

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NEUROCRINE BIOSCIENCES, INC.,
Petitioner

V.

SPRUCE BIOSCIENCES, INC.,
Patent Owner

Case PGR2022-00025
U.S. Patent 11,007,201

PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE

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PETITIONER’S UPDATED EXHIBIT LIST

Petitioner Exhibit Number	Exhibit Description
1001	U.S. Patent No. 11,007,201 to Alexis Howerton, et al. (“the ’201 patent”).
1002	U.S. Prosecution History of the ’201 Patent.
1003	Application No. PCT/US2018/046760.
1004	U.S. Provisional Application Serial No. 62/545,406.
1005	Declaration of Robert M. Carey, M.D.
1006	U.S. Patent Application Publication No. 2017/0020877 to Grigoriadis et al. (“Grigoriadis”).
1007	U.S. Patent Application Publication No. 2005/0209250 to Romano (“Romano”).
1008	Turcu et al., “Single-Dose Study of a Corticotropin-Releasing Factor Receptor-1 Antagonist in Women With 21-Hydroxylase Deficiency,” <i>J. Clin. Endocrinol. Metab.</i> , 101(3):1174–1180 (March 2016) (“Turcu”).
1009	Auchus et al., “Crinicerfont Lowers Elevated Hormone Markers in Adults With 21-Hydroxylase Deficiency Congenital Adrenal Hyperplasia,” <i>J. Clin. Endocrinol. Metab.</i> (2021) (“Auchus”).
1010	U.S. Patent Application Publication No. 2006/0078623 to Dhoot et al. (“Dhoot”).
1011	“Spruce Biosciences Presents Phase 1 and 2 Data for Tildacerfont in Adults with Congenital Adrenal Hyperplasia from Endocrine Society’s 2021 Annual Meeting,” Spruce Biosciences (Mar. 17, 2021) (“Spruce March 17, 2021 Press Release”).
1012	U.S. Patent No. 8,030,304 to Chen et al. (“Chen”).

Petitioner Exhibit Number	Exhibit Description
1013	Speiser et al., “Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society Clinical Practice Guideline,” <i>J. Clin. Endocrinol. Metab.</i> , 95(9):4133–4160 (2010) (“Speiser 2010”)
1014	Turcu A.F. & Auchus R.J., “The Next 150 Years of Congenital Adrenal Hyperplasia,” <i>J. Steroid. Biochem. Mol. Biol.</i> 153:63–71 (Sep. 2015) (“Turcu & Auchus 2015”).
1015	El Maouche et al., “Congenital Adrenal Hyperplasia,” <i>Lancet</i> 390:2194–210 (2017) (“El Maouche 2017”).
1016	Merke D.P. & Bornstein S.R., “Congenital Adrenal Hyperplasia,” <i>Lancet</i> 365:2125–36 (2005) (“Merke & Bornstein 2005”).
1017	Speiser et al., “Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society Clinical Practice Guideline,” <i>J. Clin. Endocrinol. Metab.</i> , 103(11):4043–4088 (2018) (“Speiser 2018”).
1018	Fahmy et al., “Structure and Function of Small Non-Peptide CRF Antagonists and their Potential Clinical Use,” <i>Curr. Mol. Pharmacol.</i> 10(4): 270–281 (2017) (“Fahmy 2017”).
1019	Griebel et al., “4-(2-Chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]5-methyl-N-(2-propynyl)-1,3-thiazol-2-amine Hydrochloride (SSR125543A), a Potent and Selective Corticotrophin-Releasing Factor1 Receptor Antagonist. II. Characterization in Rodent Models of Stress-Related Disorders,” <i>J. Pharmacol. Exp. Ther.</i> 301(1):333–345 (2002) (“Griebel 2002”).
1020	Gully et al., “4-(2-Chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]5-methyl-N-(2-propynyl)-1,3-thiazol-2-amine Hydrochloride (SSR125543A): A Potent and Selective Corticotrophin-Releasing Factor1 Receptor Antagonist. I. Biochemical and Pharmacological Characterization,” <i>J. Pharmacol. Exp. Ther.</i> 301(1):322-332 (2002) (“Gully 2002”).

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1021	Merke D.P. & Cutler G.B., “New Ideas for Medical Treatment of Congenital Adrenal Hyperplasia,” <i>Endocrinol. Metab. Clin. North. Am.</i> 30(1):121–135 (2001) (“Merke & Cutler 2001”).
1022	Merke et al., “Future Directions in the Study and Management of Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency,” <i>Ann. Intern. Med.</i> 136:320–334 (2002) (“Merke 2002”).
1023	“Microparticles Formulation as a Targeting Drug Delivery System,” <i>J. Nanomed. Res.</i> 6(2):00151, 1–4 (2017) (“Microparticles Formulation 2017”).
1024	Merke D.P. & Auchus R.J., “Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency,” <i>N. Engl. J. Med.</i> 383(13):1248–1261 (2020) (“Merke & Auchus 2020”).
1025	Turcu A.F. & Auchus R.J., “Novel Treatment Strategies in Congenital Adrenal Hyperplasia,” <i>Curr. Opin. Endocrinol. Diabetes Obes.</i> 23(3):225–232 (June 2016) (“Turcu & Auchus 2016”).
1026	Webb E.A. & Krone N., “Current and Novel Approaches to Children and Young People with Congenital Adrenal Hyperplasia and Adrenal Insufficiency,” <i>Best Pract. Res. Clin. Endocrinol. Metab.</i> 29:449–468 (2015) (“Webb & Krone 2015”).
1027	“Neurocrine Biosciences to Present New Data Analyses for Crinecerfont in Adults with Classical Congenital Adrenal Hyperplasia at ENDO 2021,” Neurocrine Biosciences (Mar. 20, 2021) (“Neurocrine March 20, 2021 Press Release”).
1028	“Neurocrine Biosciences Reports Positive Phase II Data for Crinecerfont in Adults with Congenital Adrenal Hyperplasia at ENDO Online 2020,” Neurocrine Biosciences (June 8, 2020) (“Neurocrine June 8, 2020 Press Release”).
1029	Williams, “Corticotropin-Releasing Factor 1 Receptor Antagonists: A Patent Review,” <i>Expert Opin. Ther. Pat.</i> 23(8):1057–68 (2013) (“Williams 2013”).

Petitioner Exhibit Number	Exhibit Description
1030	Zorrilla E.P. & Koob G.F., “Progress in Corticotropin-Releasing Factor-1 Antagonist Development,” <i>Drug Discovery Today</i> 15(9/10):371–383 (2010) (“Zorrilla & Koob 2010”).
1031	Kehne J.H. & Cain C.K., “Therapeutic Utility of Non-Peptidic CRF1 Receptor Antagonists in Anxiety, Depression, and Stress-Related Disorders: Evidence from Animal Models,” <i>Pharmacol. Ther.</i> 128(3):460–487 (2010). (“Kehne & Cain 2010”).
1032	Goodman & Gilman’s <i>The Pharmacological Basis of Therapeutics</i> (Brunton L.L. ed., 12th ed. 2011) (“Goodman & Gilman 2011”).
1033	Shargel L. & Yu A., <i>Applied Biopharmaceutics & Pharmacokinetics</i> (7th ed. 2016) (“Shargel & Yu 2016”).
1034	Shargel et al., <i>Applied Biopharmaceutics & Pharmacokinetics</i> (6th ed. 2012) (“Shargel 2012”).
1035	Bale et al., “Overview on Therapeutic Applications of Microparticulate Drug Delivery Systems,” <i>Crit. Rev. Ther. Drug Carrier Syst.</i> 33(4):309-361 (2016).
1036	U.S. Patent No. 10,849,908 to Alexis Howerton, et al. (“the ’908 patent”).
1037	U.S. Prosecution History of the ’908 Patent.
1038	Fuqua et al., “Duration of Suppression of Adrenal Steroids after Glucocorticoid Administration,” <i>International Journal of Pediatric Endocrinology</i> (2010) (“Fuqua 2010”).
1039	Sarafoglou et al., “Tildacerfont in Adults with Classic Congenital Adrenal Hyperplasia: Results from Two Phase 2 Studies,” <i>Journal of Clinical Endocrinology & Metabolism</i> (2021) (“Sarafoglou 2021”).
1040	Reif et al., “Mechanisms Involved in Placebo and Nocebo Responses and Implications for Drug Trials,” <i>Clinical Pharmacology and Therapeutics</i> (2011) (“Reif 2011”).
1041	Declaration of Gordon B. Cutler, JR., M.D.
1042	Transcript of June 5, 2024 Deposition of Dr. Adrian Dobs.

Petitioner Exhibit Number	Exhibit Description
1043	December 14, 2023 Email from Counsel Regarding Dr. Carey’s health status.
1044	Spierling & Zorilla, “Don’t stress about CRF: Assessing the translational failures of CRF1 antagonists,” <i>Psychopharmacology (Berl)</i> . 2017 May; 234(9-10): 1467–1481(“Spierling”).
1045	Recto et al., “Comparison of the Efficacy and Tolerability of Simvastatin and Atorvastatin in the Treatment of Hypercholesterolemia,” <i>Clin. Cardiol.</i> 23,682-688 (2000) (“Recto”).
1046	Auchus et al., “Phase 3 Trial of Crinecerfont in Adult Congenital Adrenal Hyperplasia,” <i>The New England Journal of Medicine</i> (2024) (“Auchus 2024”).
1047	Reply Declaration of Gordon B. Cutler, Jr., M.D.

I. INTRODUCTION

Spruce’s Patent Owner Response (“POR”) recycles arguments the Board and the Director have already rejected and provides no reason to deviate from the Board’s Institution Decision (“DI”). Grigoriadis’ disclosure of crinecerfont inherently anticipates the challenged claims because the recited androstenedione (“A4”) reductions inevitably flow from Grigoriadis’ disclosure, as shown by the Auchus reference. Spruce’s argument that the methods of these references are not the same injects unrecited features into the claims and has already been rejected in the DI and the Director’s Decision¹. DI, 22–30; Decision, 10. Spruce’s non-obviousness argument hinges on its claim construction of “baseline” and ignores that the Board has already construed that term. DI, 11.

Spruce’s written-description argument fares no better and is also premised on an argument the Board and Director have rejected. DI, 32; Decision, 12–13. Spruce’s expert admits the specification does not disclose either a representative number of species or common structural features of species that meet the claimed A4 reductions—the relevant written-description standard. Spruce’s

¹ The Director adopted her analysis in the Director Review Decision issued in PGR2021-00088 in this case. Paper 15, 3. Citation to the “Decision” herein refer to the Director’s Decision in PGR2021-00088, Paper 16.

characterization of what was known in the prior art is wrong and cannot save its deficient specification.

Having nothing new to say on the merits, Spruce resorts to personally attacking Neurocrine’s replacement expert, Dr. Cutler. These attacks are untrue, disgraceful, and speak volumes about the weakness of Spruce’s defenses. The Board should find that challenged claims 1–19 are unpatentable.

II. THE BOARD SHOULD REBUKE SPRUCE’S PERSONAL ATTACKS AGAINST DR. CUTLER

Spruce’s attacks on Neurocrine’s expert, Dr. Cutler, as “not an independent expert” are untrue, deliberately misleading, and should be disregarded by the Board. POR, 2–5. As explained in his declaration, Dr. Cutler is one of the country’s leading experts in endocrinology and metabolism disorders. EX1041 ¶¶3–13. Spruce’s expert described Dr. Cutler as “a respected endocrinologist” and testified “I have great respect for him.” EX1042, 36:11–37:4. Spruce’s allegation that Dr. Cutler “has interests in both Neurocrine and the outcome of this proceeding” is false. POR, 3. Dr. Cutler has consulted for Neurocrine’s CAH program, as he has with many other companies. EX1041 ¶7; EX1047 ¶¶17–19. He has no financial interest in Neurocrine, this proceeding, or Neurocrine’s CAH program. EX1047 ¶19; EX1041 ¶14. That Dr. Cutler knew Neurocrine’s Chief Medical Officer from when both worked at Eli Lilly and other Neurocrine scientists through his consulting work has no bearing on his opinions. *Id.*

Spruce’s allegation that “Neurocrine spent years cultivating Dr. Cutler to testify in this case” is also false. POR, 4. Dr. Cutler did not decline to serve as an expert in 2020 “given his significant conflicts,” *id.*, he declined because he had not previously been an expert witness and preferred to focus on scientific consulting rather than legal consulting. EX1047 ¶¶13–14. When Dr. Carey suffered a serious stroke and was unable to continue as Neurocrine’s expert, Dr. Cutler agreed to step in because he felt strongly that the opinions Dr. Carey had provided were correct. *Id.* ¶¶15–16.

Most egregiously, Spruce faults Dr. Cutler for not discussing the testimony with Dr. Carey. POR, 5. As Spruce was informed in a December 14 email conveying information from Dr. Carey’s daughter, this was impossible because as a symptom of his stroke, Dr. Carey suffered from severe expressive aphasia that ***made it impossible for him to communicate clearly***. EX1043. That Spruce attempts to use Dr. Carey’s illness to discredit Dr. Cutler, and faults Dr. Cutler for failing to do something Spruce knows is impossible, is disgraceful and should be rebuked by the Board.

Far from a “highly unusual situation” (POR, 5), the Board regularly permits substitution of expert witnesses when the original expert becomes unavailable, and a substitute expert adopts the testimony of the original expert—as Dr. Cutler did here. *Resmed, Inc. v. New York Univ.*, IPR2022-00994, Paper 32 (PTAB Mar. 30,

2023); *Google LLC v. Hammond Dev. Int'l, Inc.*, IPR2020-00020, Paper 18 (PTAB July 2, 2020).

III. CLAIMS 1–19 ARE UNPATENTABLE FOR LACK OF WRITTEN DESCRIPTION (GROUND 6)

The Board should find that claims 1–19 are unpatentable for lack of written-description.² Decision, 12–14; DI, 32. To show sufficient description of the claimed genus, the specification must 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 Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1350 (Fed. Cir. 2010) (*en banc*). Functionally defined genus claims, like the challenged claims, are inherently vulnerable to written-description challenges, “especially in technology fields that are highly unpredictable, where it is difficult to establish a correlation between structure and function for the whole genus or to predict what

² Neurocrine addresses Ground 6 first on reply because Spruce’s POR presents no new evidence relevant to the written-description standard. If the Board finds claims 1–19 unpatentable for lacking written-description, it need not reach the other grounds of the Petition. *See Arthrex, Inc. v. Gelfand*, IPR2023-00014, Paper 45 at 59–60 (PTAB Mar. 11, 2024); *Boston Sci. Scimed, Inc. v. Cook Grp. Inc.*, 809 F. App’x 984, 990 (Fed. Cir. 2020).

would be covered by the functionally claimed genus.” *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1301 (Fed. Cir. 2014).

As the Director found and the Board adopted on the preliminary record, “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.” DI, 32; Decision, 12. The specification indisputably discloses only a single species, tildacerfont (“Compound 1”), that can achieve the reduction in A4 results, which it classifies as “the invention.” Decision, 12. The “’201 patent specification 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 CRF1 receptor antagonists.” DI, 32 (citing Decision, 13–14). Spruce’s POR presents no new evidence contrary to these findings, instead mischaracterizing the prior art to argue the specification need not disclose a representative number of species or common structural features. POR, 65–74. As explained below, that is wrong. Nothing in the specification nor the prior art indicates that Spruce was in possession of using a class of CRF1 receptor antagonists to achieve the claimed results.

A. The Specification Does Not Show Possession of Using a Class of CRF1 Receptor Antagonists to Treat CAH

The specification does not disclose “class effects” of CRF1 receptor antagonists. POR, 67–68. The portions of the specification Spruce cites say

nothing about whether *the class* of CRF1 receptor antagonists can achieve the claimed reductions in A4. EX1047 ¶¶82–84. Rather, these citations relate either to the use of tildacerfont (12:26–29,43:4–43), the differences between CRF receptor subtypes and the role of CRF in hormone regulation (1:17–20,10:47–53,10:54–65, 11:49–12:25), or that these antagonists had been studied for other indications (11:57–64). *Id.* None of these disclosures relate to whether the specification discloses a representative number of species or common structural features of CRF1 receptor antagonists that achieve the claimed results. DI, 32.

There is no dispute that the specification fails to disclose a representative number of species that achieve the claimed reductions in A4. Tildacerfont is not “an exemplary embodiment.” POR, 69. It is the *only* embodiment described for use with the claimed methods, as the Director explained. Decision, 12 (the specification “discloses only one particular species, that may be administered to treat CAH and cause a 10% reduction in [hormones], as claimed”). Spruce’s expert agrees. EX1042, 29:18–32:19. Like *Ariad*, the “claims here recite methods of encompassing a genus of materials achieving a stated useful result... But the specification does not disclose a variety of species that accomplish the result.” Decision, 12 (citing *Ariad*, 598 F.3d at 1350).

Going even further than *Ariad*, Spruce’s specification describes the use of tildacerfont as the “*present invention*” or “*present disclosure*.” Pet. 12–16,75–79. This is further “strong evidence” that the scope of written description is limited to

the use of tildacerfont. *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). Spruce's attempt to distinguish these cases on their facts (POR, 78–79) is unavailing. Each found a patentee characterizing a feature as the “present invention” or “present disclosure” is strong evidence that the written description is limited to that feature. *Id.* The specification does exactly that, defining Spruce's invention as using tildacerfont. Pet. 12–16, 75–79.

B. The Prior Art Did Not Teach a Class of CRF1 Receptor Antagonists Could Treat CAH, or Reduce A4 Levels and Maintain the Reduction Post 24 Hours

Spruce's argument that the class of CRF1 receptor antagonists was well-known in the prior art (POR, 71–78) was already rejected by the Board and the Director. The Director found 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 CRF1 receptor antagonists that can be used to treat CAH and result in the claimed hormone reduction. Decision, 13. The Board adopted this finding. DI, 32. Moreover, Spruce argues that different species within the CRF1 receptor antagonist genus do not achieve the same results. Decision, 13; Paper 6, 42–47. Spruce's argument that there is no “*per se* rule” that a claim is invalid if there is only one working example assumes the same faulty

premise. POR, 80–83. Thus, Spruce’s reliance on *Ajinomoto*, *In re Herschler*, *Erfindergemeinschaft*, and *Merck* is inapposite. *Id.*

As Dr. Cutler explained, the prior art discussed the possibility that CRF1 receptor antagonists may be useful as a “new approach” to treat CAH, but did not provide evidence that a class of CRF1 receptor antagonists could achieve the claimed A4 reductions. EX1047 ¶¶75–76; EX1021, 130–31. Spruce’s suggestion that *Neurocrine’s prior work*, reported in Grigoriadis, shows *Spruce* was in possession of using the claimed genus to reduce A4 levels is nonsensical. POR, 72–73. If Grigoriadis’ disclosure of species of CRF1 receptor antagonists that reduce A4 provides written-description support for Spruce’s claims, then it also anticipates the claims (Ground 1). *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 971 (Fed. Cir. 2001). Either way, the claims are invalid.

Moreover, CRF1 receptor antagonists were previously studied for indications other than CAH and were *ineffective*. EX1047 ¶¶78–81; EX1030, 377–78 (two CRF1 receptor antagonists failed to show efficacy in treating depression); EX1031, 24–25 (same); EX1044, Table 1 (noting several CRF1 receptor antagonists lacked efficacy). Spruce’s expert admitted a POSA would understand that “antagonists of the CRF1 receptor have not demonstrated clinical utility despite over 30 years of research and hundreds of patents.” EX1029, 1065; EX1042, 131:18–132:14. In view of the prior art, a POSA would not have thought a class of CRF1 receptor antagonists were useful for any indication, much less

useful to treat CAH, or to lower A4 levels and maintain that reduction post 24 hours. This is particularly true because the 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.” Decision, 14 (citing *Idenix Pharms., LLC v. Gilead Sciences Inc.*, 941 F.3d 1149, 1165 (Fed. Cir. 2019)).

C. The Specification Does Not Describe Common Structural Features of CRF1 Receptor Antagonists that Achieve the Claimed A4 Reductions

As the Director found and the Board adopted here, “the ’201 patent specification does not disclose structural features common to the functional genus so that one of skill in the art can visualize or recognize the effective members of the genus of CRF₁ receptor antagonists.” DI, 32; Decision, 12–13. Spruce concedes this point, instead arguing its deficient specification is saved by what was known in the prior art. POR, 73–77; EX1042, 32:6–19. Not so.

CRF1 receptor antagonists are defined as compounds that inhibit CRF1 receptors, not by a particular structure or structures. EX1047 ¶¶86–90. Dr. Cutler explained that compounds that interact with the CRF1 receptor can have widely diverse structural features. *Id.* The broad structural features observed in some (but not all) CRF1 receptor antagonists would not tell a POSA whether any compounds in this class could accomplish the claimed results of reducing A4 from baseline. *Id.*

Spruce's own publication describes tildacerfont, the only species disclosed in the specification, as having "unique structural features" compared to other CRF1 receptor antagonists. EX1039, 4667; EX1042, 52:19–53:14.

The prior art doesn't identify common structural features of antagonists that achieve the claims A4 reductions. EX1029 (POR, 74–77) does not mention CAH. The generalized structure Spruce asserts is a "typical CRF1 receptor antagonist" is described in EX1029 as one subclass of CRF1 receptor antagonists—i.e., not reflective of the entire class. EX1029, 2, Fig. 2; EX1042, 122:8–123:16; EX1047 ¶¶91–92. It does not disclose that any antagonists falling within Figure 2's generalized structure could lower A4 but refers to these compounds as having "less-than-optimal physicochemical properties." EX1029, 2. EX1029 also reports other CRF1 receptor antagonist subclasses that do not have the same structural features as Figure 2. EX1047 ¶¶92–95; EX1029, Figs. 1 (compounds 1, 4), 6, 11. At deposition, Spruce's expert admitted she is not a chemist and did not know whether other CRF1 receptor antagonists disclosed in EX1029 were encompassed by Figure 2. EX1042, 125:5–126:7, 129:17–130:10. She also admitted other CRF1 receptor antagonists in EX1029 are different than Figure 2's structure. EX1042, 130:13–131:16.

Similarly, EX1018 does not describe structural features of CRF1 receptor antagonists that could reduce A4 from baseline. EX1047 ¶¶96–97. It merely provides a general structure that encompasses many compounds, without providing

any information on what features are important for CAH treatment or A4 reduction. *Id.*; EX1018, 3, Fig. 1. EX1018 also discloses antagonists falling outside the structure of Figure 1, with no way to distinguish compounds that are effective to reduce A4. EX1018, 7–8, Figs. 11–12; EX1047 ¶¶96–98; EX1042, 132:17–134:20. U.S. Patent 8,030,304 identifies a laundry list of 24 potential indications for CRF1 receptor antagonists but does not identify any structural features of antagonists useful to treat CAH or achieve the claimed A4 reductions. EX1012, 2:10–62.

Neither the specification nor the prior art disclose a representative number of species or common structural features of CRF1 receptor antagonists that achieve the claimed results. Thus, the claims are unpatentable. *Ariad*, 598 F.3d at 1350.

IV. CLAIM CONSTRUCTION RELEVANT TO ANTICIPATION AND OBVIOUSNESS GROUNDS

A. Spruce Does Not Dispute Neurocrine’s Proposed Construction of “A Human”/ “The Human”

Spruce doesn’t dispute that “a human” or “the human” in the challenged claims refers to an individual patient. POR, 20–27. The claims’ plain language recites administering to “a human” a CRF1 receptor antagonist, in which an A4 level in “the human” is reduced from baseline. EX1001,47:50–48:5; EX1005 ¶42; *see also* EX1042, 22:21–23:21. Neurocrine’s construction also aligns with the

specification, which presents change in A4 levels in individual patients and shows some, but not all, patients achieved the claimed reductions. EX1001, Fig. 4.

While not addressing this construction head on, Spruce argues against inherent anticipation and obviousness because “some, but not all” patients achieved the claimed reductions in A4. POR, 41–45. That is inconsistent with the plain language of the claims and the specification. If the claims require “all humans” to achieve the claimed reductions, Spruce’s data doesn’t support the claims. EX1001, Figs. 2–4; EX1042, 20:8–22:2. The Board should adopt Neurocrine’s proposal that the claims require the recited A4 reductions in “a human”—a single patient, not all patients.

B. The Board’s Construction of “Baseline” Includes Comparisons From Placebo

Spruce spends over seven pages of its POR arguing against Neurocrine’s proposed construction of “from baseline” without acknowledging that the Board construed this term. POR, 20–27. The Board, after considering these same arguments in Spruce’s preliminary response, construed the phrase “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.” DI, 8–11. Spruce’s expert did not even consider the Board’s construction in forming her opinions. EX1042, 24:11–17.

Grounds 1–3 (Grigoriadis’ disclosure of crinecerfont) and Grounds 4–5 (Grigoriadis’ disclosure of verucerfont (NBI-77860)) all meet the Board’s construction of “reduced from baseline.” The administration of crinecerfont, as disclosed in Grigoriadis, inherently results in the claimed A4 reductions compared to measurements made prior to, and/or at the beginning of, administration of the drug. This is shown by Auchus, which reported reductions in A4 after 14 days of receiving crinecerfont compared to a patient’s A4 levels 7 days before the study began. EX1009, 3, Fig. 1–3, Table 1; EX1005 ¶¶50; Pet. 32–39. The Board found, and Spruce’s expert agrees, that Auchus’ comparison of A4 levels on Day 14 and 7 days before the study is a comparison “from baseline.” DI, 22; EX1042, 79:13–83:17.

Spruce’s argument that a placebo measurement isn’t a “baseline” relates only to Grounds 4–5, Grigoriadis’ and Turcu’s disclosure of verucerfont. Pet. 39–40, 57–62; EX1005 ¶¶57–64; EX1047 ¶¶65–66. Turcu reports that 300 mg or 600 mg of NBI-77860 reduced A4 levels in six of the eight CAH patients studied compared to placebo over a 24-hour period post-dose. EX1005 ¶¶ 58–60, 86; EX1006 ¶¶91–93, Figs. 5–6; EX1008, Table 3. This is a reduction “from baseline” because the placebo is a measurement “made prior to, and/or at the beginning of, administration of the drug”—placebo is not a drug. EX1005 ¶¶ 36–41, 59; EX1047 ¶¶66–70.

As Dr. Cutler explained, determining the drug effect in relation to prior placebo administration is scientifically acceptable, and can be used to control for a placebo effect. EX1047 ¶¶67–69. Spruce’s argument that a placebo baseline can elevate stress hormones is a non-sequitur. POR, 22–27. Placebo can elevate or reduce hormones in a given patient, and Neurocrine’s data show verucerfont administration achieved reductions in A4 regardless of any placebo effect. EX1047 ¶70. Dr. Cutler did not admit “placebo was a ‘treatment’ intervention.” POR, 23. He testified about one study in which a placebo treatment was compared to a non-placebo baseline; he also testified that a placebo baseline is appropriate. EX2011, 83:6–84:11; EX2013; EX1047 ¶¶67–69. Spruce’s expert has used a placebo baseline in her own research. EX1045; EX1042, 106:8–111:10, 114:9–115:5.

C. Spruce Did Not Dispute Neurocrine’s Proposed Constructions for “Maintained at a Reduced Level [Post 24 Hours] [Post 4 Weeks] [Post 6 Weeks]”

A POSA would understand these terms to mean the A4 level is maintained at a reduced level for the specified time period with repeated dosing. Pet. 29–30; EX1005 ¶¶43–46. Spruce did not dispute this construction; Neurocrine’s proposal should be adopted.

**V. GRIGORIADIS' DISCLOSURE OF CRINECERFONT
ANTICIPATES CLAIMS 1–4, 7–9, 11–15, AND 18 (GROUND 1)**

The Board should find that Grigoriadis anticipates '201 patent claim 1.³ DI, 22–26. “[A] prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference.” *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). Grigoriadis anticipates the claims through its disclosure of crinecerfont, a CRF1 receptor antagonist, to treat CAH, resulting in the claimed reductions in A4, as shown by Auchus.

Spruce doesn't dispute the Board's initial finding that Grigoriadis teaches the administration of a therapeutically-effective amount of crinecerfont to CAH patients. DI, 23–24; EX1006 ¶¶7, 54; EX1005 ¶¶21, 53, 54, 66. The only remaining limitations recite reducing a human's A4 level from the human's baseline and maintaining that reduction post 24 hours, which as Auchus shows, inevitably flows from and is the natural result of administering crinecerfont to treat CAH. *See In re Montgomery*, 677 F.3d 1375, 1381 (Fed. Cir. 2012) (a result is inherent if “it inevitably flows from the prior art disclosure.”).

³ Spruce does not dispute that the additional limitations in claims 2-4, 7-9, 11-15, and 18 are also disclosed in Grigoriadis. As the Petition explains, Grigoriadis meets every limitation of claims 2–4, 7–9, 11–15, and 18. Pet. 45–51.

Auchus shows that administration of crinecerfont to a CAH patient, as disclosed in Grigoriadis, reduces A4 from baseline in “a human” (and indeed, in many humans) post 24 hours. That is all the claims require, and all that is required to prove inherent anticipation. *Bristol-Myers Squibb Co. v. Ben Venue Lab’ys., Inc.*, 246 F.3d 1368, 1378 (Fed. Cir. 2001). As explained above, there is no dispute the A4 reductions in Auchus are reductions “from baseline.” Section IV.B.

A. Unrecited claim elements are irrelevant to anticipation.

Spruce’s assertion that “the petition’s inherency theory depends on employing the Grigoriadis dosing protocol” (POR, 29) attempts to inject extra requirements into the claims. That is legally wrong, as the Board and Director found. DI, 29–30, Decision, 10. Auchus is not required to replicate the clinical study of Grigoriadis Example 6. DI, 29. The relevant question is whether a POSA practicing the method of Grigoriadis—administering crinecerfont—would inherently achieve the claimed results. *Id.*, 29–30. The Board answered in the affirmative. Pet. 42–57; DI, 22–30. Spruce cites no case for its assertion that “to succeed, Petitioner must demonstrate a method found in Grigoriadis that inherently satisfies the claimed method” (POR, 29) because it is not required. *See MEHL/Biophile Int’l Corp. v. Milgraum*, 192 F.3d 1362, 1366 (Fed. Cir. 1999) (holding unclaimed differences between anticipatory reference and claims “irrelevant to the anticipation analysis”); *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1326–30 (Fed. Cir. 2020) (holding importing limitations from specification for inherent anticipation analysis improper).

Spruce presents a laundry list of alleged differences between Grigoriadis and Auchus, none of which are recited in the claims. POR, 30–39. Dosing with or without food is not a requirement of the claims. EX1047 ¶¶46–52. Dosing length or dose timing are also not claim limitations. *Id.* ¶¶48–49. Patient characteristics, e.g., women or men of certain ages, are not claim limitations. *Id.* ¶51. There are no formulation requirements in the '201 patent claims. *Id.* ¶48. And claim 1 does not recite certain dose amounts. *Id.* ¶¶48–49. These unclaimed differences are “irrelevant to the anticipation analysis.” *MEHL/Biophile*, 192 F.3d at 1366.

The case law Spruce cites does not support its attempt to inject additional limitations into the claims. POR, 30–31. *Galderma* found no inherent anticipation because the reference didn't disclose the same composition claimed in the patents-in-suit and practicing the reference's general disclosure didn't necessarily achieve the claimed efficacy limitations. *Galderma Lab'ys, L.P. v. Teva Pharms. USA, Inc.*, 799 F. App'x 838, 844–46 (Fed. Cir. 2020). *Valeant* found no anticipation because the prior art disclosure for making a compound was different from the claimed compound. *Valeant Int'l (Barbados) SRL v. Watson Pharms., Inc.*, No. 10-20526-CIV, 2011 WL 6792653, at *14 (S.D. Fla. Nov. 8, 2011), *aff'd*, 534 F. App'x 999 (Fed. Cir. 2013). *Glaxo* found no inherent anticipation because the claimed polymorphic form didn't invariably result from practicing the prior art; various chemists following the prior art protocol achieved differing results. *Glaxo, Inc. v. Novopharm Ltd.*, 830 F. Supp. 871, 874–77 (E.D.N.C. 1993), *aff'd*, 52 F.3d

1043 (Fed. Cir. 1995). Here, the claims require only using a CRF1 receptor antagonist to treat CAH in a human (as disclosed in Grigoriadis), that “necessarily” or “invariably” result in a reduction of A4 from baseline that is maintained post 24 hours (as shown in Auchus). *Galderma*, 799 F. App’x at 845; *Glaxo*, 830 F. Supp. at 877. Grigoriadis anticipates claim 1 because the claimed reductions are the “natural result” flowing from the Grigoriadis method. *Valeant*, 2011 WL 6792653, at *5.

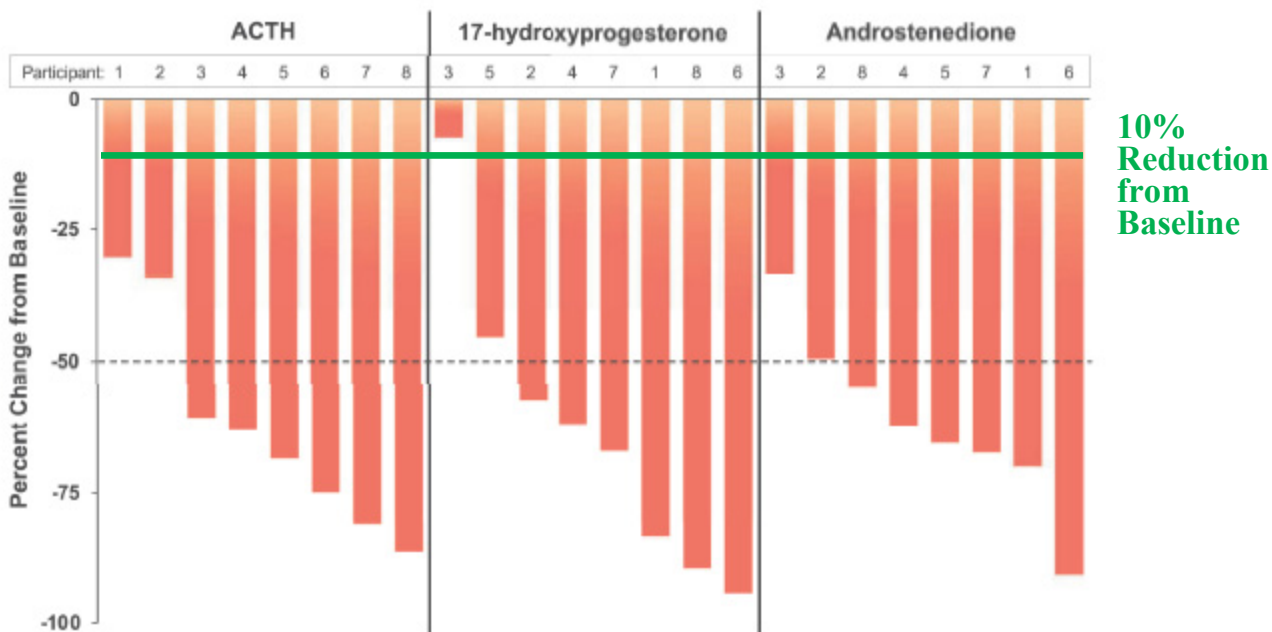
B. Auchus demonstrates the reduction in A4 from baseline inevitably flows from the disclosure in Grigoriadis.

Spruce’s argument that Auchus doesn’t show the claimed A4 reductions naturally flow from administering crinecerfont assumes *every* patient needs to achieve the claimed reductions. POR, 40–45. That is contrary to the claims, which only require “a human” to achieve the claimed A4 reductions, not every human. Auchus demonstrates inherent anticipation because at least one patient, and indeed many patients, achieved the claimed response. *See In re Montgomery*, 677 F.3d at 1384 (“For anticipation by inherency, a later-claimed invention must have necessarily resulted from the practice of a prior art reference.”); *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1352 (Fed. Cir. 2002); DI, 22–30.

Spruce’s reliance on non-precedential Board opinions (POR, 41) are distinguishable and don’t undermine the Board’s preliminary analysis or the precedential Federal Circuit authority holding inherent anticipation by “a human”

requires only one human achieve the claimed effect. DI, 30; *In re Montgomery*, 677 F.3d at 1384; *In re Cruciferous Sprout Litig.*, 301 F.3d at 1352. In *Apotex*, the Board denied institution on inherent anticipation grounds where the challenged claims recited dosing requirements that were not disclosed in the prior art. *Apotex Inc. v. Regeneron Pharms., Inc.*, No. IPR2022-01524, 2023 WL 2588222, at *15 (PTAB Mar. 10, 2023). In *Gilead*, the Board found the prior art did not disclose the claimed treatment compound or the claimed efficacy limitations. *Gilead Scis., Inc. v. United States*, No. IPR2019-01456, 2020 WL 582217, at *16–17 (PTAB Feb. 5, 2020). Here, Grigoriadis discloses all the limitations of the challenged claims. DI, 22–30.

Spruce’s assertion that Auchus does not show “any true change in hormone levels” is also wrong. POR, 44–45; EX1047 ¶¶31–42. That Auchus “was not powered to demonstrate statistical significance of a treatment effect or between-cohort difference” is irrelevant because the claims do not require statistical significance. Moreover, a POSA would understand Auchus’ A4 reductions from baseline for Cohort 4 are statistically significant and could perform a simple statistical analysis to confirm. EX1047 ¶¶44–45. *All* patients in Cohort 4 achieved a reduction in A4 from baseline. EX1047 ¶¶36–37. Consistent with Auchus, Neurocrine’s Phase III trial reported crinecerfont administration substantially reduced A4 in CAH patients. EX1046, 5, Fig.1(C); EX1047 ¶42; EX1042, 95:18–106:5.



EX1009, Fig. 4; EX1047 ¶¶36, 44–46.

VI. GRIGORIADIS’ DISCLOSURE OF CRINECERFONT AND THE A POSA’S KNOWLEDGE RENDERS CLAIMS 10, 16–17, AND 19 OBVIOUS (GROUND 2)

Spruce makes no additional arguments on obviousness of dependent claim 10 beyond its misguided arguments for Ground 1. POR, 45. As the Petition explains, a POSA would have been motivated to use a CRF1 receptor antagonist like crinecerfont to treat patients with non-classical CAH with a reasonable expectation of success. Pet. 51–52; EX1005 ¶¶82, 84.

Regarding claims 16–17, Spruce’s argument that “the petition does not even assert that Grigoriadis or Turcu discloses 14 consecutive days of repeated dosing, much less 4 weeks or 6 weeks” misses the point. Auchus reports results from dosing crinecerfont for 14 days. EX1009, 3. As previously explained, it would

have been obvious to a POSA that reduced A4 levels would be maintained for more than four weeks, or for more than six weeks, with continuous dosing. Pet. 53; EX1005 ¶¶87–88. Grigoriadis combined with the knowledge of a POSA renders claims 16 and 17 unpatentable.

Spruce’s argument that claim 19 is patentable because Grigoriadis does not disclose administering a glucocorticoid within 2 hours of the CRF1 receptor antagonist also misstates Neurocrine’s argument. POR, 46–47. As the Petition explains, Grigoriadis teaches the use of glucocorticoids as maintenance therapy for CAH patients, and that CRF1 receptor antagonists may lower the amount of glucocorticoids administered to a CAH patient, indicating co-administration. Pet. 53–54. It would be obvious to a POSA to administer a glucocorticoid concurrently or within two hours of administering the CRF1 receptor antagonist to maximize the extent of A4 reduction, and minimize the amount of glucocorticoid required. *Id.*; EX1005 ¶¶91–95.

VII. GRIGORIADIS’ AND TURCU’S DISCLOSURE OF VERUCERFONT ALONG WITH THE POSA’S KNOWLEDGE RENDERS CLAIMS 1–4 AND 7–19 OBVIOUS (GROUND 4)

Claim 1 is obvious in view of Grigoriadis’ and Turcu’s disclosure of verucerfont reducing A4 in a patient compared to placebo measurement. Pet 57–63; EX1006 ¶¶90–93; EX1008, Table 3. Spruce does not dispute that because both Grigoriadis and Turcu report the results of the same verucerfont study a POSA

would be motivated to combine their teachings. Pet. 58. As discussed above, A4 reductions compared to placebo, as reported in Turcu, are reductions “from baseline” under the Board’s construction. Section IV.B.⁴

A. Variability among patients does not undermine Grigoriadis’ and Turcu’s disclosure of the claimed A4 reductions.

Spruce’s argument that verucerfont data in Turcu is “flawed and error-filled” incorrectly conflates variability between patients with whether “a human” achieved the claimed A4 reductions. POR, 52–60. Turcu reports that 300 mg or 600 mg of verucerfont reduced A4 levels in six of the eight CAH patients studied compared to placebo over a 24-hour period after verucerfont administration. EX1047 ¶57; EX1008, Table 3. As its expert admitted, Spruce’s clinical data showed similar variability between patients for related hormones, yet Spruce characterized the data as showing “notable reductions” in A4. EX1042, 62:15–63:6; EX1039, 4671, Fig. 4.

⁴ Spruce’s reliance on the Board’s vacated decision is improper. POR, 49-52. The Director vacated that decision, and the Board has not made subsequent findings about Grigoriadis’ verucerfont disclosure. Decision, 15.

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

EX1008, Table 3.

Variability between patients is irrelevant to whether “a human” achieves an A4 reduction from baseline, and the data reflect most patients achieved the claimed reductions. EX1047 ¶¶54–56. All the claims require is that A4 levels are reduced from baseline in “the human,” i.e., *one* patient—and Turcu shows A4 levels reduced in not just one patient, but six/eight patients. EX1008, Table 3.

What Spruce calls “systemic error” in the Grigoriadis verucerfont data (POR, 57–60) simply reflect small, clinically-insignificant hormone differences in the placebo group pre-dose and between 10pm-2am (Figures 5–6 hours 1–4), a time of minimal adrenal hormone secretion. EX1047 ¶¶59–60. These small differences are apparent only because Figures 5–6 present the data as percent

change from baseline, which exaggerate these differences compared to the much larger and clinically-significant changes in the peak morning period, the time of highest adrenal production (Figures 5–6 hours 8–12). *Id.*

Fluctuation of the placebo treatment between hours 10–14 (POR, 59) does not suggest error. A POSA would understand that adrenal hormones like ACTH and 17-OHP are pulsatile, and fluctuate naturally by subject and throughout the day. EX1047 ¶¶58–64.

B. Grigoriadis' verucerfont study was appropriately designed to demonstrate the claimed reductions.

Spruce's suggestion that Grigoriadis' verucerfont study was poorly designed (POR, 61–63) is belied by the fact that this same study was published in a peer-reviewed, respected endocrinology journal. EX1008; EX1042, 48:18–49:8.

Outside of this dispute, scientists in the field found this study and its data and conclusions reliable. *Id.* Contrary to its attacks on these data here, in its own publication Spruce admitted the Turcu study showed adrenal hormones were reduced after CRF1 receptor antagonist administration. EX1039, 4677; EX1042, 74:7–75:22, 77:14–78:4.

Spruce's criticisms of the study design are irrelevant. The claims do not require a particular protocol for administering CRF₁ receptor antagonists or a specific way to measure the results. *MEHL/Biophile*, 192 F.3d at 1366; *Hospira*, 946 F.3d at 1326. That Neurocrine's verucerfont study was conducted in female

patients also does not undermine the study results. POR, 62–63. Enrolling only female patients was reasonable because ovarian production of adrenal hormones during menstruations is negligible compared to adrenal production of these hormones in CAH patients. EX1047 ¶¶72. It is also irrelevant—the claims do not require achieving the claimed A4 reductions in a particular gender.

MEHL/Biophile, 192 F.3d at 1366.

Spruce’s argument that Grigoriadis and Turcu do not disclose repeat dosing regimens (POR, 63) ignores that repeat dosing would have been obvious to a POSA. As the Petition explains, a POSA would expect a CRF1 receptor antagonist to maintain efficacy with repeat dosing. Pet. 60–62.

C. Dependent Claims 2–4 and 7–19 are obvious in light of Grigoriadis, Turcu and the knowledge of a POSA

Spruce does not dispute the obviousness of claims 2–4, 7–15, or 18 other than its arguments regarding claim 1. Accordingly, the Board should find the claims unpatentable for the unrebutted reasons stated in the petition. Pet. 62–69. Additionally, claims 16–17 and 19 are obvious considering Grigoriadis, Turcu and a POSA’s knowledge for the same reasons discussed above in Section VI. Pet. 53–55; EX1005 ¶¶87–88,91–95.

**VIII. GRIGORIADIS' DISCLOSURE OF CRINECERFONT AND
VERUCERFONT TOGETHER WITH ROMANO AND THE
KNOWLEDGE OF A POSA RENDER CLAIMS 5–6 OBVIOUS
(GROUNDS 3 AND 5)**

Spruce makes no arguments about obviousness of dependent claims 5–6 beyond its incorrect arguments for Grounds 1 and 4. POR, 47, 65–66. As the Petition explains, the combination of Grigoriadis and Romano renders these claims obvious. Pet. 55–57, 73–75; EX1005 ¶¶74–77.

Respectfully submitted,

Dated: June 20, 2024

/ Robert Oakes/
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Attorneys for Petitioner

CERTIFICATION UNDER 37 CFR § 42.24(d)

Under the provisions of 37 CFR § 42.24(d), the undersigned hereby certifies that the word count for the foregoing Petitioners' Reply to Patent Owner's Response totals 5,442, which is less than the 5,600 allowed under 37 CFR § 42.24.

Respectfully submitted,

Dated: June 20, 2024

/ Robert Oakes/
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CERTIFICATE OF SERVICE

Pursuant to 37 CFR §§ 42.6(e)(1) and 42.6(e)(4)(iii), the undersigned certifies that on June 20, 2024, a complete and entire copy of this Petitioner's Reply to Patent Owner's Response and accompanying exhibits were provided by email to the Patent Owner by serving the email correspondence addresses of record as follows:

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