

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.*

DECISION
Denying Institution of Post-Grant Review
35 U.S.C. § 324(a)

I. INTRODUCTION

On February 18, 2002, Neurocrine Biosciences, Inc. (“Petitioner”) filed a Petition for Post-Grant Review of claims 1–19 of U.S. Patent No. 11,007,201 B2 (Ex. 1001, “the ’201 patent”). Paper 1 (“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”).

Institution of post-grant review is authorized by statute only when “the information presented in the petition . . . demonstrate[s] that it is more likely than not that at least 1 of the claims challenged in the petition is unpatentable.” 35 U.S.C. § 324; *see* 37 C.F.R. § 42.4. Upon considering the Petition and the cited evidence, we conclude that Petitioner has not satisfied its burden under 35 U.S.C. § 324 to show that it is more likely than not that at least 1 of the claims challenged in the Petition is unpatentable. Therefore, we deny institution of a post-grant review.¹

¹ Patent Owner asserts that we should deny the Petition under 35 U.S.C. § 325(d) because the Office considered the same arguments raised by Petitioner here “based on the same art when deciding to issue the ’201 patent and its parent [U.S. Patent No. 10,849,908 B2 (“the ’908 patent”)] and when deciding to reject Petitioner’s PGR challenge to claims of the parent ’908 patent that are materially identical in relevant part to the claims challenged here.” Prelim. Resp. 25–26; *see also* Reply 4–6 (addressing Patent Owner’s section 325(d) challenge); Sur-Reply 3–6 (addressing Petitioner’s Reply

A. 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.

B. 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, the ’908 patent. Pet. 82. Petitioner notes that we denied institution of this petition and that requests for rehearing and for precedential opinion panel review remain pending. *Id.* Patent Owner also identifies PGR2021-00088. *See* Paper 3, 2.

C. 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), (72). 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”).” Ex. 1001, Abstr., 1:32–60.

concerning Section 325(d) challenge). Because we are denying institution of a post-grant review on the merits, we need not reach Patent Owner’s Section 325(d) argument.

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"), and thus, inhibiting release of adrenal corticotrophic 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)").

D. Challenged Claims

Petitioner challenges all nineteen claims of the '201 patent. Pet. 1, 4. All claims for 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 CFR₁ 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.

E. 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 ²	Grigoriadis ³
10, 16, 17, 19	§ 103	Grigoriadis
5, 6	§ 103	Grigoriadis and Romano ⁴
1–4, 7–19	§ 103	Grigoriadis and Turcu 2016 ⁵
5–6	§ 103	Grigoriadis, Turcu 2016, and Romano
1–19	§ 112	Lack of written description

Petitioner submits the Declaration of Robert M. Carey, M.D. (Ex. 1005) in support of institution of post-grant review.

² 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).

³ Dimitri E. Grigoriadis, US 2017/0020877 A1, published Jan. 26, 2017 (Ex. 1006, “Grigoriadis”).

⁴ Steve Romano, US 2005/0209250 A1, published Sept. 22, 2005 (Ex. 1007, “Romano”).

⁵ 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”).

II. ANALYSIS

A. Eligibility for Post-Grant Review

The post-grant review provisions set forth in Section 6(d) of the AIA apply only to patents subject to the first-inventor-to-file provisions of the AIA. *See* AIA § 6(f)(2)(A) (“The amendments made by subsection (d) . . . shall apply only to patents described in section 3(n)(1).”). Patents subject to the first-inventor-to-file provisions are those that issue from applications “that contain[] or contained at any time . . . a claim to a claimed invention that has an effective filing date as defined in section 100(i) of title 35, United States Code, that is on or after” March 16, 2013. *Id.* § 3(n)(1). Our rules require that each petitioner for post-grant review certify that the challenged patent has an effective filing date that renders the patent available for post-grant review. 37 C.F.R. § 42.204(a) (“The petitioner must certify that the patent for which review is sought is available for post-grant review.”). In addition, “[a] petition for a post-grant review may only be filed not later than the date that is 9 months after the date of the grant of the patent or of the issuance of a reissue patent (as the case may be).” 35 U.S.C. § 321(c); *see also* 37 C.F.R. § 42.202(a) (accord).

Petitioner states the following.

Neurocrine certifies that the ’201 Patent is available for PGR. The present petition is being filed within nine months of the issuance of the ’201 patent on May 18, 2021. Neurocrine has not filed a civil action challenging the validity of any claim of the ’201 patent. Neurocrine is not barred or estopped from requesting this review challenging claims 1–19

Pet. 3.

On this record, we determine that the ’201 patent is eligible for post-grant review. Specifically, 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. Ex. 1001, codes (22), (60), (63). 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 code (45).

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 Preliminary 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 to determine whether it is more likely than not that Petitioner would prevail with respect to at least one of the claims challenged in the Petition. *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, 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. 16.

Having reviewed the pleadings and evidence of record, we conclude that we need only construe the claim term “from baseline” as part of our Decision to deny institution of post-grant review.

Independent claim 1 recites a method of treating CAH by reducing an A4 level “from baseline” after administering a CRF₁ receptor antagonist to a CAH patient. *See* Ex. 1001, 47:51–48:5. We previously determined the meaning of “from baseline” with respect to the parent ’908 patent in PGR2021-00088. We stated:

The Specification expressly teaches that, with respect to the clinical phase 2 trial described in Example 4, “Patients will have overnight [pharmacokinetic/pharmacodynamics] PK/PD assessments performed at baseline, which include an [sic] pre-dose overnight assessment and a post-dose overnight assessment for PK/PD following administration of the first dose.” Ex. 1001[,], col. 42, ll. 12–16.⁶ This is the same quotation and clinical trial relied upon by Dr. Barnes in his Declaration [submitted by Patent Owner during prosecution], and is the only definition of a “baseline” in the ’908 patent. *See* Ex. 1002, 36–37. We note that placebos were evidently not employed in the phase 2 clinical study of Example 4.

Given the sole exemplary description of “baseline” in Example 4 of the Specification, we construe the claim term reciting “reduced by at least 10% from baseline” as meaning “a reduction of at least 10% in the level of ACTH (claim 1) or 17-OHP (claim 11) compared to measurements of ACTH or 17-OHP made prior to, and/or at the beginning of, administration of the drug.”

⁶ As the ’201 patent is based on a continuation application from the application that became the ’908 patent, the ’201 and ’908 patent share the same specification. *See* Ex. 1001, 41:55–59.

Neurocrine Biosciences, Inc. v. Spruce Biosciences, Inc., PGR2021-00088, Paper 11 at 8–9 (PTAB Dec. 10, 2021).

Petitioner points to clinical data in the '201 patent regarding A4 in which the A4 level is measured “before the administration of tildacerfont, a CRF1 receptor antagonist, and measuring A4 level after the administration of the first dose of tildacerfont.” Pet. 27–28. Petitioner also notes that “Figure 4 of the '201 patent presents the measurements and shows a reduction of A4 due to the administration of tildacerfont, i.e., a change from baseline.” *Id.* at 28. In line with these teachings, Petitioner asserts that it applies the definition of “from baseline” we determined in PGR2021-00088 as set forth above, which Petitioner describes as “a measurement made prior to, and/or at the beginning of, administration of the drug.” *Id.*; *see* Ex. 1005 ¶ 38.

As both parties agree that we should maintain our previously set forth construction of “from baseline,” and neither party has presented us with any reason to change our position, we apply a commensurate construction of “from baseline” that we previously determined in PGR2021-00088 as set forth above as “a reduction in A4 level compared to an A4 level measurement made prior to, and/or at the beginning of, administration of the drug.”

D. Ground 1 – Anticipation by Grigoriadis

Petitioner asserts that claims 1–4, 7–9, 11–15, and 18 are anticipated by Grigoriadis, and sets forth how each limitation is met by Grigoriadis. As

support, Petitioner cites the Declaration of Dr. Carey. *See* Pet. 42–51; Ex. 1005 ¶¶ 47–56.

1. Overview of Grigoriadis (Ex. 1006)

Grigoriadis is directed to methods for treating CAH by administering to a subject in need thereof an effective amount of a CRF₁ receptor antagonist, including (but not limited to) bedtime administration. Ex. 1006 ¶ 7. Grigoriadis teaches that “CAH is a group of autosomal recessive genetic disorders that result in little or no cortisol biosynthesis.” *Id.* ¶ 4. Grigoriadis teaches that:

Corticotropin-releasing factor (CRF)⁷ activates the CRF₁ receptor, a class B G protein-coupled receptor (GPCR), [and that] CRF₁ [receptor] antagonists have the potential to directly inhibit ACTH release in patients with CAH, thereby allowing normalization of androgen production while using lower, more physiologic doses of hydrocortisone, and reducing treatment-associated side effects.

Id. ¶ 6.

Grigoriadis lists several CRF₁ receptor antagonists including SSR-125543 that Petitioner asserts is crinecerfont and NBI-77860 that Patent Owner asserts is verucerfont. *See, e.g.*, Ex. 1006 ¶¶ 13, 51, 54; Pet. 32, 43; Prelim. Resp. 2, 8. Grigoriadis, however, only teaches administering NBI-77860 or verucerfont to a CAH patient as shown in Example 6. *See* Ex. 1006 ¶¶ 90–95; Pet. 39–40; Prelim. Resp. 44.

Example 6 of Grigoriadis teaches a clinical study titled “A Phase 1, Single-Blind, Placebo-Controlled, Fixed-Sequence, Single-Dose Study to Evaluate the Safety and Tolerability of NBI-77860 in Adult Females with

⁷ The terms “corticotropin releasing factor” (CFR) and “corticotropin releasing hormone” (CRH) as used herein are synonymous.

Congenital Adrenal Hyperplasia.” Ex. 1006 ¶ 90. This study comprised a single-blind, placebo-controlled, single center, fixed-sequence single-dose clinical trial in adult female classical CAH patients, designed to “assess the safety, tolerability, and plasma exposure of NBI-77860 [verucerfont], as well as the effect of this compound on endogenous levels of HPA [or hypothalamic-pituitary-adrenal] axis hormones.” *Id.*

The dosage regimen and experimental design of this study is depicted in Figure 4 of Grigoriadis reproduced below.

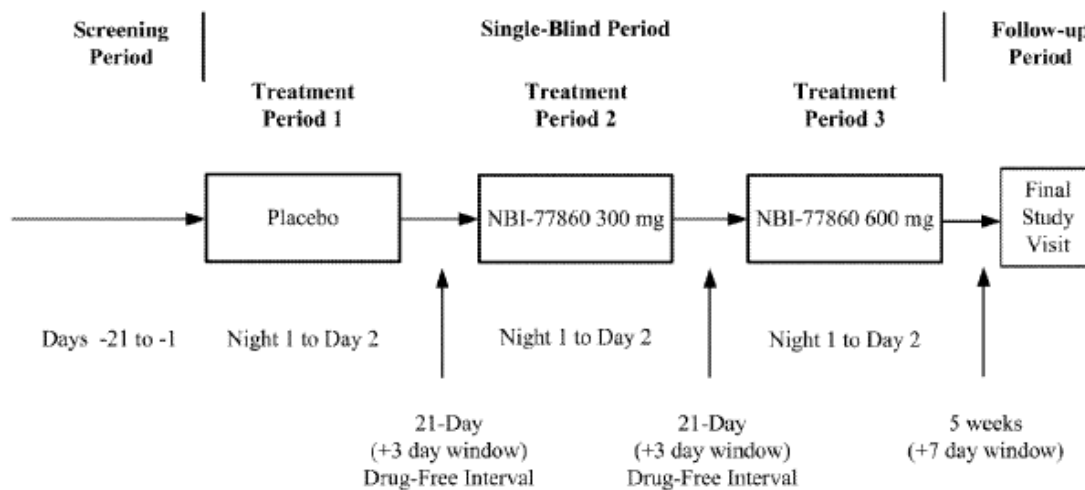


FIG. 4

Figure 4 of Grigoriadis set forth above shows the dosage regimen and experimental design of the clinical phase 1 study of Example 6. In the study, a total of eight female subjects, ages 19 to 58, with a medical diagnosis of classical 21-hydroxylase deficiency CAH were administered single bedtime doses (HS) of . . . placebo and verucerfont 300 mg, and 600 mg during three separate treatment periods. Ex. 1006 ¶ 91. The usual morning dose of concurrent steroidal treatment for the eight subjects was

delayed until after the 16-hour post-dose blood samples were collected. *Id.* The results of the study are depicted in Figure 5 of Grigoriadis reproduced below.

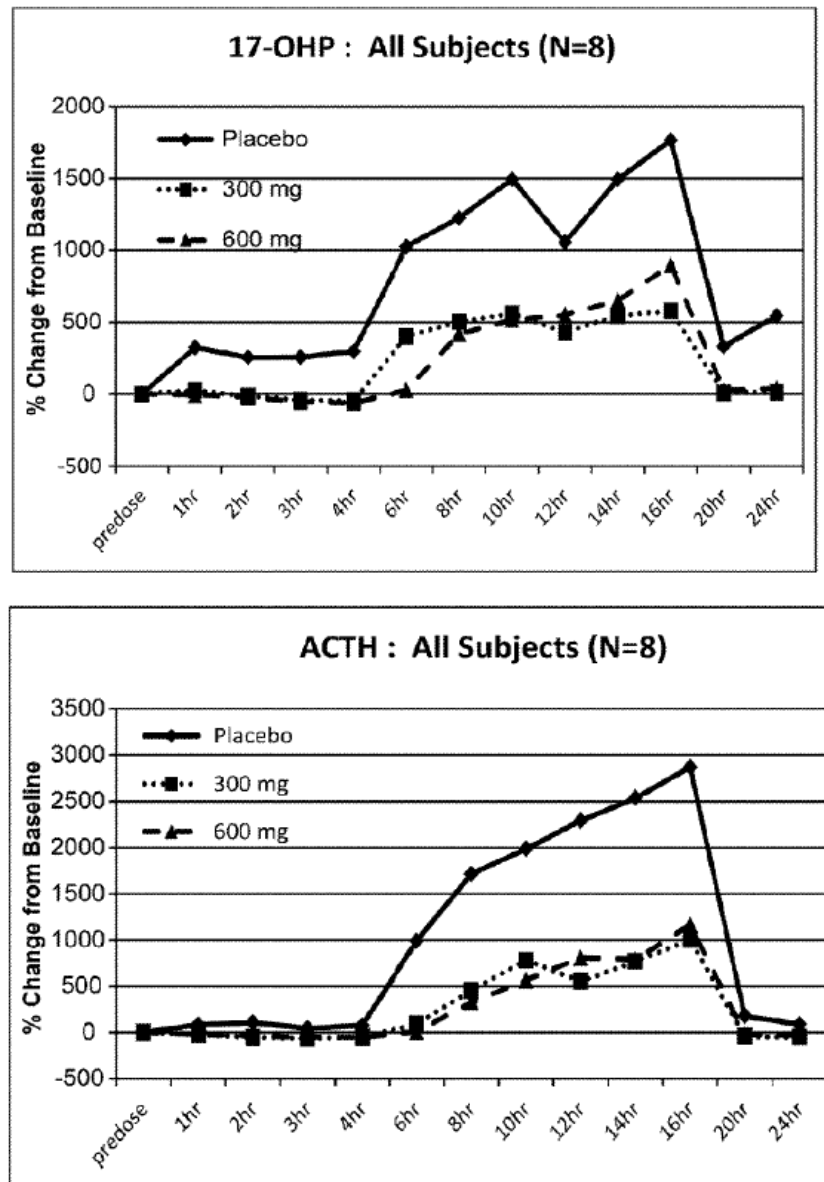


FIG. 5

Figure 5 of Grigoriadis depicts levels of 17-OHP and ACTH in response to placebo, 300 mg dose of verucerfont, and 600 mg dose of

verucerfont during the 24-hour post-dose periods. Ex. 1006 ¶ 92.

Grigoriadis concludes the following.

Consistent and clinically meaningful reductions from predose levels of both 17-OHP and ACTH were observed throughout the postdose period following administration of NBI-77860 relative to placebo in these CAH patients. In addition to the group mean data, individual responses were evaluated and treatment “responders” were conservatively defined as those subjects with at least a 50% decrease in 17-OHP and ACTH under active NBI-77860 relative to placebo during the peak morning period. This responder analysis yielded a sizeable responder rate of 50% in the study (none of these subjects were responders during the initial placebo treatment period). Furthermore, the 300 mg dose yielded nearly identical effects on 17-OHP and ACTH as the 600 mg dose.

Ex. 1006 ¶ 93.

2. Principles of Law

To show anticipation under § 102, each and every claim element, arranged as in the claim, must be found in a single prior art reference. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359 (Fed. Cir. 2008). The prior art need not, however, use the same words as the claims in order to find anticipation. *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009). It is also permissible to consider not only the literal teachings of the prior art reference, but also the inferences an ordinarily skilled person would draw from the reference. *Eli Lilly and Co. v. Los Angeles Biomedical Res. Inst. at Harbor-UCLA Med. Ctr.*, 849 F.3d 1073, 1074–75 (Fed. Cir. 2017); *In re Preda*, 401 F.2d 825, 826 (CCPA 1968).

A reference may also anticipate a claim even if it does not expressly teach all the limitations arranged or combined as in the claim, “if a person of skill in the art, reading the reference, would ‘at once envisage’ the claimed arrangement or combination.” *Microsoft Corp. v. Biscotti, Inc.*, 878 F.3d

1052, 1068 (Fed. Cir. 2017) (quoting *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015)).

To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. . . . This modest flexibility in the rule that “anticipation” requires that every element of the claims appear in a single reference accommodates situations where the common knowledge of technologists is not recorded in the reference

Continental Can Co. v. Monsanto Co., 948 F.2d 1264, 1268–69 (Fed. Cir. 1991); *see also In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981) (“Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient.”) (quoting *Hansgirk v. Kemmer*, 102 F.2d 212, 214 (CCPA 1939)).

3. Analysis

As in the petition challenging the claims of the ’908 patent, Petitioner again here relies on the disclosure of crinecerfont in Grigoriadis as “a CRF1 receptor antagonist, [that is] useful for the treatment of CAH,” combined with an admittedly non-prior art clinical study reported in Auchus 2021⁸ to show that the “administration of a therapeutically effective amount of crinecerfont to a patient as taught in Grigoriadis *inherently and necessarily* results in a reduction of a patient’s A4 level compared to the patient’s

⁸ Richard J. Auchus et al., *Crinecerfont Lowers Elevated Hormone Markers in Adults With 21-Hydroxylase Deficiency Congenital Adrenal Hyperplasia*, 20 J. CLIN. ENDOCRINOL. METAB. 1–12 (2021) (Ex. 1009, “Auchus 2021”).

baseline level, and that reduction is maintained post 24 hours.” Pet. 43 (emphasis added). Petitioner explains its inherency analysis as follows.

[A] skilled artisan would understand “maintained at a reduced level post 24 hours” to mean maintenance of reduced hormone levels for more than 24 hours when a patient is dosed repeatedly. After 14 days of administering crinecerfont once or twice daily, a patient, and indeed most patients, in the clinical study reported in Auchus 2021 experienced a reduction in A4 levels at Day 14 compared to baseline measurements. Specifically, median A4 measurements taken over 24 hours and within the morning window (6-10 a.m.) time points showed that administration of a therapeutically effective amount of crinecerfont to a patient meets the reduction in A4 level from baseline requirement recited in ’201 patent claim 1 at Day 14, *i.e.*, post 24 hours. Baseline measurement[s] were taken over a 24-hour period beginning in the evening of the seventh day before the study began (Day-7 to Day-6), and thus were made prior to administration of the study drug.

Administration of a therapeutically effective amount of crinecerfont to a patient, as taught by Grigoriadis, necessarily results in a reduction in a patient’s A4 level from baseline after 14 days of repeated dosing—*i.e.*, the A4 reduction is maintained for more than 24 hours. Thus Grigoriadis inherently anticipates ’201 patent claim 1.

Pet. 43–44 (citing Ex. 1005 ¶¶ 43–56; Ex. 1006 ¶¶ 54, 63; Ex. 1009, 3–11, Tables 2–3, Figs. 2–4).⁹

⁹ Patent Owner challenges Auchus 2021 as an improper submission under 37 C.F.R. § 42.65(b) because it is “a document containing self-funded data acquired using Neurocrine employees.” Prelim. Resp. 39. Auchus 2021, however, is a clinical research article published in a peer reviewed journal, The Journal of Clinical Endocrinology and Metabolism. *See* Ex. 1009, 1. As such, we find that section 42.65(b) does not apply to require Dr. Carey to have submitted an affidavit explaining the study and resulting data in Auchus 2021, as the reference itself provides that context.

In our previous decision addressing these same arguments with regard to the claims of the '908 patent, we found that “[t]he single clinical trial taught by Example 6 of Grigoriadis does not establish a baseline value for patients against which to compare the data obtained from patients receiving 300 mg or 600 mg of the test drug, NBI-77860 (verucerfont).” *Neurocrine Biosciences, Inc. v. Spruce Biosciences, Inc.*, IPR2021-00088, Paper 11 at 16 (PTAB Dec. 10, 2021). Therefore, we concluded that “Grigoriadis fails to disclose expressly the limitations of claims 1 and 11 severally reciting “wherein [the] . . . hormone . . . level in the human is reduced by *at least 10% from baseline.*” *Id.* at 16–17.

We noted the differences between the only study in Grigoriadis in Example 6 and the study in Auchus 2021, namely, different study drugs, treatment periods, placebo use, patient genders, dose size, and dosing regimens. *Id.* at 18. We concluded as follows.

Given these differences, and particularly the difference in the study drugs employed in Grigoriadis and Auchus [2021], we cannot agree with Petitioner that the results of the Auchus [2021] clinical trial demonstrate that the single clinical trial of a different drug, as disclosed by Grigoriadis, *necessarily* discloses “at least 10% reduction in a patient’s ACTH level from baseline, and therefore inherently anticipates claims 1 and 11 of the '908 patent. [’908 Pet. 48.] A persuasive demonstration of inherency would seem to require a study replicating that of Grigoriadis (and at least employing the identical study drug) and including baseline measurements against which to compare the Grigoriadis results. The Auchus [2021] clinical trial, for the reasons we have explained above, does not provide such proof of inherency.

To be sure, Grigoriadis discloses crinecerfont, the study drug employed in the Auchus [2021] clinical trial. *See* Ex. 1006 ¶ 54. But Grigoriadis discloses crinecerfont ([4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1 S)-2 cyclopropyl-1-(3-

fluoro-4-methylphenyl) ethyl]-5-methyl-N-(2-propyn-1-yl)-2-thiazolamine) as an example of a CRF1 receptor antagonist. However, crinecerfont is *not* disclosed by Grigoriadis as being a study drug in any clinical trial similar to its Example 6; it is mentioned only as being one of a class of CRF1 receptor antagonists. And although Grigoriadis discloses that crinecerfont is a species of CRF1 receptor antagonist, Petitioner may not attempt to import experimental results from Auchus [2021] that are not prior art to the '908 patent in an attempt to show that crinecerfont inherently has clinical properties that were not already demonstrated in Grigoriadis.

Neurocrine, PGR2021-00088, Paper 11 at 19.

We also noted that Petitioner's inherency argument was not commensurate with the scope of the claims requiring "administering to the human a therapeutically-effective amount of a CFR₁ receptor antagonist" because Petitioner had not demonstrated that at least a representative number of the genus of CFR₁ receptor antagonists would *necessarily* have demonstrated the claimed reduction in ACTH level from baseline. *Id.* at 20.

Finally, we agreed with the Examiner's reasoning of the lack of inherency because of the requirement of selecting "from various lists/locations" in the prior art references, stating "we find this finding of the Examiner to be relevant here, because we agree that the disclosure of crinecerfont as a CRF1 receptor antagonist, but the lack of any clinical showing of crinecerfont's efficacy, demonstrates that Grigoriadis does not anticipate claims 1 and 11." *Id.* at 19–20 n.5.

We find our reasoning in IPR2021-00088 sound and applicable to the case here. In its Reply, Petitioner asserts:

Patent Owner's arguments in support of discretionary denial conflate Grigoriadis' disclosure of crinecerfont with Grigoriadis' separate disclosure of a different CFR1 receptor antagonist, NBI-77860, in Example 6, which reports reduction

in hormone levels compared to placebo. The disclosure of NBI-77860 is a basis for separate Grounds of invalidity—it does not relate to Grigoriadis’ disclosure of crinecerfont.

Reply 1–2 (citing Pet. 2, 4, 42–56, 56–72; Prelim. Resp. 7, 15, 27, 29; Ex. 1006 ¶¶ 90–94; Paper 2).

Petitioner’s assertion of a distinction in Grigoriadis between the disclosure of crincerfont and NBI-77860, however, is belied by its anticipation argument that it sets forth in the Petition. For instance, Petitioner concludes that Grigoriadis anticipates claim 1 of the ’201 patent because “[a]dministration of a therapeutically effective amount of crinecerfont to a patient, *as taught by Grigoriadis*, necessarily results in a reduction in a patient’s A4 level from baseline after 14 days of repeated dosing—*i.e.*, the A4 reduction is maintained for more than 24 hours.” Pet. 44 (emphasis added). But as Patent Owner notes, “[t]he only administration of any compound to a CAH patient in Grigoriadis *is* Example 6,” in which NBI-77860 is the drug administered. Prelim. Resp. 44; Ex. 1006 ¶ 90. As we previously noted in our Decision in PGR2021-00088, “crinecerfont is *not* disclosed by Grigoriadis as being a study drug in any clinical trial similar to its Example 6; it is mentioned only as being one of a class of CRF1 receptor antagonists.” *Neurocrine*, PGR2021-00088, Paper 11 at 19.

From mere disclosure of crincerfont, Petitioner asks us to find a particular treatment protocol using this drug and the outcomes of such treatment as taught by non-prior art Auchus 2021 are inherent in the drug itself. Such outcomes of such treatment as is the subject of the challenged claims here may be inherent in a particular treatment regimen using a particular drug, but it is too far of a leap to say that disclosure of the drug

itself would render inherent any treatment outcome using any treatment protocol.

For the reasons set forth above, we determine that Petitioner has failed to establish that it is more likely than not that Grigoriadis anticipates claim 1 of the '201 patent. Because the remaining claims challenged in this ground depend either directly or indirectly on claim 1, we similarly conclude that Petitioner has not established a likelihood of prevailing with respect to these dependent claims, claims 2–4, 7–9, 11–15, 18.

E. Ground 2 – Obviousness over Grigoriadis

Petitioner asserts that claims 10, 16, 17, and 19 would have been obvious over the disclosure of crinecerfont in Grigoriadis and the knowledge of a skilled artisan. *See* Pet. 4, 51. Petitioner does not revisit how Grigoriadis teaches the limitations of claim 1 upon which the challenged claims ultimately depend, but appears to continue to rely on its arguments in ground 1 based on inherency as Petitioner makes no argument that independent claim 1 is obvious over Grigoriadis. *See* Pet. 51–55 (stating in heading of ground 2 that challenged claims “would have been obvious in view of Grigoriadis’ disclosure of crinecerfont . . .” upon which Petitioner based its inherent anticipation challenge to claim 1). Because we have found that Grigoriadis does not inherently anticipate claim 1, this ground too fails. We therefore conclude that Petitioner has failed to establish that it is more likely than not that dependent claims 10, 16, 17, and 19 would have been obvious over Grigoriadis.

F. Ground 3 – Obviousness over Grigoriadis and Romano

Petitioner asserts that claims 5 and 6 would have been obvious over the disclosure of crinecerfont in Grigoriadis, Romano, and the knowledge of

a skilled artisan. Pet. 4, 55. Again, Petitioner does not revisit how Grigoriadis teaches the limitations of claim 1 upon which the challenged claims ultimately depend, but appears to continue to rely on its arguments in ground 1 based on inherency as Petitioner makes no argument that independent claim 1 is obvious over Grigoriadis. See Pet. 55–57 (stating in heading of ground 3 that challenged claims “would have been obvious in view of Grigoriadis’ disclosure of crinecerfont . . .” upon which Petitioner based its inherent anticipation challenge to claim 1). Petitioner also does not rely on Romano for any teaching with respect to the limitations of claim 1, but for the teaching of “the use of small particle sizes with CFR₁ receptor antagonists, such as the claimed range of between about 1-20 µm.” Pet. 55–56 (citing Ex. 1007, Abst., ¶ 531; Ex. 1005 ¶¶ 74–77). Because we have found that Grigoriadis does not inherently anticipate claim 1, this ground too fails. We therefore conclude that Petitioner has failed to establish that it is more likely than not that dependent claims 5 and 6 would have been obvious over Grigoriadis and Romano.

G. Ground 4 – Obviousness over Grigoriadis and Turcu 2016

Petitioner asserts that claims 1–4 and 7–19 would have been obvious over Grigoriadis’ and Turcu 2016’s disclosure of NBI-77860 and the knowledge of a skilled artisan and sets forth how each limitation is met by Grigoriadis and Turcu 2016. Pet. 4, 57–72. As support, Petitioner cites the Declaration of Dr. Carey. See Pet. 57–72; Ex. 1005 ¶¶ 57–95.

1. Overview of Turcu 2016 (Ex. 1008)

Turcu 2016 describes a phase 1b, single-blind, placebo-controlled, fixed-sequence, single-dose study for safety and tolerability of the corticotropin-releasing factor receptor-1 antagonist, NBI-77860, in women

with 21 hydroxylase deficiency. *See* Ex. 1008, 1174. Dr. Carey explains that this study is the same study reported as Example 6 in Grigoriadis. *See* Ex. 1005 ¶ 57.

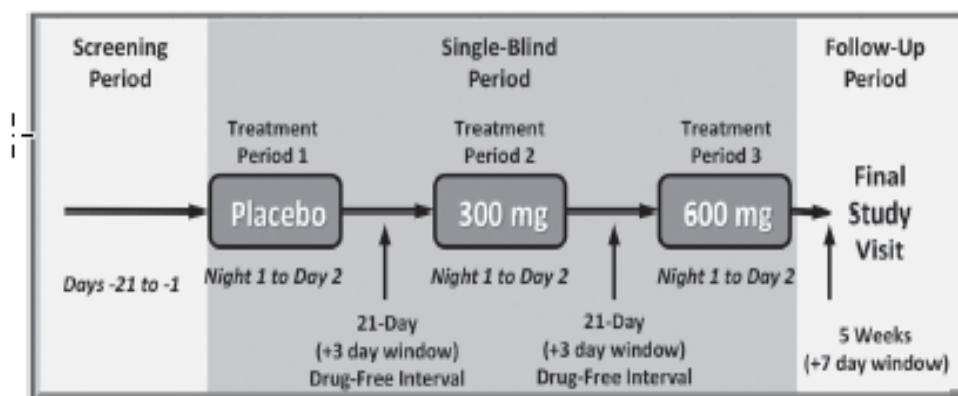
The design and results of the study are summarized as follows.

During three treatment periods separated by 3-week washout intervals, patients sequentially received placebo, NBI-77860 300 mg, and NBI-77860 600 mg at 10 pm; glucocorticoid therapy was withheld for 20 hours. We evaluated ACTH, 17OHP, androstenedione, and testosterone as well as NBI-77860 pharmacokinetics over 24 hours.

Results: Dose-dependent reductions of ACTH and/or 17OHP were observed in six of eight subjects. Relative to placebo, NBI-77860 led to an ACTH and 17OHP reduction by a mean of 43% and 0.7% for the 300 mg dose, respectively, and by 41% and 27% for the 600 mg dose, respectively. Both NBI-77860 doses were well tolerated.

Ex. 1008, 1174.

This design for Turcu 2016's study is depicted in the graphic set forth below, which is similar to Figure 4 of Grigoriadis describing Example 6.



The graphic above explains the single-blind period in which the placebo, 300 mg dose of NBI-77860, and 600 mg dose of NBI-77860 is administered to the patients 21 days apart. *Id.* at 1175.

Table 3 set forth below shows serum androstenedione and testosterone after single doses of NBI-77860, mean, and percent change from placebo during the morning window (6-10 am). *Id.* at 1177.

Table 3. Serum Androstenedione and Testosterone After Single Doses of NBI-77860, Mean, and Percent Change From Placebo During the Morning Window (6–10 AM)

Participant	Dose	Androstenedione		Testosterone	
		Mean (ng/dl)	% Change From Placebo	Mean (ng/dl)	% Change From Placebo
1011001	Placebo	303.0	0	105.3	0
	300	295.3	−2.5	131.7	25.0
	600	265.7	−12.3	122.7	16.5
1011002	Placebo	185.3	0	49.7	0
	300	190.7	2.9	42.7	−14.1
	600	78.0	−57.9	23.0	−53.7
1011003	Placebo	146.0	0	35.0	0
	300	132.7	−9.1	32.3	−7.6
	600	147.7	1.1	34.0	−2.9
1011004	Placebo	820.0	0	169.3	0
	300	747.7	−8.8	158.7	−6.3
	600	934.0	13.9	164.0	−3.1
1011005	Placebo	308.0	0	76.3	0
	300	377.0	22.4	107.3	40.6
	600	420.3	36.5	83.0	8.7
1011006	Placebo	195.7	0	59.7	0
	300	141.0	−27.9	36.7	−38.5
	600	173.3	−11.4	50.7	−15.1
1011007	Placebo	145.3	0	47.3	0
	300	135.3	−6.9	32.3	−31.7
	600	84.7	−41.7	19.0	−59.9
1011008	Placebo	914.0	0	127.0	0
	300	973.3	6.5	147.3	16.0
	600	1366.3	49.5	194.3	53.0

Table 3 above shows that five out of the eight patients had an increase in androstenedione or A4 after at least one of the two NBI-77860 doses. *Id.* The study concluded:

Interestingly, among responders, decreases in serum androstenedione and testosterone following single doses of NBI-77860 were not consistently observed, possibly because suppression of these downstream steroids requires a more sustained ACTH reduction. Chronic dosing of a CFR₁ receptor antagonist would help determine the effectiveness of this potential therapy.

Id. at 1179.

2. Principles of Law

As set forth in 35 U.S.C. § 103,

[a] patent for a claimed invention may not be obtained . . . if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains.

35 U.S.C. § 103. The question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) if in the record, objective evidence of nonobviousness.¹⁰ *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1996). Consideration of the *Graham* factors “helps inform the ultimate obviousness determination.” *Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1048 (Fed. Cir. 2016) (en banc).

“An obviousness determination requires finding both ‘that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.’” *CRFD Research, Inc. v. Matal*, 876 F.3d 1330, 1340 (Fed. Cir. 2017) (quoting *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367–1368 (Fed. Cir. 2016)). “The reasonable expectation of success requirement refers to the likelihood of success in combining references to meet the limitations of the claimed invention.” *Intelligent Bio-Sys., Inc.*, 821 F.3d at

¹⁰ At this stage in the proceeding, Patent Owner does not assert or present evidence of objective indicia supporting nonobviousness of the challenged claims. *See* Prelim. Resp.

1367. A reasonable expectation of success “does not require absolute predictability of success.” *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009) (quoting *In re O’Farrell*, 853 F.2d 894, 903–904 (Fed. Cir. 1988)).

In that regard, an obviousness analysis “need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007); see *In re Translogic Tech, Inc.*, 504 F.3d 1249, 1259 (Fed. Cir. 2007). In *KSR*, the Supreme Court also stated that an invention may be found obvious if trying a course of conduct would have been obvious to a POSITA:

When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

550 U.S. at 421. “*KSR* affirmed the logical inverse of this statement by stating that § 103 bars patentability unless ‘the improvement is more than the predictable use of prior art elements according to their established functions.’” *In re Kubin*, 561 F.3d 1351, 1359–60 (Fed. Cir. 2009) (citing *KSR*, 550 U.S. at 417).

3. Analysis

Petitioner relies on the study of NBI-77860 in Example 6 of Grigoriadis and the further disclosure of the same study in Turcu 2016 to establish that it would have been obvious to one of skill in the art “that

administering NBI-77860 to a patient would reduce that patient's A4 level compared to the patient's baseline—i.e., the patient's A4 level before receiving any drug.” Pet. 59 (citing Ex. 1005 ¶ 59). Concerning Grigoriadis and Turcu 2016's comparison of drug levels to placebo as opposed to a baseline, Petitioner makes the following remarks.

A skilled artisan would be aware that a placebo is a treatment which does not contain any drug. Therefore, a skilled artisan would reasonably expect, based on data showing administration of NBI-77860 reduced A4 in a patient compared to a placebo measurement, that administration of NBI-77680 would also reduce the patient's A4 level compared to baseline. To the extent that a placebo treatment elevated levels of A4 or its precursor hormones, the reduction in A4 from administration of NBI-77860 compared to placebo disclosed in Turcu 2016 would further indicate to a skilled artisan that administration of NBI-77860 would reduce A4 in a patient compared to the patient's baseline level.

Pet. 59–60 (citing Ex. 1005 ¶ 59; Ex. 1040, 722–723).

As for the requirement of claim 1 that the reduction in A4 from baseline in a human “is maintained at a reduced level post 24 hours,” Petitioner asserts that:

A skilled artisan would expect a drug to maintain its efficacy over time with repeated dosing. A reduction in efficacy of a drug over time is relatively rare. A skilled artisan would have reasonably expected the A4 reductions over 24 hours after administration of NBI-77860 disclosed in Turcu 2016 to extend beyond 24 hours with repeated dosing of NBI-77860.

Pet. 60 (citing Ex. 1005 ¶¶ 62–63, 87–88; Ex. 1032, 35–36; Ex. 1033, 205; Ex. 1034, 153).

Patent Owner asserts that Petitioner challenge here fails because neither Grigoriadis nor Turcu 2016 show reduction of A4 level *from baseline*, but only from administration of placebo, which is different.

Prelim. Resp. 48–50. Patent Owner concludes that “[b]ecause the Grigoriadis/Turcu study assessed hormone levels only under the influence of placebo or verucerfont treatment and never took an overnight pre-dose assessment as required for the claimed baseline, Petitioner’s proposal to combine these two references does not resolve the deficiency that already led the Board to deny institution in the prior PGR.” *Id.*; see *Neurocrine*, IPR2021-00088, Paper 11, 16–21. The impropriety of conflating from baseline and from placebo, Patent Owner asserts, is further evidenced by Dr. Cary’s definition of baseline to include a baseline measurement while a patient is taking steroid treatment. Prelim. Resp. 52 (citing Ex. 1005 ¶ 39). Such a definition, Patent Owner argues, further distances the teachings of Grigoriadis and Turcu 2016 because neither of these references discloses taking any baseline measurements while the patient was taking a steroid. *Id.* at 53 (citing Ex. 1006 ¶ 91).

Patent Owner also asserts a second reason why this ground fails, namely, that we “should be skeptical of the petition’s assumption that Turcu discloses an actual reduction of A4 levels *even from placebo*, let alone from baseline.” Prelim. Resp. 50. Patent Owner points to the variability in Turcu’s A4 measurements as set forth below.

Turcu reported measuring a nominal decrease in A4 levels from placebo after the 300 mg dose but a nominal **increase** from placebo after the 600 mg dose. EX1008, 1179 Table 3 (Participant 1011003: -9.1, +1.1; Participant 1011004: -8.8, +13.9). Turcu also reported measuring nominal **increases** in A4 levels for certain patients after the 300 mg dose. *Id.* (Participant 1011002: +2.9; Participant 1011005: +22.4; Participant 1011008: +6.5).

Prelim. Resp. 51.

Patent Owner highlights these measurements in its annotated Table 3 of Turcu 2016 set forth below.

Table 3. Serum Androstenedione and Testosterone After Single Doses of NBI-77860, Mean, and Percent Change From Placebo During the Morning Window (6–10 AM)

Participant	Dose	Androstenedione		Testosterone	
		Mean (ng/dl)	% Change From Placebo	Mean (ng/dl)	% Change From Placebo
1011001	Placebo	303.0	0	105.3	0
	300	295.3	-2.5	131.7	25.0
	600	265.7	-12.3	122.7	16.5
1011002	Placebo	185.3	0	49.7	0
	300	190.7	2.9	42.7	-14.1
	600	78.0	-57.9	23.0	-53.7
1011003	Placebo	146.0	0	35.0	0
	300	132.7	-9.1	32.3	-7.6
	600	147.7	1.1	34.0	-2.9
1011004	Placebo	820.0	0	169.3	0
	300	747.7	-8.8	158.7	-6.3
	600	934.0	13.0	164.0	-3.1
1011005	Placebo	308.0	0	76.3	0
	300	377.0	22.4	107.3	40.6
	600	420.3	36.5	83.0	8.7
1011006	Placebo	195.7	0	59.7	0
	300	141.0	-27.9	36.7	-38.5
	600	173.3	-11.4	50.7	-15.1
1011007	Placebo	145.3	0	47.3	0
	300	135.3	-6.9	32.3	-31.7
	600	84.7	-41.7	19.0	-59.9
1011008	Placebo	914.0	0	127.0	0
	300	973.3	6.5	147.3	16.0
	600	1366.3	49.5	194.3	53.0

Patent Owner concludes from Turcu’s Table 3 shown above that:

Turcu measured an **increase** in A4 levels as compared to placebo when administering verucerfont in the clear majority (>62%) of participants.

Neither the petition nor Turcu even assert that any reported reduction in A4 levels as compared to placebo is greater than the measurement variation in the experiment itself. To the contrary, Turcu concedes that “decreases in serum androstenedione...following single doses of NBI-77860 were not consistently observed[.]” *Id.*, 1179.

Prelim. Resp. 51–52.

In our decision in PGR2021-00088, we determined that:

The single clinical trial taught by Example 6 of Grigoriadis does not establish a baseline value for patients against which to compare the data obtained from patients receiving 300 mg or 600 mg of the test drug, NBI-77860 (verucerfont). *See* Ex. 1006 ¶¶ 90–94. Specifically, Example 6 does not establish a baseline “which include[s] an [sic] pre-dose

overnight assessment and a post-dose overnight assessment for PK/PD following administration of the first dose,” as disclosed by the ’908 patent.

Neurocrine, PGR2021-00088, Paper 11, 16. We concluded that Grioriadis did not disclose expressly the limitation of reducing the hormone level in a human at least 10% from baseline. *Id.* at 16–17.

Petitioner does not directly dispute this finding, but instead, equates “from baseline” with “from placebo” by asserting that because a placebo is by definition treatment without a drug, reduction in A4 from a placebo measurement would also mean a reduction in A4 from baseline. Pet. 59. Because Petitioner has not presented us with sufficient reason to depart from our previous finding, we could end our enquiry here and determine that Petitioner has failed to show it is more likely than not to succeed in showing at least one claim in this ground is unpatentable. *See* Prelim. Resp. 15.

We also agree with Patent Owner that Petitioner paints with too broad of a brush, and a reduction from placebo does not always mean a reduction from baseline as Petitioner asserts. Patent Owner points to several references that describe how the stress of medical interventions and placebo administration impacts levels of stress hormones such as ACTH and A4. Prelim. Resp. 22–25. For instance, one reference discusses “needle phobia” and release of stress hormones such as cortisol and ACTH as a result of such phobia or venipuncture. Ex. 2002, 172; *see also* Ex. 2003, 26 (finding plasma cortisol levels raised similarly in patients that underwent venous catheterization in the morning as well as the afternoon suggesting “that the first catheterization experience tended to obliterate the normal diurnal decrease in cortisol values observed in the afternoon”); Ex. 2005, Abst. (finding verbally induced nocebo (expectations of symptom worsening)

hyperalgesia caused increased adrenocorticotrophic hormone and cortisol plasma concentrations).

In contrast, Petitioner relies on Dr. Carey's unsupported statements that "[b]ecause the placebo contains no drug, there should be no effect of placebo on a patient's A-4 level." Ex. 1005 ¶ 59. Here, with regard to the challenged claims, we are dealing with the levels of stress hormones such as A4 that Patent Owner has offered evidence to show would be affected by medical intervention including the administration of a placebo. To assume no difference between comparison from baseline and placebo for levels of the stress hormones of interest is not supported by the record evidence.

We also agree with Patent Owner that the data set forth in Table 3 of Turcu 2016 does not support Petitioner's conclusion that it would have been obvious to a skilled artisan based on this data "that administering NBI-77860 to a patient would reduce that patient's A4 level compared to the patient's baseline—i.e., the patient's A4 level before receiving any drug." Pet. 59. As Patent Owner points out, the evidence in Table 3 is far from conclusive on this point; Table 3 shows that five of the eight patients had increases in A4 levels either after the 300 mg dose of NBI-77860, the 600 mg dose of NBI-77860, or both as shown by Patent Owner's annotated Table 3 set forth above. The conclusion of Turcu 2016 confirms Patent Owner's reading of Table 3: "Interestingly, among responders, decreases in serum androstenedione and testosterone following single doses of NBI-77860 were not consistently observed, possibly because suppression of these downstream steroids requires a more sustained ACTH reduction." Ex. 1008, 6.

Finally, the limitation of claim 1 that the reduction in A4 level from baseline “is maintained at a reduced level post 24 hours” has also not been shown sufficiently to have been taught or suggested by the asserted art. To establish that this claim limitation was taught by Grigoriadis and Turcu 2016, Petitioner states:

A skilled artisan would expect a drug to maintain its efficacy over time with repeated dosing. A reduction in efficacy of a drug over time is relatively rare. A skilled artisan would have reasonably expected the A4 reductions over 24 hours after administration of NBI-77860 disclosed in Turcu 2016 to extend beyond 24 hours with repeated dosing of NBI-77860. In view of the disclosure of Grigoriadis and Turcu 2016, it would have been obvious to a skilled artisan that the reduction in A4 level from baseline would be maintained for more than 24 hours with repeated dosing.

Pet. 60–61 (citing Ex. 1005 ¶¶ 62–63, 87–88; Ex. 1032, 35–36; Ex. 1033, 205; Ex. 1034, 153).

In the Reasons for Allowance set forth by the Examiner for the ’908 patent, the Examiner states:

Grigoriadis differs from the instant Invention in that Grigoriadis only discloses [see Grigoriadis’ Figure 5] measuring ACTH and 17-OHP levels in individuals throughout the 24-hour post-dose period. The prior art does not disclose or suggest maintaining the reduced hormone levels beyond 24 hours post-treatment, yet alone maintaining said reductions over a six week period.

Ex. 1037, 12. Petitioner does not address the Examiner’s findings here to convince us that the Examiner erred in this assessment of Grigoriadis, and by extension, Turcu 2016, which describes the same study as limited to the 24-hour post-dose period. *See* Pet. 40 (“Turcu 2016 (Ex. 1008) presents data from the same Phase I study disclosed in Example 6 of Grigoriadis.”).

For the reasons set forth above, we determine that Petitioner has failed to establish that it is more likely than not that claim 1 of the '201 patent would have been obvious over Grigoriadis and Turcu 2016. Because the remaining claims challenged in this ground depend either directly or indirectly on claim 1, we similarly conclude that Petitioner has not established that it is more likely than not that these dependent claims 2–4, 7–19 would have been obvious over the cited art.¹¹

H. Ground 5 – Obviousness over Grigoriadis, Turcu 2016, and Romano

Petitioner asserts that claims 5 and 6 would have been obvious over the disclosure of NBI-77860 in Grigoriadis and Turcu 2016 along with Romano and the knowledge of a skilled artisan. *See* Pet. 4, 73. Petitioner does not revisit how Grigoriadis and Turcu 2016 teach or suggest the limitations of claim 1 upon which the challenged claims ultimately depend, but appears to continue to rely on its arguments in ground 4. *See* Pet. 73–75. Petitioner also does not rely on Romano for any teaching with respect to the limitations of claim 1, but for the teaching of “the use of small particle sizes with CFR₁ receptor antagonists, such as the claimed range of between about 1-20 μm .” Pet. 73–75 (citing Ex. 1007, Abst., ¶ 531; Ex. 1005 ¶¶ 73–77). Because we have found that Grigoriadis and Turcu 2016 do not teach or suggest all of the limitations of claim 1, this ground too fails. We therefore conclude that Petitioner has failed to establish that it is more likely than not that dependent claims 5 and 6 would have been obvious over Grigoriadis, Turcu 2016, and Romano.

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*I. Ground 6 – Unpatentability of Claims 1–19
for Lack of Written Description*

Petitioner asserts that claims 1–19 lack written description support because the '201 patent only discloses a single CFR₁ receptor antagonist, tildacerfont (Compound 1) and does not disclose structural features common to the CFR₁ receptor antagonists. Pet. 75–79.

We addressed Petitioner's same argument for lack of written description support in PGR2021-00088 as set forth below.

The challenged claims recite a genus ("a CRF1 receptor antagonist or pharmaceutically acceptable salt thereof) that is not itself claimed. The claims, rather, are directed to a method of using that genus in the treatment of CAH. The prior art cited by Petitioner acknowledges that the genus of CRF1 receptor antagonists was well known in the art at the time of invention. *See* Ex. 1006, *e.g.*, ¶¶ 20, 21, 25, 26, 52–55. Furthermore, the Specification of the '908 patent discloses that CRF1 receptor antagonists were known in the art, identifies an example of a CRF1 receptor antagonist, and provides an exemplary embodiment by which a CRF1 receptor antagonist is administered to achieve the claimed effect. *See* Ex. 1001 col. 10, ll. 47–64, col. 12, ll. 27–30; Ex. 4. Finally, Petitioner's declarant, Dr. Carey, acknowledges that this genus would have been well known to a person of ordinary skill in the art. *See* Ex. 1005 ¶ 99 (citing Ex. 1029; Ex. 1018; Ex. 1030; Ex. 1031) ("Based on my review of the published literature, over 100 CRF1 receptor antagonists had been characterized or were in clinical development prior to the filing of the '908 patent, including NBI34041, verucerfont, and pexacerfont").

Neurocrine, PGR2021-00088, Paper 11, 29–30.

We concluded that "Petitioner's argument has not established that the Specification fails to 'reasonably convey to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.'"

Id. at 30 (quoting *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc)).

Petitioner has not addressed these previous findings or why these findings are in error. Therefore, we see no reason to depart from this previous ruling that is supported by the record before us here. Therefore, we determine that Petitioner has not demonstrated that it is more likely than not that any of claims 1–19 are unpatentable based on lack of written description.

III. CONCLUSION

For the foregoing reasons, we conclude that the information presented in the Petition has not established that it is more likely than not that Petitioner will prevail in showing that challenged claims 1–19 of the '201 patent are unpatentable based on grounds presented in the Petition. Accordingly, we do not institute a post-grant review of claims 1–19 of the '201 patent.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 324(a), a post grant review of claims 1–19 of the '201 patent is *denied* with respect to all grounds set forth in the Petition; and

FURTHER ORDERED that post-grant review is not instituted.

PGR2022-00025
Patent 11,007,201 B2

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