

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ACCORD HEALTHCARE INC., USA, ACCORD HEALTHCARE, INC.,
INTAS PHARMACEUTICALS LTD., AMNEAL PHARMACEUTICALS
LLC, AMNEAL PHARMACEUTICALS OF NEW YORK, LLC,
AMNEAL PHARMACEUTICALS CO. INDIA PVT. LTD., APOTEX
CORP., APOTEX INC., DR. REDDY'S LABORATORIES, LTD., DR.
REDDY'S LABORATORIES, INC., GLENMARK GENERICS INC.,
USA, GLENMARK GENERICS LTD., GLENMARK
PHARMACEUTICALS LTD., PANACEA BIOTEC LTD., SUN PHARMA
GLOBAL FZE, TEVA PHARMACEUTICALS USA, INC., ZYDUS
PHARMACEUTICALS USA, INC., CADILA HEALTHCARE LTD,
LUPIN LTD., AND LUPIN PHARMACEUTICALS, INC.

Petitioners,

v.

DAIICHI SANKYO COMPANY, LIMITED AND
UBE INDUSTRIES, LTD.,
Patent Owner.

Case IPR2015-00865

Patent 8,569,325 B2¹

Before ERICA A. FRANKLIN, TINA E. HULSE, and
CHRISTOPHER G. PAULRAJ, *Administrative Patent Judges*.

HULSE, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

¹ Case IPR2015-01881 has been joined with Case IPR2015-00865.

I. INTRODUCTION

Accord Healthcare Inc., USA, Accord Healthcare, Inc., Intas Pharmaceuticals Ltd., Amneal Pharmaceuticals LLC, Amneal Pharmaceuticals of New York, LLC, Amneal Pharmaceuticals Co. India Pvt. Ltd., Apotex Corp., Apotex Inc., Dr. Reddy's Laboratories, Ltd., Dr. Reddy's Laboratories, Inc., Glenmark Generics Inc., USA, Glenmark Generics Ltd., Glenmark Pharmaceuticals Ltd., Panacea Biotec Ltd., Sun Pharma Global FZE, Teva Pharmaceuticals USA, Inc., Zydus Pharmaceuticals USA, Inc., and Cadila Healthcare Ltd. (collectively, "Petitioner") filed a Petition requesting an *inter partes* review of claims 1–26 of U.S. Patent No. 8,569,325 B2 (Ex. 1001, "the '325 patent"). Paper 10 ("Pet."). Daiichi Sankyo Company, Ltd. and Ube Industries, Ltd. (collectively, "Patent Owner") filed a Preliminary Response to the Petition. Paper 17 ("Prelim. Resp."). We authorized Petitioner to file a Reply to the Preliminary Response to address an asserted real party-in-interest issue. Paper 21; Paper 20 (sealed version). Thereafter, Patent Owner filed an authorized Surreply. Paper 24; Paper 23 (sealed version). On September 15, 2015, we instituted an *inter partes* review of claims 1–26 on one obviousness ground. Paper 28 ("Dec. Inst."), 16.

On October 5, 2015, Lupin Ltd. and Lupin Pharmaceuticals, Inc. (collectively, "Lupin") also filed a Petition requesting an *inter partes* review of claims 1–26 of the '325 patent in case IPR2015-01881 ("the -1881 case"). IPR2015-01881, Paper 3. Lupin filed a motion to join the -1881 case with this case. *Id.*, Paper 2. On January 19, 2016, we granted Lupin's Petition and its motion for joinder. *Id.*,

Paper 11. Accordingly, we terminated the -1881 case and joined that case with this case. By that time, Patent Owner had filed a Response to the Petition in IPR2015-00865. Paper 68 (“PO Resp.”). Because the Lupin Petition included two additional arguments regarding secondary considerations in its Petition, we authorized Patent Owner to file a Supplemental Response to address those arguments.

Paper 72; *see also* Paper 74 (“PO Supp. Resp.”). Petitioner and Lupin (collectively, “Petitioners”) then filed a Reply to Patent Owner’s Response and Supplemental Response. Paper 81 (“Pet. Reply”).

Patent Owner filed a motion to exclude certain exhibits and testimony submitted by Petitioners. Paper 92 (“Mot.”). Petitioners filed an opposition (Paper 97, “Mot. Opp.”) and Patent Owner filed a reply (Paper 101, “Mot. Reply”).

Patent Owner also filed observations on the cross-examinations of Petitioners’ declarants, Jack Hirsh, Ph.D. (Paper 89), Mark Saccheti, Ph.D. (Paper 90), and Randall Zusman, M.D. (Paper 96). Petitioners filed responses to each of Patent Owner’s observations. Paper 98 (Hirsh); Paper 100 (Saccheti); Paper 99 (Zusman).

An oral hearing for this proceeding was held on May 2, 2016, a transcript of which has been entered in the record. Paper 103 (“Tr.”).

We have jurisdiction under 35 U.S.C. § 6(c). This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73.

For the reasons that follow, we determine that Petitioners have shown by a preponderance of the evidence that claims 1–26 of the ’325 patent are unpatentable.

A. *Related Proceedings*

Petitioners state that the '325 patent is asserted in the consolidated action styled *Eli Lilly & Co. v. Accord Healthcare, Inc.*, No. 14-cv-00389-SEB-TAB (S.D. Ind.). Pet. 8; IPR2015-01881, Paper 3, 7–8.

We also instituted an *inter partes* review of claims of a related patent, U.S. Patent No. 8,404,703 B2 in IPR2015-00864. Case IPR2015-00864, Paper 28.

B. *The '325 Patent (Ex. 1001)*

The '325 patent relates to a method for preventing diseases caused by thrombus or embolus. Ex. 1001, Abstract. 2-acetoxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine² (“prasugrel”) possesses inhibitory activity against platelet aggregation. *Id.* at 1:33–36. Aspirin is also well known to have low inhibiting activity against platelet aggregation. *Id.* at 1:36–38. The claimed method comprises separately administering prasugrel or a pharmaceutically acceptable salt thereof, in combination with aspirin, in their pharmacologically effective amounts, to a warm-blooded animal. *Id.*, Abstract.

² 2-acetoxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno [3,2-c]pyridine is also known as “CS-747” and “prasugrel.” See, e.g., Ex. 1044, Niitsu et al., *Pharmacology of CS-747 (Prasugrel, LY640315), a Novel, Potent Antiplatelet Agent with in Vivo p2Y₁₂ Receptor Antagonistic Activity*, 31 SEMINARS IN THROMB. HEMOST., 184–185 (2005) (characterizing the recited compound as “CS-747” and “prasugrel”). We refer to the compound as prasugrel.

According to the '325 patent, the combination of prasugrel and aspirin “possess[es] excellent inhibitory activity against platelet aggregation and thrombogenesis with short onset latency and low toxicity.” *Id.* at 2:64–3:5. The combined use of the drugs results in more potent effectiveness than the use of each component alone. *Id.* at 3:25–29. Moreover, in the case where both agents cannot be mixed technically, “each component can be administered separately.” *Id.* at 3:50–52.

C. Illustrative Claim

Petitioners challenge claims 1–26 of the '325 patent. Claim 1 is illustrative and is reproduced below:

1. A method for preventing disease caused by thrombus or embolus, said method consisting of separately administering to a human in need of prevention of said disease:

- (a) 2-acetoxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients, lubricants, binders, disintegrators, emulsifiers, stabilizers, corrigents and/or diluents, and
- (b) aspirin, and one or more pharmaceutically acceptable excipients, lubricants, binders, disintegrators, emulsifiers, stabilizers, corrigents and/or diluents,

wherein said 2-acetoxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine or the pharmaceutically acceptable salt thereof, and aspirin are administered in

pharmacologically effective amounts to prevent said disease caused by thrombus or embolus by reducing thrombogenesis or by reducing platelet aggregation in said human, after both (a) and (b) have been administered.

Claims 3, 8, 15, 20, and 24, the remaining independent claims, are similar to claim 1 but recite different intended uses for administering the combination of prasugrel and aspirin in pharmacologically effective amounts.

D. Ground of Unpatentability Instituted for Trial

We instituted trial based on the following ground of unpatentability:

Claims	Basis	References
1–26	§ 103	Coniglio, ³ Bernat, ⁴ Asai, ⁵ and Koike ⁶

II. ANALYSIS

A. The Level of Ordinary Skill in the Art

The level of ordinary skill in the art is a factual determination that provides a primary guarantee of objectivity in an obviousness analysis. *Al-Site Corp. v. VSI Int’l Inc.*, 174 F.3d 1308, 1324 (Fed. Cir. 1999) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18

³ Coniglio et al., WO 99/65500, published Dec. 23, 1999 (Ex. 1003).

⁴ Bernat et al., US 5,989,578, issued Nov. 23, 1999 (Ex. 1006).

⁵ Asai et al., CS-747, *a New Platelet ADP Receptor Antagonist*, 51 ANNU. REP. SANKYO. RES. LAB. 1–44 (1999) (Ex. 1010).

⁶ Koike et al., US 5,288,726, issued Feb. 22, 1994 (Ex. 1012).

(1966) and *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991)).

Petitioners contend that a person of ordinary skill in the art would have had a Ph.D. or M.D. with several years of training or experience in the treatment of, or research and development of treatments for, cardiovascular diseases, cardiovascular conditions, or interventional cardiology. Pet. 11 (citing Ex. 1002 ¶ 28). Petitioners also assert that a person of ordinary skill in the art would be familiar with literature relating to cardiology and thrombosis research and would know how to evaluate potential drug therapies for in vitro and in vivo activity. *Id.*

In its Response, Patent Owner states that its definition is similar to Petitioners', but argues that Petitioners' definition is incorrect because it does not require practical experience in the treatment of patients. PO Resp. 5–6 (citing Ex. 2034 ¶¶ 24–25). Accordingly, Patent Owner asserts that a person of ordinary skill in the art would be a cardiologist with experience in the treatment and/or prevention of cardiovascular disease and its thrombo-embolic consequences, such as myocardial infarction and stroke. *Id.*

As an initial matter, we note the descriptions asserted by the parties suggest that the level of ordinary skill in the art is considerably high. The parties' respective definitions for a person of ordinary skill in the art are similar, except that Patent Owner would require the artisan to be a cardiologist, rather than a Ph.D. or M.D.

Based on the record as a whole, we determine that Patent Owner's definition is overly restrictive. Rather, we find that other

types of physicians, such as a hematologist, having experience in treating or developing treatments for cardiovascular blood disorders caused by thrombus or embolus, could also be considered a person of ordinary skill in the art. *See* Ex. 1002 ¶¶ 6–22; Ex. 1071 ¶ 3.

Accordingly, we find that the record as a whole supports Petitioners’ broader description of the level of ordinary skill in the art. As such, we adopt Petitioners’ statement of the level of ordinary skill in the art. We note, however, that both parties’ declarants state that their opinions would not change if the other’s definition were adopted. Ex. 1070 ¶ 12; Ex. 2034 ¶ 25.

B. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under that standard, and absent any special definitions, we give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *See In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *See In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Neither party has asserted any specific claim constructions for any claim term in this proceeding. Based on the full trial record, we determine that the construction of any claim term is not necessary for purposes of this Decision. *See Vivid Techs., Inc. v. Am. Sci. & Eng’g*,

Inc., 200 F.3d 795, 803 (Fed. Cir. 1999) (“[O]nly those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy.”).

C. *Principles of Law*

To prevail in this *inter partes* review of the challenged claims, Petitioner must prove unpatentability by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d).

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains. *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

“[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” *KSR*, 550 U.S. at 418. “[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine elements in the way the claimed new invention does.” *Id.* Moreover, a person of ordinary skill in the art must have had a reasonable expectation of success of doing so.

PAR Pharm., Inc. v. TWi Pharms., Inc., 773 F.3d 1186, 1193 (Fed. Cir. 2014).

We analyze the instituted grounds of unpatentability in accordance with the above-stated principles.

D. Obviousness over Coniglio, Bernat, Asai, and Koike

Petitioners argue that claims 1–26 are unpatentable as obvious over Coniglio, Bernat, Asai, and Koike. Pet. 29–37. Patent Owner disagrees. PO Resp. 14–47. Based on the full trial record, we determine that Petitioners have established by a preponderance of the evidence that claims 1–26 are unpatentable over the cited art.

1. Coniglio (Ex. 1003)

Coniglio relates to a method for preventing a cerebral infarction by administering to a patient a combination of an ADP-receptor blocking antiplatelet drug in combination with an antihypertensive drug. Ex. 1003, Abstract. Coniglio states the ADP-receptor blocking drugs that may be used include “clopidogrel, ticlopidine and the like.” *Id.* at 5:33–35.⁷ Moreover, Coniglio discloses that aspirin may optionally be included in the combination of the invention. *Id.* at 11:1–2. Coniglio also states that the ADP-receptor blocking antiplatelet drug, the antihypertensive agent, and optionally drugs for preventing or treating cerebral infarction “may be employed together in the same oral dosage form or in separate oral dosage forms taken at

⁷ With the exception of U.S. patents, we cite to the unique page numbers provided by the parties for submitted exhibits according to 37 C.F.R. § 42.63(d)(2)(i).

the same time.” *Id.* at 12:28–32; *see also id.* at 13:16–19 (“According to another modification, in order to more finely regulate the dosage schedule, the active substances may be administered separately in individual dosage units at the same time or carefully coordinated times.”).

2. *Bernat (Ex. 1006)*

Bernat relates to a combination of active ingredients with anti-platelet aggregation activity consisting of clopidogrel and aspirin. Ex. 1006, 1:5–8. Bernat explains that the clopidogrel-aspirin combination exhibited synergistic activity of the two active ingredients. *Id.* at 2:58–40. Bernat also states that the combination of aspirin and another thienopyridine derivative, ticlopidine, was previously disclosed in the prior art for its use as an anti-platelet aggregation agent. *Id.* at 1:45–49. According to Bernat, however, clopidogrel is about 10 to 50 times more effective than ticlopidine and exhibits a practically immediate anti-aggregation activity compared to ticlopidine. *Id.* at 2:34–41.

3. *Asai (Ex. 1010)*

Asai is a journal review article describing CS-747 (i.e., prasugrel), a platelet ADP-receptor antagonist. Ex. 1010, Title. CS-747 (2-acetoxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4, 5, 6, 7-tetrahydrothieno[3, 2-c] pyridine) is identified as an “effective platelet aggregation inhibitor with high potency, fast onset and long duration of action.” *Id.* at 3. According to Asai, CS-747 blocks ADP-mediated platelet aggregation and exhibits more potent antithrombotic effects than clopidogrel and ticlopidine. *Id.* at 13, 42. CS-747 revealed

minimal activity in general pharmacological and toxicological studies and caused no serious adverse events when administered to Caucasian male volunteers. *Id.* at 4, 13.

4. *Koike (Ex. 1012)*

Koike is directed to tetrahydrothieno[3, 2-c]pyridine derivatives and methods of using them in compositions for inhibiting blood platelet aggregation to treat or prevent thrombosis or embolisms. Ex. 1012, 1:9–14, 39:30–34. Specific examples of the most preferred compounds of the invention include 2-acetoxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4, 5, 6, 7-tetrahydrothienol[3,2-c]pyridine (i.e., prasugrel). *Id.* at 21:52–54.

5. *Analysis*

a. *Independent Claims 1, 3, 8, 15, 20, and 24*

Independent claims 1, 3, 8, 15, 20, and 24 are directed to methods “consisting of” administering pharmacologically effective amounts of 2-acetoxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4, 5, 6, 7-tetrahydrothienol[3,2-c]pyridine (“prasugrel”), aspirin, and one or more pharmaceutically acceptable excipients, lubricants, binders, disintegrators, emulsifiers, stabilizers, corrigents, and/or diluents (“pharmaceutically acceptable additives”).

Having considered the evidence and arguments by Petitioners and Patent Owner, we conclude that Petitioners have established by a preponderance of the evidence that the combined teachings of Coniglio, Bernat, Asai, and Koike would have provided a person of ordinary skill in the art at the time of the invention a reason to combine pharmacologically effective amounts of prasugrel and

aspirin, along with a pharmaceutically acceptable excipient, to treat or prevent cardiovascular diseases caused by thrombus or embolus, as recited by the challenged claims, with a reasonable expectation of success. In particular, we agree with Petitioners and their declarant, Dr. Hirsh,⁸ that the benefits of combining thienopyridine derivatives and aspirin were well known in the prior art. *Id.* at 30; Ex. 1002 ¶¶ 64–66, 71–82. For example, Bernat teaches that combining clopidogrel, a thienopyridine derivative, with aspirin improves the inhibition of thrombogenesis and platelet aggregation over using either ingredient alone. Ex. 1006, 2:48–54, 5:18–60, Tables 1 and 2; *see also* Pet. 30.

Additionally, Coniglio teaches a method for preventing the onset of a thrombotic stroke by administering to a patient a combination that includes an ADP-receptor blocking anti-platelet drug, aspirin, and a pharmaceutically acceptable additive. Ex. 1003, 5, 11, 13. In particular, Coniglio explains that the ADP-receptor blocking anti-platelet drug may be “clopidogrel, ticlopidine and the like.” *Id.* at 5. Petitioners provide persuasive declaratory evidence that a skilled artisan would have understood from Asai and Koike that prasugrel is a “like” ADP-receptor-blocking anti-platelet drug.

⁸ Dr. Jack Hirsh is a Professor Emeritus in the Division of Hematology and Thromboembolism of the Department of Medicine at McMaster University in Hamilton, Ontario. Ex. 1002 ¶ 1. He is a hematologist with more than forty-five years of experience in thrombosis research. *Id.* We recognize Dr. Hirsh as an expert in the relevant field.

Pet. 30–32 (citing Ex. 1002, Decl. of Dr. Hirsh ¶¶ 93–106). For example, Asai teaches that, like clopidogrel and ticlopidine, prasugrel blocks ADP-mediated platelet aggregation. Ex. 1010, 10–22.

Patent Owner asserts that Coniglio does not teach or suggest the claims reciting methods “consisting of” administering prasugrel and aspirin, because Coniglio’s method includes administering an antihypertensive drug. PO Resp. 11, 27; Ex. 1003, 5. Petitioners’ proposed combination of the cited references, however, does not require applying Coniglio’s method. Rather, in the combination, Coniglio is relied upon for its teaching that ADP-receptor blocking agents similar to ticlopidine and clopidogrel may also be co-administered with aspirin. Pet. 31–32. As explained persuasively by Petitioners, in combining the teachings of the prior art, Petitioners rely upon Bernat’s disclosure of a method of administering an ADP-receptor blocking agent, aspirin, and a pharmaceutically acceptable additive to successfully treat or prevent diseases caused by a thrombus or embolus, which is independent from Coniglio’s method of additionally administering an antihypertensive agent. Pet. 32; Ex. 1006, 1:5–9, 3:29–31.

We are persuaded also by Petitioners’ assertion that a person of ordinary skill in the art would have understood that Bernat chose to combine clopidogrel with aspirin, in part, based upon clopidogrel’s superior characteristics over ticlopidine, another thienopyridine derivative known to be used in combination with aspirin. *See, e.g.*, Pet. 14–16. In particular, Bernat preferred clopidogrel in the combination, explaining that, among other things, it provided a more

effective anti-platelet aggregation than ticlopidine. Ex. 1006, 2:34–36. Petitioners articulate sound reasoning, supported by the evidence, that a person of ordinary skill in the art also would have had a reason to substitute clopidogrel in Bernat’s combination with another agent exerting an even greater anti-platelet aggregation by the same mechanism, i.e., prasugrel, as taught by Asai and Koike. Pet. 5, 30–31, 48.

Patent Owner disagrees, asserting that the state of the art at the time of the invention relating to the combination of ticlopidine or clopidogrel with aspirin would not have provided a foundation for combining prasugrel with aspirin. PO Resp. 14. In support of that contention, Patent Owner refers to the physician prescribing information for the commercial forms of ticlopidine, i.e., TICLID®, and clopidogrel, i.e., PLAVIX®, contained in the 2000 edition of the Physician’s Desk Reference (“PDR”), along with the testimony of its declarant, Dr. Gibson,⁹ regarding that information. *Id.*; Ex. 2034 ¶¶ 62–63. Patent Owner and Dr. Gibson explain that the prescribing information for TICLID® “cautioned that because TICLID® prolongs bleeding time, the ‘[c]oncomitant use of aspirin and ticlopidine is not recommended.’” PO Resp. 14–15 (quoting Ex. 2021, 2672); Ex.

⁹ Dr. C. Michael Gibson is a Professor of Medicine and chief of clinical research in the cardiovascular division at Beth Israel Deaconess Medical Center, an affiliate of Harvard Medical School. Ex. 2034 ¶ 1. We recognize Dr. Gibson as an expert in the relevant field.

2034 ¶ 62. Patent Owner and Dr. Gibson explain also that the prescribing information advised that TICLID® “should be reserved for patients who are intolerant or allergic to aspirin therapy or who have failed aspirin therapy.” PO Resp. 15. (quoting Ex. 2021, 2671); *see also* Ex. 2034 ¶ 62; Ex. 2064, 2786–88. Patent Owner and Dr. Gibson assert that the drug label for PLAVIX® also cautioned about administering clopidogrel with aspirin by stating that PLAVIX® “prolongs the bleeding time” and that drugs that may induce lesions with a propensity of bleeding “(such as aspirin and other nonsteroidal anti-inflammatory drugs [NSAIDs]) *should be used with caution* in patients taking PLAVIX.” PO Resp. 15 (quoting Ex. 2022, 844); *see also* Ex. 2034 ¶ 63; Ex. 2063, 2862–63.

Additionally, Patent Owner and Dr. Gibson assert that American College of Cardiology and American Heart Association (“ACC/AHA”) medical guidelines available at the time of the invention recommended ticlopidine and clopidogrel as alternatives to aspirin and not as adjunctive therapy. PO Resp. 15–16; Ex. 2034 ¶ 64 (citing Ex. 2023, 999 [unstable angina or non-ST elevation MI] and Ex. 2036, 904 [acute MI]). Further, Patent Owner and Dr. Gibson acknowledge that the guidelines published by the American College of Chest Physicians (“ACCP”) in 1999 “recommended use of ticlopidine and aspirin after angioplasty, but did not recommend use of clopidogrel and aspirin.” PO Resp. 16; Ex. 2034 ¶ 65; Ex. 2024, 59–60. According to Patent Owner, that guideline demonstrates that it would not have been obvious to simply substitute one thienopyridine for another. PO Resp. 16. As additional support for that contention,

Patent Owner asserts that Petitioners' declarant, Dr. Hirsh, testified that he was not aware "of any clinical guidelines published by anyone prior to the year 2000 that said that clopidogrel and aspirin should be used together for the treatment of any cardiovascular disorder." *Id.* (quoting Ex. 2029, 70:17–22).

Having considered the arguments and evidence, we do not agree with Patent Owner's assertion that the state of the art relating to the combination of ticlopidine or clopidogrel with aspirin would not have supported a reason for combining prasugrel with aspirin. *See* PO Resp. 14. In particular, we find that the prescribing information contained in the PDR addressing ticlopidine and clopidogrel in combination with aspirin may be seen as an acknowledgment regarding the practice of administering either ticlopidine or clopidogrel with aspirin. Based upon known bleeding risks associated with those drugs, the PDR included an advisory for practitioners to use caution when administering those combined therapies. Ex. 2021, 2671 (explaining that drugs, such as aspirin, that might induce lesions with a propensity to bleed "should be used with caution in patients on TICLID"); Ex. 2022, 844 (explaining that drugs, such as aspirin, that might induce lesions with a propensity to bleed "should be used with caution in patients taking PLAVIX"). In other words, the PDR provides a caution (not a prohibition) regarding a known practice of administering ticlopidine or clopidogrel with aspirin.

Similarly, to the extent that the ACC/AHA practice guidelines address the combination of aspirin with either ticlopidine or clopidogrel, the reference explains that because the mechanisms of the

antiplatelet effects of aspirin differ from the antiplatelet effects of ticlopidine or clopidogrel, “a potential exists for additive benefit with the combination.” Ex. 2023, 1002. Recognizing this potential, the reference further explains that a randomized trial was being conducted in which patients who successfully received a stent received either 500 mg ticlopidine or 75 mg clopidogrel, in addition to 100 mg aspirin, for four weeks. *Id.* As for the ACCP guidelines, Patent Owner and Dr. Gibson acknowledge that those guidelines recommend using ticlopidine and aspirin after angioplasty. PO Resp. 16; Ex. 2034 ¶ 65; *see also* Ex. 2024, 59–60. Regarding Patent Owner’s and Dr. Gibson’s assertion that the reference does not “recommend” the use of clopidogrel and aspirin, we note that the reference does not consider that combination at all, and thus does not make a recommendation for or against the combination. Ex. 2024, 59–60.

We remain unpersuaded by Patent Owner’s assertion that Petitioners’ declarant, Dr. Hirsh, testified that he was not aware of any clinical guidelines published at the time of the invention that clopidogrel and aspirin should be used together. PO Resp. 16. It is apparent from the testimony of Dr. Gibson, Patent Owner’s declarant, that even absent such guidelines, physicians used the combination of clopidogrel and aspirin at the time of the invention. *See* Ex. 1069, 64:23–65:12; Ex. 2034 ¶ 66 (testifying that he had “used [the combination of] clopidogrel and aspirin” before December 2000).

Patent Owner next contends that there was no known problem with prasugrel that would have caused a person of ordinary skill in the art to use it with aspirin. PO Resp. 17–21; Ex. 2034 ¶¶ 21, 88. Patent

Owner thus acknowledges that, at the time of the invention, physicians combined ticlopidine or clopidogrel with aspirin to address known problems with administering either ADP antagonist alone. Specifically, Patent Owner and Dr. Gibson assert that because ticlopidine is a weak anti-platelet agent, and aspirin functions by a different mechanism of antiplatelet action, “physicians began using ticlopidine with aspirin” to provide an improved antiplatelet therapy. PO Resp. 18; Ex. 2034 ¶ 88. Patent Owner also asserts that Bernat taught that “clopidogrel’s inhibition of platelet aggregation and thrombus formation could be improved by using the drug with aspirin.” *Id.* at 19; Ex. 1006, Tables 1 and 2. Further, Patent Owner and Dr. Gibson assert that “the use of aspirin with clopidogrel and ticlopidine was a way to address [a] non-responder problem and ensure that all patients receive some antiplatelet effect.” PO Resp. 19; Ex. 2034 ¶ 89.

In any event, according to Patent Owner, “the improved properties of prasugrel relative to clopidogrel and ticlopidine meant that it did not need aspirin.” PO Resp. 18; Ex. 2034 ¶ 21(b)–(c). In particular, Patent Owner asserts that “the greater potency of prasugrel would have provided the [person of ordinary skill in the art] with a reason to use prasugrel on its own rather than using it with aspirin.” PO Resp. 20 (citing Ex. 2034 ¶¶ 90–96). According to Patent Owner and Dr. Gibson, a person of ordinary skill in the art also “would have recognized that monotherapy can have significant advantages over multi-drug therapy, including avoiding drug-drug interactions and

limiting exposure to off-target side effects from one of the agents.”
PO Resp. 20–21; Ex. 2034 ¶ 96.

Having considered the arguments and evidence, we are not persuaded that the improved properties of prasugrel would have overcome the reasons established by Petitioners’ evidence, discussed above, to combine prasugrel and aspirin. That is, a person of ordinary skill in the art would have administered prasugrel and aspirin to provide a therapy that inhibits platelet aggregation by two mechanisms of action, as previously provided by therapies combining either ticlopidine or clopidogrel with aspirin. Thus, although we agree with Patent Owner that “monotherapy can have significant advantages over multi-drug therapy,” it was known in the art that a therapy combining an ADP-receptor binding antiplatelet drug with aspirin provides a beneficial effect. Further, a person of ordinary skill in the art would have had an additional reason to substitute prasugrel for clopidogrel in Bernat’s method based upon Asai’s teaching that, in addition to providing greater potency than clopidogrel, prasugrel is beneficially “less toxic” and has a “fast onset.” Ex. 1010, 3–4; Pet. 31. Indeed, in Bernat, clopidogrel was lauded, in comparison to ticlopidine, for similar reasons. *See* Ex. 1006 2:34–41, 60–62 (describing clopidogrel, as compared to ticlopidine, as more effective in terms of potency, exhibiting more immediate anti-aggregation activity in terms of onset, and as being “not very toxic”).

Patent Owner asserts also that “the prior art taught away from using prasugrel and aspirin due to the anticipated bleeding risk.” PO Resp. 22. For example, Patent Owner contends that the teachings in

Coniglio and Bernat relating to the combination of ticlopidine or clopidogrel with aspirin would not have suggested the use of prasugrel with aspirin to the person of ordinary skill in the art “because the [person of ordinary skill in the art] would have sought to avoid the risk of bleeding expected from the use of aspirin with prasugrel.” *Id.* at 29. Patent Owner also asserts that Asai and Koike taught away from that combination by teaching that prasugrel is 10-fold more potent than clopidogrel, with a more rapid onset and long-lasting antiplatelet effect. *Id.* at 29–31. According to Patent Owner and Dr. Gibson, a person of ordinary skill in the art would recognize that “the more potent the antiplatelet therapy, the greater the risk of bleeding.” *Id.* at 23; Ex. 2034 ¶¶ 21(g), 51–53; Ex. 1010, 16.

Although we agree that a person of ordinary skill in the art would have recognized a bleeding risk with the use of prasugrel, such risk was also known with respect to administering ticlopidine, clopidogrel, and aspirin, whether used alone or together. Indeed, as Patent Owner has acknowledged, antithrombotic agents, such as antiplatelet agents, “necessarily increase the risk of bleeding, because the same mechanism that prevents formation of a harmful clot can also prevent formation of a helpful one, and thus create a safety risk.” PO Resp. 22–24 (citing Ex. 2034 ¶ 42). Also, as Patent Owner has recognized, “aspirin necessarily causes bleeding because both bleeding and antithrombotic effects result from platelet inhibition.” *Id.* at 24 (citing Ex. 2034¶ 55). As discussed above, practitioners were cautioned about the bleeding risk associated with those drugs, providing them with an opportunity to weigh such risk and make an

effort to decrease that risk when prescribing those antiplatelet agents alone or in combination. As discussed below, a preponderance of the evidence indicates that a person of skill in the art would have the requisite skill to assess and address such risk in a medically acceptable manner through, for example, dosing adjustments.

Moreover, we disagree with Patent Owner's assertion that Asai and Koike teach away from combining prasugrel and aspirin. Indeed, neither of those references addresses that combination. Rather, Asai teaches that prasugrel exhibits more potent antithrombotic effects than clopidogrel or ticlopidine, with no serious adverse effects. Ex. 1010, 13, 42. Koike identifies prasugrel as one of its "most preferred" tetrahydrothieno[3, 2-c]pyridine derivatives for use in compositions for inhibiting blood platelet aggregation to treat or prevent thrombosis or embolisms. Ex. 1012, 1:9–14, 21:52–54, 39:30–34.

Based on the combined teachings of the cited prior art, we find that a person of ordinary skill in the art would have followed the rationale in Bernat of selecting the more potent, and preferred ADP-receptor-blocking anti-platelet drug, i.e., prasugrel, as disclosed by Asai and Koike, to combine with aspirin to provide a comprehensive anti-platelet therapy. Doing so would have been consistent with Coniglio's teaching that an ADP-receptor blocking agent such as ticlopidine, clopidogrel, and the like, i.e., prasugrel, may be administered together to treat thrombosis. *See, e.g., Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 719 F.3d 1346, 1351 (Fed. Cir. 2013) (recognizing a reason to modify a well-known combination therapy of two drugs having different mechanisms of action by substituting one

drug in the combination with a similar new drug having its same mechanism of action).

Patent Owner also asserts that a person of ordinary skill in the art would not have had a reasonable expectation of successfully providing a therapeutic benefit by combining prasugrel and aspirin “without creating an unacceptable risk of bleeding.” PO Resp. 33–34 (citing Ex. 2034 ¶¶ 21(n), 86). According to Patent Owner, there is a possibility that adding aspirin to prasugrel may result in too much antiplatelet potency that can “overshoot the ‘sweet spot’ between the balance of safety and efficacy, providing little benefit (if any) in terms [of] efficacy but risking further bleeding side effects.” *Id.* at 33 (citing Ex. 2034 ¶¶ 21(1), 51–53 and Fig. 1; Ex. 2029, 18:3–7).

Although a skilled artisan may not have been able to predict absolutely whether a dosage of prasugrel and aspirin will treat a disease caused by a thrombus or embolus without an undesirable bleeding event, absolute predictability is not the standard in an obviousness analysis. *In re O’Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). Rather, the proper inquiry focuses on reasonable expectations that a skilled artisan would gain from the knowledge in the art, along with the teachings or suggestions of the combined prior art. *Id.* at 903–904.

Based upon the teachings of the cited references, and the testimony regarding the skill in the art at the time of the invention, we determine that a preponderance of the evidence supports Petitioners’ assertion that a person of ordinary skill in the art would have had a reasonable expectation of successfully administering pharmaceutically

effective amounts of prasugrel and aspirin to prevent and/or treat blood clots. As Patent Owner has acknowledged, the potency of prasugrel was well characterized by Asai and Koike. PO Resp. 29–31. The relationship between potency and bleeding risk was also appreciated. *Id.* at 23; Ex. 2034 ¶¶ 21(g), 51–53. Additionally, the level of ordinary skill in the art was high. As discussed above, a person of ordinary skill in the art would have had a Ph.D. or M.D., with several years of training or experience in the treatment of, or research and development of treatments for, cardiovascular diseases, cardiovascular conditions, or interventional cardiology. That person also would be familiar with literature relating to cardiology and thrombosis research and would know how to evaluate potential drug therapies.

Further, Dr. Hirsh provided persuasive testimony that, at the time of the invention, a person of ordinary skill in the art “would have known to adjust the dose of prasugrel appropriately to mitigate the potential for any additional bleeding risks,” when substituting prasugrel for clopidogrel in Bernat’s combined therapy that included aspirin. Ex. 1070 ¶ 77. Patent Owner and Dr. Gibson do not contend otherwise. *See* PO Resp. 40 (asserting that it would have been “illogical” to adjust the dose of a prasugrel and aspirin therapy to replicate the effect of clopidogrel because it would only offer an essentially duplicative therapy).

Even if an “adjusted” dose of prasugrel and aspirin provided the same potency as an otherwise effective dosage of clopidogrel and aspirin, that does not negate the fundamental reason discussed for

combining an ADP-receptor-blocking antiplatelet drug like prasugrel with aspirin with a reasonable expectation of successfully treating or preventing thrombosis or embolism using drugs with different mechanisms of action. *See In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004) (stating a reason to combine does not require a finding that such combination is “the preferred, or more desirable combination”).

Nor does a dosage adjustment negate the potentially advantageous non-potency related benefits provided by prasugrel, e.g., fast onset and lower toxicity. Ex. 1010, 3–4. Indeed, Patent Owner and Dr. Gibson explained that a person of ordinary skill in the art had the skill to determine a safe and effective dosage amount for prasugrel and aspirin therapy using a “traditional method.” Ex. 1069, 16:23–18:5. For the foregoing reasons, we find that a preponderance of the evidence establishes that a person of ordinary skill in the art at the time of the invention would have appreciated the bleeding risk associated with administering prasugrel and aspirin and would have had the ability to determine pharmaceutically safe and effective dosage amounts for those drugs to treat or prevent a disease caused by a thrombus or embolus with a reasonable expectation of success.

b. Dependent Claims

Dependent Claims 2, 7, 9, 10, 11, 16, 21, 25, and 26

Dependent claims 2, 7, 9, 10, 11, 16, 21, 25, and 26 add the limitation “wherein the pharmaceutically acceptable salt is a hydrochloride.” Petitioners assert that Koike discloses the hydrochloride salt of prasugrel for use in anti-aggregation therapy. Pet. 33 (citing Ex. 1012, 13:43–63, 21:52–55, 28:14–21).

Additionally, Petitioners assert that Coniglio discloses using the salt forms of thienopyridine derivatives, including the hydrochloride salt. *Id.* (citing Ex. 1003, 12:16–21) (stating that “[r]eferences to the base substances are therefore intended to include those common salts known to be substantially equivalent to the parent compound”); *see also id.* (citing Ex. 1003, 4:34–35) (disclosing the hydrochloride salt as a “pharmaceutically acceptable salt”). Based on those disclosures, Petitioners assert that it would have been obvious to a person of ordinary skill in the art to use the hydrochloride salt of prasugrel because such use was known to be pharmaceutically acceptable. *Id.*

Patent Owner asserts that a person of ordinary skill in the art “would not have had a reason to use a salt form of prasugrel, much less the hydrochloride in particular.” PO Resp. 35. According to Patent Owner and its declarant, Dr. Myerson, “in evaluating drug substances for products that are suitable for appropriate delivery to a patient, one would have had no way to predict in advance whether a given salt would improve upon the free base or which salt, if any would do so.” *Id.* (citing Ex. 2048 ¶¶ 19–28). Additionally, Patent Owner asserts that the prior art did not contain any express description of prasugrel hydrochloride, and refers to Dr. Myerson’s explanation that Koike describes only prasugrel and “pharmaceutically acceptable salts thereof.” *Id.* at 36; Ex. 2048 ¶ 36.

Having considered the arguments and evidence, we agree with Petitioners that a person of ordinary skill in the art would have known that the hydrochloride salt of prasugrel may be used in a pharmaceutical formulation of the drug, as it was known to be a

pharmaceutically acceptable salt based, at least, upon the teaching of Koike that a salt of its compounds, including prasugrel, can be treated with an acid, such as hydrochloric acid. *See* Ex. 1012, 13:43–63, 21:52–55, 28:14–21.

Moreover, the claim limitation requiring the salt to be a hydrochloride relates back to an independent claim recitation of administering “2-acetoxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c] pyridine *or* a pharmaceutically acceptable salt thereof.” *See, e.g.*, Ex. 1001, independent claim 1 (emphasis added); *accord* independent claims 3, 8, 15, 20, 24. In other words, administering a pharmaceutically acceptable salt is an *alternative* requirement to administering the 2-acetoxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c] pyridine as a free base. The dependent claims do not further limit the method to administering only the specific salt forms. As acknowledged by Patent Owner, both prior art references that describe prasugrel, Asai and Koike, disclose using the free base form of prasugrel. PO Resp. 36.

Dependent Claims 6, 9, 14, and 19 and Independent Claim 8

Dependent claims 6, 14, and 19 require that the diseases caused by the thrombus or embolus are due to angioplasty, endarterectomy or stent therapy. Independent claim 8 and claim 9, which depends from claim 8, recites “treating a patient undergoing stenting or angioplasty.” Petitioners assert that a person of ordinary skill in the art would have understood that prasugrel may be used in those patients based upon Coniglio’s disclosure that ADP-receptor blocking

antiplatelet drugs such as “ticlopidine, clopidogrel and the like” may be employed in secondary prevention of ischemic events, including in patients who have had percutaneous transluminal coronary angioplasty. Pet. 28 (citing Ex. 1003, 2:9–15; Ex. 1002 ¶ 107).

Patent Owner asserts that a person of ordinary skill in the art would have expected each of the procedures recited in claims 6, 8, 9, 14, and 19 “to increase the risk of bleeding, and thus would not want to use a potent therapy like prasugrel with aspirin under such circumstances.” PO Resp. 37 (citing Ex. 2034 ¶ 112).

Having considered the arguments and evidence, we agree with Petitioners that Coniglio would have informed a person of ordinary skill in the art that ticlopidine, clopidogrel, and prasugrel would be useful in combination with aspirin as a therapy for angioplasty patients. We are not persuaded otherwise by Patent Owner’s assertion that a skilled artisan would not want to use a potent therapy like prasugrel with aspirin in those patients, as that argument is not sufficiently supported by the record. In particular, Patent Owner refers to the testimony of Dr. Gibson that a person of ordinary skill in the art “would have been even more concerned about using a potent antiplatelet agent like prasugrel with aspirin under such circumstances.” Ex. 2034 ¶ 112; PO Resp. 37. We do not find that having a “concern” about using prasugrel and aspirin in angioplasty patients means that such use may not be warranted or beneficial. As Dr. Hirsh persuasively explained, because prasugrel provides a faster onset of action, use of that drug in combination with aspirin may provide a benefit that outweighs a bleeding risk. Ex. 1070 ¶ 75.

Moreover, as Dr. Hirsh explained, any higher risk of bleeding may be mitigated by prescribing an adjusted dose. *Id.*

Dependent claims 4, 5, 12, 13, 17, 18, 22, and 23

Petitioners have explained how the teachings of the combined prior art disclose the limitations of dependent claims 4, 5, 12, 13, 17, 18, 22, and 23, and render those claims obvious in view of the skill of a person of ordinary skill in the art. Pet. 33–36. Patent Owner has not raised separate arguments specifically addressing the additional limitations of those dependent claims. Having reviewed the arguments and evidence presented by Petitioners, we adopt the reasoning therein and determine that Petitioners have established by a preponderance of the evidence that those dependent claims would have been obvious for the reasons set forth in the Petition. *Id.*

For the foregoing reasons, we are persuaded that Petitioners have shown by a preponderance of the evidence that the combined teachings of Coniglio, Bernat, Asai, and Koike provided a person of ordinary skill in the art a reason to administer pharmaceutically effective amounts of prasugrel and aspirin, along with one or more pharmaceutically acceptable additives to prevent or treat diseases cause by thrombus or embolus.

We next analyze and weigh the secondary considerations of nonobviousness asserted by Patent Owner to determine if, on balance,

that evidence renders nonobvious the methods of the challenged claims.

c. *Secondary Considerations*

“For objective evidence of secondary considerations to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the claimed invention.” *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (citing *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010)). Where objective indicia “result[] from something other than what is both claimed and *novel* in the claim, there is no nexus to the merits of the claimed invention.” *Id.* “To the extent that the patentee demonstrates the required nexus, his objective evidence of nonobviousness will be accorded more or less weight.” *In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995).

Patent Owner argues that the nonobviousness of the claims is supported by objective evidence of unexpected results. PO Resp. 47–59; PO Supp. Resp. 1–5. Petitioners assert that the obviousness of the claims is supported by objective evidence of simultaneous invention. Pet. 38–40; Pet. Reply 14–20. As explained further below, we are not persuaded by Patent Owner’s argument and evidence of secondary considerations of nonobviousness of the challenged claims.

i. *Unexpected Results*

According to the Federal Circuit, “[t]o be particularly probative, evidence of unexpected results must establish that there is a difference between the results obtained and those of the closest prior art, and that the difference would not have been expected by one of ordinary skill

in the art at the time of the invention.” *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014). Patent Owner argues that a person of ordinary skill in the art would have expected that the addition of aspirin to prasugrel would have resulted in a greater bleeding risk than the use of clopidogrel and aspirin without much gain in efficiency. PO Resp. 48 (citing Ex. 2034 ¶ 115). In other words, according to Patent Owner, an ordinary artisan would not have believed that the net clinical benefit (i.e., the ratio between the efficacy of antithrombotic therapy and any adverse effects such as bleeding) would increase by adding aspirin to prasugrel as compared to adding aspirin to clopidogrel. *Id.*

Patent Owner and its declarant, Dr. Gibson, rely on the results of the TRITON-TIMI 38 phase III trial, which was reported in Wiviott.¹⁰ PO Resp. 49; Ex. 2034 ¶ 116. Dr. Gibson—who participated in the study—explains that the data in Wiviott showing the net clinical benefit of prasugrel and aspirin when compared to clopidogrel and aspirin “would have been entirely unexpected to the [person of ordinary skill in the art] as of December 2000, as nothing in the prior art would have suggested such a result to the [person of ordinary skill in the art].” Ex. 2034 ¶ 119. Patent Owner further notes that the FDA relied on the favorable results of the TRITON study in its decision to approve EFFIENT®, a commercial

¹⁰ Wiviott et al., *Prasugrel Versus Clopidogrel in Patients with Acute Coronary Syndromes*, 357 N. ENGL. J. MED. 2001–15 (2007) (Ex. 1027) (“Wiviott”).

embodiment of prasugrel for which the label recommends the concomitant administration of aspirin. PO Resp. 51 (citing Ex. 1046). Accordingly, Patent Owner asserts that there is a nexus between the claimed invention and the results of the TRITON study. PO Resp. 51–52 (citing Ex. 2034 ¶¶ 130–31).

As an initial matter, we agree with Patent Owner that a nexus exists between the TRITON study results and the claimed invention. We are not persuaded by Petitioners’ argument that the one-time administration of antithrombins at the beginning of the 15-month trial removes the study from the scope of the claimed invention. *See* Pet. Reply 15–16 (citing Ex. 1027, 7, Tbl. 1; Ex. 1070 ¶ 94). We are persuaded, however, that a person of ordinary skill in the art would not have found the results of the TRITON study unexpected. Instead, we determine that a preponderance of the evidence demonstrates that an ordinary artisan would have expected better efficacy, and more bleeding as a result, with the combination of prasugrel and aspirin than with the combination of clopidogrel and aspirin given prasugrel’s faster onset and superior response rate. *See, e.g.*, Ex. 1070 ¶ 93. Significantly, as Petitioners note, the investigators expected prasugrel and aspirin would have an improved net clinical benefit compared to clopidogrel and aspirin, stating that “[t]he primary objective of TRITON-TIMI 38 is to test the hypothesis that prasugrel is superior to clopidogrel on a background of aspirin.” Ex. 1070 ¶ 86 (quoting Ex. 1065, 628).

Moreover, even if an ordinary artisan considered the results of the TRITON study unexpected, we are not persuaded that the results

are probative of nonobviousness. As the Federal Circuit has held, “[u]nexpected results that are probative of nonobviousness are those that are ‘different in kind and not merely in degree from the results of the prior art.’” *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013) (quoting *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004)). In *Galderma*, the claims related to topical compositions for treating acne comprising 0.3% by weight of adapalene. *Id.* at 734. The prior art indicated that many skilled artisans believed at the time of the invention that 0.1% adapalene was the optimal concentration for treating acne. *Id.* at 736. In that case, the patent owner argued that the comparable tolerability of 0.1% adapalene to 0.3% adapalene was unexpected because a person of ordinary skill in the art would have expected that tripling the concentration of adapalene would have resulted in a clinically significant increase in side effects. *Id.* at 739. The Federal Circuit determined that this difference, although unexpected, did not indicate that the claims are nonobvious because “where an unexpected increase in efficacy is measured by a small percentage, as here, and the evidence indicates that skilled artisans were capable of adjusting the percentage, the result constitutes a difference in degree, not kind.” *Id.*

Similarly, here, we determine that the difference in net clinical benefit between prasugrel and aspirin and clopidogrel and aspirin is a difference in degree, not kind. Patent Owner argues that the difference in net clinical benefit is a difference in kind because “prasugrel and aspirin interact in such a way to favorably change the

benefit/bleed risk ratio relative to clopidogrel and aspirin.” PO Resp. 57 (quoting Ex. 2034 ¶ 132). We are not persuaded. A difference in kind is “a new property dissimilar to the known property.” *Bristol-Myers Squibb*, 752 F.3d at 977. Here, we determine that the differences between prasugrel and aspirin and clopidogrel and aspirin are not due to new properties resulting from the combination. Rather, we credit the testimony of Dr. Hirsh, who explains that “the combination of prasugrel and aspirin had a different degree of antiplatelet activity (more potent inhibition of ADP-mediated platelet aggregation) compared to the prior art combinations of clopidogrel and aspirin and ticlopidine and aspirin, as a POSA would expect.” Ex. 1002 ¶ 156. Dr. Hirsh continues, stating “[t]he only alleged difference between the net clinical benefits of the respective combinations was only a difference in degree (greater efficacy and more serious bleeding).” *Id.* Patent Owner has not established persuasively that such difference was significant so as to remain probative in assessing obviousness. *See* PO Resp. 58 (citing *Bristol-Myers Squibb Co.*, 752 F.3d at 977).

Moreover, Patent Owner’s declarant, Dr. Gibson, agrees that it was within the level of ordinary skill in the art to ascertain a pharmacologically effective amount by determining the dose-response curve with respect to safety of the compound and the dose-response curve relating to the effectiveness of the compound. Ex. 1069, 16:23–18:5. Indeed, Dr. Gibson testified that that process is not unique to prasugrel and aspirin, but a “traditional method of establishing the dose of a drug.” *Id.* at 18:2–5.

Accordingly, having considered the arguments and evidence, we determine that Patent Owner has not established persuasively that the results of the TRITON study were of a “kind” or of a “significant degree” that would have been unexpected by a person of ordinary skill in the art at the time of the invention so as to support a finding of nonobviousness of the challenged claims.

ii. *Simultaneous Invention*

Petitioners argue that Ogletree¹¹ discloses the combination of prasugrel and aspirin to treat cardiovascular diseases, and filed a patent application a few months before Patent Owner filed its Japanese application to which the ’325 patent claims priority. Pet. 38–39. As such, Petitioners assert that this evidence of near-simultaneous invention supports its obviousness argument and undermines Patent owner’s evidence of nonobviousness. *Id.*

Patent Owner notes that Ogletree requires the combination of an ADP-receptor backlog antiplatelet drug (like clopidogrel), a thromboxane A₂ receptor antagonist, and optionally aspirin. Ex. 1004, 4:18–21. Because the claims recite a method “consisting of” administering only prasugrel and aspirin, Patent Owner asserts that Ogletree cannot be evidence of simultaneous invention because of the addition of the thromboxane A₂ receptor antagonist.

We agree with Patent Owner that Ogletree does not expressly disclose the claimed invention. We find, however, that Ogletree

¹¹ Martin L. Ogletree, US 6,509,348 B1, issued Jan. 21, 2003 (Ex. 1004).

provides some evidence of what constitutes the level of ordinary skill in the art. *See Ecolochem, Inc. v. So. Cal. Edison Co.*, 227 F.3d 1361, 1379 (Fed. Cir. 2000) (“The issue of simultaneous invention is directly tied to the level of knowledge attributable to one of ordinary skill in the art.”). Thus, contrary to Patent Owner’s assertion that a person of ordinary skill in the art would have only used prasugrel in monotherapy, we are persuaded that Ogletree indicates that those of ordinary skill in the art were combining the drugs with other platelet aggregation inhibitors such as thromboxane A₂ inhibitors. Pet. Reply 19–20 (citing Ex. 1070 ¶ 100).

6. *Conclusion as to Obviousness*

Having considered the parties’ arguments and evidence, we evaluate all of the evidence together to make a final determination of obviousness. In doing so, we conclude that Petitioners have shown by a preponderance of the evidence that each of the challenged claims is unpatentable as obvious over Coniglio, Bernat, Asai, and Koike.

III. PATENT OWNER’S MOTION TO EXCLUDE EVIDENCE

Patent Owner moves to exclude Petitioners’ Exhibits 1009, 1011, 1013, 1017, 1020, and 1075 (the “Challenged Exhibits”).

Mot. 1. Petitioners oppose the motion. Mot. Opp. 1. As the moving party, Patent Owner has the burden of proof to establish that it is entitled to the requested relief. 37 C.F.R. § 42.20(c).

Patent Owner asserts that each of the Challenged Exhibits are journal articles with copyright dates of 2000. Mot. 2. Patent Owner contends that Petitioners have not submitted evidence establishing that those articles are prior art printed publications. *Id.* at 1. In particular,

Patent Owner asserts that Petitioners have not established that the Challenged Exhibits “would have been available to a person of ordinary skill in the art prior to the ’703 patent’s relevant date for prior art purposes.” *Id.* at 2. Patent Owner asserts that “the parties do not dispute that the latest potential date to which the ’703 patent is entitled to priority is December 25, 2000.” *Id.* at 3. Patent Owner’s position is that the articles are not self-authenticating because the only date provided on the articles is a copyright date of “2000.” *Id.* at 2. While contending that a copyright date does not establish public availability, Patent Owner asserts that even if the copyright date could be relied upon, it would at most establish that the Challenged Exhibits were publicly accessible as of December 31, 2000, i.e., after the relevant priority date. *Id.* at 3. Thus, according to Patent Owner, the Challenged Exhibits, “as well as the declaration and deposition testimony concerning those exhibits, are irrelevant. *Id.* at 1.

Petitioners assert that Patent Owner has improperly raised the issue regarding whether the Challenged Exhibits are prior art printed publications in a motion to exclude. Mot. Opp. 2. According to Petitioners, such arguments go to the weight and sufficiency of the evidence and not to admissibility. *Id.* We agree with Petitioners. Patent Owner’s argument regarding the public accessibility of the Challenged Exhibits should have been presented in the Patent Owner Response.¹² Accordingly, we *deny* the Motion.

¹² In any event, our obviousness analysis does not rely upon any of the Challenged Exhibits, or testimony discussing those exhibits, which

IV. CONCLUSION

For the foregoing reasons, we conclude that Petitioners have shown by a preponderance of the evidence that claims 1–26 of the ’325 patent are unpatentable as obvious over Coniglio, Bernat, Asai, and Koike.

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–26 of the ’325 patent are held unpatentable;

FURTHER ORDERED that Patent Owner’s Motion to Exclude Evidence is *denied*; and

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

Petitioners characterize as only providing “relevant background on the state of the art.” Mot. Opp. 1.

IPR2015-00865
Patent 8,569,325 B2

PETITIONERS:

Douglass C. Hochstetler
dhochstetler@kelleydrye.com

PATENT OWNER:

Dov P. Grossman
dgrossman@wc.com

David M. Krinsky
dkrinsky@wc.com