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. PGR2026-00060
Patent 12,569,490

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

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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

petition challenges are both brought under 35 U.S.C. §112, are fundamentally deficient, and fail in at least three ways. First, the petition argument critically ignores *ipsis verbis* support for the challenged claim subject matter, including disclosure of originally filed claims. 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 CRF_1 receptor antagonist (crinecerfont) successfully prevented growth of TART (the male variant of OART) lesions.

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

II. OVERVIEW OF '490 PATENT

The '490 patent is directed to the treatment of two related disorders with a discrete group of ten compounds having similar structure and a shared mechanism

of action. The Examiner allowed the challenged claims after substantive examination, which included (overcome) rejections over prior art and § 112. EX2009, 1862-93, 4700-12, 4810-18.

The claims concern treatment of ovarian adrenal rest tumors (OARTs) and menstrual irregularity, both of which are adverse outcomes in patients with congenital adrenal hyperplasia. OARTs—as well as its male version, TARTs—are lesions that derive from adrenal tissue interchelated within the testes or ovaries 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 lesions and accompanying complications. *Id.*, 1:49-51. The invention disclosed the use of CRF_1 receptor antagonists for treatment of OARTs and menstrual irregularity. *See, e.g.*, EX2009, 114; EX1001, 2:4-8.

The claimed methods treat the disorders 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 CRF_1 receptor antagonists in the original application that issued as the ’490 patent. *See, e.g.*, Section III.A.1.

The claimed method of treating menstrual irregularity and OARTs with the closed group of ten compounds was supported from the outset. As originally filed,

the application's independent claim recited "[a] method of treating menstrual irregularity in a subject, comprising administering to the subject a small molecule corticotropin-releasing factor type-1 (CRF_1) antagonist" selected from the same closed group of ten compounds. The as-filed specification also provided substantial disclosure of treating OARTs with CRF_1 antagonists. *See* Section III.A.1. The treatment of menstrual irregularity and OART with these CRF_1 receptor antagonists was therefore supported in the original specification, including by the originally-filed claims, and by subject matter repeated throughout the specification. *E.g.*, EX1001, 2:4-8, 50:59-63, 79:24-27.

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 provide explicit support for the claimed subject matter. 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

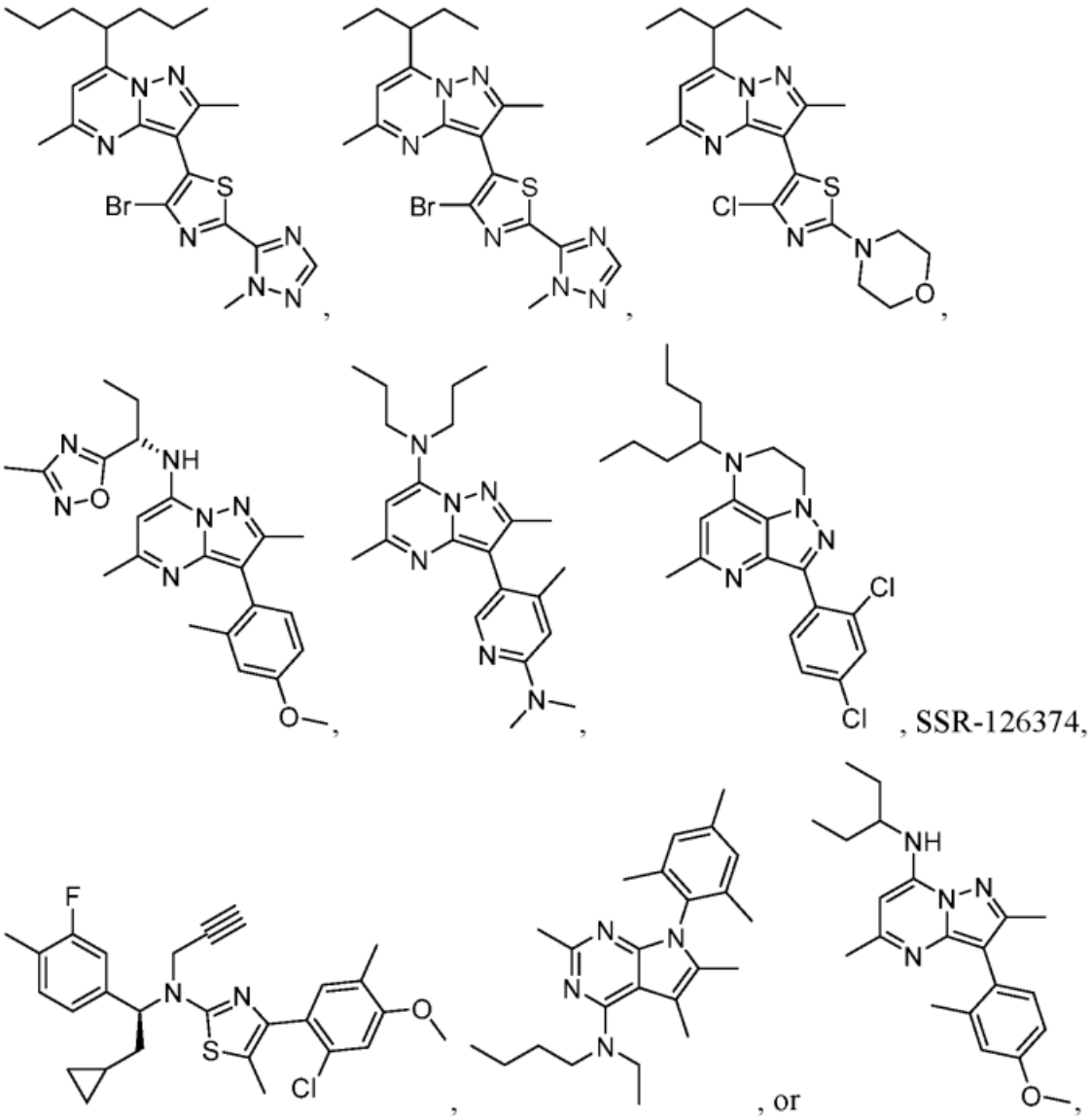
in the descriptive part of the specification.").

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, the originally-filed claims substantively support the challenged claims. The originally-filed claims ***explicitly list each of the 10 compounds***, reciting “[a] method of treating menstrual irregularity in a subject, comprising administering to the subject a small molecule corticotropin-releasing factor type-1 (CRF_1) antagonist…wherein the small molecule CRF_1 antagonist is…”



EX2009, 114 (claim 1). This substantively supports the challenged claims, which recite treating menstrual irregularity and OARTs with the same CRF_1 receptor antagonists. Petitioner's failure to account for the original claims undermines virtually every one of its written description arguments. Pet., 18-43.

Petitioner incorrectly argues (Pet., 29-33) 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 also incorrectly asserts that the specification fails to disclose "using ***any*** small molecule CRF1 receptor antagonist to treat MI." Pet., 25; *see also id.* (arguing the '490 patent discloses "only" Astressin for treating menstrual irregularity, and this "is the entirety of the '490 patent's MI treatment disclosure."); *id.*, 27 ("***sole disclosure*** relating to MI treatment is directed to Astressin…not any of the claimed selective, small-molecule CRF1 receptor antagonists."). Petitioner's argument is again contradicted by the original claims, which explicitly list ***all*** 10 claimed compounds and provide literal support for treating menstrual irregularity with the claimed CRF_1 receptor antagonists. EX2009, 114 (claim 1) ("***A method of treating menstrual irregularity*** in a subject, comprising administering to the subject a small molecule corticotropin-releasing factor type-1 (CRF1) antagonist…wherein ***the small molecule CRF1 antagonist is*** [***10 listed compounds***].").

Petitioner also erroneously states that the specification fails to disclose

"***seven of the ten*** claimed CRF1 receptor antagonists—including Neurocrine's crinecerfont and verucerfont—for treating OARTs and MI." Pet., 18. Petitioner contends these compounds "appear in the written description ***only*** as 'an additional chemotherapeutic agent' to be co-administered with a compound of Formula (I)." Pet., 29.

Again, Petitioner's argument is directly contradicted by the original claims which explicitly disclose treating menstrual irregularity using all 10 claimed CRF_1 receptor antagonists—not limited as a chemotherapeutic agent. EX2009, 114 (claim 1) ("A method of treating menstrual irregularity in a subject, comprising administering to the subject a small molecule corticotropin-releasing factor type-1 (CRF_1) antagonist…wherein the small molecule CRF_1 antagonist is [***10 listed compounds***]."). These are the same ten CRF_1 receptor antagonists and the same conditions recited in the issued claims.

The petition also wrongly states that "the '490 patent fails to show possession of a method for treating OARTS and MI ***at all***."[1] Pet., 18. Again, such argument is directly contradicted by the original claims, which provide literal support for treating MI. EX2009, 114 ("***A method of treating menstrual***

[1] Bold-italic emphases added throughout unless noted otherwise.

irregularity in a subject…."). Moreover, *ipsis verbis* support for treating OARTs and their associated complications 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 tumors (OART)***, comprising administering to a subject in need thereof a corticotropin-releasing factor type-1 (CRF_1) 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 CRF_1 (e.g.*** an endocrine disorder, a cancer including but not limited to ***TART or OART***)."), 39:30-36 ("…a CRF_1 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 arguments are thus inexplicable and wrong in light of the originally-filed specification, including the claims. Petitioner's written description challenge is deficient at least for not adequately addressing this clear *ipsis verbis* support.

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 obviousness argument in two co-pending PGRs asserting prior art with zero experimental examples; and 2) contradicted by its own later published study presenting experimental verification that a claimed CRF_1 receptor antagonist (crinecerfont) successfully prevented growth of adrenal rest tumor 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 and menstrual irregularity because the specification provided experimental data for some but not all of the 10 claimed compounds. Pet., 40 (the working example using tildacerfont "does not provide

adequate written description for ***every*** CRF1 receptor antagonist recited in claim 1."); *see also id.*, 19 ("no examples, no ***experimental data***, no ***clinical observations***" for treating OARTs or menstrual irregularity), 21 ("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.").

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 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 CRF_1 receptor antagonists useful in treating adrenal rest tumors and their associated complications. 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 CRF_1 receptor antagonist. *See, e.g.*, EX1001, 95:45-96:59, Figs. 10A-10B. Though the petition nitpicks that example,[2] Petitioner never justifies its legally erroneous assumption that one or more working example is required in the first place.

Petitioner's written description attack also is contradicted by its own prior art argument advanced in its co-pending PGR challenges. As indicated above, Petitioner's written description argument assumes that multiple working examples are required to establish disclosure of treating OARTs and menstrual irregularity. In its concurrently-filed PGR2026-00059 Ground 3, however, Petitioner takes the opposite position. There, Petitioner relies on an exhibit that provides ***zero***

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[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: Petitioner submitted it as an exhibit (EX1041).

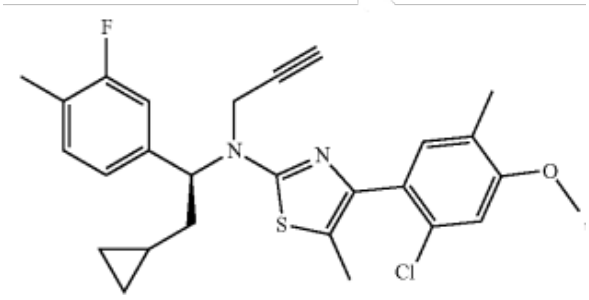
examples of CRF_1 receptor antagonists treating an adrenal rest tumor, nor even literal support for using a CRF_1 receptor antagonist for that purpose. Specifically, Petitioner alleges Grigoriadis (EX1006) demonstrates possession of TARTs treatment with CRF_1 receptor antagonists (PGR2026-00059 Pet., 65-66, 85 ("Grigoriadis expressly teaches the treatment of TARTs with a CRF1 receptor antagonist…"); PGR2026-00061 Pet., 68 ("Grigoriadis teaches administration of a CRF1 receptor antagonist in 'a subject having a testicular adrenal rest tumor (TART).'")) though Grigoriadis never says this, much less provides an example of doing so (as Petitioner says is required for disclosure). Petitioner's concurrent prior art challenges thus contradict its § 112 challenge here.

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 CRF_1 receptor antagonist (crinecerfont) successfully prevented growth of adrenal rest tumor—namely, 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

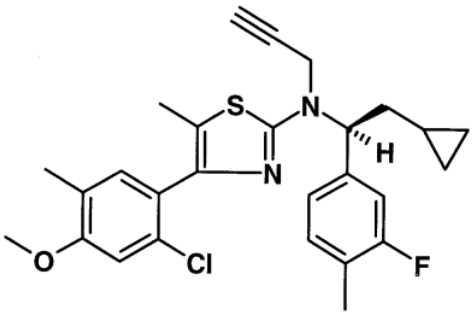
litigation position and selective evaluation of evidence undermine its erroneous assumption that multiple working examples are required to provide written description support.

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, 43-48. 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., 43-44. 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. EX2009, 4322-4326, 4366-4572. The Examiner expressly considered and evaluated these amendments, observing they "follow the certificate of correction accepted for US 11304950" and were "acknowledged and accepted." *Id.*, 4702. 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…." EX2009, 22 (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., 49-60). 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 CRF_1 inhibitors. It is inconceivable that no undue experimentation would be required for the broader class of CRF_1 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 OARTs and menstrual irregularity 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 the claimed treatment of adrenal rest tumors, and Petitioner's own publication describes common structural features among CRF_1 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 CRF_1 receptor antagonists recited in the claims—which demonstrated prevention of adrenal rest tumor 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 '490 patent's disclosure of treating adrenal rest tumors with a claimed CRF_1 receptor antagonist. EX1001, 96:39-42 ("approximately 25% shrinkage in TART…following 6 weeks treatment with a CRF_1 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., 58-59) 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 CRF_1 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 CRF_1 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).

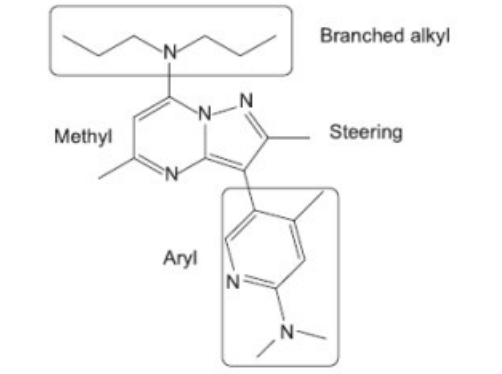


Figure 2. Regions of CRF_1 antagonist SAR.

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 CRF_1 receptor and CRF_1 receptor [antagonist]s was still largely unknown and unpredictable." Pet., 58 (quoting EX1005, 59). Petitioner presents this statement as though it was isolated to the discrete grouping of 10 small molecule CRF_1 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 CRF_1 receptor antagonists" including, e.g., peptides. EX1005, 57-59. The Board did not find the class of small-molecule CRF_1 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 CRF_1 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., 51-52), but the '490 patent claims are directed to a method of 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, even 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 using a discrete, closed group of ten known compounds

having similar structure and shared mechanisms of action. Both menstrual irregularity and OARTS are adverse outcomes in patients with congenital adrenal hyperplasia (CAH). Ovarian adrenal rest tumors in CAH patients can lead to gonadal dysfunction, and the "[c]linical consequences of gonadal dysfunction include menstrual disturbances in females." EX1069, Abstract. The claims concern treating these two conditions using a discrete class of ten previously-known compounds having shared mechanism of action (i.e., all are CRF_1 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—the male version of OART—with a CRF_1 receptor antagonist. EX1001, 96:39-42 ("approximately 25% shrinkage in TART…following 6 weeks treatment with a CRF_1 receptor antagonist"); *see also* EX1041, 10 (peer reviewed publication of the same). Petitioner's own publication demonstrated beneficial effects in treating adrenal rest tumor with a second claimed CRF_1 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 treatment of OARTs, as well as the menstrual irregularity complication.

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 adrenal rest tumors (e.g., TARTs) with a CRF_1 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. 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 '490 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., 56-57. 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 CRF_1 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., 55-56) (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., 55. Petitioner also argues "a POSA would have expected substantially more detail—such as experimental data or clinical evidence" for treatment of OARTs. Pet., 21

(incorporated into enablement argument at, *inter alia*, Pet., 54). 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, including finding and testing those OARTs subjects who also suffer from MI." Pet., 57 (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 '490 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.

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 6,093 words.

Respectfully submitted,

Date: September 18, 2026

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V. APPENDIX

Exhibit No.	Description
2001	*Neurocrine Biosciences, Inc. v. Spruce Biosciences, Inc.*, No. 1:25-cv-00059 (D. Del. June 9, 2025), ECF No. 19 (Motion to Dismiss).
2002	*Neurocrine Biosciences, Inc. v. Spruce Biosciences, Inc.*, 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	*Neurocrine Biosciences, Inc. v. Spruce Biosciences, Inc.*, No. 1:25-cv-00059 (D. Del. June 9, 2025), ECF No. 1 (Complaint).
2007	*Neurocrine Biosciences, Inc. v. Spruce Biosciences, Inc.*, 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., *4-(2-Chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]5-methyl-N-(2-propynyl)-1,3-thiazol-2-amine Hydrochloride*

	(SSR125543A): A Potent and Selective Corticotrophin-Releasing Factor1 Receptor Antagonist. I. Biochemical and Pharmacological Characterization, 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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