...wherein the endocrine disorder associated with CRF₁ activity is a testicular adrenal rest tumor (TART) or an ovarian adrenal rest tumor (OART).”). These are the same ten CRF₁ receptor antagonists and tumors recited in the issued claims.

The Petition arguments are thus inexplicable and wrong in light of the originally-filed claims. Petitioner’s written description challenge is deficient at least for not adequately addressing *ipsis verbis* support in the specification.

2. Petitioner Fails to Explain Why Literal Support in the Specification Is Insufficient.

Petitioner erroneously assumes that written description support requires actual reduction-to-practice for literally every claimed species. The petition cites

no authority supporting this impossibly heightened standard because none exists. Making matters worse, Petitioner's legally erroneous written description attack is 1) inconsistent with its own argument in Ground 3 asserting prior art with zero experimental examples; and 2) contradicted by its own later published study presenting experimental verification that a claimed CRF₁ receptor antagonist (crinecerfont) successfully prevented growth of TART lesions. The petition's written description arguments additionally fail for at least these reasons.

Despite the petition argument, there is no *per se* rule requiring experimental verification of every claimed species. “[T]he written description requirement does not demand either examples or an actual reduction to practice; a constructive reduction to practice that in a definite way identifies the claimed invention can satisfy the written description requirement.” *Ariad*, 598 F.3d at 1352 (Fed. Cir. 2010). Written description does not require experimental data demonstrating effectiveness, nor does it require actual reduction to practice. *Falkner v. Inglis*, 448 F.3d 1357, 1366 (Fed. Cir. 2006) (“[W]e hold, in accordance with our prior case law, that (1) examples are not necessary to support the adequacy of a written description (2) the written description standard may be met (as it is here) even where actual reduction to practice of an invention is absent....”); *see also Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1309 (Fed. Cir. 2015). It is well-settled that “all that the written description requirement demands” is that the specification

demonstrate the inventors “conceived of and described their invention at the time the respective original patent applications were filed.” *Alcon Research Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180, 1191 (Fed. Cir. 2014).

Contrary to these precedents, Petitioner argues the specification fails to show possession of a method for treating OARTs (Pet., 19-24) or TARTs (Pet., 24-32) because the specification provided experimental data for some but not all of the 10 claimed compounds. Pet., 43 (the working example using tildacerfont “does not provide adequate written description for *every* CRF1 receptor antagonist recited in claim 1”); *see also id.*, 31 (“the written description of the ’491 patent still *fails to provide any data or disclosure* demonstrating possession of methods of treating TARTS across the full scope of the claims”), 22 (“a POSA would have expected...*experimental data or clinical evidence*—to demonstrate that the named inventors were, in fact, in possession of a method of treating OARTs.”); *id.*, 21 (the ’491 patent “contains no examples, no *experimental data*, no clinical observations, and no other indicia related to the treatment of OARTs”).

Petitioner cites no supporting legal authority requiring experimental verification of every claimed compound and offers no meaningful analysis of the specification as a whole. First, as discussed in Section III.A.1 above, there is indisputably literal support in the specification for what is claimed. Second, the specification explains that adrenal rest tumors on the testicles and ovaries are

related disorders with shared etiology. EX1001, 1:41-51 (“lesions of the testes and ovaries derived from adrenal tissue interchelated within these organs [testes and ovaries] during embryogenesis. In response to high ACTH, hyperplasia of this tissue occurs, resulting in single or multiple lesions that may cause pain and infertility.”). Third, the as-filed specification describes a shared mechanism of action by the CRF₁ receptor antagonists useful in treating adrenal rest tumors. EX1001, 39:44-52 (“an endocrine disorder associated with CRF1 activity or function or a CRF1 associated disease (e.g., an endocrine disorder including but not limited to TART or OART), may be treated with a compound described herein (e.g., CRF1 modulator, CRF1 inhibitor, or CRF1 antagonist), in the instance where increased CRF1 activity or function (e.g. signaling pathway activity) causes the disease (e.g., an endocrine disorder such as TART or OART).”); *see also id.*, 90:20-41. Finally, the specification provides a working example demonstrating successful treatment of an adrenal rest tumor using a CRF₁ receptor antagonist. *See, e.g.*, EX1001, 95:51-96:37, Figs. 10A-10B. Though the petition nitpicks that example,² Petitioner never justifies its legally erroneous assumption that one or

² Petitioner conspicuously fails to inform the Director that this very study had been peer-reviewed and published in the highly reputable *Journal of Clinical Endocrinology and Metabolism*. Petitioner was certainly aware of this publication:

more working example is required in the first place.

Petitioner's written description attack also is contradicted by its own prior art argument here. As indicated above, Petitioner's written description argument assumes that multiple working examples are required to establish disclosure of treating TARTS. In Ground 3, however, Petitioner takes the opposite position. There, Petitioner relies on an exhibit that provides *zero examples* of CRF₁ receptor antagonists treating an adrenal rest tumor, nor even literal support for using a CRF₁ receptor antagonists for that purpose. Specifically, Petitioner alleges Grigoriadis (EX1006) demonstrates possession of TARTs treatment with CRF₁ receptor antagonists (Pet., 65-66, 85 "Grigoriadis expressly teaches the treatment of TARTs with a CRF₁ receptor antagonist...") though Grigoriadis never says this, much less provides an example of doing so (as Petitioner says is required for disclosure). Petitioner's prior art challenge thus contradicts its § 112 challenge.

Petitioner submitted it as an exhibit (EX1041). Additionally, Petitioner did not inform the Office that this peer-reviewed publication contradicts Petitioner's mischaracterizations of the study. *Compare, e.g.*, EX1041, 10 ("the volume of this participant's TART was reduced 23%") with EX1003, ¶108 (Dr. Lodish characterizing shrinkage as little as 10.5%).

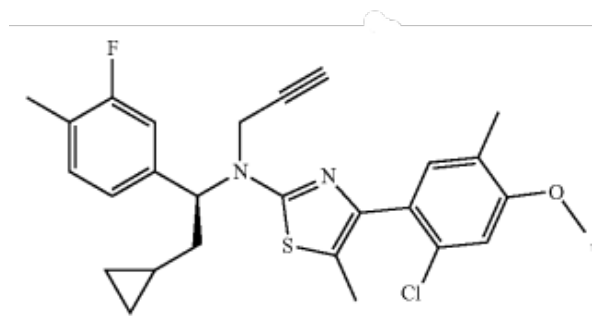
Finally, Petitioner's written description challenge is inconsistent with (and ignores) its own published work. Petitioner's post-critical date studies describe that another claimed CRF₁ receptor antagonist (crinecerfont) successfully prevented growth of TART lesions. EX1052 ("no increase in the mean TART volume, despite a substantial reduction in the glucocorticoid dose with crinecerfont"). Despite being fully aware of this evidence corroborating the written description support in the specification, Petitioner elected not to address it for the Director. *Cf.* 37 C.F.R. § 42.51(b)(1)(iii) (requiring service of relevant information inconsistent with a party's position); *see also* 37 C.F.R. § 42.11(b) (requiring a duty of candor and good faith to the Office). Petitioner's shifting litigation position and selective evaluation of evidence undermine its erroneous assumption that multiple working examples are required to provide written description support.

3. A (Corrected) Typographical Error is Not Worth Exhausting Board Resources

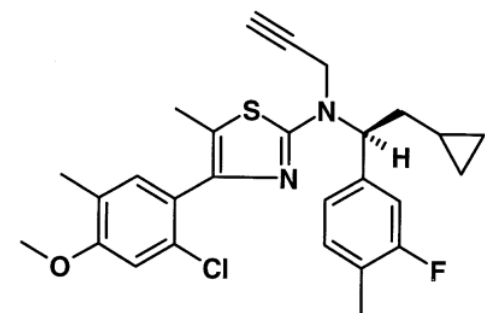
Next, Petitioner second-guesses the Examiner's conclusion that the specification contained an unambiguous typo amenable to correction. Pet., 18-19, 46-52. Petitioner asserts the originally filed specification "disclosed a compound having...an impossible carbon-carbon quadruple bond" that "cannot exist" rather than the structure of crinecerfont. Pet., 46-47. This very issue was considered by the Examiner, and the Office already properly accepted the correction of this typographical error. As explained during examination, an amendment to the

specification and claims addressing the chemical structure of crinecerfont was made consistent with a Certificate of Correction previously accepted by the Office for related U.S. Patent No. 11,304,950. EX2008, 4535, 4296. The Examiner expressly considered and evaluated these amendments, observing they were “to correct typographical errors” and were “acknowledged and accepted.” *Id.*, 4551. There is no dispute that the accepted correction of the typographical error conforms with the actual crinecerfont compound, which was known in the art.

Compare EX1001, Claim 1:



with EX2011 (compound SSR125543A):



Despite this issue having already been settled by the Office, Petitioner now seeks to waste Board resources by revisiting it again. The Office has previously warned that it will not rehash its prior decisions without the ***Petitioner*** providing good reason to do so. *See Dabico Airport Sol'ns Inc. v. AXA Power APS*, IPR2025-

00408, Paper 21 (PTAB, June 18, 2025) (informative) (“Petitioner does not provide any persuasive reasoning why an *inter partes* review is an appropriate use of Office resources.”). It was Petitioner’s burden to provide persuasive reasoning why the Office should use its resources to address something already corrected during examination. Petitioner provides no good reason to do so here.

Even if a ministerial issue is to be revisited, Petitioner ignores the four corners of the original specification. The petition never addresses the specification disclosure explaining that any chemical substitutions are understood by those skilled in the art “to comply with principles of chemical bonding and to give compounds which are not inherently unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions....” EX2008, 154 (original paragraph [0095]). The original specification thus supported the Examiner’s conclusion that the “impossible” quadruple bond was a rightfully corrected typographical error. Rehashing the Office’s prior correction of a typographical error is not an appropriate basis of challenge and a waste of Office resources.

B. Ground 2: Petitioner Fails to Demonstrate Lack of Enablement

Petitioner’s enablement challenge largely mirrors its written description theory and extensively cross-references to its written description argument (Pet., 52-61). The petition enablement challenge fails for many related reasons.

As an initial matter, Petitioner fails to adequately inform the Director that the Office previously rejected a similar enablement argument directed at broader claims in PGR2021-00088. In that case, the same Petitioner as here (Neurocrine) argued lack of enablement, but the Board found undue experimentation was not required to practice the claims using the broader class of known CRF1 inhibitors:

....Petitioner's declarant, Dr. Carey, testifies that the genus of CRF1 receptor antagonists was known in the art.... The Specification of the '908 patent discloses, as Patent Owner points out, an explanation of the mechanism of action, a working example, and clinical trial protocols used to verify efficacy.... Against these disclosures, we find that Petitioner's argument that practicing the claimed invention of the '908 patent would require undue experimentation, without further evidentiary support, would be unsustainable at trial. We consequently conclude that Petitioner has failed to establish that it is more likely than not that any claim in Ground V [enablement] is unpatentable.

PGR2021-00088, Paper 11 at 34-35. After Director Review, the Board reached the same conclusion: "The Specification of the '908 patent discloses, as Patent Owner points out, an explanation of the mechanism of action, a working example, and clinical trial protocols used to verify efficacy.... Petitioner has failed to establish that it is more likely than not that any claim in Ground 5 [enablement] is unpatentable." PGR2021-00088, Paper 21 at 49-50. Recognizing its enablement argument was meritless, Petitioner did not even argue lack of enablement in its second PGR. PGR2022-00025, Paper 2 at 4.

Petitioner now rehashes its previously rejected enablement theory against materially narrower claims—*i.e.*, 10 specific CRF₁ inhibitors. It is inconceivable that no undue experimentation would be required for the broader class of CRF₁ inhibitors, yet experimentation somehow becomes undue for a narrower subset of only 10 specifically claimed compounds. The petition provides no explanation because none exists. Petitioner's enablement challenge (Ground 2) can be rejected for at least this reason alone.

If enablement is considered further here, it can be rejected for additional reasons.

1. Petitioner's Own Publications Undermine Its Enablement Challenge

Petitioner's arguments that the art is unpredictable (*Wands* Factor 7), that the state of the art is nascent (*Wands* Factor 5), and that treating TARTs and OARTs is complex (*Wands* Factor 4) cannot be reconciled with Petitioner's own publications and clinical results. Petitioner did not factor these publications into its enablement or *Wands* analysis. This omission is telling. Petitioner's own crinecerfont study corroborates enablement of what is claimed, and Petitioner's own publication describes common structural features among CRF₁ receptor antagonists.

First, Petitioner fails to address its own post-critical date publication that corroborates enablement of the challenged claims. Post-critical date evidence is relevant to determining enablement and must be considered. *Amgen Inc. v. Sanofi*,

872 F.3d 1367, 1374-75 (Fed. Cir. 2017) (“evidence could have been relevant to determining if the claims were enabled as of the priority date and should not have been excluded simply because it post-dated the claims’ priority date”). Petitioner’s evidence includes its own clinical study of crinecerfont—one of the ten CRF₁ receptor antagonists recited in the claims—which demonstrated prevention of TART growth even with reduced glucocorticoid dosing. EX1052 (“no increase in the mean TART volume, despite a substantial reduction in the glucocorticoid dose with crinecerfont”). Petitioner omitted this information when presenting its enablement challenge, though it corroborates the ’491 patent’s disclosure of treating TART with a claimed CRF₁ receptor antagonist. EX1001, 96:17-20 (“approximately 25% shrinkage in TART...following 6 weeks treatment with a CRF₁ receptor antagonist”); *see also* EX1041, 10 (peer reviewed publication of the same). Petitioner’s omission is detrimental to its enablement challenge, at least to its allegations of unpredictability and complexity (*Wands* Factors 4 and 7).

Second, Petitioner’s contention that the claimed compounds do not share structural features (Pet., 60-61) is contradicted by its own publication and evidence submitted with its challenge. Petitioner’s exhibits include prior art references that teach the “basic pharmacophore” of a CRF₁ receptor antagonist comprises “three moieties: a hydrophobic moiety up” (e.g., a branched alkyl group), “a proton accepting moiety in the middle” (e.g., the core nitrogen heterocycle), “and an

aromatic moiety down” (e.g., an aryl substituent). EX1018. This is consistent with pharmacophores in the claims. Petitioner was certainly aware of the prior art demonstrating known structural features of the class: Petitioner submitted as evidence its own prior art reference which explained a “typical CRF₁ antagonist consists of a ‘core’ nitrogen heterocycle with an ‘aryl’ substituent adjacent to the core nitrogen atom and a ‘branched alkyl’ group attached at the opposite end of the core.” EX1029, 2; *see also id.*, Fig. 2 (reproduced below).

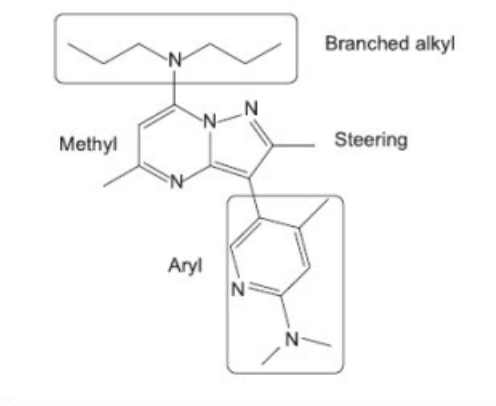


Figure 2. Regions of CRF₁ antagonist SAR.

Petitioner’s failure to address these references is detrimental to its enablement challenge, at least to its allegations regarding the state of art (*Wands* Factor 5).

Petitioner misrepresents the Board’s prior statement that “the structure-function relationship between CRF₁ receptor and CRF₁ receptor [antagonist]s was still largely unknown and unpredictable.” Pet., 61 (quoting EX1005, 59). Petitioner presents this statement as though it was isolated to the discrete grouping of 10 small molecule CRF₁ receptor antagonists in the challenged claims. To the

contrary, the Board was describing the broader genus that included “a wide variety of large and small molecule compounds that can act as CRF₁ receptor antagonists” including, e.g., peptides. EX1005, 57-59. The Board did not find the class of small-molecule CRF₁ receptor antagonists was unknown, much less the closed list of ten claimed compounds. Petitioner’s reliance on the Board’s prior findings is misplaced.

Thus, Petitioner’s enablement challenge is incurably deficient at least for failure to account for its own publications which corroborate enablement and demonstrate shared structural features common to CRF₁ receptor antagonists. Petitioner’s failure to address these references demonstrates the superficiality of the petition’s enablement analysis, as well as Petitioner’s failure to carry its burden to demonstrate lack of enablement.

2. Narrow Scope of Claims Defeats Petitioner’s Enablement Challenge

Where, as here, there is a very narrow claim scope, this weighs in favor of finding enablement (*Wands* Factor 8). Petitioner’s challenge fails to demonstrate that practicing the narrow claims would require undue experimentation. For the inquiry concerning undue experimentation, “[t]he key word is ‘undue,’ not ‘experimentation.’” *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The petition challenge is premised on breadth (Pet., 54-55), but the ’491 patent claims are directed to a method of treating two related disorders using a discrete group of ten

known compounds having similar structure and a shared mechanism of action. The narrowness of the claims is ignored in Petitioner’s argument and underscores that Petitioner failed to meet its burden of showing non-enablement.

a. Petitioner’s Arguments Are Misplaced In View of a Narrow Scope of Explicitly Disclosed Compounds

Petitioner’s arguments regarding broadly claimed subject matter are misplaced and inapt here. Where claims cover a narrow scope, less is required to enable the full scope of the claimed invention. *Amgen Inc. v. Sanofi*, 598 U.S. 594, 610, 143 S. Ct. 1243, 1254 (2023) (“The more one claims, the more one must enable.”).

Enablement does not require “disclosure of a test with every species covered by a claim.” *In re Angstadt*, 537 F.2d 498, 502 (C.C.P.A. 1976). Where, as here, claims are directed toward the use of known compounds for a specified purpose rather than toward the compounds themselves, a single working example can sufficiently enable the claimed scope. *Teva Pharms. Int’l GmbH v. Eli Lilly & Co.*, 172 F.4th 1367, 1381 (Fed. Cir. 2026) (patent owner did “not claim humanized anti-CGRP antagonist antibodies *themselves*; instead, they claim only the use of such antibodies for the different, limited purpose of treating headache”). There is no requirement for the specification to exhaustively demonstrate experimentally every embodiment covered by the claims, especially when the POSA is highly skilled. *In re Fisher*, 427 F.2d 833, 839 (C.C.P.A. 1970) (“the claims must bear a

reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.”).

Petitioner’s enablement argument fails to meaningfully account for the narrow scope of claims and explicit disclosure in the specification. The challenged claims are directed toward treating two related endocrine disorders with a discrete, closed group of ten known compounds having similar structure and shared mechanisms of action. The specification explains that adrenal rest tumors on the testicles and ovaries arise from the same etiology. EX1001, 1:39-51 (“Testicular adrenal rest tumors (TART) and ovarian adrenal rest tumors (OART) are ACTH-responsive lesions of the testes and ovaries derived from adrenal tissue interchelated within these organs during embryogenesis. In response to high ACTH, hyperplasia of this tissue occurs, resulting in single or multiple lesions that may cause pain and infertility.”). The claims concern treating these two endocrine disorders using a discrete class of ten previously-known compounds having shared mechanism of action (i.e., all are CRF₁ receptor antagonists) and structural features common to the class. *Supra*, Section III.B.1; *see also* EX1018, EX1029 (Petitioner’s own prior art demonstrating the same). The specification provides a working example demonstrating successful treatment of TART with a CRF₁ receptor antagonist. EX1001, 96:17-20 (“approximately 25% shrinkage in TART...following 6 weeks treatment with a CRF₁ receptor antagonist”); *see also*

EX1041, 10 (peer reviewed publication of the same). Petitioner's own publication demonstrated beneficial effects with a second claimed CRF₁ receptor antagonist. EX1052 ("no increase in the mean TART volume, despite a substantial reduction in the glucocorticoid dose with crinecerfont"). Given the shared etiology of TARTs and OARTs and the shared mechanism of action of the ten known compounds, the specification's disclosure reasonably correlates to the scope of the narrow claims.

That the specification's disclosure reasonably correlates to the narrowly claimed scope is further reinforced by Petitioner's definition of the POSA. *In re Fisher*, 427 F.2d 833, 839 (C.C.P.A. 1970) ("the claims must bear a ***reasonable correlation*** to the scope of enablement provided by the specification ***to persons of ordinary skill in the art.***"). The specification provides, *inter alia*, a working example of treating TARTs with a CRF₁ receptor antagonist, guidance for clinical trials, and a discrete list of related compounds. Petitioner opines that the POSA is highly skilled and experienced in the field of endocrinology with special familiarity in treating TARTs and OARTs. Pet., 16-17. Specifically, according to Petitioner, the POSA "would have possessed a medical degree or Ph.D. in a field related to endocrinology" with "knowledge of the treatment regimens employed to treat such disorders" and "at least three years of experience researching endocrine disorders, including TARTS, OARTs, or other adrenal disorders." Such a skilled, capable POSA would find reasonable correlation to the claims from that which was

disclosed by the specification. Petitioner’s definition of a highly specialized POSA supports a finding of enablement rather than cutting against it (*Wands* Factor 6).

Thus, the petition fails to show that the narrow claims of the ’491 patent are not reasonably enabled by the specification.

b. Petitioner’s Relied-Upon Caselaw is Inapt

Petitioner’s authorities address far broader genus claims and do not fit the analysis of the narrow claims at issue here. Pet., 57-58. The petition invokes cases concerning multitudes of compounds, where the sheer volume of testing them would result in unnecessary experimentation. In contrast, the challenged claims concern a discrete group of just ten known CRF₁ receptor antagonists. Petitioner’s cases do not support finding lack of enablement under these circumstances.

Petitioner argues that *Idenix* and *Amgen* support a finding of non-enablement for the full scope of claims (Pet., 57-58) (discussing *Idenix Pharms. LLC v. Gilead Scis. Inc.*, 941 F.3d 1149 (Fed. Cir. 2019) and *Amgen Inc. v. Sanofi*, 598 U.S. 594 (2023)). But both *Idenix* and *Amgen* dealt with exceptionally broad claims. Indeed, the Federal Circuit subsequently recognized that *Idenix* “encompassed ‘at least many, many thousands of [claimed species]’...[and] rendered the amount of necessary experimentation high.” *Teva Pharms.*, 172 F.4th 1382. In *Amgen*, the “claims cover[ed] potentially millions more **undisclosed** antibodies” outside what Amgen had described. *Amgen* 598 U.S. at 603. Here, the claims are not directed to

“many, many thousands” or “millions” of “undisclosed” compounds. The claims are instead directed to just 10 compounds. Accordingly, the petition has no legal authority to support its enablement challenge and the cases cited are inapposite.

c. Petitioner’s Demand For Clinical Proof of Each Compound Is Not The Standard

The petition essentially demands that each claimed compound be clinically validated for the claimed therapeutic effect, but this is not what enablement requires.

Enablement has never required clinical trials for each claimed embodiment. “Testing for the full safety and effectiveness...is more properly left to the [FDA]. Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings.” *Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994); *see also United Therapeutics Corp. v. Liquidia Techs., Inc.*, 74 F.4th 1360, 1369 (Fed. Cir. 2023). “[C]laims do not require FDA-type clinical safety or efficacy standards.” *Wyeth LLC v. Astrazeneca Pharms. LP*, 180 F.4th 1371, 1378 (Fed. Cir. 2026). Moreover, a specification need not experimentally demonstrate every possible embodiment that falls within the scope of a claim in order to be enabling. *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1336 (Fed. Cir. 2003)). In evaluating whether claims are enabled, “[t]he key word is ‘undue,’ not ‘experimentation.’” *In re Wands*, 858 F.2d at 737.

The petition faults the specification’s disclosure of a phase 2 open-label

study protocol because it “contains no clinical data.” Pet., 57-58. Petitioner also argues “a POSA would have expected substantially more detail—such as experimental data or clinical evidence” for treatment of OARTs. Pet., 22 (incorporated into enablement argument at, *inter alia*, Pet., 57). But as explained above, clinical trials are not required for enablement. Petitioner’s argument is thus premised on a false notion that is legally erroneous. Relatedly, Petitioner argues that “the definition of undue experimentation” is where “POSA would be forced to conduct years of costly testing of the claimed CRF1 receptor antagonists across the extremely small population of subjects with OARTs.” Pet., 59-60 (citing *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318 (Fed. Cir. 2005)). But *Rasmusson* concerned a lack of right to priority to earlier filed applications where the claim of using finasteride for treating cancer was unsupported by those earlier filings. *Rasmusson* does not concern time or cost of testing, and Petitioner’s reliance on this case is inapposite. It certainly did not establish a rule requiring clinical trials to enable a claim.

Thus, the ’491 patent claims are narrow, the compounds are known, the specification supplies a working example (validated by peer-reviewed publication), and Petitioner’s own data corroborates a second claimed compound. Petitioner fails to carry its burden to show that practicing the claims would require undue experimentation. Petition Ground 2 fails.

C. Ground 3: Petitioner Fails to Demonstrate Obviousness

Independent claim 1—and thus all claims of the '491 patent—require the claim element “wherein the endocrine disorder associated with CRF₁ activity is a testicular adrenal rest tumor (TART) or an ovarian adrenal rest tumor (OART).” EX1001, Claims 1-19. Petitioner contends this claim element is obvious based on the disclosure of Grigoriadis, or Grigoriadis in combination with Yu. Pet., 85. Because neither Grigoriadis nor Yu disclose treating TART or OART with a CRF₁ receptor antagonist, Petitioner fails to establish a *prima facie* case of obviousness for this claim feature.

Petitioner has the “burden to prove that all claimed limitations are disclosed in the prior art.” *Par Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1194 (Fed. Cir. 2014). “[T]he petition must specify where each element of the claim is found in the prior art.” 37 C.F.R. § 42.204(b)(4). Where, as here, a petition does not demonstrate that all claimed limitations are disclosed in the prior art, then the petitioner’s obviousness challenge fails as a matter of law.

Petitioner first relies on Grigoriadis as purportedly disclosing this claim element, though Grigoriadis makes no such disclosure—as the Examiner expressly observed during examination. The petition alleges that “Grigoriadis expressly teaches the treatment of TARTs with a CRF₁ receptor antagonist[.]” Pet., 85. But Grigoriadis discusses TARTs only once, and that is within the context of treatment

with glucocorticoids—not CRF₁ receptor antagonists. EX1006, [0044] (“Thus, *the goals of glucocorticoid treatment* include cortisol replacement and suppression of ACTH to prevent virilization and menstrual disturbances in women and to *inhibit testicular adrenal rest tumors* in men.”). Thus, Petitioner misrepresents the direct teaching of Grigoriadis. This was not lost on the Examiner who, during examination, identified that in “Grigoriadis...treating of the subject having an ovarian adrenal rest tumor or a testicular adrenal rest tumor, as required by the claims, *is not taught or suggested.*” EX2008, 4671.

Petitioner next relies—in the alternative—on Grigoriadis in combination with Yu as purportedly disclosing this claim element. Pet., 85 (“Grigoriadis expressly teaches the treatment of TARTs with a CRF₁ receptor antagonist, or, at minimum, renders it obvious in combination with Yu.”). But Petitioner’s reliance on Yu does not resolve the deficiency of Grigoriadis because Petitioner never argues or demonstrates that Yu suggests or teaches treating TARTs or OARTs with a CRF₁ receptor antagonist. Because Petitioner fails to demonstrate that either Grigoriadis or Yu disclose treating TARTs or OARTs with a CRF₁ receptor antagonist, the petition fails to establish a *prima facie* case for obviousness.

Because the asserted art does not disclose this required claim element, Petitioner’s challenge as a whole fails and the Office need not reach the remaining claim limitations. For at least this reason, Ground 3 fails.

IV. CONCLUSION

Petitioner has failed to make a facial case of unpatentability for any challenged claim, so institution is unwarranted and should be denied.

Respectfully submitted,

Date: September 18, 2026

/ Michael T. Rosato /
Michael T. Rosato, Lead Counsel
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CERTIFICATION UNDER 37 C.F.R. §42.24(d)

Pursuant to §42.24(d), the undersigned certifies that this paper contains no more than 18,700 words, not including the portions of the paper exempted by §42.24(b). According to the word-processing system used to prepare this paper, the paper contains 6,836 words.

Respectfully submitted,

Date: September 18, 2026

/ Michael T. Rosato /

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V. APPENDIX

Exhibit No.	Description
2001	<i>Neurocrine Biosciences, Inc. v. Spruce Biosciences, Inc.</i> , No. 1:25-cv-00059 (D. Del. June 9, 2025), ECF No. 19 (Motion to Dismiss).
2002	<i>Neurocrine Biosciences, Inc. v. Spruce Biosciences, Inc.</i> , No. 1:25-cv-00059 (D. Del. June 9, 2025), ECF No. 26 (Memorandum Opinion).
2003	E-mail Letter from Mike Morin, Counsel representing Neurocrine Biosciences, to Dr. Javier Szwarcberg, CEO Spruce Biosciences Inc. (Dec. 10, 2024).
2004	E-mail from Mike Morin, Counsel representing Neurocrine Biosciences, to Michael Rosato, Counsel representing Spruce Biosciences Inc. (Jan. 11, 2025).
2005	E-mail Letter from Mike Morin, Counsel representing Neurocrine Biosciences, to Michael Rosato, Counsel representing Spruce Biosciences Inc. (Jan. 6, 2025).
2006	<i>Neurocrine Biosciences, Inc. v. Spruce Biosciences, Inc.</i> , No. 1:25-cv-00059 (D. Del. June 9, 2025), ECF No. 1 (Complaint).
2007	<i>Neurocrine Biosciences, Inc. v. Spruce Biosciences, Inc.</i> , CASEBOARD (Jan. 30, 2025), https://caseboard.io/cases/ac09fc0e-6e6e-497b-adc5-4bc46d1541be .
2008	File History – US Pat. No. 12,569,491.
2009	File History – US Pat. No. 12,569,490.
2010	File History – US Pat. No. 12,576,084.
2011	Danielle Gully et al., <i>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</i>

	<i>(SSR125543A): A Potent and Selective Corticotrophin-Releasing Factor1 Receptor Antagonist. I. Biochemical and Pharmacological Characterization</i> , 301(1) J. PHARMACOLOGY & EXPERIMENTAL THERAPEUTICS 322-332 (2002).
2012	Notice of Opposition Proceedings to EPO Pat. No. 3784233

CERTIFICATE OF SERVICE

The undersigned certifies that the foregoing Patent Owner's Preliminary Response pursuant to 37 C.F.R. § 42.207 was served on September 18, 2026, on the Petitioner at the electronic correspondence address of the Petitioner as follows:

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