UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

TEVA PHARMACEUTICALS USA, INC.
Petitioner

v.

CORCEPT THERAPEUTICS, INC.
Patent Owner

Case PGR2019-00048
Patent 10,195,214 B2

PETITIONER'S NOTICE OF APPEAL OF FINAL WRITTEN DECISION

via PTAB E2E
Patent Trial and Appeal Board

via U.S.P.S. Priority Mail Express®
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United States Patent and Trademark Office
Mail Stop 8, Post Office Box 1450
Alexandria, VA 22313-1450

via CM/ECF
United States Court of Appeals for the Federal Circuit

INTRODUCTION

Petitioner Teva Pharmaceuticals USA, Inc.'s appeal stems from the Patent Trial and Appeal Board's Final Written Decision Determining No Challenged Claims Unpatentable pursuant to 35 U.S.C. § 328 entered on November 18, 2020 (Paper 51) in the above-captioned post-grant review of United States Patent No. 10,195,214. This notice is timely filed within 63 days of the Final Written Decision. 37 C.F.R. § 90.3(a)(1).

PETITIONER'S APPEAL

Please take notice that under 35 U.S.C. §§ 141(c), 142, 329; 37 C.F.R. §§ 90.2(a), 90.3(a), and Federal Rule of Appellate Procedure and Federal Circuit Rule 15, Petitioner appeals to the United States Court of Appeals for the Federal Circuit from the Final Written Decision (Paper 51).

PETITIONER'S ISSUES ON APPEAL

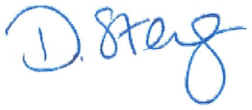
In accordance with 37 C.F.R. § 90.2(a)(3)(ii), Petitioner's issues on appeal include at least: (i) the Board's finding that claims 1–13 of the '214 patent are not unpatentable as obvious over the combination of Korlym Label and Lee; (ii) the Board's finding that claims 1–13 of the '214 patent are not unpatentable as obvious over the combination of the Korlym Label, Lee, and FDA Guidance; and (iii) any finding or determination supporting or related to these issues, including claim

constructions, as well as all other issues decided adversely to Petitioner in any order, decision, ruling, phone conference decision, and/or opinion.

Simultaneously with this submission, Petitioner is filing a true and correct copy of this Notice of Appeal with the Director of the United States Patent and Trademark Office and a true and correct copy of the same, along with the required docketing fee, with the Clerk of the United States Court of Appeals for the Federal Circuit as set forth in the accompanying Certificate of Filing.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



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Case PGR2019-00048
U.S. Pat. No. 10,195,214

CERTIFICATION OF FILING

The undersigned certifies that, along with being electronically filed through PTAB E2E, a true and correct copy of the above-captioned **PETITIONER'S NOTICE OF APPEAL OF FINAL WRITTEN DECISION** is being filed by U.S.P.S. Priority Mail Express® with the Director on November 24, 2020 at the following address:

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The undersigned also hereby certifies that a true and correct copy of the above-captioned **PETITIONER'S NOTICE OF APPEAL OF FINAL WRITTEN DECISION** and the filing fee is being filed via CM/ECF with the Clerk's Office of the United States Court of Appeals for the Federal Circuit on November 24, 2020.

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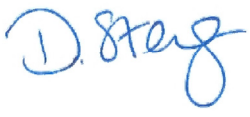

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Case PGR2019-00048
U.S. Pat. No. 10,195,214

CERTIFICATION OF SERVICE

The undersigned hereby certifies that the foregoing **PETITIONER'S NOTICE OF APPEAL OF FINAL WRITTEN DECISION** was served electronically via e-mail on November 24, 2020, in its entirety on the following:

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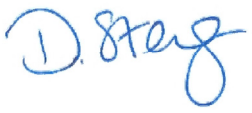

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Paper No. 51
Date: November 18, 2020

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

TEVA PHARMACEUTICALS USA, INC.,
Petitioner,

v.

CORCEPT THERAPEUTICS, INC.,
Patent Owner.

PGR2019-00048
Patent 10,195,214 B2

Before JAQUELINE WRIGHT BONILLA, *Deputy Chief Administrative Patent Judge*, ROBERT A. POLLOCK, and DAVID COTTA, *Administrative Patent Judges*.

COTTA, *Administrative Patent Judge*.

Final Written Decision

Determining No Challenged Claims Unpatentable
35 U.S.C. § 328

Dismissing Patent Owner's Motion to Exclude Evidence
37 C.F.R. § 42.64

I. INTRODUCTION

On May 7, 2019, Teva Pharmaceuticals USA, Inc., ("Petitioner") filed a Petition for Post Grant Review of claims 1–13 of U.S. Patent No. 10,195,214 B2 ("the '214 patent").[1] Paper 2 ("Pet."). On August 23, 2019, Corcept Therapeutics, Inc. ("Patent Owner") filed a Preliminary Response to the Petition.[2] Paper 8 ("Prelim. Resp."). On September 23, 2019, with the authorization of the Board, Paper 14, Petitioner filed a Reply to Patent Owner's Preliminary Response. Paper 15 ("Reply"). On October 3, 2019, also with the authorization of the Board, Patent Owner filed a Sur-Reply to Petitioner's Reply. Paper 17 ("Sur-reply"). We determined, based on the information presented in papers and evidence before us at that time, that there was a reasonable likelihood that Petitioner would prevail in showing that at least one of the challenged claims was unpatentable over the cited art. Pursuant to 35 U.S.C. § 324, the Board instituted trial on November 20, 2019. Paper 19 ("Institution Decision" or "Inst. Dec.").

After institution, Patent Owner filed a Response to the Petition (Paper 29, "PO Resp."), Petitioner filed a Reply to Patent Owners' Response (Paper 34, "Reply"), and Patent Owner filed a Sur-Reply (Paper 43, "Sur-Reply").

Patent Owner also filed a Motion to Exclude (Paper 44, "Mot."), Petitioner filed an Opposition to Patent Owner's Motion to Exclude (Paper 45, "Mot. Opp."), and Patent Owner filed a Reply in Support of its Motion to Exclude (Paper 47, "Mot. Reply").

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[1] Petitioner identifies Teva Pharmaceutical USA Inc. as the real party in interest. Pet. 65.

[2] Patent Owner identifies Corcept Therapeutics, Inc. as the real party in interest. Paper 5, 1.

On September 2, 2020, the parties presented arguments at an oral hearing. The transcript of the hearing has been entered into the record. Paper 50 ("Tr.").

We have jurisdiction under 35 U.S.C. § 6. We issue this Final Written Decision pursuant to 35 U.S.C. § 328(a) and 37 C.F.R. § 42.73. Based on the record before us, we conclude that Petitioner has not demonstrated by a preponderance of the evidence that claims 1–13 are unpatentable. We dismiss Patent Owners' Motion to Exclude as moot.

A. Related Proceedings

Petitioner and Patent Owner represent that the '214 patent was asserted in district court in *Corcept Therapeutics, Inc. v. Teva Pharmaceuticals USA, Inc*., Civil Action No. 18-3632 (SDW) (CLW) (D.N.J.). Pet. 65; Paper 5, 1. Petitioner additionally identifies pending U.S. Patent Application Nos. 16/219,564 and 15/627,368 as relating to the '214 patent. Pet. 65.

B. The '214 Patent (Ex. 1001)

The '214 patent, entitled "Concomitant Administration of Glucocorticoid Receptor Modulators and CYP3A Inhibitors," issued February 5, 2019, identifying Joseph K. Belanoff as the inventor. Ex. 1001, codes (45), (54), (72). The '214 patent discloses "methods of treating diseases including Cushing's syndrome and hormone-sensitive cancers by concomitant administration of a glucocorticoid receptor antagonist (GRA) and steroidogenesis inhibitors, and by concomitant administration of [] GRA and CYP3A inhibitors." Ex. 1001, Abstract.

The '214 patent teaches that Cushing's syndrome is a disorder caused by dysregulation of cortisol. *Id.* at 1:27–37. "Clinical manifestations of

Cushing's syndrome include abnormalities in glucose control, requirement for anti-diabetic medication, abnormalities in insulin level, abnormal psychiatric symptoms, cushingoid appearance, acne, hirsutism, and increased or excessive body weight, and other symptoms." *Id.* at 1:37–42.

The '214 patent discloses that "[o]ne effective treatment of cortisol dysregulation is to block the binding of cortisol to cortisol receptors, or to block the effect of cortisol binding to cortisol receptors." *Id.* at 1:43–45. The '214 patent also discloses that "[m]ifepristone binds to cortisol receptors, and acts to block such binding and to block the effect of cortisol on tissues." *Id.* at 1:45–49.

According to the '214 patent, "[a]nother effective treatment of cortisol dysregulation is to reduce the synthesis of cortisol, e.g., by reducing or blocking steroid synthesis." *Id.* at 1:50–53. "CYP3A enzymes play important roles in the synthesis of steroid hormones such as cortisol." *Id.* at 1:61–62. The '214 patent discloses a number of drugs that inhibit CYP3A including, *inter alia,* ketoconazole, itraconazole, and clarithromycin. *Id.* at 1:63–2:12.

The '214 patent teaches that "[t]he simultaneous, or nearly simultaneous (e.g., concomitant) presence of two drugs in a subject may alter the effects of one or the other, or both, drugs." *Id.* at 2:64–66. More specifically, "[c]oncomitant administration of different drugs often leads to adverse effects since the metabolism and/or excretion of each drug may reduce or interfere with the metabolism and/or excretion of the other drug(s), thus increasing the effective concentrations of those drugs as compared to the effective concentrations of those drugs when administered alone." *Id.* at

3:15–22. In addition, "the risk of . . . toxic effects is believed to be increased when other drugs are concomitantly administered." *Id.* at 3:24–29.

The '214 patent discloses that "CYP3A inhibitors such as, e.g., ketoconazole, may be concomitantly administered with glucocorticoid receptor modulators (GRMs) such as the GR antagonik [sic, antagonist] (GRA) mifepristone." *Id.* at 3:47–50; *see also id.* at 4:1–21. For example, the '214 patent asserts that "concomitant administration of ketoconazole and mifepristone surprisingly does not increase the risk of ketoconazole toxicity in the patient, and is believed to be safe for the patient." *Id.* at 4:51–55.

C. Challenged Claims

Petitioner challenges claims 1–13 of the '214 patent. Claim 1 is representative and is reproduced below.

> 1. A method of treating Cushing's syndrome in a patient who is taking an original once-daily dose of 1200 mg or 900 mg per day of mifepristone, comprising the steps of:
>
> reducing the original once-daily dose to an adjusted once-daily dose of 600 mg mifepristone,
>
> administering the adjusted once-daily dose of 600 mg mifepristone and a strong CYP3A inhibitor to the patient,
>
> wherein said strong CYP3A inhibitor is selected from the group consisting of ketoconazole, itraconazole, nefazodone, ritonavir, nelfmavir, indinavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, cobicistat, troleandomycin, tipranivir, paritaprevir and voriconazole.

Ex. 1001, 68:2–16.

D. The Asserted Ground of Unpatentability

Petitioner challenges the patentability of claims 1–13 of the '214 patent on the following grounds:

Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1–13	103(a)	Korlym Label,[3] Lee[4]
1–13	103(a)	Korlym Label, Lee, FDA Guidance[5]

Petitioner submits two Declarations of Dr. David J. Greenblatt (Ex. 1002; Ex. 1067) and the Declaration of Dr. Adrian Dobs (Ex. 1068) in support of its Petition and Reply to Patent Owners' Response. Patent Owner submits the Declarations of Dr. F. Peter Guengerich (Ex. 2056), Dr. Ty Carroll (Ex. 2057), and Dr. Laurence Katznelson (Ex. 2058) in support of its Response to the Petition and Sur-Reply to Petitioner's Reply.

E. 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*.).

[3] Corcept Therapeutics Inc., *Korlym™ (mifepristone) 300 mg Tablets,* (2012) (Ex. 1004, "Korlym Label").
[4] Lee et al., Office of Clinical Pharmacology Review NDA 20687 (Addendum, Korlym™, Mifepristone) (2012) (Ex. 1005, "Lee").
[5] U.S. Department of Health and Human Services, Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), *Guidance for Industry, Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling,* (2006) (Ex. 1041, "FDA Guidance").

Petitioner contends that the person of ordinary skill in the art ("POSA") "would have had an M.D., a Pharm. D., and/or a Ph.D. in pharmacology or a related discipline" as well as "at least four years of experience either treating patients with mifepristone and/or CYP3A inhibitors or, alternatively, studying drug-drug interactions involving CYP3A inhibitors." Pet. 22. Petitioner further contends that a POSA might also "have worked as part of a multidisciplinary team that included researchers and clinicians in the field and drawn upon not only her own skills, but also the specialized skills of others, to solve a given problem." *Id.* Petitioner's proposal thus embraces three distinct possibilities: 1) that the POSA is just a clinician with experience treating patients, 2) that the POSA is just a researcher with experience studying drug-drug interactions, and 3) that the POSA is part of a multidisciplinary team including researchers and clinicians.

Patent Owner contends that Petitioner's definition of the POSA is "incomplete." PO Resp. 20. According to Patent Owner, "the POSA for purposes of the '214 patent needs to include an M.D. or related medical professional with at least four years of experience treating patients with Cushing's syndrome with mifepristone." *Id.* at 22. Patent Owner does not otherwise object to Petitioner's definition and, in fact, notes that Petitioner's definition allows for the inclusion of a POSA having such experience, but does not require it. *Id.* at 21 n. 2.

We agree with Petitioner that the "problem" addressed in the '214 patent focused on "determining the extent and clinical significance of the DDI [drug-drug interaction] between mifepristone and strong CYP3A inhibitors." Pet. Reply. 3–4 (citing Ex. 1001, 3:40–57; Ex. 1035, 339). This

supports that the POSA should include someone having experience studying drug-drug interactions. In addition, we agree with Patent Owner that the POSA should have some experience treating patients with Cushing's syndrome because all of the claims of the '214 relate to treating patients with Cushing's syndrome,[6] and because both of the prior art references relied upon in connection with Ground 1, and two of the three prior art references relied upon in connection with Ground 2, relate to Cushing's syndrome. Ex. 1004, 1 (prescribing information for Korlym, a drug indicated for treating "patients with endogenous Cushing's syndrome"); Ex. 1005 (an FDA Office of Clinical Pharmacology Review Memorandum, included in the 2012 drug approval package for Korlym). *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (the prior art itself can reflect the appropriate level of ordinary skill in the art).

The definition of a POSA that best incorporates both experience with drug-drug interaction and experience treating patients is Petitioner's proposed multidisciplinary team. Patent Owner does not object to defining the POSA as part of a multidisciplinary team, so long as that team includes a person with experience treating Cushing's syndrome, which, as discussed above, is appropriate. Tr. 38. Accordingly, we define the POSA as: a multidisciplinary team that includes researchers and clinicians in the field and is able to draw upon not only the individual skills of each team member, but also the specialized skills of others to solve a given problem. The

[6] Claim 5 and its dependents are directed to "[a] method of treating symptoms associated with elevated cortisol levels." Cushing's syndrome is "caused by excess levels of cortisol." Ex. 1001, 1:31–33. Accordingly, claim 5 relates to Cushing's syndrome even if it does not specifically recite that the patient has Cushing's syndrome. All of the other claims expressly recite Cushing's syndrome.

researchers and clinicians would have an M.D., a Pharm. D., and/or a Ph.D. in pharmacology or a related discipline. The clinician would have at least four years of experience treating patients with Cushing's syndrome using mifepristone and/or CYP3A inhibitors. The researcher would have at least four years of experience studying drug-drug interactions involving CYP3A inhibitors.

Notwithstanding the parties' differences with respect to whether the POSA must have experience treating patients with Cushing's syndrome, we do not perceive our identification of the POSA to impact our patentability analysis. In this regard, we note that while some of the individuals who have offered testimony in this proceeding may lack certain attributes encompassed within the multi-disciplinary team, all are qualified to contribute to the multidisciplinary team. We further note that by incorporating experience with treating Cushing's syndrome in the definition of the POSA, as proposed by Patent Owner, we have adopted a higher level of skill than proposed by Petitioner.

F. Claim Construction

In a post-grant review, we construe the 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)." *See* Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51,340, 51,340, 51,358 (Oct. 11, 2018) (amending 37 C.F.R. § 42.200(b) effective November 13, 2018) (now codified at 37 C.F.R. § 42.200(b) (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) and its progeny. 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.*, 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)).

As discussed in more detail below, the Petition, Patent Owner's Response, the testimonial evidence, and our Institution Decision implicitly treat the claims as requiring co-administering mifepristone with a strong CYP3A inhibitor in a manner that is safe for the patient being treated. Pet. 33; *id.* at 41; Ex. 1002 ¶¶ 61, 69, 86, 105; Inst. Dec. 21; PO Resp. 29–33. In its Reply, Petitioner argues, for the first time, that "the claims do not require safety; they require only 'treating' Cushing's syndrome or its symptoms." Reply 14. We address this argument *infra* p. 16–21. Other than our discussion of claim construction in connection with this new argument, for purposes of resolving whether Petitioner has demonstrated that claims 1–13 of the '214 patent are unpatentable, we need not expressly construe any claim terms.

II. GROUND 1: OBVIOUSNESS OVER KORLYM LABEL AND LEE

Petitioner asserts that the combination of the Korlym Label and Lee renders claims 1–13 of the '214 patent obvious. Pet. 24–41. Patent Owner opposes. PO Resp. 29–77. We have considered the question of patentability in view of all the evidence and arguments presented in this proceeding.

Based on the record developed during this proceeding, we determine that Petitioner has not shown by a preponderance of the evidence that claims 1–13 of the '214 patent would have been obvious over the combination of the Korlym Label and Lee.

A. Disclosures of the Asserted Prior Art

The Korlym Label

The Korlym Label is "the original FDA-approved prescribing information for Korlym® from February 2012." Prelim. Resp. 28. It discloses that Korlym (mifepristone) is "a cortisol receptor blocker indicated to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery." Ex. 1004, 1. "The recommended starting dose is 300 mg once daily." *Id.* "Based on clinical response and tolerability, the dose may be increased in 300 mg increments to a maximum of 1200 mg once daily." *Id.* The Korlym Label cautions:

> Medications that inhibit CYP3A could increase plasma mifepristone concentrations and dose reduction of Korlym may be required.
>
> Ketoconazole and other strong inhibitors of CYP3A, such as itraconazole, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir and fosamprenavir, boceprevir, clarithromycin, conivaptan, lopinavir, mibefradil, nefazodone, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, or voriconazole may increase exposure to mifepristone significantly. The clinical impact of this interaction has not been studied. Therefore, extreme caution should be used when these drugs are prescribed in combination with Korlym. The benefit of concomitant use of these agents should be carefully weighed against the potential risks. The dose of Korlym should be limited to 300 mg and used only when necessary.

Id. at 9–10.

Lee

Lee is "an FDA Office of Clinical Pharmacology Review Memorandum, included in the 2012 drug approval package for Korlym®." Prelim. Resp. 30. Lee discloses that there is a "high potential of [ketoconazole's] concomitant use with mifepristone." Ex. 1005, 4.[7] In view of the high potential for concomitant use, Lee recommends a drug-drug interaction ("DDI") study. It states:

> The degree of change in exposure of mifepristone when co-administered with strong CYP3A inhibitors is unknown and may present a safety risk or deprive the patients on strong inhibitors the use of Mifepristone due to lack of accurate knowledge of this potential drug interaction. Thus the quantitative data for effect of ketoconazole on the pharmacokinetics of mifepristone would be beneficial to the target populations. A drug-drug interaction study with ketoconazole is recommended as a Post Marketing Requirement (PMR). The goal of this study is to get a quantitative estimate of the change in exposure of mifepristone following co-administration with ketoconazole. Based on the results of this study, the effect of moderate CYP3A inhibitors on mifepristone pharmacokinetics may need to be addressed. This will help provide more therapeutic options available to Cushing's patients and appropriate labeling of mifepristone when co-administered with CYP3A inhibitors.

Id. at 4–5.

Lee also discloses that the FDA recommended a DDI study, and that the drug-drug interaction data provided by the sponsor (Patent Owner) did not allow for "reasonable interpretation." Lee explains:

> The Agency recommended a drug-drug interaction study with a strong CYP3A4 inhibitor prior to the submission because the DDI study with a cimetidine, could not adequately address the DDI with CYP3A4 inhibitors. Instead of conducting a DDI

[7] All references to Lee are to the exhibit page numbers added by Petitioner.

> study with ketoconazole, the sponsor provided two randomly-timed concentrations of mifepristone obtained from one patient who w[as] on the concomitant use of 400 mg TID ketoconazole during [a] Phase 3 clinical trial on page 122 in [the] Clinical Pharmacology Summary. Those concentrations were 8,520 and 8,770 ng/mL (75 minutes apart between the two samples), which were more than 4 times higher than average trough concentrations (~2,000 ng/mL). However, reasonable interpretation of these concentrations was not possible, because detailed information was not provided further.

Id. at 38. Lee notes, however, that "[t]he mechanism-based inhibition of mifepristone on its own metabolism, may not allow an adequate assessment of drug-interaction at steady state or the remaining capacity of metabolizing enzyme may not be sensitive to any influence by inhibitors." *Id.* at 76.

B. The Parties' Positions

Petitioner contends that the Korlym Label and Lee disclose administering mifepristone in doses ranging from 300–1200 mg to treat Cushing's syndrome. Pet 30–31 (citing Ex. 1004, 3; Ex. 1005, 3, 11). Petitioner also contends that the Korlym Label and Lee disclose co-administration of mifepristone and a strong CYP3A inhibitor, such as ketoconazole, to treat Cushing's syndrome. *Id.* at 32 (citing Ex. 1004, 9; Ex. 1005, 37). Petitioner acknowledges, however, that "[t]he Korlym Label does not expressly teach lowering the once-daily dose from 1200 or 900 mg to 600 mg, specifically, when used in combination with strong CYP3A inhibitors . . . [i]nstead . . . recommend[ing] limiting mifepristone dosages to 300 mg per day in such cases." *Id.* (citing Ex. 1004, 6).

Petitioner contends that "arriving at the specific once-daily dose of 600 mg in conjunction with strong CYP3A inhibitors would have been merely the product of routine optimization." Pet. 32. Petitioner provides the testimony of Dr. David J Greenblatt, who testifies that,

> a POSA would have expected that co-administration of strong CYP3A inhibitors and mifepristone—at some dose—would be safe and effective to treat Cushing's syndrome and other symptoms associated with elevated cortisol levels, and it would be a matter of routine experimentation to determine precisely how much to adjust the dosage of mifepristone when co-administered with a strong CYP3A inhibitor to achieve the optimum balance of safety and therapeutic efficacy.

Ex. 1002 ¶ 61.

Petitioner contends that the POSA would have been motivated to optimize mifepristone dosage with a reasonable expectation of success for three reasons. First, "the label instructs clinicians to make dosage adjustments 'based on a clinical assessment of tolerability and degree of improvement in Cushing's syndrome manifestations.'" Pet. 33. According to Petitioner, the label thus "explicitly contemplates that physicians prescribing Korlym will optimize the dosage on a trial-and-error basis." *Id.* Second, Petitioner contends that the label "expressly permits once-daily doses up to 1200 mg per day, and skilled artisans would have known from prior studies that mifepristone was well tolerated and effective in patients with Cushing's syndrome at doses even higher than that." *Id.* (internal citations omitted). Petitioner thus argues that "a skilled artisan would have had a reasonable expectation that 600 mg could be administered safely, even in combination with a strong CYP3A inhibitor." *Id.* Third, Petitioner notes that the POSA would have known exactly how to test an optimized dosage of mifepristone using studies that were "routine in the art." *Id.* at 34.

Patent Owner argues, *inter alia,* that Petitioner "failed to show that a POSA would have had a reasonable expectation of success of developing the methods claimed in the '214 patent based on the Korlym Label and Lee, with or without FDA Guidance." PO Resp. 29. Patent Owner contends that

Dr. Greenblatt, upon whom Petitioner relied to establish a reasonable expectation of success, testified that "a POSA at the time of invention would have ***no expectation*** regarding whether co-administration of greater than 300 mg mifepristone with a strong CYP3A inhibitor would be safe and effective." *Id.* at 33. According to Patent Owner, this is dispositive because "[i]f a POSA does not have ***any*** expectation based on the prior art, he or she cannot have a reasonable expectation of successfully arriving at the claimed inventions." *Id.* at 34.

C. Analysis

This case turns on whether Petitioner has carried its burden to establish that a POSA had a reasonable expectation of success in performing the claimed methods. We begin our analysis by considering the argument, advanced by Petitioner for the first time in its Reply, that the claims do not require safety. For the reasons discussed below, we determine that Petitioner has waived this argument and that, even if it is not waived, it is not persuasive.

We then consider the three reasons identified in the Petition as to why "[a] skilled artisan would have been motivated to [optimize the treatment regimen as claimed], and the skilled artisan would have had a reasonable expectation of success of using that optimized treatment regimen to treat Cushing's syndrome." Pet. 33. As noted above, these reasons are: 1) that the Korlym label "explicitly contemplates that physicians prescribing Korlym will optimize dosage on a trial-and-error basis"; 2) that "the label expressly permits once-daily doses of up to 1200 mg per day" in monotherapy; and 3) that "a skilled artisan would have known exactly how to . . . run a clinical study to determine the extent and significance of the

drug-drug interaction" and "how to adjust the dosage based on the results of the DDI study." *Id.* at 33–35.

We next consider below Petitioner's argument that the 300 mg/day limitation recited in the Korlym Label is not supported by clinical experience. *Id*. 35–37. It appears that Petitioner relies on this argument to support the notion that the 300 mg/day limitation would not have discouraged the POSA from trying higher doses, rather than as support for an expectation that such doses would be safe and effective. *See id*. at 35 ("Nor would the 300-mg-per-day dose limitation on the Korlym Label have discouraged a skilled artisan from titrating the dose to 600 mg when used in combination with strong CYP3A inhibitors."). Nevertheless, for completeness, and so as not to omit discussion of any evidence potentially supporting a reasonable expectation of success, we consider below whether this argument supports an expectation of success.

Finally, we also address below evidence identified for the first time in Petitioner's Reply disclosing administration of more than 300 mg of mifepristone with ketoconazole.

After considering all of the evidence before us, we find that Petitioner has not carried its burden to establish a reasonable expectation of success. Because we find that Petitioner has not carried its burden, we decline to consider Patent Owner's arguments that the POSA would have expected failure in co-administering mifepristone with a strong CYP3A inhibitor and that objective indicia support the non-obviousness of the claimed methods.

1. Petitioner's new argument that the claims do not require safety

Prior to the filing of Petitioner's Reply, the parties implicitly agreed that the claims required co-administering mifepristone with a strong CYP3A inhibitor in a manner that is safe for the patient being treated. For example, when asserting a reasonable expectation of success in the Petition, the Petitioner posits that the POSA "would have had a reasonable expectation that 600 mg could be administered ***safely***, even in combination with a strong CYP3A inhibitor." Pet. 33 (emphasis added); *see also id.* at 41 (arguing that "a skilled artisan would have had a reasonable expectation that the resulting method of treatment would be successful in effectively and ***safely*** treating these conditions.") (emphasis added); PO Resp. 29–33 (arguing that the POSA would have lacked an expectation of success because there was no expectation that mifepristone could be co-administered safely with a strong CYP3A inhibitor). Similarly, Dr. Greenblatt's initial testimony (pre-institution) supporting a reasonable expectation of success states that it was "reasonably likely that 600 mg would be ***well tolerated*** and therapeutically effective when co-administered with a strong CYP3A inhibitor." Ex. 1002 ¶¶ 69, 86, 105 (emphasis added); *see also id* ¶ 61 ("[A] POSA would have expected that co-administration of strong CYP3A inhibitors and mifepristone—at some dose—would be ***safe*** and effective to treat Cushing's syndrome and other symptoms associated with elevated cortisol levels, and it would be a matter of routine experimentation to determine precisely how much to adjust the dosage of mifepristone when co-administered with a strong CYP3A inhibitor ***to achieve the optimum balance of safety and therapeutic efficacy***.") (emphasis added). Based on the parties' implicit construction of the challenged claims as requiring safety, our Institution

Decision also treated the claims as requiring safety. *See, e.g.,* Inst. Dec. 21 (crediting Dr. Greenblatt's testimony in rejecting Patent Owner's argument that there was "nothing in the prior art that would have indicated to a POSA that 600 mg of mifepristone could safely be administered to a patient concomitantly being treated with a strong CYP3A inhibitor").

In its Reply, Petitioner changed its position, arguing for the first time that "the claims do not require safety; they require only 'treating' Cushing's syndrome or its symptoms." Reply 14. Not only is this an inappropriate new argument (*see* Pet. 23 (arguing that the claims should be given their plain and ordinary meaning and that "no further claim construction is required for purposes of this PGR")), it contradicts the obviousness rationale set forth in the Petition. *See supra* p. 16–17.

Our regulations require the Petition to identify "[h]ow the challenged claim is to be construed" and "[h]ow the construed claim is unpatentable." 37 C.F.R. § 42.104(b)(3),(4). A reply is not an opportunity to start anew, to fill in gaps or to remedy omissions in a petition. *See SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1357 (2018) (explaining that "petitioner's contentions [in a petition] ... define the scope of the litigation all the way from institution through to conclusion."); *see also* Patent Trial and Appeal Board Consolidated Trial Practice Guide 73 (Nov. 2019), https://www.uspto.gov/sites/default/files/documents/tpgnov.pdf. We therefore decline to consider Petitioner's belatedly presented new argument in its Reply that the claims do not require safety. *See Acceleration Bay, LLC v. Activision Blizzard Inc*., 908 F.3d 765, 775 (Fed. Cir. 2018) (concluding that the Board did not abuse its discretion in refusing to consider portions of a reply declaration "rais[ing] a new obviousness argument for [a claim]

limitation that could have been made in the petition" but was not); *Intelligent Bio-Sys*., 821 F.3d at 1369–70 (concluding that the Board did not abuse its discretion in refusing to consider reply brief arguments advocating a "new theory" of unpatentability under 37 C.F.R. § 42.23(b)).

Even if we were to consider Petitioner's new argument regarding claim construction, we would not find it persuasive because Petitioner's obviousness rationale incorporates an expectation of safety. Irrespective of whether the claims require safety, Petitioner cannot carry its burden to establish that the claimed methods would have been obviousness without establishing that – as posited in the Petition – the POSA would have expected co-administration to be safe.

Further, if we were to consider Petitioner's new argument, we would find that the claims do require safety, as entirely consistent with what both parties unmistakably understood, as evidenced by their patentability arguments throughout the proceeding (until Petitioner's new argument in its Reply). In this regard, we note that the preambles in the independent claims at issue, i.e., in claims 1, 5, and 10, are necessarily limiting and we consider the scope of the challenged claims as a whole, including preambles, in our patentability analysis. The preamble in claim 1, for example, recites a "method of treating Cushing's syndrome in a patient who is taking an original once-daily dose of 1200 mg or 900 mg per day of mifepristone." Ex. 1001, 68:2–16. Claims 5 and 10 contain similar language relating to a patient taking an "original once-daily dose" of 1200 mg or 900 mg per day of mifepristone, although claim 5 is directed to a "method of treating symptoms associated with elevated cortisol levels," and claim 10 is directed

to a "method of controlling hyperglycemia secondary to hypercortisolism in a patient with endogenous Cushing's syndrome." *Id*. at 68:23–38, 46–63.

A claim's preamble is limiting when it is "necessary to give life, meaning, and vitality to the claim." *MBO Labs., Inc. v. Becton Dickinson & Co.*, 474 F.3d 1323, 1330 (Fed. Cir. 2007). Here, the bodies of independent claims 1, 5, and 10 all recite "reducing the original once-daily dose to an adjusted once-daily dose" and "administering the adjusted once-daily dose of 600 mg mifepristone and a strong CYP3A inhibitor to the patient." Ex. 1001, 68:5–9, 68:27–32, 68:52–57. The terms "original," "adjusted," and "patient" refer back to the preamble in the claims, i.e., the preamble language provides the antecedent basis and meaning for the "original" dose to be "adjusted," as well as "the patient," to which the claims are directed. *Eaton Corp. v. Rockwell Int'l Corp*., 323 F.3d 1332, 1339 (Fed. Cir. 2003) ("When limitations in the body of the claim rely upon and derive antecedent basis from the preamble, then the preamble may act as a necessary component of the claimed invention.").

In addition, when considering the recited methods of treatment (or controlling hyperglycemia) in a patient in the context of the specification, we interpret the recited methods to require administration of drugs in a manner that is safe for a patient. The summary section in the specification of the '214 patent, for example, states that:

> concomitant administration of a CYP3A inhibitor such as ketoconazole and a GRM such as mifepristone is believed *to be safe for the subject, and to provide the therapeutic benefits of both drugs to the subject*, and may allow the reduction in the amount of a GRM, or of a CYP3A inhibitor, administered to the subject; such reduction may reduce the risk of toxic effects of

> the CYP3A inhibitor concomitantly administered with the GRM.

Ex. 1001, 3:50–58 (emphasis added); *see id.* at 4:4–21. That disclosure, along with many other statements in the specification, clarify that safety and efficiency are important aspects of the recited methods, especially in relation to toxic effects that might preclude treatment in patients. *See also id*. at 13:1–3 (stating "Applicant discloses herein methods for the safe concomitant administration of both a glucocorticoid receptor modulator (GRM) and steroidogenesis inhibitor to a subject."), 13:10–23 (same).

Consistently, all examples in the specification evaluate safety in patients. *See id*. at 54:29–60:24 (Examples 1 and 2, referring to "safety evaluation," "safety monitoring," and "SAFETY RESULTS"), 60:24–63:48 (Example 3, describing Phase 1 clinical studies in patients and "safely administered" doses), 63:50–64:51 (Examples 4-7, noting that "liver function of the patient is not significantly compromised").

Moreover, the specification, including the abstract, repeatedly refers to the "surprising discovery" that mifepristone, at the recited levels, can be administered safely to patients concomitantly receiving a strong CYP3A inhibitor, such as ketoconazole. *See, e.g, id.* at Abstract ("Applicant has surprisingly found that GRAs may be administered to subjects receiving CYP3A inhibitors or steroidogenesis inhibitors such as ketoconazole without increasing risk adverse reactions . . providing safe concomitant administration"), 4:22–5:3 (describing how "Applicant has surprisingly discovered that mifepristone may be administered to patients concomitantly receiving ketoconazole"), 6:63–7:13 (referring to the "surprising" discovery that the recited drug combination "may provide safe and effective treatment of a patient in need of treatment"), 12:21–51; 13:10–14:40; *see also* Ex.

1002 (Declaration by Petitioner's expert witness, Dr. Greenblatt), ¶ 40 (noting that, according to the specification, Patent Owner "made the 'surprising[]' discovery that 'concomitant administration of ketoconazole and mifepristone . . . does not increase the risk of toxicity in the patient, and is believed to be safe for the patient.'") (quoting Ex. 1001, 13:67–14:3).

We interpret a claim "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)." *See* Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51,340, 51,340, 51,358 (Oct. 11, 2018) (amending 37 C.F.R. § 42.200(b) effective November 13, 2018) (now codified at 37 C.F.R. § 42.200(b) (2019)). Thus, we construe the claims in accordance with the ordinary and customary meaning, as understood by one of ordinary skill in the art reading the claims in light of the intrinsic evidence, including the claims and specification. *Id.*; *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–14 (Fed. Cir. 2005) (en banc) (stating that "the person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification"). Here, if we were to consider Petitioner's new argument that the claim do not require safety, we would find that the challenged claims and specification of the '214 patent make it clear that the recited methods of treatment or controlling hyperglycemia necessarily require reducing an original dose of mifepristone and co-administering mifepristone with a strong CYP3A inhibitor in a manner that is safe for the patient being treated.

2. Petitioner's argument that the Korlym Label instructs clinicians to make dosage adjustments based on a clinical assessment

The first reason provided by Petitioner as to why a POSA would have been motivated to optimize the treatment regimen used to treat Cushing's syndrome, and would have expected success in doing so, is that the Korlym label "instructs clinicians to make dosage adjustments 'based on a clinical assessment of tolerability and degree of improvement in Cushing's syndrome manifestations.'" Pet. 33. Thus, according to Petitioner, "the label explicitly contemplates that physicians prescribing Korlym will optimize the dosage on a trial-and-error basis." *Id.* We do not find this argument persuasive of a reasonable expectation of success in practicing the claimed methods.

Petitioner is correct that the Korlym label instructs clinicians to make dosage adjustments based on clinical assessments. It states:

> The daily dose of Korlym may be increased in 300 mg increments. The dose of Korlym may be increased to a maximum of 1200 mg once daily but should not exceed 20 mg/kg per day. Increases in dose should not occur more frequently than once every 2-4 weeks. Decisions about dose increases should be based on a clinical assessment of tolerability and degree of improvement in Cushing's syndrome manifestations. . . . Careful and gradual titration of Korlym accompanied by monitoring for recognized adverse reactions (*See Warnings and Precautions 5.1 and 5.2*) may reduce the risk of severe adverse reactions.

Ex. 1004, 3. However, as Petitioner's expert, Dr. Greenblatt, concedes, the instruction to adjust dosage based on clinical assessments appears in a portion of the label addressing the administration of Korlym in monotherapy, i.e., when giving Korlym (mifepristone) by itself to a patient, without co-administering it with another drug. Ex. 2059, 172:16–173:5.

Notably, the portion of the Korlym label addressing co-administration with CYP3A inhibitors expressly cautions against administering more than 300 mg/day of mifepristone. It states:

> Korlym should be used with extreme caution in patients taking ketoconazole and other strong inhibitors of CYP3A. . . . Mifepristone should be used in combination with strong CYP3A inhibitors only when necessary, and in such cases the dose should be limited to 300 mg per day.

Ex. 1004, 6; *see also id.* at 9–10 ("Ketoconazole and other strong inhibitors of CYP3A . . . may increase exposure to mifepristone significantly. . . . The benefit of concomitant use of these agents should be carefully weighed against the potential risks. The dose of Korlym should be limited to 300 mg and used only when necessary."). The instruction in the Korlym label to adjust the dosage to higher than 300 mg based on a clinical assessment, therefore, does not apply when Korlym is co-administered with a strong CYP3A inhibitor. *See* Ex. 2057 ¶ 66 (Dr. Carroll's testimony that the POSA would have understood the 300 mg/day limitation on co-administration to supersede the instruction to titrate up to a dose of 1200 mg/day). Accordingly, we do not find the instruction in the Korlym label to adjust the dosage based on a clinical assessment to support an expectation that Korlym could be co-administered safely with a strong CYP3A inhibitor at dosages above 300 mg/day.

3. Petitioner's argument that the POSA would expect success based on the fact that mifepristone is well tolerated at doses as high as 1200 mg/day in monotherapy

The second reason provided by Petitioner as to why a POSA would have been motivated to optimize the treatment regimen used to treat Cushing's syndrome and would have expected success in doing so is that

"the label expressly permits once-daily doses of up to 1200 mg per day" in monotherapy "and skilled artisans would have known from prior studies that mifepristone was well tolerated and effective in patients with Cushing's syndrome at doses even higher than that." Pet. 33 (citing Ex. 1004, 3 (Korlym label permitting doses up to 1200 mg/day in monotherapy); Ex. 1018, 436 (study finding that mifepristone was "well tolerated" at doses of 300, 600, and 1200 mg); Ex. 1012, 539 ("high doses of a glucocorticoid antagonist [e.g. mifepristone] may . . . alleviate the toxic effects of hypercorticolism on tissues."); Ex. 1021 (study in which mifepristone was administered at doses ranging from 200 – 1000 mg/day)). According to Petitioner, this supports that "a skilled artisan would have had a reasonable expectation that 600 mg could be administered safely, even in combination with a strong CYP3A inhibitor." *Id.*

To establish a connection between the high doses of mifepristone permitted in monotherapy and the expectation that doses above 300 mg/day would be safe when co-administered with a strong CYP3A inhibitor, Petitioner relies on the testimony of Dr. Greenblatt. *Id.* In his declaration submitted prior to institution, Dr. Greenblatt testified that because the Korlym label "expressly permits doses of up to 1200 mg per day [of mifepristone in monotherapy] . . . it was ***reasonably likely that 600 mg would be well tolerated*** and therapeutically effective when co-administered with a strong CYP3A inhibitor." Ex. 1002 ¶¶ 69, 86, 105 (emphasis added).[8] Our Institution Decision credited this testimony as supporting a

[8] The Petition cites to paragraphs 70, 87, and 106. Pet. 33. This appears to be a typographical error as the testimony in paragraphs 69, 86, and 105 relates more directly to this argument. Our analysis here thus focuses on paragraphs 69, 86, and 105. The testimony in paragraphs 70, 87, and 106 is

reasonable expectation of success. Inst. Dec. 21 (citing this testimony as the reason we were not persuaded by Patent Owner's argument that there was "nothing in the prior art that would have indicated to a POSA that 600 mg of mifepristone could safely be administered to a patient concomitantly being treated with a strong CYP3A inhibitor."). However, on the full trial record, we struggle to harmonize this pre-institution testimony with testimony Dr. Greenblatt provided after institution.

In a post-institution deposition, Dr. Greenblatt, Petitioner's expert, was asked a series of questions about a study conducted by Dat Nguyen (published after the effective filing date of the '214 patent) in which "healthy adult men received mifepristone 600 mg orally daily for 12 days (period 1) followed by mifepristone 600 mg daily plus ketoconazole 200 mg orally twice daily for 5 days (period 2)." Ex. 1034, 2371 (Nguyen study); Ex. 2059, 159:17–164:20 (Greenblatt deposition testimony). Dr. Greenblatt testified unequivocally that the POSA would have no expectation as to whether the co-administration of 600 mg of mifepristone with ketoconazole would be safe.

> [Patent Owner's Counsel]: So the Nguyen study concluded – this is on the front -- first page of Teva 1034 – that systemic exposure to mifepristone increased following multiple doses of mifepristone 600 mg daily, plus ketoconazole 200 mg twice daily, and little to no increase in adverse events occurred, correct?
>
> [Dr. Greenblatt]: Yes, you read that correctly.

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discussed *infra* in connection with Petitioner's argument that the POSA would have known how to conduct a DDI study to determine the optimum dosage.

> [Patent Owner's Counsel]: So the testing that underlied the patent showed that a dose of 600 mg of mifepristone could be safely administered with ketoconazole, correct?
>
> [Dr. Greenblatt]: Partly correct. In this study in healthy men, healthy men without the disease, which would -- who would not ordinarily be candidates for treatment, there was little or no increase in adverse events.
>
> [Patent Owner's Counsel]: Well, okay. With all those assumptions built into this, was this -- was the result set forth here that there was little to no increase in adverse events, was that result predictable?
>
> [Dr. Greenblatt]: It's -- ***the result is neither predictable or unpredictable***. It is what it is. It's the study was done as mandated by the FDA to get at the truth, and here's the outcome of the study.
>
> [Patent Owner's Counsel]: So a person of skill in the art would not have expected there to be no increase in adverse events?
>
> [Dr. Greenblatt]: The study was done to, in part, to answer that question, not to address an expectation. ***I don't believe that there would be any expectation. You don't know what's going to happen,*** which is why you do the study.
>
> [Patent Owner's Counsel]: So if the same testing had shown that a dose of 600 mg mifepristone could not be safely administered with ketoconazole, would that have been expected by a person of skill in the art?
>
> . . .
>
> [Dr. Greenblatt]: Yeah, the same answer. ***I don't think there's an expectation.*** You're doing the study to find out what the result is to get the scientific truth.

Ex. 2059, 160:9–163:2 (emphasis added) (objections omitted for readability). Thus, according to Dr. Greenblatt's deposition testimony, the

POSA would have had no expectation as to whether co-administering 600 mg/day of mifepristone with ketoconazole would be safe.

This testimony is consistent with additional testimony Dr. Greenblatt provided in his deposition about what a POSA would have expected with respect to mifepristone blood levels before a DDI study was conducted. In the declaration he submitted prior to institution, Dr. Greenblatt stated that a POSA would have "known that a wide array of outcomes – ranging from a few-percentage-point increase to a 15- or 20-fold increase [in mifepristone blood levels] – were possible" when mifepristone was co-administered with ketoconazole. Ex. 1002 ¶ 142. When asked about this statement in his deposition after institution, Dr. Greenblatt testified that the POSA would not have known beforehand where the dividing line between safe and effective and unsafe would be within the range of possible outcomes. Dr. Greenblatt testified:

> [Patent Owner's Counsel]: You -- you know, you talk about the range of outcomes from a few percentage points to a 15- to 20-fold increase, right?
>
> [Dr. Greenblatt]: Yes.
>
> [Patent Owner's Counsel]: Where in that range would a person of skill in the art think the demarcation between safe and effective and not safe and effective would be?
>
> [Dr. Greenblatt]: That judgment is not available, at least to me. I don't -- I don't think it can be reliably made.
>
> [Patent Owner's Counsel]: So a person of skill in the art would not have had an expectation as to where the dividing line would be?
>
> [Dr. Greenblatt]: In my opinion, that is correct.

Ex. 2059, 231:18–232:9 (objections omitted for readability). Thus, Dr. Greenblatt testified not only that the POSA would not have known how co-administration of mifepristone and ketoconazole would affect mifepristone blood levels, but also that the POSA would not have known what particular blood level would be safe.

Dr. Greenblatt's deposition testimony is also consistent with the testimony he provided in a declaration submitted subsequent to his deposition, in which he stated that a POSA would not have been able to say whether co-administration would be safe or unsafe. More specifically Dr. Greenblatt testified that a POSA looking at the five factors Dr. Greenblatt previously identified as affecting drug-drug interaction:[9]

> would not be able to say, one way or another, whether co-administration of 600 mg mifepristone and a strong CYP3A inhibitor was likely to be safe or unsafe. Instead, the POSA would have had to run a clinical DDI study to quantify the magnitude of the DDI. I have published articles making precisely this point.

Ex. 1067 ¶ 23; *see also* Ex. 1023 (article referenced in the above statement, in which Dr. Greenblatt stated: "we still have not achieved a predictive paradigm having accuracy sufficient to justify bypassing all, or even most, clinical DDI studies in the course of drug development").

As noted above, Dr. Greenblatt's pre-institution testimony with regard to expectations of safety is difficult to harmonize with Dr. Greenblatt's post-institution testimony. In particular, it is not clear how a POSA who would

[9] The five factors include: "(i) whether the substrate is also metabolized by other enzymes; (ii) the route of administration; (iii) the hepatic clearance of the substrate; (iv) the half-life of the substrate; (v) the extent to which the substrate is metabolized in the intestine." Ex. 1002 ¶ 33.

have had no expectation as to whether 600 mg/day of mifepristone can be safely co-administered with ketoconazole, as set forth in Dr. Greenblatt's post-institution testimony, would have found it "reasonably likely that 600 mg would be well tolerated . . . when co-administered with a strong CYP3A inhibitor," as set forth in Dr. Greenblatt's pre-institution testimony.

At oral argument, when asked to address Dr. Greenblatt's deposition testimony on the expectations of the POSA with respect to safety, Petitioner's counsel sought to limit the import of Dr. Greenblatt's testimony to "specific outcomes" and continued to assert that the POSA would have had a reasonable expectation that co-administration with 600 mg of mifepristone would be safe:

> [The Board]: Counsel, one concern I have with that argument is reconciling that with the -- with Dr. Greenblatt's deposition testimony, which is featured prominently in Patent Owner's briefing, about what the expectation would be with respect to adverse events when mifepristone is administered together with ketoconazole. Could you address that, please?
>
> [Petitioner's Counsel]: Yes, I can. Your Honor, that testimony was -- Dr. Greenblatt was being asked about specific outcomes. And his testimony has been clear since the start of this proceeding that you do not have an a priori expectation of exactly what outcome you're going to get.
>
> So the being, he's knows that you're going to end up with an increase in exposure, between a few percentage points, up to, possibly, 20-fold. The art gives you the safe range of monotherapy for mifepristone, which goes up to 2000 mg, and within that, and knowing that the majority of the drug-drug interactions end up at fivefold, or much lower, there's evidence to that in the record, Your Honor, person of ordinary skill in the art would have had a reasonable expectation that 600 mg would be safe.

> Now, would they have had an absolute predictability? No, and that's what that line of questioning goes to, it's asking specifically, would [you] have expected this, would you have expected that?

Tr. 20–21. We do not find the arguments of Petitioner's counsel regarding Dr. Greenblatt's deposition testimony to be persuasive.

While Petitioner's counsel is correct that Dr. Greenblatt was asked at his deposition (after institution) about a "specific outcome," the outcome he was asked about – co-administration of 600 mg of mifepristone with ketoconazole – was one that he had previously testified (prior to institution) would have been "reasonably likely" to be "well tolerated." Ex. 2059, 160:8–163:2 (Dr. Greenblatt's deposition testimony); Ex. 1002 ¶¶ 69, 86, 105 (Dr. Greenblatt's prior testimony). Moreover, the specific outcome on which Dr. Greenblatt was questioned was the only dose above 300 mg/day on which Dr. Greenblatt provided testimony that the POSA would have had a reasonable expectation of success in practicing the claimed methods, i.e., in treating patients safely.

Petitioner does not identify persuasive evidence that a POSA would have expected other outcomes (for example, outcomes for other doses above the 300 mg limit set forth in the Korlym label) to be safe.[10] *See generally* Pet. 33–35. Finally, the specific outcome on which Dr. Greenblatt was questioned corresponds to the dose recited in the claims of the '214 patent. Accordingly, Dr. Greenblatt's deposition testimony bears directly on

[10] Petitioner identifies 600 mg as the "next logical dose to try" after the 300 mg countenanced by the Korlym label, because "Korlym comes in 300 mg increments." Tr. 66; *see also,* Ex. 1068 ¶ 27 (Dr. Dobs testimony that 600 mg of mifepristone would be "the most reasonable choice in conducting a DDI study" because it was "the next highest dose" after 300 mg).

whether the POSA would reasonably have expected success, notwithstanding that the testimony was focused on the specific outcome of co-administration of 600 mg/day of mifepristone with ketoconazole.

With respect to Petitioner's counsel's argument during the oral hearing that there is evidence in the record that "the majority of drug-drug interactions end up at fivefold, or much lower" (Tr. 21), the Petition does not identify evidence that the POSA would have extended this teaching to drug-drug interactions involving mifepristone.[11] *See Johnston v. IVAC Corp.*, 885 F.2d 1574, 1581 (Fed. Cir. 1989) ("Attorneys' argument is no substitute for evidence."); *In re Pearson*, 494 F.2d 1399, 1405 (CCPA 1974). In addition, Dr. Greenblatt testified in his deposition that the POSA would have had no expectation as to where, within the range of outcomes from a few percentage points to a 15- to 20-fold increase in mifepristone blood levels, the line of demarcation between safe and unsafe would fall. Ex. 2059, 231:18–232:9. Accordingly, even if the POSA would have expected mifepristone/CYP3A inhibitor drug-drug interactions to "end up at fivefold, or much lower," the evidence does not support that the POSA would have concluded from this information that co-administration was reasonably likely to be safe.

Having considered all of the evidence and arguments of record, we find that Dr. Greenblatt's post-institution testimony on expectations of safety is more persuasive and more consistent with other evidence of record than his pre-institution testimony. *See, e.g.,* Ex. 1023, abstract (article authored

[11] We infer that the evidence in the record that Petitioner's counsel referred to is Exhibit 1074. Exhibit 1074 was not identified in the Petition as supporting a reasonable expectation of success. *See generally* Pet. 33–35. Nor did Dr. Greenblatt rely on Exhibit 1074 as supporting an expectation of success with respect to mifepristone's drug-drug interactions. *See* Ex. 1002 ¶¶ 69, 86, 105.

by Dr. Greenblatt stating: "we still have not achieved a predictive paradigm having accuracy sufficient to justify bypassing all, or even most, clinical DDI studies in the course of drug development"); Ex. 1070, 65:4–18 (Dr. Guengerich deposition testimony that the POSA would not have been able to predict with certainty at what dose a drug could be administered with another drug before conducting a DDI study); Ex. 1068 ¶ 26 (testimony from Dr. Dobs that "it would not have been possible for a POSA to form an expectation about the extent and clinical significance of the drug-drug interaction between mifepristone and strong CYP3A inhibitors based on a single data point" and thus a POSA would have "awaited the results of a clinical DDI study . . . and *then* formed an opinion about the extent of the DDI").

Accordingly, we credit Dr. Greenblatt's post-institution testimony on the expectations of the POSA with respect to safety over his pre-institution testimony on that subject. More specifically, we credit Dr. Greenblatt's post-institution testimony that the POSA "would not be able to say, one way or another, whether co-administration of 600 mg mifepristone and a strong CYP3A inhibitor was likely to be safe or unsafe." Ex. 1067 ¶ 23. We likewise credit Dr. Greenblatt's deposition testimony that the POSA would not have known how co-administration of mifepristone and ketoconazole would affect mifepristone blood levels or what particular blood level would be safe (Ex. 2059, 231:18–232:9) and, more generally, that the POSA would have had no expectation as to whether co-administration of 600 mg/day of mifepristone with ketoconazole would be safe (Ex. 2059, 160:8–163:2; *see also id.* at 226:7–17). We do not credit Dr. Greenblatt's testimony that the POSA would have concluded that because the Korlym label "expressly

permits doses of up to 1200 mg per day [of mifepristone in monotherapy] . . . it was reasonably likely that 600 mg would be well tolerated and therapeutically effective when co-administered with a strong CYP3A inhibitor." Ex. 1002 ¶¶ 69, 86, 105.

4. Petitioner's argument that the POSA would have known how to run a DDI study and how to adjust the dosage based on the results of that study

The third reason Petitioner provides as to why the POSA would have been motivated to optimize the treatment regimen used to treat Cushing's syndrome and would have expected success in doing so is that the POSA "would have known how to . . . run a clinical study to determine the extent and significance of the drug-drug interaction" and "how to adjust the dosage based on the results of the DDI study." Pet. 34–35. As support, Petitioner cites the testimony of Dr. Greenblatt. *Id.* (citing Ex. 1002 ¶¶ 70–71, 87–88, 106–107, and 142–143). We do not find this persuasive of an expectation of success in performing the claimed methods.

The mere ability of a POSA to conduct a DDI study does not support an expectation that such a study would have shown the interaction between two drugs to be safe. Nor does the ability to adjust dosage based on the results of a DDI study support that any dosage tested in that study would have been safe. Petitioner does not identify, and we do not find, evidence in the record to the contrary. Indeed, the evidence of record supports that the ability to conduct a DDI study and identify a dose based on that study is independent of the POSA's expectations with respect to the outcome of that study. *See e.g.,* Ex. 1002 ¶ 33 (Dr. Greenblatt testimony that "one simply does not know the precise extent or clinical significance of a specific DDI until the interaction is tested"); Ex. 1068 ¶ 26 (Dr. Dobs testimony that the

POSA would not have been able to form an expectation about the significance of the interaction between mifepristone and a strong CYP3A inhibitor based on one data point and thus the POSA would have "awaited the results of the clinical DDI study that the FDA asked Corcept to perform and *then* formed an opinion about the extent of the DDI"); Ex. 1070, 65:4–18 (Dr. Guengerich deposition testimony that the POSA would not have been able to predict with certainty at what dose a drug could be administered with another drug before conducting a DDI study).

Similarly, the fact that Lee recommended that Patent Owner conduct a DDI study with a strong CYP3A inhibitor does not itself support an expectation that the study would show doses of mifepristone above 300 mg/day to be safe when co-administered with a strong CYP3A inhibitor. As Dr. Dobs (expert witness for Petitioner) concedes, the results of this study could well have been that there was no safe dose of mifepristone that could be administered with a strong CYP3A inhibitor. Ex. 2071, 104:10–21 (deposition transcript of cross-examination of Dr. Dobs subsequent to his declaration (Ex. 1068) submitted with Petitioner's Reply). Indeed, Lee contemplates that after the DDI study with ketoconazole (a strong CYP3A inhibitor) is completed, an additional study with a moderate CYP3A inhibitor may be necessary. Ex. 1005, 38 ("DDI studies to evaluate the inhibitory effects of strong CYP3A4 inhibitor (ketoconazole is recommended) is recommended. Based on the results further evaluation to determine the effect of a moderate CYP3A4 inhibitor on mifepristone pharmacokinetics may be needed."). In unrebutted testimony, Dr. Guengerich testifies that the "the only reason to run a DDI study with a moderate CYP3A inhibitor ***after*** running a DDI study with ketoconazole is if

the first study showed that coadministration with ketoconazole causes a clinically significant increase in mifepristone exposure." Ex. 2056 ¶ 47. Lee also states that "[u]se of strong CYP3A4 inhibitors is proposed to be contraindicated by the sponsor" and that the sponsor recommended that "administration of moderate CYP3A4 inhibitors . . . be also avoided until further information is provided." Ex. 1005, 37–38. Lee's recommendation to conduct a DDI study thus does not support an expectation that the study would show co-administration to be safe.

Accordingly, we do not find that the ability of the POSA to have carried out a DDI study, or Lee's recommendation to conduct such a study, establishes that a POSA would have had a reasonable expectation of success in safely administering more than 300 mg/day of mifepristone with a strong CYP3A inhibitor when treating patients as recited in the challenged claims.

5. Petitioner's argument that the 300 mg/day limitation is not supported by clinical evidence.

Petitioner argues that the POSA would have recognized that the 300 mg/day restriction in the Korlym Label was "not put on the label because there was any evidence that higher doses would be unsafe." Pet. 35. According to Petitioner, "there *was no* evidence about the extent of the drug-drug interaction, so the 300 mg limitation was put on the label as a precautionary measure pending the completion of the Nhuyen-Mizne [DDI] study." *Id.* Although Petitioner does not identify the absence of data as a reason to expect success in co-administering more than 300 mg/day of mifepristone with a strong CYP3A inhibitor, Petitioner does make the somewhat-related contention that the "300-mg-per-day dose limitation on the Korlym Label [would not] have discouraged a skilled artisan from

titrating the dose to 600 mg when used in combination with strong CYP3A inhibitors." *Id.* at 35.

We find that the evidence supports that the caution expressed in the Korlym label was not based on clinical data showing dosages above 300 mg/day to be unsafe. In particular, Lee teaches that "[t]he degree of change in exposure of mifepristone when co-administered with strong CYP3A inhibitors is unknown," and recommends conducting a drug-drug interaction study with the goal of generating "a quantitative estimate of the change in exposure of mifepristone following co-administration with ketoconazole." Ex. 1005, 4–5. Consistent with Lee, the Korlym Label suggests that its instruction to limit the dosage of mifepristone when used together with a strong CYP3A inhibitor is based on the absence of clinical data. It states:

> Ketoconazole and other strong inhibitors of CYP3A . . . may increase exposure to mifepristone significantly. ***The clinical impact of this interaction has not been studied. Therefore, extreme caution should be used*** when these drugs are prescribed in combination with Korlym. The benefit of concomitant use of these agents should be carefully weighed against the potential risks. The dose of Korlym should be limited to 300 mg and used only when necessary.

Ex. 1004, 9–10 (emphasis added). Based on these teachings, Dr. Greenblatt testifies that "[a] POSA at the time of the claimed invention would have in fact known that the 300-mg limitation was *not* founded in clinical experience." Ex. 1002 ¶ 129. Dr. Greenblatt's testimony on this point is consistent with the Korlym Label and with Lee. Accordingly, we agree with Petitioner that the POSA would have recognized that the 300 mg limitation was not founded in clinical experience.

While we agree that the 300 mg limitation was not based on clinical experience, it was not spun out of whole cloth. We find that the POSA still

would have given that limitation weight. This finding is supported by numerous contemporaneous references repeating the caution set forth in the label. *See, e.g.,* Ex. 1030, 327 (article on using mifepristone to manage Cushing's syndrome citing Korlym label for the proposition that "[i]f used with a CYP3A inhibitor, the maximum dose should not exceed 300 mg/day"); Ex. 2012, 320 (review article on mifepristone citing Korlym label, stating: "Until additional drug-drug interaction data become available, we suggest discontinuing ketoconazole 14 days prior to initiating mifepristone, unless it is medically necessary to use these drugs in combination. In such cases, the maximum daily dose of mifepristone should be 300 mg."); Ex. 2006, 457 (article on treatment of Cushing's disease citing Ex. 2012 (which cites the Korlym label), stating "Ketoconazole and other CYP3A inhibitors could increase mifepristone levels in the blood, so discontinuing ketoconazole 14 days before starting mifepristone is advisable"); *see also,* Ex. 2035, 515 (article on the use of mifepristone to treat Cushing's syndrome, teaching "inhibitors of CYP3A . . . may increase concentrations of mifepristone with concomitant use" and [f]or this reason, these drugs should be used with extreme caution with mifepristone"); Ex. 2057 ¶¶ 58–73, 75, 76 (Dr. Carroll's testimony regarding interpretation of the caution in the Korlym label); Ex. 2058 ¶¶ 68–78, 82 (Dr. Katznelson's testimony regarding interpretation of the caution in the Korlym label).

More importantly for purposes of this decision, although the absence of data might have somewhat lessened the weight a POSA would have accorded to the caution against co-administering more than 300 mg/day of mifepristone, the absence of data does not itself support that a POSA would have expected co-administration of more than 300 mg/day of mifepristone

with a strong CYP3A inhibitor to be safe. Put another way, it is Petitioner's burden to demonstrate that the POSA would have a reasonable expectation of success in safely co-administrating to a patient doses above 300 mg/day of mifepristone with a strong CYP3A inhibitor, and the absence of data does not meaningfully contribute toward proving that the POSA would have formed such an expectation.

6. Evidence identified for the first time in Petitioner's Reply

In its Reply, Petitioner argues that the Van der Lelij thesis (Ex. 1075) "suggested that co-administration of a strong CYP3A inhibitor with more than 300 mg/day mifepristone *would* be safe." Pet. Reply 20. Petitioner contends that the Van der Lelij thesis has been publicly available since 1992 and "reports that a Cushing's syndrome patient received 1200 mg ketoconazole and 600 mg mifepristone and then 'recovered.'" *Id.* Petitioner also contends that Exhibits 1078 and 1079 (two purported prior art patent applications) disclose "co-administration of more than 300 mg mifepristone with ketoconazole." *Id.*

Patent Owner contends that Petitioner's arguments regarding the Van der Lelij thesis and Exhibits 1078 and 1079 should be disregarded because they are new arguments that should have been presented in the Petition. PO Sur-Reply 19–20. We agree.

Our rules require that a petition must identify "[t]he supporting evidence relied upon to support the challenge and the relevance of the evidence to the challenge raised, including identifying specific portions of the evidence that support the challenge." 37 C.F.R. § 42.204(b)(5). Our rules provide that we "may exclude or give no weight to the evidence where

a party has failed to state its relevance or to identify specific portions of the evidence that support the challenge" in the petition. *Id.*

Here, the requirement that Petitioner identify "[t]he supporting evidence relied upon to support the challenge" necessarily includes evidence supporting the position that the POSA would reasonably have expected success in performing the claimed methods. *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367–68 (Fed. Cir. 2016) ("It was [Petitioner's] burden to demonstrate . . . that the skilled artisan would have had a reasonable expectation of success."). More specifically, under the theory of unpatentability articulated in the Petition, Petitioner was required to identify evidence supporting that the POSA would have expected co-administration of 600 mg/day of mifepristone with a strong CYP3A inhibitor to be safe in a patient being treated according to the recited claims. Pet. 33 (arguing that the POSA "would have had a reasonable expectation that 600 mg could be administered ***safely***, even in combination with a strong CYP3A inhibitor."); *see also, infra.* 16–21 (discussing new argument in Petitioner's Reply that claims do not require safety).

Thus, to the extent Petitioner sought to rely on the Van der Lelij thesis and Exhibits 1078 and 1079 to establish that the POSA would have expected co-administration to be safe, Petitioner should have cited that evidence in its Petition. As stated in our Trial Practice Guide, "Petitioner may not submit new evidence or argument in reply that it could have presented earlier, e.g. to make out a prima facie case of unpatentability." Patent Trial and Appeal Board Consolidated Trial Practice Guide 73. Thus, it is inappropriate for Petitioner to rely on new evidence, i.e., the Van der Lelij thesis and Exhibits

1078 and 1079, for the first time in its Reply that it could have, and should have, presented earlier in its Petition.

At oral argument, Petitioner represented that it submitted the Van der Lelij thesis with its Reply to rebut Dunnigan (Ex. 2036), a prior art reference that Patent Owner cites as evidence in its Patent Owner Response that the POSA would have expected co-administration of more than 300 mg/day of mifepristone with a strong CYP3A inhibitor to be unsafe. Tr. 75 (arguing that the Van der Lelij thesis was presented to rebut Patent Owner's argument that Dunnigan was "the only case study in existence"). As noted above, Petitioner could have, and should have, cited such evidence in its Petition to make its prima facie case of unpatentability, and it would be appropriate for us to decline to consider this evidence at all.

Even if we consider the Van der Lelij thesis and Exhibits 1078 and 1079 for the purposes of assessing a reasonable expectation of success, however, we do not find them persuasive. As an initial matter, Petitioner's discussion of the Van der Lelij (Ex. 1075) and Exhibits 1078 and 1079 appears to present mere attorney argument. Pet. Reply 20. Petitioner does not explain how, nor identify persuasive evidence supporting how, if at all, the Van der Lelij thesis or Exhibits 1078 and 1079 would have impacted the expectations of the POSA. *Johnston*, 885 F.2d at 1581; *In re Pearson*, 494 F.2d at 1405.

In addition, the Van der Lelij thesis, assuming it qualifies as prior art,[12] represents at best a single data point. Ex. 1075, 138 (discussing treatment of a single patient). While Petitioner does not direct us to any

[12] Patent Owner challenges whether Petitioner has presented sufficient information to establish that the Van der Lelij thesis was publicly accessible as of the priority date of the '214 patent. Mot. 1–5.

testimony discussing the Van der Lelij thesis, in discussing another reference that provided a single data point, Petitioner's own expert, Dr. Dobs, testified: "it would not have been possible for a POSA to form an expectation about the extent and clinical significance of the drug-drug interaction between mifepristone and strong CYP3A inhibitors based on this one data point." Ex. 1068 ¶ 26 (discussing the Dunnigan reference). This supports that the Van der Lelij thesis, if considered, also would not support an expectation about the extent and clinical significance of the drug-drug interaction between mifepristone and strong CYP3A inhibitors.

With respect to Exhibits 1078 and 1079, Petitioner is correct that both disclose co-administration of more than 300 mg of mifepristone with ketoconazole in very general terms. TEVA1078 ¶ 37 (disclosing co-administration of 5–1000 mg mifepristone and 100–800 mg ketoconazole); TEVA1079 ¶¶ 47, 60, 63, 80 (disclosing co-administration of 400 mg mifepristone and ketoconazole). However, Petitioner does not adequately explain how Exhibit 1078 or 1079 establishes that the POSA would have had a reasonable expectation of success in safely treating a patient when administering 600 mg/day mifepristone with a strong CYP3A inhibitor, such as ketoconazole, as recited in the challenged claims. Similarly, Petitioner does not identify, in either of Exhibits 1078 and 1079, any specific working examples of co-administering in a patient more than 300 mg mifepristone with ketoconazole. *Johnston*, 885 F.2d at 1581; *In re Pearson*, 494 F.2d at 1405. Thus, these references lack even the single data point that Dr. Dobs testified was insufficient to support an expectation of success. Ex. 1068 ¶ 26.

Finally, and notably, Petitioner's ultimate conclusion with respect to the Van der Lelij thesis and Exhibits 1078 and 1079 is not that they would have caused the POSA to believe that co-administration would be safe, but rather that the POSA would have had no expectation regarding whether it was safe. Thus, after discussing the Van Der Lelij thesis and Exhibits 1078 and 1079, Petitioner's Reply concludes:

> Thus, a POSA aware of all pertinent prior art (as opposed to just the art cherry-picked by Corcept's attorneys) would not have expected co-administration of 600 mg and a strong CYP3A inhibitor to be dangerous. ***A POSA would not have had any particular expectation at all***; she would have simply run a routine DDI study to find the answer. TEVA1002, ¶¶70–71.

Pet. Reply. 21 (emphasis added). Accordingly, even crediting Petitioner's argument, the Van der Lelij thesis and Exhibits 1078 and 1079 do not support an expectation by a POSA that co-administering more than 300 mg/day of mifepristone with a strong CYP3A inhibitor would have been safe for the treatment of Cushing's syndrome or related symptoms in patients.

7. Conclusion with respect to expectation of success

The evidence of record supports that the POSA would have expected to be able to safely administer 300 mg/day of mifepristone with a strong CYP3A inhibitor because the Korlym Label permits co-administration of this dose. Ex. 1004, 6. However, we do not find support in the record for an expectation that administering more than 300 mg/day of mifepristone would have been safe. Indeed, the only evidence identified by Petitioner that a dose above 300 mg/day would have been safe is the pre-institution testimony of Dr. Greenblatt that, because the Korlym label "expressly permits doses of up to 1200 mg per day [of mifepristone in monotherapy] . . . it was

reasonably likely that 600 mg would be well tolerated and therapeutically effective when co-administered with a strong CYP3A inhibitor." Ex. 1002 ¶¶ 69, 86, 105.[13] For the reasons discussed *supra*, we do not credit this testimony in view of conflicting testimony by the same witness post-institution. Instead, we find that the POSA would have given weight to the 300 mg/day limitation recited in the Korlym Label and that the POSA would have had no expectation, one way or another, as to whether more than 300 mg/day of mifepristone could be safely be co-administered with a strong CYP3A inhibitor.

We recognize that absolute certainty is not required and that some level of unpredictability in the art cannot defeat a showing of a reasonable expectation of success. *See, e.g.*, *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) ("the expectation of success need only be reasonable, not absolute."). Nonetheless, when there is a high enough quantum of unpredictability – e.g., where the chance of failure is equal to the chance of success or where the prior art supports at best a cautious optimism that a particular course of action will work – the party that bears the burden of proving unpatentability may not have met its burden of showing a

[13] Dr. Greenblatt also testifies that "a POSA would have expected that co-administration of strong CYP3A inhibitors and mifepristone—at some dose—would be safe and effective to treat Cushing's syndrome." Ex. 1002 ¶ 61. We find that this testimony does not speak to whether the safe and effective dose Dr. Greenblatt expects to find would have exceeded 300 mg/day. In addition, to the extent Petitioner might argue that this testimony supports an expectation of safety for doses above 300 mg/day, we do not find this argument persuasive for the reasons discussed in connection with Dr. Greenblatt's pre-institution testimony that he expected co-administration of 600 mg/day to be "well tolerated," when also considering his post-institution testimony.

reasonable expectation of success. *See Honeywell International, Inc. v. Mexichem Amanco Holding SA DE CV,* 865 F.3d 1348, 1355 (Fed. Cir. 2017) (finding that the Board "made what amounts to a finding that one of ordinary skill would *not* have had a reasonable expectation of success" when it found that "one of ordinary skill would no more have expected failure than success"); *Sanofi v. Watson Laboratories, Inc.*, 875 F.3d 636, 647, 650 (Fed. Cir. 2017) (rejecting argument that district court "appli[ed] too high a standard for proving a reasonable expectation of success," affirming the determination that a defendant failed to prove obviousness where a person of ordinary skill in the art "would have been at best cautiously optimistic that dronedarone could reduce the risk of cardiovascular hospitalization and hospitalization for AF in the ATHENA patient population").

We determine that Petitioner has not demonstrated that a person of ordinary skill in the art would have had a reasonable expectation of success in safely co-administering more than 300 mg/day of mifepristone with a strong CYP3A inhibitor in a patient. We find that, as in *Honeywell,* the expectation of failure would have been at least equal to the expectation of success and, as in *Sanofi*, the POSA would have been "at best cautiously optimistic" that such a dose would be safe.

Absent persuasive evidence that it would have been safe to co-administer mifepristone with a CYP3A inhibitor at doses above 300 mg/day, Petitioner argues that the POSA would have arrived at an optimal dose of 600 mg/day by conducting a routine DDI study. Pet. Reply 8–17. We do not find this persuasive because the ability to arrive at the claimed invention through a particular method – in this case by conducting an allegedly routine DDI study – does not obviate the requirement to show that the POSA would

reasonably have expected a successful outcome based on prior art available at the time of filing of the patent at issue. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation*, 676 F.3d 1063, 1070 (Fed. Cir. 2012) ("While it may have been obvious to experiment with the use of the same PK profile when contemplating an extended-release formulation, there is nothing to indicate that a skilled artisan would have had a reasonable expectation that such an experiment would succeed in being therapeutically effective.").

The decision of our reviewing court in *Honeywell* is instructive in this regard. In *Honeywell*, the Board found that "the evidence presented by Patent Owner as a whole show[ed] . . . unpredictability" and "[t]hus . . . the skilled artisan would no more have expected failure . . . than would have expected success." 865 F.3d at 1355 (emphasis omitted). The Board nonetheless found that the claims at issue would have been obvious. In so doing, the Board:

> determined that, because stability in the art was entirely unpredictable, one of ordinary skill would have made no predictions at all, but rather would have expected to undertake efforts to find an optimal combination and thus that "routine testing" would have led the skilled artisan to the claimed combination.

Id. The Federal Circuit reversed, finding that the Board had made a finding of "'overall unpredictability' in the art, but then glossed over that finding with a 'routine testing' rationale because Honeywell did not persuasively prove an expectation of failure." *Id.* at 1356 (emphasis omitted). The Federal Circuit pointed to the provision in 35 U.S.C. § 103 that "[p]atentability shall not be negated by the manner in which the invention

was made" and explained that this provision "was enacted to ensure that routine experimentation does not necessarily preclude patentability." *Id.*

Here, the evidence supports that the POSA would have had no expectation as to whether co-administering dosages of mifepristone above the 300 mg/day threshold set forth in the Korlym label would be successful. In the absence of evidence supporting an expectation that dosages above 300 mg/day would be safe, we find that Petitioner has not carried its burden to establish that the POSA would have had a reasonable expectation of success in carrying out the claimed methods. *See Honeywell*, 865 F.3d at 1355 (finding that the Board made "what amounts to a finding that one of ordinary skill would *not* have had a reasonable expectation of success" when it stated that "one of ordinary skill would no more have expected failure than success"). We decline Petitioner's invitation to, in the terminology used by the *Honeywell* court, "gloss over" this finding "with a 'routine testing rationale.'" *Id.* at 1356.

Petitioner cites *Pfizer*, as support for its argument that "a skilled artisan employing 'routine testing,' . . . would have arrived at the claimed method[s]." Pet. 37; *see also id.* at 57 (citing *Pfizer* in its discussion of unexpected results). The patent at issue in *Pfizer* claimed a particular salt form – the besylate form – of the drug amlodipine. 480 F.3d at 1356. In *Pfizer*, the Federal Circuit accepted the district court's finding that, at the time of the invention, "it was generally unpredictable as to whether a particular salt would form and what its exact properties would be." *Id.* at 1364. Based on this finding, the district court concluded that the claimed salt was non-obvious because "the skilled artisan would have had no expectation of success in making a besylate salt of amlodipine because there

was no reliable way to predict the influence of a particular salt species on the active part of the compound." *Id.* The Federal Circuit reversed, explaining that it could not be the "proper standard" that "any new salt . . . would be separately patentable, simply because the formation and properties of each salt must be verified through testing." *Id.* Applying this reasoning to the present case, Petitioner contends that it cannot be the case "any new drug-drug interaction involving CYP3A inhibitors 'would be separately patentable, simply because the [extent of interaction] must be verified through testing.'" Pet. 57–58.

This argument is not persuasive because *Pfizer* did not dispense with the requirement to show a reasonable expectation of success. To the contrary, the record in *Pfizer* included evidence that in response to "tablet processing problems," Dr. James Wells, who had been assigned the project of formulating the commercial drug product, "readily compiled a list of seven alternative ions – including the besylate – each of which he expected would form an amlodipine acid addition salt." *Pfizer*, 480 F.3d at 1353, 1364. The record also included testimony from Dr. Wells that "he expected these seven amlopidine acid addition salts would show improved physiochemical characteristics over the maleate salt." *Id.* at 1364. According to the Federal Circuit, this testimony "amply reflected" a reasonable expectation of success. *Id.* In addition, the record in *Pfizer* included "a suggestion in [patentee's] supplemental filing with the FDA that it was known that the besylate salt of amlodipine would work for its intended purpose." *Id.* at 1365. The Federal Circuit thus summarized that "the evidence would convince a reasonable finder of fact that the skilled artisan would have had that reasonable expectation of success that an acid

addition salt of besylate would form and would work for its intended purpose." *Pfizer*, 480 F.3d at 1364; *see also id.* at 1367 ("our conclusion here relies on the fact that one skilled in the art would have had a reasonable expectation of success at the time the invention was made, and merely had to verify that expectation"). Here, unlike *Pfizer*, the evidence does not support an expectation of success that the POSA merely had to verify through routine testing.

Petitioner asserts that "[t]his case . . . presents a straightforward application of the principle that 'where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.'" Pet. 51 (*citing E.I Dupont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018)). This argument is not persuasive because Petitioner has not established that the "general working conditions" disclosed in the prior art encompass co-administration of 600 mg/day of mifepristone with a strong CYP3A inhibitor.

Here, the evidence of record supports that the general working conditions limited co-administration of mifepristone with a strong CYP3A inhibitor to just 300 mg/day. Ex. 1004, 6; *see also* Ex. 1030, 326–327 (article on using mifepristone to manage Cushing's syndrome citing Korlym label for the proposition that "[i]f used with a CYP3A inhibitor, the maximum dose should not exceed 300 mg/day"); Ex. 2012, 320 (review article on mifepristone citing Korlym label, stating: "Until additional drug-drug interaction data become available, we suggest discontinuing ketoconazole 14 days prior to initiating mifepristone, unless it is medically necessary to use these drugs in combination. In such cases, the maximum

daily dose of mifepristone should be 300 mg."); Ex. 2006, 457 (article on treatment of Cushing's disease citing Ex. 2012 (which cites the Korlym label), stating "Ketoconazole and other CYP3A inhibitors could increase mifepristone levels in the blood, so discontinuing ketoconazole 14 days before starting mifepristone is advisable").

Considering all of the evidence and arguments of record with respect to Ground 1, we find that Petitioner has not established by a preponderance of the evidence that a POSA would reasonably have expected co-administration of more than 300 mg of mifepristone with a strong CYP3A inhibitor to be safe for the treatment of Cushing's syndrome or related symptoms in patients. Accordingly, we find that Petitioner has not established that the combination of the Korlym Label and Lee would have rendered claims 1–13 obvious.

II. GROUND 2: OBVIOUSNESS OVER KORLYM LABEL, LEE, AND FDA GUIDANCE

Petitioner asserts that the combination of the Korlym Label, Lee, and FDA Guidance renders claims 1–13 of the '214 patent obvious. Pet. 42–46. Patent Owner opposes. PO Resp. 29–77. We have considered the question of patentability in view of all the evidence and arguments presented in this proceeding. Based on the record developed during this proceeding, we determine that Petitioner has not shown by a preponderance of the evidence that claims 1–13 of the '214 patent would have been obvious over the combination of the Korlym Label, Lee, and the FDA Guidance.

A. Disclosures of the Asserted Prior Art

The Korlym Label and Lee

The disclosures of the Korlym Label and Lee are discussed *supra* 10–11.

FDA Guidance

The FDA Guidance is a "draft guidance" document distributed by the FDA for "comment purposes" providing "recommendations for sponsors of new drug applications (NDAs) and biologics license applications (BLAs) for therapeutic biologics who are performing in vitro and in vivo drug metabolism, drug transport, and drug-drug interaction studies." Ex. 1041, 1, 4.[14] The FDA Guidance provides instruction on the design of drug-drug interaction studies. *Id.* at 9–18. More specifically, the FDA Guidance provides instruction on the design of drug-drug interaction studies where the drug being studied is a substrate of CYP enzymes. *Id.* at 13–14. The FDA Guidance states "if the investigational drug is shown to be metabolized by CYP3A and the contribution of this enzyme to the overall elimination of this drug is either substantial (>25% of the clearance pathway) or unknown, the choice of inhibitor and inducer could be ketoconazole and rifampin, respectively, because they are the most sensitive in identifying an effect of interest." *Id.* at 13.

B. Analysis

Petitioner does not rely on the FDA Guidance as providing additional evidence that the POSA would reasonably have expected success in carrying out the claimed methods. *See generally* Pet. 44–46. Rather, Petitioner

[14] All references to the FDA Guidance are to the exhibit page numbers added by Petitioner.

argues that the FDA Guidance "would have provided a skilled artisan with the motivation and all the necessary tools to perform the routine optimization that would lead to the once-daily 600 mg dose." *Id.* at 46. As support for a reasonable expectation of success, Petitioner appears to rely principally on the fact that the Korlym Label permits doses up to 1200 mg/day in monotherapy. *Id.* ("As already discussed, the Korlym Label expressly permits doses of up to 1200 mg per day, TEVA1004, 3—meaning that a POSA would have reasonably expected that 600 mg would be well tolerated and therapeutically effective for treating a patient with Cushing's syndrome."). For the reasons discussed in connection with Ground 1, we do not find this persuasive.

Accordingly, for the reasons discussed in connection with Ground 1, we determine that Petitioner has not shown by a preponderance of the evidence that claims 1–13 of the '214 patent would have been obvious over the combination of the Korlym Label, Lee, and the FDA Guidance.

III. MOTION TO EXCLUDE

Patent Owner moves to exclude Exhibit 1075, the Van der Lilij thesis, on the basis that Petitioner "has failed to offer sufficient information establishing its authenticity as a publicly accessible document as of the priority date of the '214 patent." Mot. 1. As discussed above, we recognize that Petitioner could have, and should have, submitted such evidence with its Petition and, therefore, other reasons exist for us to not consider this reference. Even if we were to consider the Van der Lilij thesis, however, it would not change our determination that Petitioner has not carried its burden to establish a reasonable expectation of success in practicing the claimed

methods, as also discussed above. Accordingly, we dismiss Patent Owner's Motion to Exclude as moot.

IV. CONCLUSION

Claims	35 U.S.C. §	Reference(s)/Basis	Claims Shown Unpatentable	Claims Not Shown Unpatentable
1–13	103	Korlym Label, Lee		1–13
1–13	103	Korlym Label, Lee, FDA Guidance		1–13
Overall Outcome				1–13

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that Petitioner not proven by a preponderance of the evidence that claims 1–13 are unpatentable;

FURTHER ORDERED that Patent Owner's Motion to Exclude is dismissed as moot;

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