Trials@uspto.gov
571.272.7822

Paper No. 62
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NEUROCRINE BIOSCIENCES, INC.,
Petitioner,

v.

SPRUCE BIOSCIENCES, INC.,
Patent Owner.

PGR2022-00025
Patent 11,007,201 B2

Before JOHN G. NEW, SUSAN L. C. MITCHELL, and TINA E. HULSE, *Administrative Patent Judges*.

MITCHELL, *Administrative Patent Judge*.

JUDGMENT

Final Written Decision
Determining All Challenged Claims Unpatentable
35 U.S.C. § 328(a)

Denying in Part and Dismissing in Part
Petitioner's Motion to Exclude Evidence
37 C.F.R. § 42.64(c)

Denying in Part and Dismissing in Part
Patent Owner's Motion to Exclude Evidence
37 C.F.R. § 42.64(c)

Dismissing Petitioner's Motion to Strike
37 C.F.R. § 42.23(b)

I. INTRODUCTION

We have jurisdiction to hear this post-grant review under 35 U.S.C. § 6. This Final Written Decision is issued pursuant to 35 U.S.C. § 328(a) and 37 C.F.R. § 42.73. For the reasons set forth below, we determine that Petitioner Neurocrine Biosciences, Inc. ("Petitioner") has established, by a preponderance of the evidence, that challenged claims 1–19 of Patent Owner Spruce Biosciences, Inc.'s ("Patent Owner") U.S. Patent No. 11,007,201 B2 (Ex. 1001, "the '201 patent") are unpatentable. We also *deny in part* and *dismiss in part* Petitioner's Motion to Exclude Evidence, *deny in part* and *dismiss in part* Patent Owner's Motion to Exclude Evidence, and *dismiss* Petitioner's Motion to Strike.

II. BACKGROUND

A. Procedural History

On February 18, 2022, Neurocrine Biosciences, Inc. ("Petitioner") filed a Petition for Post-Grant Review of claims 1–19 of the '201 patent. Paper 2 ("Pet."). On June 17, 2022, Spruce Biosciences, Inc. ("Patent Owner") filed a Preliminary Response. Paper 6 (Prelim. Resp.).

Petitioner requested leave to file a reply brief addressing Patent Owner's arguments in its Preliminary Response, which we granted along with authorization for Patent Owner to file a sur-reply in response. *See* Paper 7. On July 14, 2022, Petitioner filed its Reply, *see* Paper 8 ("Reply"), and on July 28, 2022, Patent Owner filed its Sur-Reply, *see* Paper 9 ("Sur-Reply"). On September 15, 2022, we denied institution of post-grant review. *See* Paper 10.

On October 13 2022, Petitioner filed a Rehearing Request, and Petitioner additionally filed a request for Precedential Opinion Panel

("POP") review. *See* Papers 11, 12. On July 20, 2023, the Director *sua sponte* initiated Director Review of our decision, *see* Paper 13, and ordered dismissal of the requests for rehearing and POP review, *see* Paper 14. On August 4, 2023, the Director issued a decision vacating our decision denying institution and remanding the case to the panel "for further proceedings consistent with my Decision in PGR2021-00088." Paper 15. When we refer in this Decision to the "Director's Decision" or "Dir. Dec.," we are referring to the Decision in PGR2021-00088, Paper 16. We instituted post-grant review of the challenged claims of the '201 patent on December 1, 2023. Paper 20 ("Institution Decision" or "Dec. Inst.").

After institution of trial, Patent Owner filed a Response (Paper 27, "PO Resp."), Petitioner filed a Reply (Paper 30, "Pet. Reply"), and Patent Owner filed a Sur-reply (Paper 43, "PO Sur-reply"). A consolidated oral argument was held in this proceeding and PGR2021-00088 on September 3, 2024, and a copy of the transcript was entered into the record. Paper 57 ("Tr."). We authorized additional briefing on claim construction on September 6, 2024 (Paper 56). Both Petitioner (Paper 58) and Patent Owner (Paper 59) filed additional briefing on claim construction and Oppositions (Papers 60 and 61, respectively) to the opposing party's additional briefing.

Both Petitioner (Paper 44) and Patent Owner (Paper 45) filed Motions to Exclude Evidence ("[Pet./PO] Mot. Exclude") and filed Oppositions (Papers 47 and 48, respectively) to the opposing party's Motion to Exclude Evidence ("[Pet./PO] Opp. Mot. Exclude"). Both parties also filed a Reply to their opponent's Opposition to their Motions to Exclude ("[Pet./PO] Reply Mot. Exclude"). Paper 51 (Petitioner); Paper 50 (Patent Owner). Petitioner filed an authorized Motion to Strike (Paper 49, "Pet. Mot.

Strike"), and Patent Owner filed an Opposition (Paper 53, "Opp. Mot. Strike").

Petitioner also filed a Statement of Objections to Patent Owner's Demonstrative Evidence, *see* Paper 55, which we took under advisement at oral hearing. *See* Tr. 4.

B. Real Parties in Interest

Petitioner identifies itself as the real party in interest. Pet. 82. Patent Owner also identifies itself as the real party in interest. Paper 3, 2.

C. Related Matters

Petitioner asserts that it "is not aware of any disclaimers, reexamination certificates, or petitions for *inter partes* or post grant review for the '201 Patent, nor is Petitioner aware of any pending civil actions involving the '201 patent." Pet. 82.

Petitioner does identify PGR2021-00088 in which Petitioner sought post-grant review of the parent patent for the '201 patent, U.S. Patent No. 10,849,908 B2 ("the '908 patent"). Pet. 82. Patent Owner also identifies PGR2021-00088. *See* Paper 3, 2.

D. The '201 Patent (Ex. 1001)

The '201 patent, titled "Corticotropin Releasing Factor Receptor Antagonists," issued May 18, 2021, identifying Patent Owner as the applicant and assignee. Ex. 1001, codes (54), (71), (73). The '201 patent is directed to "pharmaceutical compositions comprising -(4-Chloro-2-(morpholin-4-yl) thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo (1,5-α) pyrimidine ("Compound 1"), and methods of using the same for the

treatment of congenital adrenal hyperplasia ("CAH")." *Id*. at Abstr., 1:32–60.

Relevantly, the '201 patent is directed to the administration of Compound 1, or another antagonist of the corticotropin releasing factor ("CRF") receptor type 1 ("CRF1" or "CRF_1"), and thus, inhibiting release of adrenal corticotropic hormone ("ACTH") by the secretory cells of the adenohypophysis, for the treatment of CAH. Ex. 1001, 10:47–12:25. The Specification of the '201 patent explains the necessity of controlling the level of ACTH to prevent the overproduction of androgens, such as androstenedione ("A4"). *Id*. at 11:65–12:25, 48:3; *see also id*. at 43:47–53 (explaining in Example 4 that "Compound 1 attenuates morning rise in A4 which indicates an ability to control excess androgen production and associated symptoms (*see* FIG. 4)").

E. Challenged Claims

Petitioner challenges all nineteen claims of the '201 patent. Pet. 1, 4. All claims of the '201 patent are method claims. Claim 1 is the sole independent claim. Claims 2–5, 7, and 9–18 depend directly from claim 1, claim 6 depends from claim 5, claim 8 depends from claim 7, and claim 19 depends from claim 18.

Claim 1 is representative and reproduced below:

> 1. A method of treating congenital adrenal hyperplasia (CAH) in a human comprising administering to the human a therapeutically-effective amount of a CFR_1 receptor antagonist or a pharmaceutically acceptable salt thereof, wherein an androstenedione (A4) level in the human is reduced from baseline and is maintained at a reduced level post 24 hours.

Ex. 1001, 47:51–48:5.

F. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1–19 of the '201 patent on the following grounds, *see* Pet. 4:

Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1–4, 7–9, 11–15, 18	102[1]	Grigoriadis[2]
10, 16, 17, 19	103	Grigoriadis
5, 6	103	Grigoriadis and Romano[3]
1–4, 7–19	103	Grigoriadis and Turcu 2016[4]
5, 6	103	Grigoriadis, Turcu 2016, and Romano
1–19	112	Lack of written description

Petitioner initially relied upon the Declarations of Dr. Robert M. Carey (Ex. 1005, the "Carey Declaration"). When Dr. Carey became medically incapable of testifying at deposition or otherwise participating in the proceeding, the Board approved Petitioner's request to submit additional

[1] The Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112-29, 125 Stat. 284, 287–88 (2011), amended 35 U.S.C. §§ 102, 103, and 112, effective March 16, 2013. Because the earliest application on which the '201 patent claims priority was filed after the effective date of the AIA, we apply the AIA version of 35 U.S.C. §§ 102, 103, 112. *See* Ex. 1001, codes (22), (60), (63).

[2] Dimitri E. Grigoriadis, US 2017/0020877 A1, published Jan. 26, 2017 (Ex. 1006, "Grigoriadis").

[3] Steve Romano, US 2005/0209250 A1, published Sept. 22, 2005 (Ex. 1007, "Romano").

[4] Adina F. Turcu, et al., *Single-Dose Study of a Corticotropin-Releasing Factor Receptor-1 Antagonist in Women with 21-Hydroxylase Deficiency*, 101 J. CLIN. ENDOCRINOL. METAB. 1174–1180 (2016) (Ex. 1008, "Turcu 2016").

documentation to allow Gordon B. Cutler, Jr., M.D., to succeed Dr. Carey, with the affirmative proviso that Dr. Cutler adopt Dr. Carey's existing testimony and be made available for cross-examination by Patent Owner (Ex. 1041, "the Cutler Declaration"; Ex. 1047, "the Cutler Reply Declaration"; Ex. 1049). Patent Owner relies upon the Declaration of Adrian Dobs, M.D., M.H.S. (Ex. 2014, the "Dobs Declaration"). We have reviewed the credentials of Petitioner's and Patent Owner's declarants, and consider each to be qualified to provide the opinions for which their testimony has been submitted. *See* Section IV.C.

III. MOTIONS TO EXCLUDE EVIDENCE, MOTION TO STRIKE, AND OBJECTIONS TO DEMONSTRATIVES

As we have previously described, *see* Section I.A., both parties have submitted Motions to Exclude Evidence, *see* Papers 46 and 47, and Petitioner has filed a Statement of Objections to Patent Owner's Demonstrative Evidence based on exhibits it asks us to exclude, *see* Paper 55. Petitioner also filed an authorized Motion to Strike. *See* Paper 51.

We now consider each party's Motion to Exclude in turn, along with Petitioner's Objections to Patent Owner's demonstratives, and we also consider Petitioner's Motion to Strike.

A. Petitioner's Motion to Exclude and Motion to Strike

Petitioner moves to exclude portions of "the written description opinions of Patent Owner's expert, Dr. Dobs (Exhibit 2014, ¶¶20, 75–87), and to exclude Exhibit 2016 and Exhibits 2020–2026 in their entireties." Pet. Mot. Exclude 1. We address each of Petitioner's arguments in turn.

1. *Dr. Dobs' Written Description Opinions (Exhibit 2014 ¶¶ 20, 75–87)*

a. *Parties's arguments*

Petitioner asserts that the Board should exclude from evidence Dr. Dobs' written description opinions set forth in paragraphs 20 and 75–87 of Dr. Dobs' Declaration, *see* Exhibit 2014, because "Dr. Dobs is not qualified as an expert to opine on written description of the challenged claims under FRE 702." Pet. Mot. Exclude 3.

According to Petitioner, Dr. Dobs admitted during her deposition that she "lacks specialized knowledge, skill, experience, training, or education that would assist the Board in understanding the evidence relating to whether the challenged claims lack adequate written description under 35 U.S.C. §112(a)." Pet. Mot. Exclude 3–4; *see also id.* at 8–9. More specifically, Petitioner contends "Dr. Dobs admitted that she is not familiar with medicinal chemistry, and demonstrated she is not qualified to opine on the chemical structures described in the prior art references she cited to support her written description opinions." *Id.* at 7. Petitioner argues further that "Dr. Dobs repeatedly admitted she is not a chemist, was not comfortable with chemical terminology, and could not answer questions regarding the chemical structures described in the Williams and Fahmy articles." *Id.* at 2, 7 (citing Ex. 1042, 32:12–14, 125:18–126:7, 128:8–130:10); *see id.* at 7–8 (citing Ex. 2014 ¶¶ 83–84; Ex. 1042, 32:21–35:2, 126:15–128:7, 128:8–130:10, 130:13–131:16, 132:17–134:20). Finally, Petitioner states that "Dr. Dobs admitted that tildacerfont (the only antagonist described in the specification) 'was developed with structureally unique features' compared to the other CFR1 receptor antagonists." *Id.* at 8 (citing Ex. 1042, 52:19–53, 14; Ex. 1039, 8).

Patent Owner responds that Petitioner's rationale for its Motion to Exclude Evidence "ignores its own definition of relevant skill level in the art, which says nothing about expertise in medicinal chemistry or that a POSA must be 'a chemist.'" PO Opp. Mot. Exclude 2. Patent Owner asserts that Dr. Dobs is qualified as an endocrinologist to testify about the perspective of one of skill in the art as defined by the Petitioner. *Id*. at 1–2.

Petitioner replies that although it agrees that Dr. Dobs, as an endocrinologist, qualifies as one of ordinary skill in the art for this proceeding, but reiterates Dr. Dobs testimony that Petitioner asserts are "all contrary to her opinion that the prior art discloses a structure-function correlation (Ex. 2014 ¶ 84)." Pet. Reply Mot. Exclude 3. Petitioner concludes that "Dr. Dobs' testimony shows that she lacks the required expertise to opine on the structural features of CRF1 receptor antagonists, and whether common structural features result in the claimed function lowering A4 levels." *Id*. at 3–4.

b. *Analysis*

Dr. Dobs attested that she is a physician and Board-certified endocrinologist with expertise in endocrinology and hormone disorders, and has been an expert in this field since well before 2017. Ex. 2014 ¶ 3. Dr. Dobs is presently Professor of Medicine and Oncology in the Division of Endocrinology, Diabetes and Metabolism, and Director, Johns Hopkins Clinical Research Network Johns Hopkins Institute for Clinical and Translational Research (ICTR) at The Johns Hopkins University School of Medicine. Ex. 2015, 1.

Dr. Dobs also attested that by 2017, the year when the provisional application that is the first application in the priority chain of the '201 patent

was filed, she had a medical degree, experience in the field of endocrinology, knowledge of hormone regulation and disorders, and knowledge of the regimens employed to treat such disorders. Ex. 2014 ¶ 4. Dr. Dobs testified that she also had at least three years of experience conducting research concerning endocrine disorders, including congenital adrenal hyperplasia ("CAH") and other adrenal disorders, and she thus satisfies the description of a skilled artisan in this field. *Id.*

Dr. Dobs states that she has published extensively on topics including hormones and hormone disorders including cortical adrenal hyperplasia, is the author or co-author of over 250 scientific articles, and has served on numerous editorial boards. Ex. 2014 ¶¶ 8–9. Dr. Dobs has also participated in more than fifty clinical trials evaluating endocrine therapeutics and hormones. *Id.* ¶ 10. She has also participated in several FDA panels and has presented in front of several FDA advisory boards. *Id.*

Dr. Dobs testified that, in her clinical practice, she has treated patients with CAH as well as Cushing's syndrome, which may be associated with over-administration of glucocorticoids during the treatment of CAH. Ex. 2014 ¶ 11.

Petitioner's proffered definition of a person of ordinary skill in the art, which we adopt below, is one who "[possesses] a medical degree or a Ph.D. in a field related to endocrinology, and would have knowledge of hormone regulation and disorders, as well as knowledge of the treatment regimens employed to treat such disorders." Pet. 26 (citing Ex. 1005 ¶ 34). Petitioner also argues that such a person of ordinary skill would also have at least three years of experience conducting research concerning endocrine disorders, including CAH or other adrenal disorders. *Id.* at 26–27.

By this definition, Dr. Dobs is at least a person of ordinary skill in the art, as Petitioner admits. *See* Pet. Reply 2. She possesses a medical degree and is Board-certified in endocrinology, and has sufficient clinical and research experience in the diagnosis and methods of treatment of treating patients with endocrinological disorders. Dr. Dobs is therefore qualified to testify at least as to the knowledge of a skilled artisan. *Kyocera Senco Indus. Tools Inc. v. Int'l Trade Comm'n*, 22 F.4th 1369, 1376–77 (Fed. Cir. 2022). Furthermore, given her past research and clinical experience, her current position as a tenured medical professor at a major research university, and her extensive record of publication, we find Dr. Dobs qualified to opine as an expert in the causes and nature of endocrine disorders, including CAH, and the diagnosis, and treatment of patients with such disorders.

To the extent that Dr. Dobs has admitted that she is "not comfortable with chemical terminology"; "could not answer questions regarding the chemical structures in the prior art articles"; "did not know whether CRF_1 receptor antagonists contained the structural features she deemed 'essential' in her Declaration"; and "agreed that tildacerfont has structurally unique features" (*see* Ex. 1042, 52–53, 125–126, 126–128, 128–130) goes to the weight that we assign to such testimony, but we do not find that such testimony, in light of Dr. Dobs' extensive qualifications as an endocrinologist set forth above, deems Dr. Dobs unqualified to testify concerning the written description issue in this proceeding.

For these reasons explained above, Petitioner's Motion to Exclude Dr. Dobs' written description opinions in paragraphs 20 and 75–87 of Exhibit 2014 is *denied*.

2. *Exhibits 2016 and 2020–2026*

a. *Petitioner's arguments*

Petitioner argues that "Patent Owner relies on Exhibit 2016 for the proposition that Dr. Eiry Roberts, Neurocrine's Chief Medical Officer, 'prepared' the peer-reviewed Auchus article, and 'has known Dr. Cutler for decades and recruited him' to work with Neurocrine." Pet. Mot. Exclude 10 (citing PO Resp. 1, 3). Petitioner argues the Board should exclude Exhibit 2016 from evidence because "it does not show whether Dr. Roberts 'prepared' the Auchus article, nor whether Dr. Roberts and Dr. Cutler had a pre-existing relationship," and "neither of these issues have any consequence on the outcome of this case." *Id.* at 13.

Petitioner also argues that the Board should exclude from evidence Exhibits 2016 and 2020–2026 "as irrelevant under FRE 401" because, *inter alia*, "none of Exhibits 2020–2026 are relevant to whether Grigoriadis anticipates the '201 patent claims or renders those claims obvious, as set forth in the Petition." Pet. Mot. Exclude 10 (citing Pet. 4). According to Petitioner, "Exhibits 2020–2026 are documents filed in the prosecution of Neurocrine's own patent applications," Exhibits 2020, 2021, and 2024 "are ministerial papers filed with the Office in connection with Neurocrine's patent applications that have nothing to do with the merits of this PGR," and "Exhibits 2022 and 2025 are Information Disclosure Statements." *Id.* at 10–11.

Petitioner further contends that Exhibits 2023 and 2026 are irrelevant because "Exhibit 2023 is a Preliminary Amendment and Exhibit 2026 is a Reply to a Restriction Requirement" in which the claims in the exhibits are merely pending, Petitioner has made no substantive arguments about

patentability of those pending claims, and the pending claims "are fundamentally different than Grigoriadis' disclosure of administrating crinecerfont as a CRF_1 receptor antagonist useful to treat CAH, and the inherent result of that administration (reducing ACTH, 17-OHP, and/or A4 levels in a human)." Pet. Mot. Exclude 11–12.

Patent Owner responds that Petitioner's arguments apply to the weight to be given Patent Owner's evidence and does not support the exclusion of that evidence. PO Opp. Mot. Exclude 9. Patent Owner also asserts that when considering the substance of the Exhibits Petitioner seeks to exclude, these exhibits support Patent Owner's argument that Petitioner "cannot credibly assert that differences between the generic disclosure in Grigoriadis and the detailed protocol in Auchus are immaterial because Neurocrine filed patent alleging those differences matter critically." *Id.*

Finally, Petitioner replies that "any alleged differences between Grigoriadis' and Auchus' respective protocols are immaterial because the protocols are not in the challenged claims." Pet. Reply Mot. Exclude 5.

b. *Analysis*

We do not need to rely on Patent Owner's Exhibits 2016 and 2020–2026 to resolve the disputes before us in this proceeding. Therefore, these Exhibits play no part in our reasoning, and were not relied upon by the Board in reaching our Decision. Petitioner's Motion to Exclude Exhibits 2016 and 2020–2026 is *dismissed* as moot.

Petitioner also moved to strike Exhibits 2020–2026 as irrelevant. Pet. Mot. Strike 2–3. For the same reasons that we dismiss as moot Petitioner's Motion to Exclude these same exhibits, we also dismiss as moot Petitioner's Motion to Strike.

Petitioner also submitted a Statement of Objections to Patent Owner's Demonstrative Evidence objecting to Patent Owner's demonstrative slides 19, 22, 25, and 66 in Exhibit 2028. *See* Paper 55, 1. Petitioner objects to these slides because they cite and rely "on information contained in Exhibits 2020, 2021, 2023, and 2026." *Id.* Because we do not need to rely on any information in these Exhibits to resolve the disputes before us, we do not need to rule on these objections.

3. *Summary*

For the reasons we have explained in the preceding sections, we *deny* Petitioner's Motion to Exclude Dr. Dobs' written description opinions in paragraphs 20 and 75–87 of Exhibit 2014 and *dismiss* as moot Petitioner's Motion to Exclude Exhibits 2016 and 2020–2026.

B. Patent Owner's Motion to Exclude

Patent Owner moves to exclude Exhibits 1005 and 1046, and portions of Exhibit 1047. PO Mot. Exclude 1, 5. We address each of the parties' arguments in turn.

1. *The Carey Declaration (Exhibit 1005)*

a. *Parties' Arguments*

Patent Owner argues the Board should exclude Petitioner's Exhibit 1005 because Petitioner replaced Dr. Carey with Dr. Cutler. PO Mot. Exclude 1–2. According to Patent Owner, Petitioner filed Dr. Cutler's Declaration because Dr. Carey is medically unable to participate in this proceeding and was not made available for cross-examination. *Id.* Patent Owner contends "[w]hile it is believed that EX1005 has now been withdrawn given the circumstances, Petitioner has not expressly

acknowledged its withdrawal and even improperly cited EX1005 in its briefing." *Id.* at 1 (citing Pet. Reply 11, 13–15, 20–21, 25, 26).

Petitioner responds that Dr. Cutler expressly adopted Dr. Carey's existing testimony in his supplemental declaration, a substitution to which Patent Owner was amenable, as well as being made available for cross-examination on those opinions. Pet. Opp. Mot. Exclude 1–2. Petitioner further asserts that Patent Owner did not provide sufficient reasoning for its expectation that Dr. Carey's declaration would be withdrawn, and Dr. Carey's declaration is of record as incorporated into Dr. Cutler's supplemental declaration. *Id.* at 2. Therefore, Petitioner concludes, any objection to the declaration has been waived. *Id.*

Patent Owner replies that Exhibit 1005 should be excluded "[t]o avoid confusion and/or prejudice" because Petitioner withdrew Dr. Carey as a witness. PO Reply Mot. Exclude 1. Patent Owner contends that Dr. Cutler adopted the content of Dr. Carey's Declaration by appending a copy of Dr. Carey's Declaration (Ex. 1005) to his own Declaration (Ex. 1041) "rather than reproducing the content in the body of his own declaration." *Id.*

Patent Owner argues that this creates two problems, namely that the record now contains two copies of Dr. Carey's Declaration, and "the parties in briefing are burdened with separately referencing two documents" which "risks the prejudicial false impression that Petitioner has two supporting witnesses (Dr. Cutler and Dr. Carey), when in fact only one exists." PO Reply Mot. Exclude 1–2.

b. *Analysis*

Petitioner initially relied upon the Declaration of Dr. Robert M. Carey (Ex. 1005). When Dr. Carey became medically incapacitated and incapable

of testifying at deposition, the Board approved Petitioner's request to submit additional documentation to allow Gordon B. Cutler, Jr., M.D., to "step into the shoes" of Dr. Carey, with the affirmative proviso from the Board that Dr. Cutler adopt Dr. Carey's existing testimony and be made available for cross-examination by Patent Owner. *See* Ex. 1049. Dr. Cutler subsequently submitted a Declaration (Ex. 1041) and a Reply Declaration (Ex. 1047) and was deposed by Patent Owner on February 29, 2024 (Paper 26), and a second time on July 25, 2024 (Paper 33).

In his Declaration, Dr. Cutler testifies that "I have reviewed Dr. Carey's declaration (attached as Appendix B) and the opinions and exhibits cited therein. I agree with Dr. Carey's opinions in full, and hereby adopt the opinions set forth in Dr. Carey's declaration as my own." Ex. 1041 ¶ 16. Dr. Cutler's Declaration adds nothing more that is substantial, except to describe his background and qualifications, and to note that Dr. Carey cited an article co-authored by Dr. Cutler in his Declaration "proposing the study of CFR1 receptor antagonists for potential use in the treatment of CAH." *Id.* ¶¶ 2–13, 8.

Patent Owner adduces no legal authority for us to exclude the Carey Declaration, nor does it provide any evidence that inclusion of the Carey Declaration colorably prejudices its case. Patent Owner deposed Dr. Carey twice. Patent Owner's arguments that failing to exclude the Carey Declaration: (1) will cause the parties in briefing to be burdened with separately referencing two documents; and (2) "risks the prejudicial false impression that Petitioner has two supporting witnesses (Dr. Cutler and Dr. Carey), when in fact only one exists" have no merit. *See* PO Reply Mot. Exclude 1–2.

Dr. Cutler's Declaration appropriately adopts the Carey Declaration in full and makes no additional substantial argument with respect to the merits of the case as we prescribed. *See* Ex. 1049, 1. Petitioner properly relied upon the Carey Declaration, which was appropriately incorporated in full into Dr. Cutler's Declaration essentially becoming Dr. Cutler's testimony, in its Reply Brief as the Declaration on the merits supporting its Petition. Indeed, excluding the Carey Declaration would potentially prejudice *Petitioner*, by depriving it of the expert opinion supporting its arguments as cited in the Petition and the Reply and fully attested to by Dr. Cutler. Finally, excluding Exhibit 1005 is more likely to introduce confusion into the record by removing an Exhibit upon which the Petition expressly relies.

Similarly, the record is sufficiently clear as to why Dr. Cutler, with the Board's approval, stepped in for the medically incapacitated Dr. Carey. *See* Ex. 1041 ¶ 15[5]; Ex. 1046, 1–2. Any risk of prejudice against Patent Owner by the mistaken impression that Petitioner has two supporting witnesses has ben elimated. Patent Owner's motion to exclude Exhibit 1005 is *denied*.

2. *Exhibit 1046 and Paragraphs 24, 31–34, 42, 44, 45, 54–64, 67–70, and 77–99 of Dr. Cutler's Reply Declaration (Exhibit 1047)*

a. *Patent Owner's arguments*

Patent Owner argues Petitioner presents "untimely and improper new argument and evidence not relevant to the petition case," which pled an anticipation theory, in Exhibit 1046 and paragraphs 24, 31–34, 42, 44, 45,

[5] Dr. Cutler testified in his Declaration that "I understand that Dr. Robert M. Carey, M.D., submitted a declaration in support of Neurocrine's Petition . . . (EX. 1005). I understand that Dr. Carey . . . at present is not able to work, or to participate further in this matter." Ex. 1041 ¶ 15.

54–64, 67–70, and 77–99 of Exhibit 1047. PO Mot. Exclude 3–6. According to Patent Owner, Petitioner relies on Exhibit 1046 "to bolster its ever-evolving pivot from anticipation to the different theory of obviousness" and to "argue that while neither Grigoriadis nor Auchus demonstrate[s] clinical efficacy, that was eventually demonstrated in a different and later published Phase III trial." *Id.* at 2–3 (citing Ex. 1047 ¶¶ 30, 34, 42).

Patent Owner further contends "Petitioner's argument and reliance on this newly submitted document [Ex. 1046] demonstrate that its abandonment of the anticipation theory of the petition and improper pivot to an (unpled) obviousness theory is complete" and "[t]o the extent such argument and evidence is considered at all, it should only be to confirm the petition failed to demonstrate Grigoriadis, alone or properly viewed in combination with Auchus, satisfies each element of the challenged claims." PO Mot. Exclude 3 (citing Ex. 1047 ¶ 24).

b. *Petitioner's response*

Petitioner responds that Patent Owner's argument that Exhibit 1046 and portions of Exhibit 1047 "should be excluded as 'untimely and improper new argument and evidence not relevant to the petition case' violates the Board's procedures by cloaking arguments about scope of reply in a motion to exclude." Pet. Opp. Mot. Exclude 3. Accordingly, Petitioner contends on this basis alone the Board should deny Patent Owner's Motion to Exclude. *Id.*

Petitioner also argues that the Board should deny Patent Owner's Motion to Exclude on the merits because Petitioner "cited to Exhibit 1046 *once* in its Reply as further evidence—'*[c]onsistent with Auchus*'—that the administration of crinecerfont substantially reduced A4 in CAH patients"

and to "simply refute[] Patent Owner's (irrelevant) argument that Auchus' A4 reductions from baseline for Cohort 4 were not statistically significant." Pet. Opp. Mot. Exclude 4–5 (emphasis and footnote omitted, first alteration in original, citing Pet. Reply 19–20; Ex. 1046, 5, Fig. 1; Ex. 1047 ¶¶ 31–42; PO Resp. 44–45).

Petitioner contends that Patent Owner fails to explain how any paragraphs of Exhibit 1047 are "outside the scope of proper reply" because "[e]ven a cursory look at Patent Owner's parenthetical citations shows that all of Dr. Cutler's explanations rebut Patent Owner's arguments." Pet. Opp. Mot. Exclude 6 (explaining how each of the following paragraphs of Exhibit 1047—24, 31–34, 42, 44, 45, 54–64, 67–70, and 77–99—rebut Patent Owner's arguments) (citing PO Mot. Exclude 3–4).

c. *Patent Owner's reply*

Patent Owner responds that its Motion to Exclude is not limited to the issue of improper reply brief scope, but instead seeks to exclude evidence that goes "to an unpled obviousness theory" that has "no tendency to make the pled inherent anticipation theory more or less probable and fails to support facts 'of consequence in determining the action' as required by FRE 401." PO Reply Mot. Exclude 2. Patent Owner contends Petitioner's Opposition does not demonstrate otherwise because it "never squarely deals with the lack of relevance to its petition case" and "doesn't grapple with testimony of Dr. Cutler that clearly illustrates the improper abandonment of its anticipation theory." *Id.* at 2–3. Patent Owner disagrees that Exhibit 1046 and the portions of Exhibit 1047 it seeks to exclude rebut Dr. Dobs' testimony because Dr. Cutler repeatedly agrees with Dr. Dobs and "pivot[s]

to different and unpled arguments and theories." *Id.* at 3–4 (citing Ex. 1047 ¶ 34).

d. *Analysis*

As an initial matter, our reasoning and conclusions in this Decision involving analysis of whether appropriate written description support exists do not rely upon what is taught in Exhibit 1046, nor do we cite to it to support our analysis. We consequently dismiss as moot Patent Owner's Motion to Exclude Exhibit 1046.

With respect to the cited paragraphs of Exhibit 1047, paragraphs 24, 31–34, 42, 44, 45, 54–64, 67–70, and 77–99, that Patent Owner seeks to exclude, we determine that these paragraphs are part of a direct response to the testimony of Patent Owner's expert, Dr. Dobs, with respect to the Grigoriadis reference and to Dr. Carey's expert opinion regarding what is taught by that reference. As such, we find that these paragraphs are relevant under Fed R. Evid. 401 as rebuttal to the responsive arguments made by Patent Owner in this case. Because we find the challenged paragraphs are responsive to Patent Owner's evidence and because "the introduction of new evidence in the course of the trial is to be expected in *inter partes* review trial proceedings," we are not persuaded that the challenged paragraphs are untimely and irrelevant. *See Genzyme Therapeutic Prod. Ltd. P'ship v. Biomarin Pharm. Inc.*, 825 F.3d 1360, 1366 (Fed. Cir. 2016) (stating "the introduction of new evidence in the course of the trial is to be expected in *inter partes* review trial proceedings"); *see also Corephotonics, Ltd. v. Apple Inc.*, 84 F.4th 990, 1009 (Fed. Cir. 2023) (finding "a reply may be proper if it is responsive and simply expands on previously raised arguments") (stating new evidence may be introduced during an *inter partes* review as

long as it is an expansion on and fair extension of a previously raised argument and has a nexus or is responsive to an argument made by the Patent Owner or the Board).

For instance, challenged paragraphs 77–99 of Exhibit 1047, directly relate to Dr. Cutler's rebuttal of Dr. Dobs' argument that the prior art teaches that all CRF_1 receptor antagonists could be used to treat CAH, or achieve A4 reductions. As such, they form a coherent part of Petitioner's argument in reply to Patent Owner's evidence. They are consequently relevant to the issues in this case and, particularly, to the issue of whether the challenged claims have sufficient written descriptive support in the '201 Specification, which is dispositive of this post grant review. Patent Owner has not sufficiently shown how the challenged paragraphs are irrelevant under Rule 401, or how, by failing to exclude them, Patent Owner's case is unduly prejudiced.

3. *Summary*

For the reasons we have explained in the preceding sections, we *deny* Patent Owner's motion to exclude Exhibit 1005; we *dismiss* as moot Patent Owner's Motion to Exclude Exhibit 1046, and we *deny* Patent Owner's Motion to Exclude paragraphs 24, 31–34, 42, 44, 45, 54–64, 67–70, and 77–99 of Exhibit 1047.

IV. ANALYSIS

A. Eligibility for Post-Grant Review

In our Institution Decision, we determined that the '201 patent is eligible for post-grant review based on Petitioner's certification and effective filing dates for the claims of the '201 patent. Dec. Inst. 6–7. Specifically, we found the application leading to the '201 patent was filed on October 22,

2020, and asserts that it is a continuation of the application that led to the '908 patent, which in turn claims priority to a previously filed PCT application and a provisional application, the first of which was filed on August 14, 2017. *Id*. (citing Ex. 1001, codes (22), (60), (63)). We also found that all of these dates fall after March 16, 2013. Also, this Petition was filed on February 18, 2022, which is within nine months after the May 18, 2021, issue date of the '201 patent. *Id.* at 7 (citing Ex. 1001, code (45)). Patent Owner has not challenged this determination. *See generally* PO Resp.

B. Person of Ordinary Skill in the Art

Factual indicators of the level of ordinary skill in the art include "the various prior art approaches employed, the types of problems encountered in the art, the rapidity with which innovations are made, the sophistication of the technology involved, and the educational background of those actively working in the field." *Jacobson Bros., Inc. v. U.S.*, 512 F.2d 1065, 1071 (Ct. Cl. 1975); *see also Orthopedic Equip. Co. v. U.S.*, 702 F.2d 1005, 1011 (Fed. Cir. 1983) (quoting with approval *Jacobson Bros*.).

According to Petitioner, a person of ordinary skill in the relevant art ("POSA") "would have a medical degree or a Ph.D. in a field related to endocrinology, and would have knowledge of hormone regulation and disorders, as well as knowledge of the treatment regimens employed to treat such disorders . . . [and] would also have at least three years of experience conducting research concerning endocrine disorders, including CAH or other adrenal disorders." Pet. 26–27 (citing Ex. 1005 ¶ 34 (Dr. Carey Declaration)).

Patent Owner does not expressly contest this definition of a person of ordinary skill in the art in its Response. Because Petitioner's definition of a

person of skill in the art appears commensurate with the level of skill reflected in the asserted art in this case as well as the '201 patent itself, *see, e.g.*, Exs. 1024, 1025, 2003, 2004, 2005, we apply Petitioner's proposed level of ordinary skill in the art. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (stating prior art itself can reflect the appropriate level of ordinary skill in the art).

C. Claim Construction

We construe claims "using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. [§] 282(b)." 37 C.F.R. § 42.200 (2019). Therefore, we construe the challenged claims under the framework set forth in *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–19 (Fed. Cir. 2005) (en banc). Under this framework, claim terms are given their ordinary and customary meaning, as would be understood by a person of ordinary skill in the art, at the time of the invention, in light of the language of the claims, the specification, and the prosecution history of record. *Id.* Only those terms that are in controversy need be construed, and only to the extent necessary to resolve the controversy. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, *Matal*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (citing *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

Petitioner proposes constructions for the claim terms "baseline/from baseline," "human," and "maintained at a reduced level post 24 hours [4 weeks or 6 weeks]." *See* Pet. 27–30. Patent Owner responds that "it is sufficient for the Board to maintain its decision in Petitioner's prior PGR [PGR2021-00088], rejecting Petitioner's argument that the claimed reduction 'from baseline' is satisfied by the reduction relative to placebo in

Grigoriadis, as also was established during prosecution." Prelim. Resp. 15. Patent Owner continues to maintain in its Response that placebo measurements should not be equated with baseline. PO Resp. 20–27.

In our Institution Decision, we concluded that we need only construe the claim term "from baseline" as part of our decision granting institution of post-grant review. Dec. Inst. 9. We construed the claim language reciting "reduced from baseline" as meaning "a reduction in A4 level compared to an A4 level measurement made prior to, and/or at the beginning of, administration of the drug." *Id.* at 11.

After the oral argument, we concluded that our construction of "from baseline" was inadequate because "the endocrine hormonal system controlling release of adrenocorticotropic hormone ('ACTH') and 17-hydroxprogesterone ('17-OHP') is not in a physiological steady state, but is rather subject to a circadian rhythmicity." Paper 56, 2. We "construe[d] the claim term 'baseline' to mean 'a series of samples taken from an untreated patient with CAH, prior to treatment at intervals that are time-matched to the sampling intervals to be taken from the patient treated with either a CRF_1 receptor antagonist or placebo.'" *Id.* at 3. We stated our proposed new construction at oral argument and offered the parties an opportunity to express their views on this construction. *Id.* at 4. We authorized both parties "to submit briefing upon this new proposed construction as it relates to . . . Grounds 1–5" of this proceeding and "to submit an opposition to the other party's arguments." *Id.* Both Petitioner (Paper 58) and Patent Owner (Paper 59) filed additional briefing on claim construction and Oppositions (Papers 60 and 61, respectively) to the opposing party's additional briefing.

Given our conclusion below that the challenged claims are unpatentable under 35 U.S.C. § 112(a) as lacking written description support, we determine that no claim construction by the Board is necessary to resolve the dispute at issue here.

D. Principles of Law

1. Burden of Proof

To prevail in this post-grant review of the challenged claims, Petitioner must prove unpatentability by a preponderance of the evidence. 35 U.S.C. § 326(e); 37 C.F.R. § 42.1(d). Petitioner has the burden from the onset to show with particularity why the challenged claims are unpatentable. *See Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016). This burden of persuasion never shifts to the patent owner. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015) (discussing the burden of proof in *inter partes* review).

2. Written Description

The test for written description support is "whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date" based on an "objective inquiry into the four corners of the specification." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). The written description requirement is satisfied when the specification "set[s] forth enough detail to allow a person of ordinary skill in the art to understand what is claimed and to recognize that the inventor invented what is claimed." *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 928 (Fed. Cir. 2004).

The written description inquiry is a question of fact, is context-specific, and must be determined on a case-by-case basis. *Ariad*, 598 F.3d at 1351 (citing *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985); *Capon v. Eshhar*, 418 F.3d 1349, 1357–58 (Fed. Cir. 2005)). "[T]he level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology." *Id.* (citing *Capon*, 418 F.3d at 1357–58). Factors used to evaluate the sufficiency of a disclosure include: 1) "the existing knowledge in the particular field"; 2) "the extent and content of the prior art"; 3) "the maturity of the science or technology"; and 4) "the predictability of the aspect at issue." *Id.* (citing *Capon*, 418 F.3d at 1359).

E. Ground 6: Claims 1–29 Lack of Written Descriptive Support

1. Petitioner's arguments

Petitioner argues that the claims of the '201 patent fail the written description requirement because the '201 patent does not show possession of the claimed subject matter. Pet. 76. Petitioner contends that the '201 patent "discloses only a single CRF1 receptor antagonist, tildacerfont (Compound 1)," and "repeatedly characterizes the 'present invention' or 'present disclosure' as relating to Compound 1." *Id.* (citing Ex. 1005 ¶ 96).

Petitioner further asserts that written description support is lacking for the challenged claims because (1) "all of the Examples and clinical data in the '201 patent relate to tildacerfont;" (2) there is no disclosure of any other CRF1 receptor antagonist to treat CAH in the '201 patent; (3) there are no disclosed "structural features common to the members of the genus so that one of skill in the art can visualize or recognize the members of the genus;"

(4) Patent Owner distinguished tildacerfont from other CRF1 receptor antagonists as having "structurally unique features that lower the lipophilicity and volume of distribution of the compound and improve solubility resulting in more predictable pharmacokinetic properties;" (5) Patent Owner failed to provide any specific support for the challenged claims when they were added to the application; and (6) Patent Owner relied on allegedly unexpected results of administering tildacerfont to overcome rejections of Grigoriadis in the prosecution history. *Id*. at 76–79 (citing Ex. 1001, 1:30–38, 34:5–47:58, Tables 5–8; Ex. 1039, 2; Ex. 1003, 38–52; Ex. 1004, 52–61; Ex. 1037, 328–330).

2. *Patent Owner's arguments*

Patent Owner responds that Petitioner's written description challenge fails because the '201 patent discloses using CRF_1 receptor antagonists, which constitute a well-known genus of compounds. PO Resp. 66–78. First, according to Patent Owner, the Specification "describes inventing the use of this known class for the treatment of CAH in a human by administering the antagonist to achieve a pre-defined reduction in a specified hormone level." *Id.* at 67. Patent Owner contends "[t]he specification confirms that its description of using the CRF1 receptor antagonist class refers to a known class by explaining the class effects of this particular type of antagonist" such as by explaining that "CRF and its two receptor subtypes were well-characterized," explaining "the differences between the receptor subtypes," and explaining "the effects of using the CRF1-specific antagonists instead of non-specific antagonist." *Id.* at 68 (citing Ex. 1001, 1:17–20, 10:47–65, 11:49–56, 11:65–12:25; Ex. 2014 ¶ 82).

Patent Owner argues further that the Specification also includes an exemplary embodiment using tildacerfont, which is an example of a particular CRF_1 receptor antagonist. PO Resp. 69 (citing Ex. 1001, 14:15–36; Ex. 2014 ¶ 78). Patent Owner contends that the Specification teaches administering the CRF_1 antagonist "until the desired reduction in hormone levels (e.g., A4, ACTH, or 17-OHP) is achieved" and describes experimental results of such a method of administering tildacerfont. *Id.* at 69–71 (citing Ex. 1001, 26:12–27:38, 33:52–59, 41:43–43:47, 43:34–53, Figs. 2–4; Ex. 2014 ¶¶ 78–80).

Based on testimony from the parties' experts and references submitted by Petitioner, Patent Owner also argues that CRF_1 receptor antagonists were well-known and characterized. PO Resp. 71–78. Patent Owner contends that Dr. Carey describes CRF_1 receptor antagonists and their effects and admits in the proceeding in PGR2021-00088 that as of the relevant time, 'over 100 CRF1 receptor antagonists had been characterized or were in clinical development prior to the filing of the [parent] '908 patent, including NBI34041, verucerfont, and pexacerfont.'" *Id.* at 72 (citing Ex. 1005 ¶ 99 in PGR2021-00088; Ex. 1029; Ex. 1018, Ex. 1030; Ex. 1031; Ex. 1041 ¶ 16; Ex. 2014 ¶ 75) (alteration in original).

Second, Patent Owner argues that "Dr. Dobs agrees with Drs. Carey and Cutler that, by the critical date, a [person of ordinary skill in the art] would have recognized that CRF1 receptor antagonists were a well-known class." PO Resp. 73 (citing Ex. 2014 ¶¶ 75–82). According to Patent Owner, Petitioner's references describe structural characteristics common to CRF_1 receptor antagonists, such as 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. *Id.* at 74–75 (citing Ex. 1018, 272, Fig. 1; Ex. 1029, 2, Fig. 2; Ex. 2014 ¶ 83). Patent Owner also contends that Petitioner's expert and references recognize that tildacerfont is a CRF_1 receptor antagonist. *Id.* at 77 (citing Ex. 1005 ¶ 27; Ex. 1041 ¶ 16; Ex. 1012, 6:54–60; Ex. 1018; Ex. 1029, 5–9, Figs. 1,9; Ex. 2014 ¶¶ 75–76).

Third, Patent Owner contends that Petitioner's written description arguments are flawed because they are based on an erroneous legal standard. PO Resp. 78–83. Patent Owner argues that Petitioner incorrectly assumes there is a *per se* rule that a claim is invalid if there is only one working example in the specification. *Id*. at 80–82. Patent Owner contends that *Ariad* states no such rule, noting that *Ariad* involved a patent application that disclosed no example of any species actually being used to achieve the claimed result. *Id.* at 80–81 (citing *Ariad*, 598 F.3d at 1356). Patent Owner argues that instead, as the Federal Circuit explains, "the number of species required to be representative decreases when there is additional information already available in the prior art." *Id.* at 81 (citing *Ajinomoto Co. v. Int'l Trade Comm'n*, 932 F.3d 1342, 1359 (Fed. Cir. 2019)).

Patent Owner contends that because the '201 patent discloses that CRF_1 antagonists were already known in the field, "the genus 'was already well explored in the relevant art by the time of the . . . patent's invention,'" such that "the specification, read in light of the background knowledge in the art, [provides] a representative number of species for the genus." PO Resp. 81–82 (citing *Ajinomoto*, 932 F.3d at 1359). Patent Owner argues that the Specification of the '201 patent need not recite multiple structures with common structural features to satisfy the written description requirement because Petitioner does not challenge that the prior art describes known

structures and identifies common structural features, and Petitioner does not identify any evidence that the disclosed working example is not representative of the well-known class of compounds. *Id.* at 83.

3. *Petitioner's Reply*

Petitioner replies by noting that the Board has adopted the Director's finding that "the '201 patent specification does not disclose a representative number of species falling within the scope of the recited genus of CRF1 receptor antagonists that can be used in the claimed" method." Pet. Reply 5 (quoting Dir. Dec. 12; Dec. Inst. 32). Petitioner asserts that the '201 Specification discloses but a single species, tildacerfont ("Compound 1"), that can achieve the claimed reduction in A4 levels, which it classifies as "the invention." *Id.* (quoting Dir. Dec. 12). Petitioner also cites to our finding that the Specification also "does not disclose structural features common to the members of the functional genus so that one of skill in the art can visualize or recognize the effective members of the genus of CFR1 receptor antagonists." *Id.* (Dec. Inst. 32 (citing Dir. Dec. 13–14)).

Turning to the merits, Petitioner first argues that the Specification of the '201 patent does not show possession of a class of CRF_1 receptor antagonists for the treatment of CAH. Pet. Reply 5–7. Petitioner argues that the portions of the Specification cited by Patent Owner are silent with respect to whether the class of CRF_1 receptor antagonists can achieve the claimed reduction in A4. *Id.* at 5–6 (citing Ex. 1047 ¶¶ 82–84). According to Petitioner, these citations relate to the use of tildacerfont, or the differences between CRF receptor subtypes and the role of CRF in hormone regulation, or that these antagonists had been studied for other indications. *Id.* at 6 (citing Ex. 1001, 1:14–20, 10:47–65, 11:49–12:25, 11:47–64, 12:26–

29, 43:4–43). Petitioner asserts that none of these disclosures relates to whether the Specification discloses a representative number of species or common structural features of CRF_1 receptor antagonists that achieve the claimed results. *Id.* (citing Dec. Inst. 32).

Petitioner contends that there is no dispute that the Specification fails to disclose a representative number of species that achieve the claimed reduction in A4. Pet. Reply 6. Petitioner argues that tildacerfont is not "an exemplary embodiment," as Patent Owner argues, but is rather the *only* embodiment described for use with the claimed methods. *Id.* (citing PO Resp. 69, Dir. Dec. 12). Furthermore, argues Petitioner, Patent Owner's expert, Dr. Dobs, agrees that tildacerfont is the only compound disclosed by the Specification. *Id.* (citing Ex. 1042, 29:18–32:19).

Additionally, Petitioner argues, the Specification of the '201 patent describes the use of tildacerfont as the "present invention" or "present disclosure," which Petitioner argues, is further "strong evidence" that the scope of written description is limited to the use of tildacerfont. Pet. Reply 6–7 (citing Pet. 12–16, 75–79; *SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc.*, 242 F.3d 1337, 1343 (Fed. Cir. 2001); *Gentry Gallery Inc. v. Berkline Corp.*, 134 F.3d 1473, 1478–80 (Fed. Cir. 1998); *In re Lew*, 257 F. App'x 281, 285 (Fed. Cir. 2007)). Petitioner argues that, contrary to Patent Owner's arguments, each of these cited cases found that a patentee's characterization of a feature as the "present invention" or "present disclosure" is strong evidence that the written description is limited to that feature. *Id.* at 7. According to Petitioner, the Specification of the '201 patent does the same thing, defining Patent Owner's invention as using tildacerfont. *Id.* (citing Pet. 12–16, 75–79).

Petitioner next argues that the prior art did not teach a class of CRF_1 receptor antagonists that could treat CAH, or reduce A4 levels and maintain the reduction post twenty-four hours. Pet. Reply 7–9. Petitioner points to the Director's finding, adopted by the Board, that Dr. Carey's testimony that "over 100 CRF1 receptor antagonists had been characterized or were in clinical development" before the priority date does not support claims to a class of CRF_1 receptor antagonists that can be used to treat CAH and result in the claimed hormone reduction. *Id.* at 7 (quoting Dir. Dec. 13; Dec. Inst. 32). Petitioner notes that Patent Owner has acknowledged that different species within the CRF_1 receptor antagonist genus do not achieve the same results. *Id.* (citing Dir. Dec. 13; Prelim. Resp. 6, 42–47). According to Petitioner, Patent Owner's argument that there is no "*per se* rule" a claim is invalid if there is only one working example is similarly faulty. *Id.* at 7–8 (citing PO Resp. 80–83).

Petitioner points to the testimony of its expert, Dr. Cutler, who explains that, although the prior art discussed the possibility that CRF_1 receptor antagonists may be useful as a "new approach" to treat CAH, it did not provide evidence that a class of CRF_1 receptor antagonists could achieve the claimed A4 reductions. Pet. Reply 8 (citing Ex. 1047 ¶¶ 75–76; Ex. 1021, 130–31). Petitioner also disputes Patent Owner's suggestion that Petitioner's prior work, as reported in Grigoriadis, shows that Patent Owner was in possession of using the claimed genus to reduce A4 levels. *Id.* (citing PO Resp. 72–73). Petitioner contends that, if Grigoriadis' disclosure of species of CRF_1 receptor antagonists that reduce A4 provides written-description support for Patent Owner's claims, then it must also anticipate

the claims, which is the basis for Ground 1. *Id.* (citing *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 971 (Fed. Cir. 2001)).

Petitioner argues further that CRF_1 receptor antagonists were previously studied for indications other than CAH, and were ineffective. Pet. Reply 8 (citing Ex. 1047 ¶¶ 78–81; Ex. 1030, 377–78; Ex. 1031, 24–25; Ex. 1040, Table 1). Petitioner points out that Patent Owner's expert admitted that a person of ordinary skill in the art would have understood that "antagonists of the CRF1 receptor have not demonstrated clinical utility despite over 30 years of research and hundreds of patents." *Id.* (citing Ex. 1029, 1065; Ex. 1042, 131:18–132:14). Petitioner argues that, in view of the prior art, a skilled artisan would not have thought a class of CRF_1 receptor antagonists were useful for any indication, much less being useful to treat CAH, or to lower A4 levels and maintain that reduction post 24 hours. *Id.* at 8–9. Petitioner contends that this is particularly true because the '201 Specification discloses only tildacerfont and does not provide any way "to distinguish effective from ineffective compounds among those encompassed by the broad genus so claimed." *Id.* at 8 (quoting Dir. Dec. 14 (citing *Idenix Pharms., LLC v. Gilead Sciences Inc.*, 941 F.3d 1149, 1165 (Fed. Cir. 2019))).

Finally, Petitioner contends that the '201 Specification does not describe common structural features of CRF_1 receptor antagonists that achieve the claimed reductions in A4. Pet. Reply 9 (citing Dir. Dec. 12–13; Dec. Inst. 32). Petitioner asserts that CRF_1 receptor antagonists are defined as compounds that inhibit CRF_1 receptors, not by a particular structure or structures. *Id.* (citing Ex. 1047 ¶¶ 86–90). Petitioner again points to the testimony of Dr. Cutler, who explains that compounds that interact with the

CRF_1 receptor can have widely diverse structural features. *Id.* Dr. Cutler opines that the broad structural features observed in some (but not all) CRF_1 receptor antagonists would not tell a person of ordinary skill in this art whether any compounds in this class could accomplish the claimed results of reducing A4 from baseline. *Id.* Petitioner also notes that Patent Owner's own publication describes tildacerfont (the only species disclosed in the '201 Specification) as having "unique structural features" compared to other CRF_1 receptor antagonists. *Id.* at 10 (citing Ex. 1039, 4667; Ex. 1042, 52:19–53:14).

Petitioner notes that the generalized structure Patent Owner asserts is a "typical CRF1 receptor antagonist" is described in Williams[6] as one subclass of CRF_1 receptor antagonists, i.e., not reflective of the entire class. Pet. Reply 10 (citing Ex. 1029, 2, Fig. 2; Ex. 1042, 122:8–123:16; Ex. 1047 ¶¶ 91–92). Petitioner argues that Williams does not disclose that any of the antagonists falling within Figure 2's generalized structure could lower A4, but refers to these compounds as having "less-than-optimal physicochemical properties." *Id.* (citing Ex. 1029, 2). Furthermore, argues Petitioner, Williams also reports other CRF_1 receptor antagonist subclasses that do not have the same structural features as Figure 2. *Id.* (citing Ex. 1047 ¶¶ 92–95; Ex. 1029, Figs. 1 (compounds 1, 4), 6, 11; Ex. 1044 ¶¶ 95–99). Petitioner also notes that, at her deposition, Patent Owner's expert admitted she is not a chemist and did not know whether other CRF_1 receptor antagonists disclosed in Williams were encompassed by Figure 2. *Id.* (citing Ex. 1042, 125:5–

[6] J.P. Williams, *Corticotropin-Releasing Factor 1 Receptor Antagonists: A Patent Review*, 23(8) EXPERT OPIN. THER. PATENTS 23(8) 1057–1068 (2013) ("Williams") Ex. 1029.

126:7, 129:17–130:10). According to Petitioner, Dr. Dobs also admitted that other CRF_1 receptor antagonists disclosed by Williams have different structures from that shown in Figure 2. *Id.* (citing Ex. 1042, 130:13–131:16).

Similarly, Petitioner argues, Fahmy[7] does not describe structural features of CRF_1 receptor antagonists that could reduce A4 from baseline. Pet. Reply 10 (citing Ex. 1047 ¶¶ 96–97). Rather, Petitioner contends, Fahmy provides a general structure that encompasses a large number of compounds, without providing any information on what features are important for CAH treatment or A4 reduction. *Id.* at 10–11 (citing Ex. 1018, 3, Fig. 1). According to Petitioner, Fahmy also discloses antagonists falling outside the structure of Figure 1, and provides no way to distinguish compounds that are effective to reduce A4. *Id.* at 11 (citing Ex. 1018, 7–8, Figs. 11–12; Ex. 1047 ¶¶ 96–98; Ex. 1042, 132:17–134:20). Furthermore, argues Petitioner, Chen[8] discloses a list of 24 potential indications for CRF_1 receptor antagonists, but does not identify any structural features of antagonists useful to treat CAH or achieve the claimed reductions in A4. *Id.* (citing Ex. 1012, 2:10–62).

Consequently, Petitioner contends, neither the '201 Specification nor the prior art discloses a representative number of species or common structural features of CRF_1 receptor antagonists that achieve the claimed results. Pet. Reply 11.

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[7] H. Fahmy, *Structure and Function of Small Non-Peptide CRF Antagonists and their Potential Clinical Use*, 10(4) CURRENT MOL. PHARMACOL. 270–281 (2017) ("Fahmy") Ex. 1018.

[8] Chen et al. (US 8,030,304 B2, October 4, 2011) ("Chen") Ex. 1012.

4. *Patent Owner's Sur-Reply*

Patent Owner replies that Petitioner attacks the prior art as not demonstrating a reduction from baseline and attacks the '201 Specification, which demonstrates a reduction from baseline, for not repeating structural features already provided in the prior art. PO Sur-Reply 19. Patent Owner contends, however, Petitioner fails to address the adequacy of the Specification in view of the knowledge provided in the prior art. *Id.*

Patent Owner contends that Petitioner and its expert, Dr. Cutler, acknowledged that the '201 Specification discloses CRF_1 receptor antagonists as a known class. PO Sur-Reply 19–20 (citing Pet. Reply 6; Ex. 1047, ¶ 83). According to Patent Owner, Dr. Cutler never retracted his and Dr. Carey's testimony that CRF_1 receptor antagonists were a well-known and characterized class. *Id.* (citing PO Resp. 7; Ex. 1005 ¶¶ 23, 24; Ex. 2010 ¶ 99; Ex. 2014 ¶¶ 20, 75–77). Patent Owner therefore contends that Petitioner has failed to prove the inventors lacked constructive possession of the class at the critical date. *Id.*

Patent Owner disputes Petitioner's contention that a method patent using a known class must itself list out the "species or common structural features" of the class even when structural features of the class already were well-known. PO Sur-Reply 20 (citing Pet. Reply 1, 5–6, 9–12). To the contrary, Patent Owner argues, a patent identifying a well-known class need not repeat structural information that was already known and available in the prior art. *Id.* (citing PO Resp. 66–67, 73–74).

Nor, Patent Owner argues, does Petitioner dispute the well-known class of CRF_1 receptor antagonists was characterized structurally in the prior art. PO Sur-Reply 20. Rather, argues Patent Owner, Petitioner does not

contest that there was a known structure-activity relationship for CRF_1 receptor antagonists, that the basic pharmacophore for inhibition had been defined, or that the inventors were already in at least constructive possession of the class. *Id.* Instead, Patent Owner contends, Petitioner argues that exceptions exist. *Id.* (citing Pet. Reply 9–11). Patent Owner argues the law, however, does not require that there be structural features ubiquitous to the class; the law requires structural features common to the class. *Id.* (citing *Ariad*, 598 F.3d at 1350). According to Patent Owner, Petitioner's own evidence establishes such features had been identified. *Id.* (citing PO Resp. 71–78).

According to Patent Owner, Petitioner argues that a post-critical date publication explains that second-generation CRF_1 antagonists have lower lipophilicity and volume of distribution to improve solubility, resulting in more predictable pharmacokinetic properties. PO Sur-Reply 21 (citing Pet. Reply 10 (citing Ex. 1039, 4667; Ex. 1042, 52:19–53:14)). However, argues Patent Owner, Petitioner identifies no evidence that the pharmacodynamic ability of CRF_1 receptor antagonists is absent from the class; to the contrary, Patent Owner notes, Dr. Cutler testified that the opposite was true. *Id.* (citing Ex. 1047 ¶ 23; Ex. 2027, 73:3–12). Patent Owner asserts that Petitioner's own evidence demonstrates art-recognized structural characterization, including identification of structural features common to the class. *Id.*

Patent Owner next argues that the '201 Specification provides a method of identifying effective compounds in the class. PO Sur-Reply 21. According to Patent Owner, Petitioner's expert, Dr. Cutler, testified that a 14-day oral dosing protocol was able to identify whether a CRF_1 receptor

antagonist reduces A4 from baseline as required by the claims. *Id.* (citing Ex. 2027, 18:10–21:5). Patent Owner states that Dr. Cutler also testified that determining a therapeutic effect of CRF_1 receptor antagonists was well within the level of ordinary skill in the art. *Id.* (citing Ex. 2027, 75:21–76:14). Patent Owner notes that the '201 Specification discloses the claimed reduction during the 14-day dosing trial protocol. *Id.* (citing PO Resp. 33–35, 67–71; Ex. 2014 ¶¶ 43, 78–80; Ex. 1001, 14:60–15:11, 26:12–27:39, 39:8–40:19, 41:42–44:47, 43:47–53, Fig. 4; Ex. 1039, Fig. 5.).

Patent Owner notes that although Dr. Cutler points to the 14-day dosing protocol as disclosed in Auchus, Auchus in fact borrowed the protocol that Patent Owner published. PO Sur-Reply 22. According to Patent Owner, if Auchus is probative of anything in this case, it is evidence corroborating written description support in the '201 Specification. *Id.* (citing *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1374 (Fed. Cir. 2017) (holding that "post-priority-date evidence of a particular species" can bear on whether the disclosure is representative)).

Patent Owner next disputes Petitioner's argument that the '201 Specification says nothing about whether the class can achieve the claimed reductions in A4 and "define[s]" the invention as limited to using tildacerfont. PO Sur-Reply 22 (citing Pet. Reply 5–7) (alternation in original). Patent Owner argues that the Specification explains that: (1) CRF binding to CRF_1 receptor triggers ACTH release and downstream 17-OHP and A4 production; (2) CRF_1 receptor antagonists are biologically-active small molecules that bind CRF_1 receptor; and (3) CRF_1 receptor antagonists treat CAH by reducing production of ACTH, 17-OHP, and A4 by antagonizing CRF-CRF_1 receptor binding, and that tildacerfont is one

embodiment of that genus. *Id.* at 23 (citing PO Resp. 79–80; Ex. 1001, 10:61–65, 11:49–12:29).

Patent Owner contends that, contrary to Petitioner's arguments, it is the dosing protocol that is material to the results for CRF_1 receptor antagonism and that Grigoriadis does not disclose a method that inherently achieves the claimed results. PO Sur-Reply 23. Patent Owner argues that Petitioner has failed to prove Grigoriadis' (1) generic mention of crinecerfont (no real method) or (2) a flawed single-dose verucerfont study achieves a reduction from baseline—that provides no evidence that Patent Owner's examples were unrepresentative. *Id.* Patent Owner asserts that even prior art disclosure that the class of CRF_1 receptor antagonists are useful in CAH would not constitute an anticipatory disclosure of using them in a manner specifically to achieve a maintained reduction from baseline. *Id.* at 23–24.

Finally, Patent Owner contends that Petitioner's arguments that some CRF receptor antagonists have been ineffective for indications such as alcoholism, anxiety and depression are irrelevant, because these studies are, as admitted by Petitioner's expert, unrelated to the treatment of CAH. PO Sur-Reply 23–24 (citing Pet. Reply 8–9; Ex. 1047 ¶ 78, Ex. 2027, 103:1–106:15). Patent Owner notes that Dr. Cutler also admitted that there is no reason that a person of ordinary skill in the art would expect or require that a CAH treatment also would be effective for depression, anxiety, or alcoholism. *Id.* (citing Ex. 2027, 39:14–40:5, 46:1–50:14).

Patent Owner concludes that Petitioner has not presented any evidence demonstrating a failed CRF_1 receptor antagonist studied for CAH treatment, and that Petitioner's expert testified that it was known in the prior

art that there is a therapeutically effective dose for any CRF_1 receptor antagonist. PO Sur-Reply 25 (citing Ex. 1047 ¶ 23; Ex. 2027, 73:3–12).

5. *Analysis*

The written description requirement of Section 112(a) requires that:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

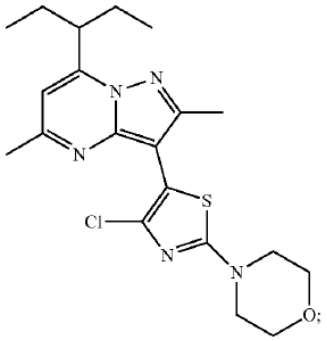
35 U.S.C. § 112(a). In *Regents of the University of California v. Eli Lilly & Co.*, our reviewing court held that an adequate written description of genetic material "'requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention." 119 F.3d 1559, 1566 (Fed. Cir. 1997) (quoting *Fiers v. Revel*, 984 F.2d 1164, 1171 (Fed. Cir. 1993)).

In *University of Rochester v. G.D. Searle & Co.*, the Federal Circuit held that this standard also applies to *all* inventions, including proteins and other biological compounds:

> We see no reason for the rule to be any different when non-genetic materials are at issue; in fact, where there might be some basis for finding a written description requirement to be satisfied in a genetics case based on the complementariness of a nucleic acid and, for example, a protein, that correspondence might be less clear in a non-genetic situation.

358 F.3d at 925. We consequently apply herein the standard set forth in *Regents* to our written description analysis.

Independent claim 1 of the ’201 patent recite, in relevant part, “[a] method of treating congenital adrenal hyperplasia (CAH) in a human comprising administering to the human a therapeutically-effective amount of a CRF_1 receptor antagonist or a pharmaceutically acceptable salt thereof.” There is no dispute that the ’201 Specification names but a single CRF_1 receptor antagonist, Compound 1 (i.e., tildacerfont). The ’201 patent characterizes Compound 1 as being “3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-α) pyrimidine.” Ex. 1001, 1:33–35. The ’201 Specification also repeatedly provides a structural formula for Compound 1:



Compound 1 (tildacerfont) of the ’201 Specification

See, e.g., *id.* at 1:41–57. Consequently, the ’201 Specification provides ample description of Compound 1.

Challenged independent claim 1, however, is not restricted to Compound 1, but recite “a therapeutically-effective amount of *a* CRF_1 receptor antagonist” (emphasis added), which encompasses not only Compound 1, but essentially, all members of the genus of CRF_1 receptor antagonists that reduce the level of A4 in a human “from baseline and is maintained at a reduced level post 24 hours.” *See, e.g.*, *Ariad*, 598 F.3d at 1341.

"[A]n adequate written description of a claimed genus requires more than a generic statement of an invention's boundaries." *Ariad*, 598 F.3d at 1349 (citing *Regents*, 119 F.3d at 1568). Rather:

> [A] sufficient description of a genus instead requires the disclosure of either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can "visualize or recognize" the members of the genus.

Id. at 1350 (citing *Regents*, 119 F.3d at 1568–69). Moreover, "an adequate written description requires a precise definition, such as by structure, formula, chemical name, physical properties, or other properties, of species falling within the genus sufficient to distinguish the genus from other materials." *Id.* (citing *Regents*, 119 F.3d at 1568 (quoting *Fiers*, 984 F.2d at 1171)). Furthermore, "functional claim language can meet the written description requirement when the art has established a correlation between structure and function." *Id.* (citing *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 964 (Fed. Cir. 2002) (quoting 66 Fed. Reg. 1099 (Jan. 5, 2001))). "[M]erely drawing a fence around the outer limits of a purported genus is not an adequate substitute for describing a variety of materials constituting the genus and showing that one has invented a genus and not just a species." *Id.*

Given the large number of CRF_1 receptor antagonists with varying structures and effectiveness (*see* Ex. 1018, 270–271; Ex. 1029, 1065) the '201 Specification's disclosure of a single species of CRF_1 receptor antagonists, i.e., Compound 1, therefore fails, on its face, to meet *Ariad's* requirement that the Specification disclose "a representative number of species falling within the scope of the genus or structural features common

to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus." *Ariad*, 598 F.3d at 1350.

Although the '201 Specification does not expressly disclose "a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus," the larger test for the sufficiency of Section 112's written description requirement is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date. *Ariad*, 598 F.3d at 1351 (citing *Vas–Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1562–63 (Fed. Cir. 1991) (quoting *Ralston Purina*, 772 F.2d at 1575)). For generic claims, the Federal Circuit has set forth a number of factors for evaluating the adequacy of the disclosure, including "the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, [and] the predictability of the aspect at issue." *Capon*, 418 F.3d at 1359.

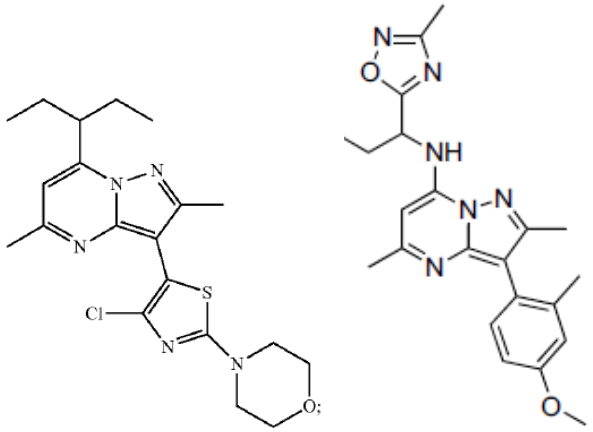
In other words, the question is whether a person of ordinary skill would, given the factors set forth in *Capon*, recognize from the disclosures of the '201 Specification the "structure, formula, chemical name, physical properties, or other properties, of species falling within the claimed genus" of CRF_1 receptor antagonists. *Ariad*, 598 F.3d at 1350. Alternatively, because the claimed genus is characterized in the language of the claims by what it *does* (i.e., reduces the level of A4 from baseline and is maintained at a reduced level post 24 hours), would a person of skill in the art recognize that the art has established a recognizable correlation between the structure of the claimed genus and its function in reducing the level of A4 from

baseline and maintaining the reduction post 24 hours? *See Enzo*, 323 F.3d at 964.

In arguing that the '201 Specification meets this requirement, despite the Specification's silence with respect to defining the claimed genus of CRF_1 receptor antagonists, Patent Owner contends that a person of ordinary skill would recognize the genus claimed by the '201 patent by either test. PO Resp. 71–78. In support of this argument, Patent Owner relies upon Fahmy and Williams. *Id.*

a. *Fahmy (Ex. 1018)*

The Fahmy reference is a review of small non-peptide CRF antagonists, with an emphasis upon their clinical relevance and with emphasis on those members that showed great promise or those that were advanced to clinical trials. Ex. 1018, Abstr. Fahmy teaches that dysfunction of the CRF system has often been correlated with anxiety or symptoms closely-related to anxiety, and to various diseases such as major depression, anxiety, eating disorders and drug addiction. *Id.* at 271. Fahmy also notes that CRF may be involved in the stress-induced relapse and the anxiety-like behaviors observed during acute drug withdrawal and drug addiction. *Id.* Fahmy makes only a single mention of using CRF_1 receptor antagonists in the treatment of CAH, noting that verucerfont, a CRF_1 receptor antagonist related to tildacerfont, "is under investigation as a possible treatment for the typical congenital adrenal hyperplasia." *Id.* at 276. The comparative structures of tildacerfont and verucerfont are depicted below:



Comparative structures of tildacerfont (right) and verucerfont (left)

Ex. 1001, 1:41–57; Ex. 1018, 276.

Fahmy teaches that both peptide and non-peptide CRF receptor antagonists are known in the art, although, due to the peptide nature of the former, their physical properties posed a boundary for their use in clinical settings.[9] Ex. 1018, 272. Therefore, Fahmy teaches, non-peptide antagonists have been pursued as a better alternative. *Id.* Fahmy teaches that "[h]undreds of accounts of small molecule antagonists have appeared in the literature and the preclinical and clinical pharmacology have been reported for many of these agents," and that "[t]he main research into CRF antagonists to date has focused on non-peptide CRF1 receptor antagonists to target health problems arising as a result of chronic stress and thus as potential treatment options for anxiety-related and stress-related disorders." *Id.* Fahmy also teaches that "[s]everal classes of small molecule non-peptide

[9] Fahmy teaches that peptides acting as selective agonists and antagonists for CRF_1 and CRF_2 receptors include the peptides astressin and anti-sauvagine1-30. Ex. 1018, 272. Presumably, the difficulties in employing peptidergic CRF_1 receptor antagonists relates to the obstacle posed in crossing the blood brain barrier.

CRF receptor antagonists have been synthesized and many are commonly used in research." *Id.* Fahmy further discloses that "[t]he synthesis of more non-peptide CRF1 receptor antagonists with . . . diverse structure scaffolds as well as further clinical investigations may shed more light on how CRF is implicated in mental disorders." *Id.*

More specifically, Fahmy teaches that:

> The relationship between structures of non-peptide CRF1 antagonists and their affinity to CRF1 receptors indicates that CRF1 antagonists are typically built of three moieties: a hydrophobic moiety up, a proton accepting moiety in the middle, and an aromatic moiety down. Thus the basic pharmacophore is proposed to be made of a monocyclic or bicyclic heterocyclic ring carrying a hydrophobic dialkylamino group on one flank and an aryl ring, usually substituted at the 2-, 4- and 6-positions, on the opposite flank. Having the aromatic ring orthogonal to the heterocyclic core appears to be essential for the affinity. A methyl group on the heterocyclic core also appears to enhance the CRF1 antagonist properties (Fig. 1).

Ex. 1018, 272 (internal citations omitted). Figure 1 of Fahmy, reproduced below, illustrates that the X-ray structure of several non-peptide CRF_1 antagonists confirms these characteristics that are required for optimum CRF receptor binding affinity:

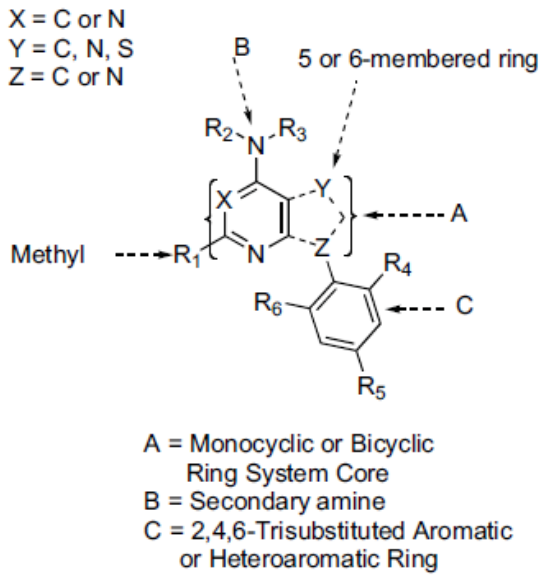
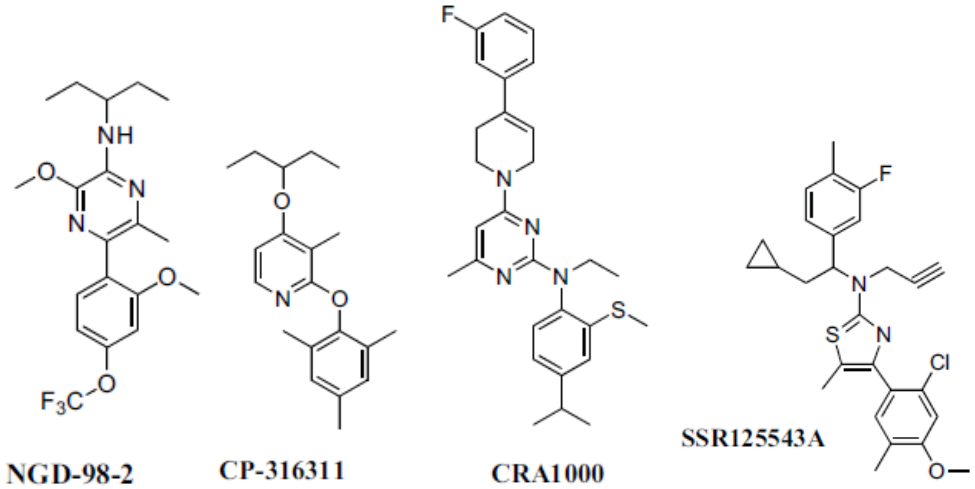


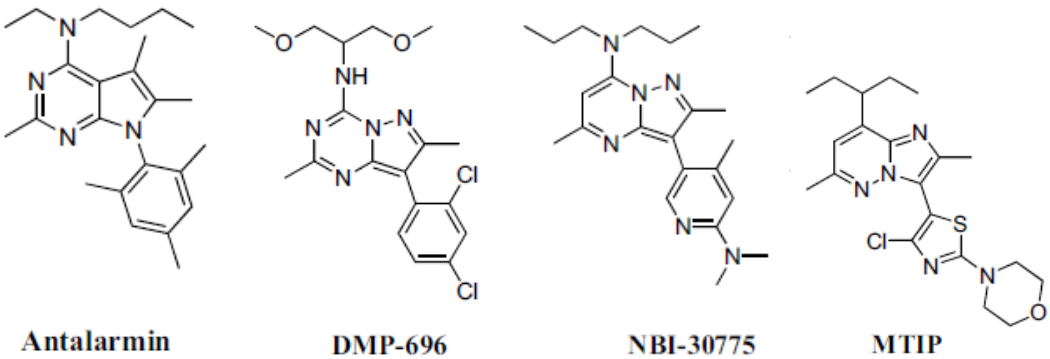
Figure 1 of Fahmy depicts the structure of the pharmacophore of CRF1 antagonists

Fahmy teaches that, based on the number of rings in the heterocyclic core ring system, small molecule CRF_1 receptor antagonists can be classified to the following classes: (1) monocyclic; (2) bicyclic; and (3) tricyclic CRF_1 receptor antagonists. Ex. 1018, 272–276. The first category, monocyclic CRF_1 receptor antagonists, can be further sub-classified, based upon the nature of the central ring structure, into: (a) pyrazines; (b) pyridines; (c) pyrimidines; and (d) thiazoles. *Id.* at 272–274. Examples of each of these sub-classifications taught by Fahmy are depicted below:



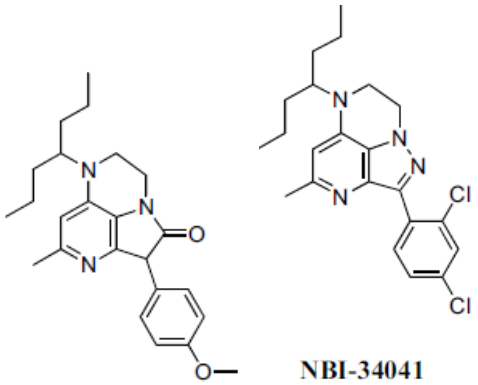
Illustrations from Figures 2–5 of Fahmy depicting examples of (from left to right), pyrazine (NGD-98-2), pyridine (CP-316311), pyrimidine (CRA1000) and thiazole (SSR125543A) monocyclic CRF_1 receptor antagonists

Similarly, bicyclic CRF_1 receptor antagonists can be subdivided into: (a) pyrrolo[2,3-d]pyrimidines; (b) pyrazolo[1,5-α]1,3,5-triazines; (c) pyrazolo[1,5-α]pyrimidines; and (d) imidazo[1,2-b]pyridazines. Ex. 1018, 274–276. Examples of each of these sub-classes are depicted in Fahmy, and selected examples are reproduced below:



Illustrations from Figures 6–8 and 10 of Fahmy depicting examples of (from left to right), pyrrolo[2,3-d]pyrimidine (Antalarmin), pyrazolo[1,5-α]1,3,5-triazine (DMP-696), pyrazolo[1,5-α]pyrimidine (NBI-30775) and imidazo [1,2-b] pyridazine (MTIP) bicyclic CRF_1 receptor antagonists

Fahmy also teaches that tricyclic CRF_1 receptor antagonists can be sub-classified into: (a) triazaacenaphthylenes; and (b) tetraazaacenaphthylenes. Ex. 1018, 276–277. Fahmy illustrates examples of each, which are reproduced below:



Illustrations from Figures 11 and 12 of Fahmy depicting examples of (from left to right), triazaacenaphthylene (unlabeled) and tetraazaacenaphthylene (NBI-34041) tricyclic CRF_1 receptor antagonists

Fahmy concludes that "the design of small molecule, non-peptide CRF antagonists may afford new treatment options and a new class of antidepressants and anti-anxiety agents from this class may emerge in the near future." Ex. 1018, 277.

b. *Williams (Ex. 1029)*

Williams is a review article covering "the disclosures of non-peptide CRF_1 antagonists in the patent literature since 2006." Ex. 1029, Abstr. Williams teaches that:

> Animals display anxiety-like behaviors when CRF is administered centrally and these behaviors can be reversed by centrally administered peptide antagonists of the CRF_1 receptor. This plus a vast amount of CRF-associated research not reviewed here suggested that blockade of the CRF_1 receptor may result in new therapies to treat human stress-related disorders like anxiety and depression.

Id. at 1057 (internal citation omitted). Williams does not address the treatment of CAH, but obliquely mentions the subject, stating that:

> [C]ompound 12 has a longer 'residence time' on the receptor and CRF_1 antagonists with longer residence times were more effective in reducing plasma ACTH levels in adrenalectomized rats. Adrenalectomized rats are unable to regulate the ACTH levels since they lack the negative feedback of adrenal cortisol that controls ACTH release thus providing a sustained elevated level of the ACTH biomarker. The CRF_1 antagonist R121919 (2), with a preliminary hint of clinical efficacy, has a longer residence time versus CP-316,311 which may prove to be an important factor in future CRF_1 antagonist development.

Id. at 1058 (internal citations omitted).

Williams teaches that:

> The 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. The most prevalent subclass (designated Type I for the purpose of this review) of CRF_1 antagonists are those with two atoms separating the aryl region moiety from the requisite core nitrogen atom (which may play the role of a hydrogen bond acceptor when bound by the receptor). This is illustrated by compound 2 (Figure 2) with the 3-pyridyl group serving in the role as the aromatic substituent attached at the C-3 position of the pyrazolo [1,5-α]pyrimidine core and the dipropylamino group at C-7 represents the branched alkyl region. The methyl group at the C-4 position of the pyridyl and the methyl at C-2 of the core serve to steer the aryl group out of plane relative to the central heterocycle.

Id. at 1058 (internal citations omitted). Figure 2 of Williams is reproduced below:

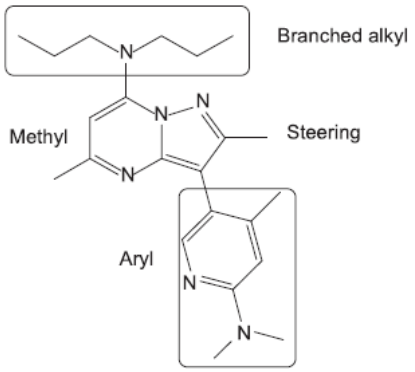


Figure 2 of Williams depicts regions of CRF_1 antagonist structure-activity relationship (SAR)

Figure 2 of Williams corresponds to the pyrazolo[1,5-α]pyrimidine core subclass (bicyclic CRF receptor antagonist subclass (c)) of Fahmy (compound NBI-30775).

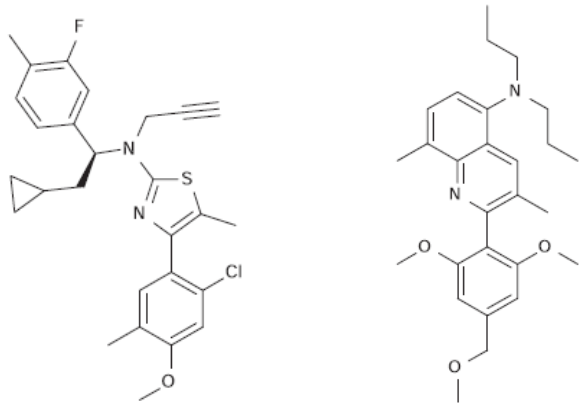
Williams identifies several classes and subclasses of CRF_1 receptor antagonists. The first class, which Williams identifies as Type I CRF_1 antagonists, is characterized by:

> [T]wo atoms separating the aryl region moiety from the requisite core nitrogen atom (which may play the role of a hydrogen bond acceptor when bound by the receptor). This is illustrated by compound 2 (Figure 2) with the 3-pyridyl group serving in the role as the aromatic substituent attached at the C-3 position of the pyrazolo [1,5-α]pyrimidine core and the dipropylamino group at C-7 represents the branched alkyl region. The methyl group at the C-4 position of the pyridyl and the methyl at C-2 of the core serve to steer the aryl group out of plane relative to the central heterocycle.

Ex. 1029, 1058. Figure 2 of Williams is reproduced above. Williams' Type I CRF_1 receptor antagonists comprise monocyclic, bicyclic, and tricyclic CRF_1 receptor antagonists taught by Fahmy. *See id.* at 1058–1061, Figs. 1–6. Williams also teaches that Type I CRF_1 receptor antagonists can include CRF_1 antagonists with additional rings adjacent to the core nitrogen

heterocycle and those with the branched alkyl region supported by additional ring. *Id.* at 1061, Figs. 7, 8.

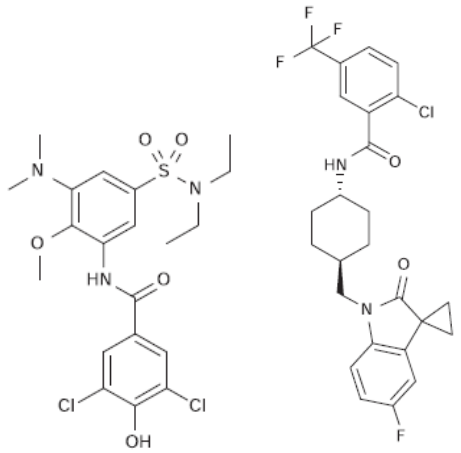
Williams also teaches Type II CRF_1 receptor antagonists. Ex. 1029, 1061. Williams discloses that Type II CRF_1 antagonists "have many of the same features in common with the Type I antagonists but the branched alkyl region initially appeared to require more complicated side chains for biological activity." *Id.* Williams teaches that both monocyclic and bicyclic CRF_1 receptor antagonists are known in the art; one of each type is depicted below:



<u>Monocyclic (left) and bicyclic (right) Type II CRF_1 receptor antagonists</u>

Id. at Figs. 6, 5.

Williams further teaches that there are other, atypical CRF_1 receptor antagonists that "do not appear to be directly related to the traditional Type I or II CRF_1 antagonists." Ex. 1029, 1062. These include benzimidazole-containing amides, a "very unusual phenol," amidrazones, and N-phenylphenyl glycines, and a trans-4-aminomethylcyclohexylamine with links to two aryl groups. *Id.* at 1062–1063. Two examples of these atypical CRF_1 receptor antagonists are depicted below:



"Atypical" CRF_1 receptor antagonists: a phenol (left) and a cyclohexyl amide (right)

Id. at Figs. 11, 12.

Finally, Williams teaches that "[a]ntagonists of the CRF_1 receptor have not demonstrated clinical utility despite over 30 years of research and hundreds of patents," a point with which Patent Owner's expert, Dr. Dobs, agreed. Ex. 1029, 1065; Ex. 1038, 132. Williams also discloses that "[i]t may be that small molecule (< 500 MW) CRF receptor antagonists will never effectively compete with peptide agonists that are > 10 times larger in molecular weight." Ex. 1029, 1065. Williams, like Fahmy, however, discloses that the majority of studies investigating the clinical utility of small-molecule CRF_1 receptor antagonists are directed to stress-related conditions such as anxiety, depression, post-traumatic stress disorder, substance abuse, and stress-induced relapse in craving responses to food, nicotine and alcohol. *Id.* at 1057–1058.

Summarizing, the teachings of the prior art of record as of the critical date indicate a very considerable structural diversity of molecules that can act as CRF_1 receptor antagonists. Such antagonists can be peptidergic or small molecule receptor antagonists, the latter including Type I and Type II antagonists, as well as "atypical" CRF_1 receptor antagonists. Furthermore,

Type I and II CRF_1 receptor antagonists can be either monocyclic or bicyclic in their core structure, and there are also known tricyclic and "atypical" Type I CRF_1 receptor antagonists.

Moreover, at the time of filing, very few studies existed demonstrating that CRF_1 receptor antagonists are effective in the treatment of CAH, as recited in the challenged claims. Fahmy mentions a single study of a CRF_1 receptor antagonist, verucerfont, being studied for this clinical application, and Williams is altogether silent on the subject, noting only that, at the time (i.e., 2013), "despite over 30 years of research and hundreds of patents" no small molecule CRF_1 receptor antagonists had demonstrated any clinical utility. Ex. 1018, 276; Ex. 1029, 1065.

For these reasons, we do not find persuasive the testimony of Patent Owner's expert, Dr. Dobs, that:

> By describing adjustments of dosing protocols to achieve an A4 reduction from baseline, and describing this use of tildacerfont as just one embodiment of the claimed use of the entire well-known, well-characterized, and discrete class, the specification reasonably conveyed to a POSA that the invention extended to the particularly claimed use of the entire recited class.

Ex. 2014 ¶ 82. On the contrary, far from being a "well-known, well-characterized, and discrete class" the prior art teaches a heterogeneous assembly of different classes of small molecule CRF_1 receptor antagonists (Type I, Type II, and "atypical") displaying a very considerable variety of structures, both in terms of the core pharmacophore (e.g., monocyclic, bicyclic, tricyclic, phenolic, cyclohexyl amide, etc.) as well as in the various side groups. Moreover, the challenged claims recite only "a CRF_1 receptor antagonist or a pharmaceutically acceptable salt thereof," the scope of which also encompasses the much larger (and, according to Williams) much more

effective large-molecule (peptide) CRF_1 receptor antagonists, about which the Specification is entirely silent. *See* Ex. 1029, Abstr., 1065.

Furthermore, despite Dr. Dobs' testimony that "[t]he [prior art] references explain the 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," Dr. Dobs also acknowledged that the "atypical CRF1 receptors depicted in Figures 11 and 12 of Williams had different structures, and lacked the nitrogen heterocyclic core." Ex. 1042, 127:9–14, 130:13–131:16; *see also* Ex. 2014 ¶ 83. Additionally, Petitioner's expert, Dr. Cutler, testified, by way of example, in his Reply Declaration that two of the '"first-generation CRF1 antagonists' identified in Figure 1 of the Williams article do not fall within the Figure 2 structure Dr. Dobs relies upon." Ex. 1047 ¶ 93.

Indeed, with respect to the alleged core pharmacophore that Dr. Dobs describes as being taught by the prior art, we find more persuasive Dr. Cutler's opinion that "this general description, which comprises a large and indeterminate number of unique chemical structures, does not provide any information on what structural features of CRF1 receptor antagonists would be important to a CAH treatment, or to achieve a reduction in A4." Ex. 1047 ¶ 97. Based upon the evidence of record, we also find more persuasive Dr. Cutler's opinion that:

> [T]he '201 patent itself does not describe structural features common to CRF1 receptor antagonists that could be administered to treat CAH or result in a reduction in A4 compared to baseline that is maintained at a reduced level post 24 hours. The prior references described by Dr. Dobs also do not identify any such common structural features that would achieve these results.

Id. ¶ 99.

Capon states that:

> [T]he determination of what is needed to support generic claims to biological subject matter depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter.

Capon, 418 F.3d 1359.

In view of these factors, and summarizing our findings of the disclosures of the prior art set forth above, we find that: (1) the '201 Specification discloses only a single species of the claimed genus (*see* Ex. 1001, 1:42–57), and does not disclose "either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus" (*Ariad*, 598 F.3d at 1350 (citing *Regents*, 119 F.3d at 1568–69)); (2) Patent Owner's own publication noted the single species disclosed in the '201 Specification as having "unique structural features" compared to other CRF1 receptor antagonists (Ex. 1039, 4667; Ex. 1042, 52:19–53:14); (3) there was very little knowledge disclosed by the prior art relied upon by Patent Owner of the ability of CRF_1 receptor antagonists to decrease the level of A4 from baseline that is maintained at a reduced level post 24 hours as claimed, or to even have any therapeutic effectiveness at all (*see generally* Exs. 1018, 1029); (4) the extent and content of the two prior art review articles relied upon by Patent Owner also demonstrate a wide variety of large and small molecule compounds that can act as CRF_1 receptor antagonists (*see generally* Exs. 1018, 1029); (5) the effective use of CRF_1 receptor antagonists in the treatment of CAH, or indeed in any clinical application, at the time of filing, was far from being

mature, and was unpredictable (*see, e.g.*, Ex. 1018, 276; Ex. 1029, 1065); and (6) given the variety of structures that had been shown to act as CRF_1 receptors, the structure-function relationship between CRF_1 receptor and CRF_1 receptors was still largely unknown and unpredictable (*see* Ex. 1029, 1065–66).

We conclude, by a preponderance of the evidence of record, including the declaration and deposition testimony of Patent Owner's expert, that a person of ordinary skill in the art would not have recognized, either from the express disclosures of the '201 Specification or from the knowledge of the prior art, the "structure, formula, chemical name, physical properties, or other properties, of species falling within the genus" of claimed CRF_1 receptor antagonists. *See Ariad*, 598 F.3d at 1350. We therefore conclude that the challenged claims fail to meet the written description requirement of 35 U.S.C. § 112(a) and are unpatentable.

F. Grounds 1–5

Because we find that all of the challenged claims are unpatentable for lack of written description support under 35 U.S.C. § 112(a) on Ground 6, we do not reach Petitioner's arguments on Grounds 1–5.

V. CONCLUSION

For the reasons we have explained, we conclude that Petitioner has demonstrated by a preponderance of the evidence, that challenged claims 1–19 of the '201 patent are unpatentable as lacking adequate written description support. Furthermore, Petitioner's Motion to Exclude Evidence is *denied in part* and *dismissed in part* as moot. Patent Owner's Motion to Exclude Evidence is *denied in part* and *dismissed in part* as moot. Petitioner's Motion to Strike is also *dismissed* as moot.

In summary:

Claim(s) Rejected	35 U.S.C. §	Reference(s)/ Basis	Claim(s) Shown Unpatentable	Claim(s) Not Shown Unpatentable
1–19	112(a)	Written Description	1–19	

VI. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that based on a preponderance of the evidence, claims 1–19 of the '201 patent are unpatentable;

FURTHER ORDERED that Petitioner's Motion to Exclude is denied in part and dismissed in part; and

FURTHER ORDERED that Patent Owner's Motion to Exclude is denied in part and dismissed in part;

FURTHER ORDERED that Petitioner's Motion to Strike is dismissed; and

FURTHER ORDERED that because this is a final written decision, the parties to this proceeding seeking judicial review of our Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

FOR PETITIONER:

W. Karl Renner
Robert Oakes
FISH & RICHARDSON P.C
axf-ptab@fr.com
oakes@fr.com

FOR PATENT OWNER:

Michael T. Rosato
Jad A. Mills
WILSON SONSINI GOODRICH & ROSATI
mrosato@wsgr.com
jmills@wsgr.com