

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

JANSSEN PHARMACEUTICALS, INC.
and JANSSEN PHARMACEUTICA NV,

Plaintiffs,

v.

TEVA PHARMACEUTICALS USA, INC.,

Defendant.

Civil Action Nos.:

2:18-00734

2:19-16484

OPINION

JANSSEN PHARMACEUTICALS, INC.
and JANSSEN PHARMACEUTICA NV,

Plaintiffs,

v.

MYLAN LABORATORIES LTD.,

Defendant.

CECCHI, District Judge.

Janssen Pharmaceuticals, Inc. and Janssen Pharmaceutica NV (collectively, “Janssen” or “Plaintiffs”) sued Teva Pharmaceuticals USA, Inc. (“Teva” or “Defendant”) for infringing U.S. Patent No. 9,439,906 (the “’906 Patent”). ECF No. 133 (“Final Pretrial Order” or “FPTO”) at 2–3. Teva stipulated to infringement of the ’906 Patent but challenged the patent’s validity. *Id.* Specifically, Teva asserted that all representative claims were invalid as obvious and that several claims were also invalid as indefinite. *Id.* This Court held an eleven-day bench trial¹ and

¹ The bench trial was held on various days between October 13, 2020, and October 30, 2020. ECF Nos. 135–37, 140–41, 145–49, 151. Closing arguments were held on March 5, 2021. ECF No. 199.

concluded that Teva had not proven invalidity through obviousness or indefiniteness. *Janssen Pharms., Inc. v. Teva Pharms. USA, Inc.* (“*Teva P*”), 571 F. Supp. 3d 281 (D.N.J. 2021). Following an appeal by Teva, ECF No. 275, the Federal Circuit affirmed this Court’s holding on indefiniteness² but vacated and remanded its obviousness determination. *Janssen Pharms., Inc. v. Teva Pharms. USA, Inc.* (“*Teva IP*”), 97 F.4th 915, 918 (Fed. Cir. 2024).³

This Opinion constitutes the Court’s findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52(a). The findings of fact are based on the Court’s observations and credibility determinations of the witnesses who testified at trial and a review of the evidence admitted. Although the Court has reviewed all the evidence presented, this Opinion only includes references to the evidence most pertinent to its analysis.⁴ For the reasons set forth below, the Court finds that the ’906 Patent has not been proven invalid.

I. BACKGROUND

Janssen sells Invega Sustenna, which is an injectable paliperidone palmitate medication used to treat schizophrenia in adults. FPTO at 2. Teva filed an Abbreviated New Drug Application (“ANDA”) in 2017 seeking approval from the Food and Drug Administration (“FDA”) to

² Therefore, indefiniteness will not be discussed in this Opinion.

³ Janssen also sued Mylan Laboratories Ltd. (“Mylan,” together with Teva, “Defendants”) in a separate action before this Court, No. 19-16484. In that case, the parties stipulated to be bound by the final judgment in the instant matter with respect to infringement and validity. No. 19-16484, ECF No. 71. Arguments presented by Teva are “presented by both Teva and Mylan.” Def. Br. at 1 n.1. Mylan was also an appellant in the appeal before the Federal Circuit. *See Teva II*, 97 F.4th 915, 918 n.1 (Fed. Cir. 2024).

⁴ The parties submitted post-trial briefs and proposed findings of fact and conclusions of law in December 2020, after the conclusion of the bench trial. ECF Nos. 164 (“Pltf. Post Trial Br.”), 165 (“PFOF”), 167 (“Def. Post Trial Br.”), 167-1 (corrected at 168-1 (“DFOF”). The parties submitted responsive briefs in January 2021. ECF Nos. 188 (“Pltf. Post Trial Reply Br.”), 189 (“Def. Post Trial Reply Br.”). The parties agree that the issues to be determined on remand should be based on the existing trial record. ECF No. 293 at 2. The parties have also submitted post-remand briefing. ECF Nos. 299 (“Def. Br.”), 300 (“Pltf. Br.”), 311 (corrected at 314 (“Pltf. Reply Br.”)), 312 (“Def. Reply Br.”). The Court also considered Plaintiffs’ Notice of Supplemental Authority (ECF No. 313) and Defendants’ response (ECF No. 318). Unless otherwise noted, the Court will refer to the corrected documents submitted by the parties.

manufacture and sell a generic version of Janssen’s Invega Sustenna. *Id.* In response, Janssen sued for patent infringement under the Hatch-Waxman Act, asserting various claims of the ’906 Patent. ECF No. 1. The ’906 Patent discloses dosing regimens of paliperidone palmitate and is listed in the FDA’s “Orange Book” as covering Invega Sustenna-brand paliperidone palmitate extended-release suspension products. FPTO at 2.

Schizophrenia is a psychotic disorder typified by disorganized speech and behavior, delusions and hallucinations. PFOF ¶ 11. Individuals diagnosed with schizophrenia often struggle to adhere to treatment regimens, particularly those that require daily intake of oral medication. *Id.* ¶ 14. This failure to take medication often leads to psychotic episodes that result in further difficulty complying with treatment. *Id.*

In order to help solve this adherence problem, long-acting injectables (“LAIs”)—otherwise known as “depots”—were developed. *Id.*; DFOF ¶¶ 57–58. LAIs deposit a large amount of drug into the body which is then slowly released. PFOF ¶ 14; DFOF ¶ 58. This slow release allows for the administration of medication once or twice a month, versus the daily administration required when taking the oral versions. PFOF ¶ 14; DFOF ¶ 59. Therefore, LAIs, including Invega Sustenna, “may greatly enhance compliance with dosing.” PTX/DTX 1 at 1:58–61.

A. The ’906 Patent

The ’906 Patent is titled “Dosing Regimen Associated with Long Acting Injectable Paliperidone Esters.” *Id.* at 1. It was filed on December 17, 2008, and claims the benefits of provisional applications filed on December 19, 2007, and December 5, 2008. *Id.* Although Teva previously contended that the priority date of the ’906 Patent was “no earlier than December 5, 2008,” DFOF at 112 ¶ 2, it has since revised this position. Def. Br. at 67 (“The priority date of Janssen’s ’906 Patent is 2007.”).

The parties agree that claims 2, 10, 13, 20 and 21 are representative. FPTO at 9. The asserted claims relate to “[a] dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment for schizophrenia.”⁵ PTX/DTX 1 at 32:11–13. Claim 2 relates to a dosing regimen for a psychiatric patient without renal impairment, claims 10 and 13 relate to a dosing regimen for a psychiatric patient with renal impairment and claims 20 and 21 relate to the characteristics of the paliperidone palmitate formulation. PFOF ¶¶ 7–9.

The Court underscores that the ’906 Patent’s claims relate to dosing regimens for *a* patient, not to generalized dosing regimens. Further, the renal impairment claims themselves do not specify a level of renal impairment. Finally, the claims do not include any safety and efficacy requirement. The analysis conducted throughout this Opinion recognizes these distinctions and is in accordance with the Federal Circuit’s instructions.

Turning to the claims, Claim 2 depends from Claim 1 and relates to a dosing regimen for a psychiatric patient without renal impairment. Most notably, the claims disclose a loading dose regimen consisting of an initial 150 mg-eq.⁶ dose followed by a 100 mg-eq. dose, both injected in the deltoid, and subsequent maintenance doses of 25 to 150 mg-eq. injected in the deltoid or the gluteus. The claims are reproduced in full below.

1. A dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment for schizophrenia, schizoaffective disorder, or schizophreniform disorder comprising

(1) administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of about 150 mg-eq. of paliperidone as

⁵ Some claims discuss treatment for a different psychiatric disorder. However, the parties’ arguments focus on schizophrenia, so this Opinion does the same. *See Teva II*, 97 F.4th 915, 925 n.3 (Fed. Cir. 2024).

⁶ Paliperidone palmitate is converted to paliperidone once it is introduced into the body. PFOF ¶ 6; DFOF ¶ 80. As such, doses are not expressed in terms of their actual weight, but rather in terms of the equivalent amount of paliperidone they contain. PFOF ¶ 6. This measurement is referred to as a “milligram-equivalent” or “mg-eq.” for short. *Id.*

paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

- (2) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of about 100 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 6th to about 10th day of treatment; and
- (3) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a first maintenance dose of about 25 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation a month (± 7 days) after the second loading dose.

2. The dosing regimen of claim 1 wherein after administration of the first maintenance dose, subsequent maintenance doses of from about 25 mg-eq. to 150 mg-eq. are administered in the deltoid or gluteal muscle of the psychiatric patient in need of treatment at monthly (± 7 days) intervals.

PTX/DTX 1 at 32:11–36.

Claim 10 depends from Claim 8 and relates to a dosing regimen for a psychiatric patient with renal impairment. Among other things, the claims disclose a loading dose regimen consisting of two 75 mg-eq. injections in the deltoid and a subsequent maintenance dose of between 25 mg-eq. and 75 mg-eq. injected in the deltoid or the gluteus. The claims are reproduced in full below.

8. A dosing regimen for administering paliperidone palmitate to a renally impaired psychiatric patient in need of treatment for schizophrenia, schizoaffective disorder, or schizophreniform disorder comprising

- (a) administering intramuscularly in the deltoid of a renally impaired psychiatric patient in need of treatment a first loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;
- (b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 6th to about 10th day of treatment; and
- (c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a first maintenance dose of about 25 mg-eq. to about 75 mg-eq. of paliperidone as paliperidone palmitate in a

sustained release formulation a month (± 7 days) after the second loading dose.

10. The dosing regimen of claim 8 wherein the sustained release formulation is an aqueous nanoparticle suspension.

Id. at 32:66–33:20, 33:26–27. Claim 13 primarily differs from Claim 10 by disclosing a maintenance dose of between 25 mg-eq. and 50 mg-eq. *Id.* at 33:26–52.

Claims 20 and 21 are only representative as they depend from claims 1 or 8. Both claims further depend from Claim 19, which is reproduced below. Most relevant is the particle-size limitation of Claim 19 (italicized below).

19. The dosing regimen of claims 1, 4, 8 or 11 wherein the sustained release depot formulation is an aqueous nanoparticle suspension consists essentially of

- (a) *156 mg/ml of the paliperidone palmitate having an average particle size (d50) of from about 1600 nm to about 900 nm;*
- (b) 12 mg/ml of polysorbate 20;
- (c) one or more buffering agents sufficient to render the composition neutral to very slightly basic (pH 8.5);
- (d) 30 mg/ml of a suspending agent wherein the suspending agent is polyethylene glycol 4000; and
- (f) water q.s. ad 100%.

Id. at 34:32–43 (emphasis added).⁷

The '906 Patent describes several different dosing regimens for administering paliperidone palmitate. *See generally* PTX/DTX 1. For a patient without renal impairment, the patent discloses a first loading dose of 150 mg-eq. of paliperidone palmitate, followed by a second loading dose of 100 mg-eq. of paliperidone palmitate, both injected in the deltoid. *Id.* at 32:11–24. The specification explains that “deltoid injections result in a faster rise in initial plasma concentration”

⁷ Subsection (e) of Claim 19 is omitted in the patent. *See* PTX/DTX 1 at 34:32–43.

and that injecting the loading doses in the deltoid “facilitate[s] patients’ attaining a rapid therapeutic concentration of paliperidone.” *Id.* at 5:2–8. The two loading doses are followed by maintenance doses of 25 mg-eq. to 150 mg-eq of paliperidone palmitate, injected in either the deltoid or the gluteal muscle. *Id.* at 32:25–30. For a patient with renal impairment, the ’906 Patent adjusts the dosing regimen so that the two loading doses are both 75 mg-eq., and the maintenance dose ranges from 25 mg-eq. to 75 mg-eq. *Id.* at 32:66–33:20.

The history leading up to this invention is discussed below for helpful context.

B. Antipsychotic Drugs and Research

1. Antipsychotic Drugs

Schizophrenia patients are treated with antipsychotic medication, such as Invega Sustenna, to control and treat their symptoms. PFOF ¶ 12; DFOF ¶ 53. The “first generation” of antipsychotics that were developed included dozens of oral medications and a few LAIs. PFOF ¶ 15. However, first-generation medications were plagued by serious side effects such as tremors, stiffness and cognitive symptoms like mental dulling and impaired functioning. *Id.* ¶ 16. Consequently, these medications were mostly used with chronically ill patients. *Id.* ¶ 17. Seeking to improve upon the side effects profile, “second-generation” antipsychotics were subsequently developed. *Id.* ¶ 19. These medications were an improvement over their predecessors, significantly reducing the severity and likelihood of side effects. *Id.*

2. Janssen’s Research and Clinical Trials

Many second-generation oral antipsychotics were developed, including Janssen’s risperidone product, Risperdal. *Id.* However, the only second-generation LAI available before Invega Sustenna was Janssen’s Risperdal Consta—an injectable form of risperidone. *Id.* ¶¶ 19–20. But Risperdal Consta is not rapidly effective, and thus requires oral supplementation during

the first three weeks of treatment. *Id.* ¶ 20. In addition, the drug requires subsequent dosing every two weeks. *Id.* This short dosing interval contributes to treatment nonadherence and the problems that ensue. *Id.* Janssen set out to overcome these shortcomings by developing a second-generation LAI that required *monthly* dosing and was rapidly effective without the need for oral supplementation. *Id.* ¶ 21.

i. Phase I

Recognizing the problems with injectable risperidone, Janssen began research into paliperidone palmitate. *Id.* ¶¶ 20–21. Janssen’s first Phase I study looked at a *single* 50 mg-eq. dose injected in the gluteus. *Id.* ¶ 27. Results of the study showed that the paliperidone palmitate released too slowly to allow for the desired once-monthly dosing. *Id.* Hypothesizing that smaller particle size would provide for a quicker release, Janssen developed several formulations with smaller particle sizes. *Id.* Janssen later finalized one of those formulations, which is used in Invega Sustenna and meets the elements of claims 20 and 21. *Id.*

Janssen next undertook Phase I studies evaluating loading doses. *Id.* ¶ 28. One clinical trial tested two potential loading dose regimens: (1) a larger dose on day one and (2) smaller, equal doses on days one and eight. *Id.* The larger dose on day one proved more effective and tolerable, and was chosen for further study. *Id.* Meanwhile, Janssen also researched the effects of the injection site. *Id.* ¶ 29. Based on the prior art, Janssen believed that the main injection sites—the deltoid and the gluteus—would be interchangeable. *Id.* However, Janssen found that deltoid injections led to a 45 percent higher peak plasma concentration of the drug. *Id.* Because higher plasma concentrations increase the risk of severe side effects, Janssen utilized gluteal injections for future studies. *Id.*

ii. Phase II

Based on its Phase I results, Janssen conducted a Phase II clinical trial studying equal doses of either 50 or 100 mg-eq. in the gluteus on days 1, 8 and 36. *Id.* ¶ 30. Results of the study were “very promising”—both dose amounts proved rapidly effective and were superior to placebo on the eighth day of treatment without the need for oral supplementation. *Id.* ¶ 31. Janssen decided to build on these favorable results with several Phase III trials. *Id.* ¶ 32.

iii. Phase III

Ultimately, Janssen considered the pertinent Phase III trials (PSY-3003 and PSY-3004) to be failures. The results showed no dose amounts in either study were effective in subjects in the United States. *Id.* ¶¶ 34–35. Janssen responded to this “crisis moment” by organizing a “task force” of clinical, pharmaceutical and other specialists. *Id.* ¶¶ 36, 38. The task force explored several possible explanations for the failures, as well as potential solutions including doses as high as 400 mg-eq. *Id.* ¶ 39. After undertaking advanced modeling led by Dr. An Vermeulen, co-inventor of the ’906 Patent, the task force determined that body weight and the injection site had impacted the efficacy of the treatment regimen. *Id.* ¶¶ 42–43. The task force then modeled numerous solutions to this problem before recommending a dosing strategy consisting of an initial 150 mg-eq. dose in the deltoid on day one, followed by doses of either 25, 50, 100 or 150 mg-eq. in the deltoid or the gluteus on day eight and monthly thereafter. *Id.* ¶ 43.

Based on this recommendation, Janssen designed two additional Phase III studies: PSY-3006 and PSY-3007. *Id.* ¶ 44. Both studies began with a 150 mg-eq. deltoid injection on day one. *Id.* ¶¶ 44–45. PSY-3007 then used 25, 100 or 150 mg-eq. deltoid or gluteal injections while PSY-3006 used 50 mg-eq. deltoid or gluteal injections on day eight and flexible dosing afterwards. *Id.* The PSY-3007 study compared the regimens to placebo, whereas the PSY-3006 study compared to Risperdal Consta. *Id.*

Dr. Mahesh Samtani, one of the co-inventors of the '906 Patent, worked to improve upon the modeling previously conducted under Dr. Vermeulen. *Id.* ¶ 48. As part of this work, Dr. Samtani determined that the absorption of paliperidone palmitate proceeds in two phases (biphasic): for the first two weeks, there is a steady, fast input into the blood circulation. *Id.* ¶ 49. After those two weeks, the “slow process takes over.” *Id.* (quoting Tr. 1349:16–20, 1351:6–9 (Samtani)). Additionally, Dr. Samtani discovered that higher doses of paliperidone palmitate do not result in proportionally higher increases in peak concentration in the body, and that with higher doses there is a longer half-life. *Id.* (citing Tr. 1353:23–25 (Samtani)). Dr. Samtani then used the updated model to run simulations of different dosing regimens to determine the optimum sequence, dosage, and administration site for paliperidone palmitate. *Id.* ¶ 50.

As Dr. Samtani was working with the model, Janssen received the results from its earlier PSY-3002 study. *Id.* ¶ 52. The PSY-3002 study failed to show that paliperidone palmitate was an improvement on Risperdal Consta. *Id.* After a “heated debate” regarding how to respond to this failure, Janssen employees decided to modify the PSY-3006 study to increase the injection on day eight to 100 mg-eq. and to require its administration in the deltoid—thus resulting in the patented regimen. *Id.* ¶ 53. This determination was made based upon the modeling and simulations previously conducted. *Id.*

As PSY-3006 and PSY-3007 continued, Dr. Samtani worked to update his model, conducting internal and external validation processes. *Id.* ¶ 55. Dr. Samtani’s simulations ultimately showed that the 150/100 mg-eq. loading dose regimen would be safe and effective. *Id.* This finding was confirmed by the results of PSY-3006 and PSY-3007, which demonstrated that the loading dose regimen achieved rapid and long-term efficacy without oral supplementation. *Id.*

¶¶ 55, 60. In short, Janssen achieved what it had set out to do. *See id.* ¶ 21. The FDA approved Invega Sustenna and the claimed dosing regimen in 2009. *Id.* ¶ 60.

C. *Janssen v. Tolmar*

While Teva’s appeal was pending in this matter, Federal Circuit Judge William C. Bryson, sitting by designation in the District of Delaware, presided over a case involving an obviousness challenge to the ’906 Patent, the same patent at issue here. After consideration of the prior art reference NCT00210548, a protocol for one of Janssen’s Phase III clinical trials (the “’548 Protocol” or “NCT 548”), which is also the closest prior art in this case, Judge Bryson concluded that the ’906 Patent had not been proven invalid. *Janssen Pharms., Inc. v. Tolmar, Inc.* (“*Tolmar I*”), 718 F. Supp. 3d 394 (D. Del. 2024). Following the Federal Circuit’s decision in *Teva II*, Tolmar filed a motion for reconsideration asserting, *inter alia*, that Judge Bryson’s opinion was inconsistent with the Federal Circuit’s opinion. Judge Bryson denied Tolmar’s motion. *Janssen Pharms., Inc. v. Tolmar, Inc.* (“*Tolmar II*”), No. CV 21-1784, 2024 WL 2972832 (D. Del. June 13, 2024).

Regardless, the Court acknowledges that Judge Bryson reached his decision based on the record presented to him. The findings and conclusions in this Opinion are based on the record presented and discussed herein.

D. *Prior Art Summary*

To demonstrate obviousness of the claims discussed above, Teva relies on three primary prior art references. Def. Br. at 9. These include: (1) the ’548 Protocol; (2) U.S. Patent No. 6,555,544, a patent owned by Janssen describing a single dose of LAI formulations of paliperidone palmitate (the “’544 Patent”) and (3) International Publication No. WO 2006/114384,

a patent application by Janssen disclosing the formulation and a single dose of paliperidone palmitate (the “WO ’384”).⁸

II. DISCUSSION

Issued patents are presumed valid. *See* 35 U.S.C. § 282(a). To rebut this presumption, a defendant bears the burden of proving invalidity by clear and convincing evidence. *Titan Tire Corp. v. Case New Holland, Inc.*, 566 F.3d 1372, 1376 (Fed. Cir. 2009) (“Because of this presumption, an alleged infringer who raises invalidity as an affirmative defense has the ultimate burden of persuasion to prove invalidity by clear and convincing evidence, as well as the initial burden of going forward with evidence to support its invalidity allegation.”).

A. **Applicable Law**

To prove that a patent claim is invalid as obvious, a party must show that the “differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art.” 35 U.S.C. § 103; *see also Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1360–61 (Fed. Cir. 2007). In particular, the “party seeking to invalidate a patent as obvious must demonstrate ‘by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so.’” *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 973 (Fed. Cir. 2014) (quoting *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009)). This determination is a question of law based on underlying findings of fact,

⁸ To the extent Teva relies on additional prior art references throughout its arguments, they will be discussed in the relevant sections.

see *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966), including “the scope and content of the prior art, the differences between the prior art and the claimed invention, the level of ordinary skill in the art, and any relevant secondary considerations.” *Galderma Lab’ys, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 736 (Fed. Cir. 2013) (citing *Graham*, 383 U.S. at 17–18).

“The obviousness analysis should not be conducted ‘in a narrow, rigid manner,’ but should instead focus on whether a claimed invention is merely ‘the result[] of ordinary innovation,’ which is not entitled to patent protection.” *Pernix Ir. Pain DAC v. Alvogen Malta Operations Ltd.*, 323 F. Supp. 3d 566, 595 (Fed. Cir. 2018) (alteration in original) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 427–28 (2007)). The analysis is “expansive and flexible” and “need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.” *KSR Int’l Co.*, 550 U.S. at 415, 418.

B. Person of Ordinary Skill in the Art

The parties offer slightly different definitions of a person of ordinary skill in the art (a “POSA”). Janssen asserts that a POSA would have “an M.D., Ph.D., PharmD, or equivalent work experience in drug formulation, pharmacy, pharmacokinetics, or medicine.” PFOF ¶ 77 n.7 (citation omitted). Teva argues that “[a] POSA is a person who would have an advanced degree such as an M.D., Ph.D., PharmD, master’s degree, or other advanced degree in an area related to chemistry, pharmaceuticals, medicine or biology, with several years of experience in the pertinent field and be capable of working in a team comprising others in the field or related fields.” DFOF ¶ 136 (internal quotation marks and citation omitted). However, the parties agree that any differences are “not meaningful for purposes of this case.” ECF No. 200 at 122:9–123:10 (Closing Argument).

C. The Prior Art

As noted above, Teva relies on three primary prior art references to show that the representative claims of the '906 Patent would have been obvious to a POSA: (1) the '548 Protocol; (2) the '544 Patent and (3) the WO '384. Def. Br. at 9. These references are further described below.

1. The '548 Protocol

The '548 Protocol is a summary of the protocol for Janssen's PSY-3003 clinical trial with the brief title: "A Study to Evaluate the Effectiveness and Safety of 3 Doses of Paliperidone Palmitate in Treating Subjects with Schizophrenia." See PTX 54/DTX 55 at 1; PFOF ¶ 89. It does not contain results or data, but rather details a 14-week study designed to test the hypothesis that three fixed-dose regimens of paliperidone palmitate would be more effective than placebo. Tr. 1578:25–1579:15 (Sinko); PFOF ¶ 89; PTX 54/DTX 55 at 1. Participants would receive equal doses of either 50, 100 or 150 mg-eq. in the gluteal muscle on days 1, 8, 36 and 64. Tr. 1579:17–1580:1 (Sinko); PTX 54/DTX 55 at 1; PFOF ¶ 91. Thus, for example, a patient who received a 50 mg-eq. dose on day one would continue to receive a 50 mg-eq. dose for each subsequent dose.

The '548 Protocol presents a unique situation—it merely proposes a hypothesis. Both sides agree that the protocol contains no information about the study's results. Tr. 480:16–20 (Wermeling), 1579:8–15 (Sinko). To be clear, the Court does not discard the teachings of the '548 Protocol because it lacks both data and results. Instead, the Court considers what a POSA would infer from the '548 Protocol in light of its lack of data and results. Courts must consider prior art "not only for what it expressly teaches, but also for what it fairly suggests" to a POSA. *Bradium Techs. LLC v. Iancu*, 923 F.3d 1032, 1049 (Fed. Cir. 2019) (quoting *In re Baird*, 16 F.3d 380, 383 (Fed. Cir. 1994)); accord *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). A

POSA will typically “view a reference, understand its strengths and weaknesses, its advantages and deficiencies, and attempt to overcome the flaws in the prior art by employing ordinary creativity, related references, and general background knowledge.” *Tolmar I*, 718 F. Supp. 3d 394, 426 (D. Del. 2024); *see also Adapt Pharma Operations Ltd. v. Teva Pharms. USA, Inc.*, 25 F.4th 1354, 1365 (Fed. Cir. 2022).

A POSA would know that Janssen likely would not have pursued the '548 Protocol and invested significant funds in a Phase III clinical trial without a belief that its hypothesis was correct. But without the data and results from the clinical trial, which were only known to Janssen, a POSA would have only understood that Janssen believed the dosing regimens were likely safe and effective. *Tolmar II*, No. CV 21-1784, 2024 WL 2972832, at *2 (D. Del. June 13, 2024) (explaining that a POSA would have “credit[ed] Janssen’s hypothesis that the NCT 548 dosing regimens would be safe and effective based on the regimen’s status as a phase III clinical trial”).

In the end, Janssen developed a novel dosing strategy that differed from the '548 Protocol dosing regimens in several ways, including the dose sequence, dose amount, relationship between loading doses and maintenance doses, and injection site.

2. The '544 Patent

The '544 Patent is an expired patent owned by Janssen titled “Aqueous Suspensions of Submicron 9-Hydroxyrisperidone Fatty Acid Esters.” PTX 55/DTX 54. Granted in 2003, the patent discloses a “pharmaceutical composition suitable as a depot formulation for administration by intramuscular or subcutaneous injection, comprising” among other things, a “therapeutically effective amount” of paliperidone palmitate. *Id.* at 9:65–10:4; *see* Tr. 276:21–277:2 (Wermeling). The '544 Patent taught administration of a single dose of paliperidone palmitate that is effective for approximately three weeks or longer. *See* PTX 55/DTX 54 at 8:17–19. It does not teach

loading doses to initiate treatment, discuss a multi-dose regimen or address the complexities that present themselves when administering multiple doses of varying amounts at different times. Tr. 1538:2–1539:2, 2256:12–14 (Sinko); Tr. 506:24–507:1 (Wermeling).

The '544 Patent discusses particle size, describing an “effective average particle size of less than 2,000 nm.” PTX 55/DTX 54 at 10:28–29; Tr. 294:2–11 (Wermeling). In the '544 Patent, “effective average particle size” refers to a d90 value, meaning at least 90 percent of the particles are smaller than the size indicated. *See* PTX 55/DTX 54 at 5:15–21. The '544 Patent also discloses an experiment using four formulations of paliperidone palmitate—termed A, B, C and D—that range in particle size. *See id.* at 9:25–31; Tr. 295:3–8 (Wermeling). All four formulations were “administered to four beagle dogs intramuscularly,” *see* PTX 55/DTX 54 at 9:48–51, but only formulations C and D “were put on a three month stability test” for further study, *id.* at 9:33–35; Tr. 1529:24–1530:8 (Sinko). Notably, Formulation B—one of the formulations *not* chosen for further study—is the only formulation within the range disclosed in the '906 Patent. Tr. 1795:5–18 (Sinko).

3. The WO '384 Publication

International Publication WO '384 is a patent application by Janssen published in 2006, titled “Preparation of Aseptic 3-[2-[4-(6-Fluoro-1,2-Benzisoxazol-3-yl)-1-Piperidinyl]Ethyl]-6,7,8,9-Tetrahydro-9-Hydroxy-2-Methyl-4H-Pyridio[1,2-a]Pyrimidin-4-One Palmitate Ester.” PTX 66/DTX 72. The WO '384 does not disclose a dosing regimen like the '906 Patent. Tr. 1548:23–1549:5 (Sinko). The invention relates to “a process for preparing aseptic crystalline” paliperidone palmitate. PTX 66/DTX 72 at 1:5–9. Among other things, in an example in the application, it discloses specific amounts of active and inactive ingredients for an LAI paliperidone palmitate formulation. The example states that the “suspension was filled aseptically into sterile

syringes” in dose volumes corresponding to a range of 25 to 150 mg-eq. of paliperidone. *See id.* at 18:10–15; Tr. 305:9–21 (Wermeling).

D. Obviousness of Claim 2

The parties agree that the closest prior art is the ’548 Protocol. Def. Br. at 24–25, 37; Pltf. Br. at 16, 51 n.11. Teva alleges that based on various pieces of prior art discussed herein, “a POSA would have found it obvious to modify the ’548 Protocol” to reach Claim 2. Def. Br. at 25. The ’548 Protocol discusses three regimens of four equal doses of 50, 100 or 150 mg-eq. As discussed above, in light of its lack of results, a POSA would only have inferred that Janssen believed its hypothesis would result in safe and effective dosing regimens.

Teva must show by clear and convincing evidence that a POSA “would have had reason to combine the teaching of the prior art references to achieve the claimed invention” and “would have had a reasonable expectation of success from doing so.” *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1068–69 (Fed. Cir. 2012) (quoting *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009)). The prior art references must not be analyzed in isolation, but with consideration of their “interrelated teachings.” *See KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). In short, the obviousness analysis must not proceed “in a narrow, rigid manner.” *Id.* at 427–28.

A POSA would not have known merely from the ’548 Protocol itself which, if any, of the many aspects of the protocol should be altered. *See Tolmar I*, 718 F. Supp. 3d 394, 428 (D. Del. 2024). “[A] conclusion of obviousness does not follow from merely ‘vary[ing] all parameters or try[ing] each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.’” *Grunenthal GmbH*

v. Alkem Lab'ys Ltd., 919 F.3d 1333, 1345 (Fed. Cir. 2019) (second and third alterations in original) (quoting *In re Kubin*, 561 F.3d 1351, 1359–60 (Fed. Cir. 2009)). This is especially true in the pharmaceutical field, where each clinical trial testing any slight modification yields extremely high costs. *Tolmar I*, 718 F. Supp. 3d at 428. Instead, Teva must prove that a POSA would have had a motivation to modify or combine the teachings from the prior art to reach the specific dosing regimen in Claim 2, and have a reasonable expectation of success in doing so.⁹ See *KSR Int'l Co.*, 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 the elements *in the way the claimed new invention does.*” (emphasis added)).

Specifically, Teva must prove that a POSA would have been motivated and have a reasonable expectation of success in modifying the '548 Protocol to address the following distinctions between the '548 Protocol and the '906 Patent's Claim 2. The '548 Protocol discusses equal doses throughout the treatment plan, PTX 54/DTX 55 at 1, whereas the '906 Patent discloses a high, unequal, decreasing loading dose regimen of 150 mg-eq. followed by 100 mg-eq., *see, e.g.*, PTX/DTX 1 at 32:11–30. Further, the maintenance doses in the '906 Patent are independent of the loading doses and can range from 25 mg-eq. to 150 mg-eq., PTX/DTX 1 at 32:25–30, whereas the '548 Protocol requires the maintenance doses to be equivalent with the loading doses, PTX 54/DTX 55 at 1 (disclosing regimens of 150 mg-eq., 100 mg-eq. and 50 mg-eq.). The '548 Protocol also calls for gluteal injections, *id.*, whereas the '906 Patent discloses loading doses administered in the deltoid, PTX/DTX 1 at 32:15, 32:20.

⁹ Contrary to Teva's arguments regarding loading doses (Def. Br. at 26–29), Teva must prove that a POSA would have been motivated to change or combine the prior art to arrive at the specific dosing regimen of Claim 2. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418–19 (2007) (“[I]nventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.”).

Ultimately, as discussed in detail below, Teva's arguments are unsupported by the record, contradicted by the prior art and inconsistent with its own expert's testimony. Teva is unable to overcome these deficiencies to prove the obviousness of Claim 2.

1. Unequal, Decreasing Loading Doses

In an attempt to carry its burden to prove obviousness by clear and convincing evidence, Teva puts forth several unavailing arguments as to why a POSA would be motivated to modify the '548 Protocol to achieve the high, unequal, decreasing loading dose regimen (150/100 mg-eg.) of Claim 2. *See* Def. Br. at 29–35. Given that Teva's arguments center around a motivation to *modify* the '548 Protocol, and because a motivation need not originate from the reference to be modified, Teva relies on various other pieces of prior art. *See Tolmar I*, 718 F. Supp. 3d at 427 (“In the absence of a reason to modify the NCT dosing regimens, NCT 548 would not render the '906 claims obvious.”).

Although Teva includes the WO '384 and the '544 Patent in its disclosed obviousness combinations, FPTO at 11, these pieces of prior art do not provide a motivation to achieve Claim 2's dosing regimen. As Teva's expert in pharmacokinetics, Dr. Daniel Paul H. Wermeling,¹⁰ acknowledged, neither reference discloses a loading dose regimen. *See* Tr. 512:5–8 (Wermeling) (“Q: Does WO '384 give you a reason to give a Day 1 dose of 150 mg equivalents in the deltoid and a second dose in the deltoid of 100 mg equivalents on Day 6 to 10? A: It does not.”), 506:24–507:1 (Wermeling) (“Q: And the '544 patent doesn't say anything about giving any doses on Day 1 and Day 8, right? A: Correct. There's nothing about that kind of schedule.”);

¹⁰ Dr. Wermeling is a named author on over 35 peer-reviewed publications related to pharmacokinetics, pharmacodynamics and bioavailability. FPTO at 41–42. He has also worked as a clinical investigator on studies related to pharmacokinetics and pharmacodynamics, has received over 60 grants for such studies and is a named inventor on six U.S. patents. *Id.*

see also Tr. 2256:12–14 (Sinko) (testifying that the ’544 Patent would not have “taught or suggested to a skilled artisan to use a loading dose regimen”). Thus, neither piece of prior art would motivate a POSA to modify the ’548 Protocol to achieve the loading dose regimen of Claim 2.¹¹

Teva also relies on two articles by Dr. Larry Ereshefsky et al. from 1990 (“Ereshefsky 1990”) and 1993 (“Ereshefsky 1993”) (collectively, the “Ereshefsky References”),¹² a 2001 article by Dr. James L. Karagianis et al. (“Karagianis”)¹³ and a May 2007 label for Haldol Decanoate (“Haldol Label”).¹⁴ Teva asserts these pieces of prior art provide a motivation to reach the 150/100 mg-eq. loading dose regimen, and its arguments are addressed in turn below.¹⁵

i. Motivation Based on Treating an Acutely Agitated Patient and Bringing the Patient into the Therapeutic Window Faster

Teva argues that a POSA would be motivated by the prior art to select an initial loading dose of 150 mg-eq. because it was the “maximum effective and safe dose” from the ’548 Protocol. Def. Br. at 30 (citation omitted). At trial, Dr. Wermeling testified regarding a POSA’s motivation to modify the first dose related to treatment of an “acutely agitated” patient. *See, e.g.*, Tr. 321:11–

¹¹ Teva’s argument regarding modification to the loading dose regimen based on a patient’s body weight, relying on the ’544 Patent (Def. Br. at 30–31), is unpersuasive. Teva does not provide sufficient support in the record for this theory, and as discussed above, the ’544 Patent does not provide a motivation to arrive at Claim 2’s dosing regimen.

¹² Larry Ereshefsky et al., *Kinetic and Clinical Evaluation of Haloperidol Decanoate Loading Dose Regimen*, 26 *Psychopharmacology Bull.* 108 (1990); Larry Ereshefsky et al., *A Loading-Dose Strategy for Converting From Oral to Depot Haloperidol*, 44 *Hosp. & Cmty. Psychiatry* 1155 (1993).

¹³ James L. Karagianis et al., *Rapid Tranquilization With Olanzapine in Acute Psychosis: A Case Series*, 62 (suppl. 2) *J. Clinical Psychiatry* 12 (2001).

¹⁴ Haldol is the brand name for LAI haloperidol decanoate. Def. Br. at 16.

¹⁵ The Court notes that the parties presented minimal testimony and evidence on the Janicak and Revill prior art references at trial. On remand, Teva only mentions the Janicak reference once, in passing as a cumulative citation (Def. Reply Br. at 12), and does not mention the Revill reference. Nonetheless, the Court has considered these references and finds that they do not alter the Court’s obviousness analysis. *See* PFOF ¶¶ 118–19; DFOF ¶¶ 232–33, 264–67.

22, 426:6–8 (Wermeling). Now, Teva appears to pivot to a revised theory that a POSA would choose an initial high loading dose to bring a patient “into the therapeutic window as quickly as possible.” Def. Br. at 30 (citation omitted). However, Teva’s arguments rely on Dr. Wermeling’s testimony that is both contradicted and unpersuasive, as well as prior art that does not support its contentions. Without credible evidence, Teva’s motivation theories as to the first loading dose are unavailing.

Dr. Wermeling explained that a POSA would have been motivated to use a high first loading dose in “life-threatening circumstance[s].” Tr. 321:11–16 (Wermeling). But the premise of Dr. Wermeling’s argument—that a POSA would use an LAI to treat a patient in an acute situation—was contradicted by Teva’s own psychiatrist expert, Dr. René Kahn.¹⁶ Dr. Kahn testified that LAIs would *not* be used for an acutely agitated patient. Tr. 90:12–19 (Kahn) (Q: “And do you use long-acting injectable medications in emergency situations? A: No, one doesn’t. Q: Why not? A: Because long-acting injectables are not designed to be used in emergency situations. They don’t work fast enough.”). Dr. Kahn explained that an LAI, as indicated by its name, is “long acting,” and in an “emergency situation, it is much more important to acutely and immediately control the symptoms.” Tr. 90:20–23 (Kahn). Janssen’s expert on the treatment of psychotic disorders, Dr. Christian G. Kohler,¹⁷ agreed, stating that “short-acting medications” are “*always*” used for the “treatment of acute agitation.” Tr. 1931:23–1932:1

¹⁶ Dr. Kahn is the Esther and Joseph Klingenstein Professor and System Chair of Psychiatry at the Icahn School of Medicine at Mount Sinai. FPTO at 40–41. Dr. Kahn has conducted extensive research on schizophrenia and its treatment, has published over 900 research papers and has been awarded multiple honors for his work in the field of psychiatry. *Id.*

¹⁷ Dr. Kohler is the Clinical Director of Neuropsychiatry in the Neuropsychiatry Division of the Department of Psychiatry at the Perelman School of Medicine at the University of Pennsylvania. FPTO at 37–38. Dr. Kohler has over twenty years of experience teaching psychiatry to medical students and residents in medical schools and hospitals, has extensive research experience in neuropsychiatric disorders and is the author of over 80 peer-reviewed research publications. *Id.*

(Kohler) (emphasis added). Prior art also supports this testimony. For example, one reference explains that “[i]n the acute phase of schizophrenia, short-acting injections may be required because of their quick action.” PTX 64 at 282.

Teva also relies on the Ereshefsky References as teaching a POSA to “increase the first dose.” Def. Br. at 34. But in the Ereshefsky References, all patients were required to be “stabilized for at least two weeks on oral haloperidol before starting the depot regimen,” and the study reported a drop in plasma concentration of haloperidol in the first 14 days. PTX 60/DTX 89 at 1157 (Ereshefsky 1993); Tr. 1568:21–1569:13 (Sinko) (discussing Ereshefsky 1990 and noting that those “patients were established and stabilized on oral haloperidol, and then they were switching them to the haloperidol decanoate”). Thus, a POSA analyzing the Ereshefsky References would understand that LAIs did not work fast enough to treat acute conditions. Although Dr. Wermeling also relied on Karagianis at trial, his testimony on this prior art is similarly unavailing. Dr. Wermeling testified that Karagianis was “relevant” because it taught to use “loading strategies” with oral doses of olanzapine to achieve “rapid neuroleptization,” which is related to treating an “agitated patient.” Tr. 313:11–314:22 (Wermeling). However, Dr. Kahn explained that rapid neuroleptization “has nothing to do with the use of long-acting injectables.” Tr. 2382:8–2384:11 (Kahn). In short, Dr. Kahn’s testimony and the prior art undermine Dr. Wermeling’s theory regarding a POSA’s motivation to give the maximum safe and effective dose to an acutely agitated patient.

On remand, Teva reframes its argument and contends that a POSA would choose to employ this “maximum effective and safe dose” to bring a patient “into the therapeutic window as quickly as possible.” Def. Br. at 30 (citing ECF No. 167-1 ¶ 343). The only testimony cited by Teva in support of this argument is Dr. Wermeling explaining his acute agitation theory. *Id.* (citing ECF

No. 167-1 ¶ 343, which in turn cites Tr. 321:1–22, 426:2–8 (Wermeling)). But as described above, the acute agitation theory was unpersuasive, and therefore Teva’s revised motivation theory fares no better.

Furthermore, Janssen’s expert in pharmacokinetics, Dr. Patrick J. Sinko,¹⁸ rejected the idea that one can “reach the therapeutic threshold faster” simply by increasing the dose of paliperidone palmitate. Tr. 2109:22–2110:04 (Sinko). Dr. Sinko explained that increasing the dose may “get[] more drug into the body, but it’s not occurring more quickly.” Tr. 1592:22–1594:25 (Sinko); *see also* Tr. 2111:6–13 (Sinko) (recommending “a faster formulation [rather] than an increased dose” to reach a concentration sooner), 1779:22–1780:1 (Sinko). Indeed, Dr. Wermeling testified that to adjust the release characteristics of the drug, a POSA would change the *particle size*. *See* Tr. 299:7–8 (Wermeling) (“The particle sizes in the formulation are managed to provide release characteristics that are desirable.”), 293:23–24 (Wermeling) (“[P]harmacokinetic properties can be altered by altering the particle sizes made in the formulation.”), 291:15–19 (Wermeling). Reinforcing this testimony, Dr. Sinko credibly conveyed that the Goodman and Gilman reference (“Goodman & Gilman”)¹⁹ explains that the “formulation is controlling the absorption.” Tr. 1536:8–21 (Sinko). Thus, contrary to Teva’s assertion, both sides’ experts agreed that a POSA seeking to achieve rapid therapeutic effects would be motivated to modify the particle size of paliperidone palmitate, not its dose size.²⁰ *See* Tr. 581:24–582:2 (Block) (“[S]maller particles,

¹⁸ Dr. Sinko is a Distinguished Professor of Pharmaceutics in the Ernest Mario School of Pharmacy at Rutgers. FPTO at 36–37. Dr. Sinko has over thirty years of research experience in drug formulation, drug delivery technology and drug targeting. *Id.* Dr. Sinko has given over 160 invited lectures, has published 175 articles in scientific journals and serves as a grant reviewer for the National Institute of Health. *Id.*

¹⁹ Goodman & Gilman’s *The Pharmacological Basis of Therapeutics* (Laurence L. Brunton ed., McGraw-Hill, 11th ed. 2006).

²⁰ The Court acknowledges that a POSA can be motivated to do more than one thing. *See Teva II*, 97 F.4th 915, 930 (Fed. Cir. 2024). Here, however, the evidence demonstrates a POSA would be motivated

having a larger surface area, provide a more substantial release rate than larger particles, which have a relatively smaller surface area. And dissolution or release . . . is surface area dependent.”).

In sum, Teva’s argument that a POSA would be motivated to modify the initial loading dose of the ’548 Protocol is unpersuasive; it is not sufficiently supported by Teva’s own expert testimony and is contradicted by the prior art.

ii. Motivation Based on Excessive Accumulation

Teva further argues that a POSA would be motivated to select a second loading dose of 100 mg-eq. because reducing the second dose would avoid excessive accumulation of paliperidone palmitate. Def. Br. at 31. However, the prior art does not support Teva’s asserted motivation.

Ereshefsky 1993 teaches the reduction of *maintenance* doses, not *loading* doses, to avoid excessive accumulation. See PTX 60/DTX 89 at 1156. Teva’s expert Dr. Wermeling acknowledged as much, stating that Ereshefsky 1993 teaches reduced *maintenance* dosages of haloperidol decanoate in the “second and third months” of the study “to avoid this excessive accumulation.” Tr. 322:17–323:1 (Wermeling). As Dr. Wermeling recognized on several occasions, loading doses and maintenance doses are distinct concepts. See Tr. 372:15–24 (Wermeling) (testifying that FDA guidance that is “true for maintenance dosing” is “not correct as applied to” loading doses), 211:8–12 (Wermeling) (stating that loading doses are given “more frequently than” maintenance doses), 312:12–13 (Wermeling) (explaining that a “loading dose is the use of higher doses than maintenance at a shorter dosing interval”). A POSA would not infer that Ereshefsky’s teachings on maintenance doses would apply equally to loading doses. See PTX 59/DTX 88 at 109 (Ereshefsky 1990 explaining that “[a] loading-dose regimen is used to obtain

to modify the particle size to achieve therapeutic effects more rapidly, and there is insufficient evidence to support that a POSA would be motivated to modify the loading dose size to achieve the same.

therapeutic steady-state [plasma concentrations] earlier in the course of therapy. . . . then subsequent doses reflect maintenance treatment to maintain the desired steady-state [plasma concentrations]”); PTX 65 at 26–27 (explaining different equations for calculating loading and maintenance dose amounts); *see also Endo Pharms. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1385 (Fed. Cir. 2018) (recognizing distinction in prior art teachings towards maintenance versus loading doses).

Of course, a motivation “does not have to be found explicitly in the prior art,” *In re Kahn*, 441 F.3d 977, 987 (Fed. Cir. 2006), and a POSA can employ “inferences and creative steps” to get from the prior art to the claimed invention, *KSR Int’l Co.*, 550 U.S. at 418. But Teva has the burden to show by clear and convincing evidence *how* the prior art would motivate a POSA to achieve the claimed regimen. Here, Teva points to the reduced maintenance doses of Ereshefsky 1993 and asserts that a POSA would accordingly be “motivated to select a 100 mg-eq. dose for the second loading dose.” Def. Br. at 31. Missing from Teva’s argument is a credible explanation of *how* a POSA would reasonably infer from the reduction of a *maintenance* dose a motivation to reduce a second *loading* dose. *See In re Magnum Oil Tools, Int’l, Ltd.*, 829 F.3d 1364, 1376 (Fed. Cir. 2016) (“[T]he ultimate burden of persuasion of obviousness must remain on the patent challenger.”).

Teva also argues that a POSA would select a 100 mg-eq. second loading dose to “avoid possible overexposure” in “patients with smaller bodies or milder symptoms.” Def. Br. at 31. However, Teva does not point to persuasive testimony to establish its point. Teva’s cited testimony does not even appear to mention smaller bodies or milder symptoms. *See id.* (citing Tr. 148:17–19 (Kahn); Tr. 321:1–323:1, 474:20–475:22 (Wermeling)). Moreover, Teva does not explain why a “smaller patient” or one with “milder symptoms” would require a reduced *second* loading dose

while still maintaining the *initial*, high 150 mg-eq. dose. Indeed, Teva’s expert testimony regarding reduction of doses for a renally-impaired patient advocated for a reduction in *both* loading doses, not just the second dose. *See* Tr. 148:13–16 (Kahn). Teva’s assertion that a POSA would be motivated to reduce dosage for a “smaller patient” or one with “milder symptoms” appears to be attorney argument without sufficient support in the record. *Icon Health & Fitness, Inc. v. Strava, Inc.*, 849 F.3d 1034, 1043 (Fed. Cir. 2017) (“Attorney argument is not evidence.”).

Therefore, Teva’s argument that a POSA would be motivated to reduce the second loading dose of the ’548 Protocol to achieve the claimed regimen is unpersuasive.

iii. Motivation Based on the 20 Times Multiplier

In another attempt to prove motivation, Teva asserts that the Ereshefsky References, as well as the Haldol Label, provide guidance to arrive at the 150/100 mg-eq. loading dose regimen in Claim 2. *See* Def. Br. at 32.²¹ Specifically, Teva argues that the Ereshefsky References and the Haldol Label teach a POSA to multiply the *oral* dose of haloperidol by 20 times to reach the *injectable* dose. Def. Br. at 32. Applying this 20 times multiplier to the maximum recommended dose of Invega ER, which is oral paliperidone (12 mg), PTX 57 at 25, Teva argues that a POSA would be motivated to use a 240 mg-eq. loading dose of paliperidone palmitate to treat a patient, Def. Br. at 32. According to Teva, the 240 mg-eq. dosage amount “could be approximated” into the 150/100 mg-eq. dosing regimen of Claim 2. *Id.*

The record does not support that a POSA would take the specific dosing recommendations from these references and apply them to reach Claim 2. The Ereshefsky References and the Haldol

²¹ As Janssen points out (Pltf. Reply Br. at 24 n.10), the Haldol Label was not disclosed in the Final Pretrial Order, including the Final Pretrial Order’s obviousness combinations, and Teva failed to comply with Local Patent Rule 3.3. *See Celgene Corp. v. Hetero Labs Ltd.*, No. 17-3387, 2021 WL 3701700 (D.N.J. June 15, 2021). Regardless, even considering the Haldol Label, the Court finds Teva’s arguments regarding such to be unsubstantiated.

Label study haloperidol decanoate, not paliperidone palmitate. PTX 59/DTX 88; PTX 60/DTX 89. Haloperidol decanoate has a different pharmacokinetic profile than paliperidone palmitate. Tr. 513:17–24 (Wermeling); *see also* Tr. 515:9–21 (Wermeling) (noting that the drugs are “inherently” different, in part because “one is a solution and one is a particle, so you have different rate processes”). Dr. Sinko explained that because each drug acts differently in a patient, studies on drugs with different pharmacokinetics cannot be directly correlated. Tr. 1566:18–1567:11 (Sinko). Although a POSA would not disregard the teachings of the Ereshefsky References and the Haldol Label because they study a different drug, Teva’s argument requires a POSA to be motivated to apply the specific quantitative amounts recommended based on haloperidol decanoate to paliperidone palmitate.²² Teva does not provide sufficient evidence as to *why* a POSA would do so.

Further, in testimony cited by Teva in support of this argument, Dr. Wermeling does not explain why a POSA would be motivated to achieve the specific sequence and dosing amounts of Claim 2. *See* Def. Br. at 32 (citing ECF No. 167-1 ¶ 352, which in turn cites Tr. 557:16–22 (Wermeling)). Although Dr. Wermeling explains generally the teachings of the Ereshefsky References and that “20 times 12” is “240,” Tr. 557:16–22 (Wermeling), this testimony does not credibly support how a POSA would be motivated to choose the size of the two loading doses at each point in time. Despite presenting attorney argument regarding the Haldol Label, Teva does not cite any persuasive testimony supporting its argument. This is unsurprising, given that Teva did not identify the Haldol Label as prior art in the Final Pretrial Order. FPTO at 11. Instead,

²² Indeed, as the Federal Circuit acknowledged when discussing references involving different antipsychotic LAIs, “the specific *amounts* of medication given in these references would not correlate to the amount of paliperidone palmitate claimed.” *Teva II*, 97 F.4th 915, 930 (Fed. Cir. 2024) (emphasis in original).

Teva relies on its already-rejected reasoning that a POSA would seek to rapidly achieve the “therapeutic window” before decreasing dosage to avoid “excessive accumulation.” Def. Br. at 32. As discussed above, these arguments are unavailing because they are not sufficiently supported by the record and misconstrue the prior art. Therefore, Teva’s argument that a POSA would be motivated to select the dosing amounts from the ’906 Patent based on the 20 times multiplier contained in the prior art is unpersuasive.

iv. Motivation Based on the Haldol Label’s Dosing

Teva advances another argument regarding the Haldol Label and its recommendation to multiply the oral dose by 20 times to reach the injectable dose. As an initial matter, although a POSA would recognize the prior art’s teachings, a patent challenger must show that the prior art “suggest[s] that the *specified elements* should be selected and combined.” *Orexo AB v. Actavis Elizabeth LLC*, 903 F.3d 1265, 1273 (Fed. Cir. 2018) (emphasis added). The Haldol Label instructs to “begin with lower initial doses and to adjust the dose upward as needed,” see Tr. 2392:19–2393:1 (Kahn); DTX 149 at 12, whereas the ’906 Patent’s dosing regimen starts higher and decreases. As presented by Teva, the Haldol Label teaches the opposite of Claim 2’s dosing regimen. See *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1360 (Fed. Cir. 2007) (noting evidence presented must be considered in its “totality”).

Teva cites to a hypothetical presented to Janssen’s expert, Dr. Kohler, that is inconsistent with the Haldol Label. Def. Br. at 16, 33–34. The hypothetical inquired about the loading dose regimen under the Haldol Label’s teachings if 180 mg was being administered. Given that the Haldol Label recommends a maximum first loading dose of 100 mg, DTX 149 at 12–13, Dr. Kohler agreed, following the hypothetical, that the Haldol Label would instruct a 100/80 mg loading dose regimen. Tr. 1967:24–1968:15 (Kohler). But as Janssen points out, the premise of

the hypothetical presented to Dr. Kohler is contrary to the Haldol Label. The Haldol Label only recommends multiplying the oral medication by 20 times if a patient received *more than 10 milligrams* a day of the oral equivalent. Pltf. Reply Br. at 26; DTX 149 at 12. Therefore, if applying the Haldol Label's 20 times conversion, a patient receiving an injectable would receive *more than 200 mg*, split into two doses: a first loading dose of 100 mg, and a second loading dose of more than 100 mg. Since the Haldol Label recommends a maximum 100 mg initial dose, the *second* loading dose would increase (not the first) as the overall dosage amount increased. In short, applying the Haldol Label's 20 times conversion instructs an increasing regimen that is unlike the decreasing regimen of Claim 2. Thus, Teva's argument is unpersuasive.

v. *Prior Art's Teachings on Motivation in Toto*

Considering the evidence discussed in detail above *in toto*, Teva fails to prove by clear and convincing evidence that a POSA would be motivated to employ Claim 2's loading dose regimen.

Beginning with the '548 Protocol, as many of Teva's arguments do, a POSA would credit Janssen's hypothesis that the doses tested are likely to be safe and effective. However, this would not provide a motivation to achieve the novel, high, unequal, decreasing loading dosing regimen of Claim 2. Teva then turns to other theories purportedly grounded in the prior art to establish a motivation to modify the '548 Protocol. Teva asserts that a POSA would be motivated to increase the initial loading dose to achieve therapeutic effects more rapidly. However, the Goodman & Gilman reference and expert testimony explain that a POSA would change the particle size, not dosing amounts, to reach the therapeutic window faster. Next, Teva asserts that a POSA would be motivated by the prior art to decrease the second loading dose to avoid excessive accumulation. Once again, this theory is unsupported by the prior art, which teaches a reduction in *maintenance* doses, not loading doses. Teva also points to the Ereshefsky References and the Haldol Label but

does not adequately explain why a POSA would straightforwardly apply the specific values from haloperidol decanoate in those studies to paliperidone palmitate. In any event, the Haldol Label in fact appears to teach *increasing* loading doses, directly contrary to Claim 2.

Of course, Teva could always show that a POSA would be able to use “inferences and creative steps” to get from these prior art references to the claimed regimen. *KSR Int’l Co.*, 550 U.S. at 418. But as discussed above, Teva’s arguments are unpersuasive, misconstrue the prior art or are contradicted by the record. And although a motivation “does not have to be found explicitly in the prior art,” there must still be “some articulated reasoning . . . to support the legal conclusion of obviousness.” *In re Kahn*, 441 F.3d at 987–88. Combining the teachings from the prior art references, a POSA would understand that Janssen believed the ’548 Protocol’s regimens would be safe and effective, and that the prior art taught to reduce maintenance doses (not loading doses) or an increasing loading dose regimen—contrary to the dosing regimen of Claim 2. Therefore, Teva has failed to meet its burden.

vi. Reasonable Expectation of Success

Teva’s failure to establish that a POSA would be motivated to achieve Claim 2’s dosing regimen is fatal to its obviousness argument. *See Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367–68 (Fed. Cir. 2016) (noting that it is patent challenger’s burden to establish both motivation and reasonable expectation of success). Nonetheless, the Court will address a POSA’s reasonable expectation of success.

The Court notes that the below discussion, as well as this entire Opinion, analyzes whether Teva proves that a POSA would possess a reasonable expectation of success in administering paliperidone palmitate to *a* patient according to the claimed dosing regimen. Additionally, the Court acknowledges that there is no safety and efficacy limitation in the ’906 Patent itself.

Efficacy data is not “always required for a reasonable expectation of success,” *OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375, 1385 (Fed. Cir. 2019), and obviousness does not require “[c]onclusive proof of efficacy,” *Acorda Therapeutics, Inc. v. Roxane Lab’ys, Inc.*, 903 F.3d 1310, 1333 (Fed. Cir. 2018) (alteration in original) (quoting *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014)). But “[u]nclaimed factors relevant to the feasibility of creating a useful claimed invention can impact the motivation to combine analysis if a skilled artisan would reasonably consider them.” *Natera, Inc. v. NeoGenomics Lab’ys, Inc.*, 106 F.4th 1369, 1378 (Fed. Cir. 2024) (holding there was no clear error in the district court’s findings on motivation or reasonable expectation of success where the court referenced unclaimed factors). Indeed, Dr. Wermeling explained that a POSA would be motivated to use a dosing regimen that is safe and effective. *See, e.g.*, Tr. 320:5–12, 324:18–325:11, 426:6–12 (Wermeling). Further, the fact that the ’548 Protocol does not contain safety and efficacy data, as discussed above, surely impacts what the protocol would suggest to a POSA. *See OSI Pharms.*, 939 F.3d at 1385 (noting that presence of “no efficacy data” impacts the “reasonable expectation of success” to be drawn from references).

In arguing for expectation of success, Teva points to the three primary prior art references—the ’548 Protocol, the ’544 Patent and the WO ’384. Def. Br. at 36–38. The ’548 Protocol alone does not establish an expectation of success in achieving the dosing regimen of Claim 2 for a patient. Although a POSA would credit Janssen’s hypothesis and the ’548 Protocol’s Phase III status, drug trials routinely fail. *See* Tr. 543:7–10 (Wermeling) (explaining that “most drugs fail” and that the drug development process is “very difficult”). The ’548 Protocol, even as a Phase III clinical trial, was only a hypothesis. *See OSI Pharms.*, 939 F.3d at 1378, 1384–85 (finding no reasonable expectation of success because creating drugs

to treat cancer is a “highly unpredictable art” and a Phase II clinical trial had “no efficacy data or any other reliable indicator of success” for claims directed to treating “a mammal”).

Additionally, the ’548 Protocol is different from the claimed dosing regimen. For example, the ’548 Protocol only discloses equal doses whereas the claimed regimen discloses high, unequal and decreasing doses. A clinical trial protocol for a *different* dosing regimen does not establish a reasonable expectation of success for the Claim 2 dosing regimen. Even if a POSA would expect the ’548 Protocol to succeed because it was a Phase III clinical trial, that does not demonstrate an expectation of success in achieving the specific dosing regimen of Claim 2. *See Salix Pharms., Ltd. v. Norwich Pharms. Inc.*, 98 F.4th 1056, 1062 (Fed. Cir. 2024) (finding that the disclosure of a Phase II “clinical trial plan” was not enough, standing alone, to render obvious a distinct dosing regimen “that was not included within the planned clinical trial”).

Teva also argues that the WO ’384 and the ’544 Patent create a reasonable expectation of success because both “disclose effective treatment options.” Def. Br. at 38. However, these prior art references only disclose the use of a single dose. *See* PTX 55/DTX 54 at 8:18–20; PTX 66/DTX 72 at 2; Tr. 1538:2–6 (Sinko) (explaining that the ’544 Patent “does not” include loading doses), 511:15–17 (Wermeling) (agreeing that the WO ’384 “does not disclose anything about a dosing regimen”). Single-dose regimens are not as complex or unpredictable as multi-dose regimens, such as the ’906 Patent, which encounter difficulties such as potentially toxic “accumulat[ion]” and “fluctuation between administrations” that single-dose regimens do not. Tr. 1597:21–1600:10 (Sinko); *see also Eli Lilly & Co. v. Teva Pharms. Int’l GmbH*, 8 F.4th 1331, 1349 (Fed. Cir. 2021) (“Unpredictability of results equates more with nonobviousness rather than obviousness.”) (quoting *Honeywell Int’l Inc. v. Mexichem Amanco*

Holding S.A. DE C.V., 865 F.3d 1348, 1356 (Fed. Cir. 2017)). Therefore, these references fall short of providing a reasonable expectation of success for treating *a* patient.

Considered altogether, the evidence discussed above still does not create a reasonable expectation of success. The '548 Protocol's dosing regimens are different than Claim 2's regimen, and a clinical trial for a different dosing regimen, without more, does not create an expectation of success. When evaluating the '548 Protocol, a POSA would also take into consideration that most drugs fail during the development process. Tr. 543:7–10 (Wermeling); *see also KSR Int'l Co.*, 550 U.S. at 418. Further, neither the '544 Patent nor the WO '384 provides information that is critical to achieving a multi-dose regimen. *See Teva Pharms. USA, Inc. v. Corcept Therapeutics, Inc.*, 18 F.4th 1377, 1381 (Fed. Cir. 2021) (noting that “reasonable-expectation-of-success analysis” must be “frame[d] . . . around th[e] specific dosage” claimed). Multi-dose regimens are unpredictable in ways that single-dose regimens are not. With multi-dose regimens, as discussed, a POSA must account for “accumulation” of the drug in a patient's body, Tr. 1598:16–1599:1 (Sinko), “fluctuations” in blood levels, Tr. 1597:17–1599:14 (Sinko), and avoiding “adverse effects” from too much of the drug, Tr. 1597:17–1599:14 (Sinko). These concepts are inherently “more complicated” with a dosing regimen like Claim 2, Tr. 1600:21–1601:10 (Sinko), because there are different dose amounts being given at different intervals to a patient. Although the '548 Protocol includes multi-dose regimens, without results, what a POSA can infer from it is limited. *See Tolmar I*, 718 F. Supp. 3d at 426 (“But without knowing the results of the Phase III clinical trial, a person of ordinary skill in the art would have learned nothing from NCT 548 beyond crediting Janssen's hypothesis.”).

Moreover, Teva fails to overcome evidence in the record that a POSA would likely utilize a *low and increasing* dosing regimen when administering an antipsychotic medication, contrary to

the dosing regimen of Claim 2.²³ Dr. Kahn explained that a POSA would understand that the recommended dosing for antipsychotics is to start at a low dose before “adjust[ing] the dose upward as needed” or “slowly work[ing] up to a higher dose.” *See* Tr. 2392:19–2393:1, 168:19–169:5 (Kahn). This is because it was known that severe symptoms occurred more frequently at higher doses. *See* Tr. 2392:19–2393:1 (Kahn); Tr. 1903:6–1905:24 (Kohler); DTX 93 at 313 (“Low doses of risperidone have been reported to attenuate negative symptoms of schizophrenia with a low incidence of extrapyramidal side effects. Extrapyramidal effects are commonly seen, however, with doses of risperidone in excess of 6 mg/day.”); PTX 808 at s122 (“[A]typical antipsychotics should be used as first-line therapy, commencing with a low dose and titrating upwards very slowly over a period of several weeks.”). In consideration of this evidence, contrary to the premise of Teva’s arguments, a POSA would not likely start with the 150 mg-eq. loading dose, nor have a reasonable expectation of success in doing so. *See Pfizer, Inc.*, 480 F.3d at 1360 (“The trial court has the responsibility to determine whether the challenger has met its burden by clear and convincing evidence by considering the totality of the evidence, *including any rebuttal evidence presented by the patentee.*” (emphasis added)).

In sum, Teva fails to carry its burden to prove that a POSA cognizant of the prior art would have a reasonable expectation of success in achieving the claimed dosing regimen.

²³ The conventional wisdom is relevant to the background knowledge of a POSA. Regardless, even if the Court did not consider this conventional wisdom, the Court’s conclusion would remain the same: a POSA would not have a reasonable expectation of success in achieving the claimed dosing regimen. But as instructed by the Federal Circuit in *Teva II*, 97 F.4th 915, 933–34 (Fed. Cir. 2024), the Court will not compare the results of the claimed dosing regimens to the conventional wisdom when discussing unexpected results in its analysis of secondary considerations. *See supra* § II.H.3.

2. Deltoid Injection Site

Having determined that the loading dose regimen is not obvious, the Court concludes that Claim 2 is not obvious “when considered ‘as a whole.’” *Jones v. Hardy*, 727 F.2d 1524, 1529 (Fed. Cir. 1984) (quoting 35 U.S.C. § 103); *see also In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000) (noting that patent challenger must establish obviousness of “the specific combination that was made by the applicant”). Nevertheless, the Court will analyze the obviousness of the deltoid as the injection site.

i. Motivation

It was known that sites for intramuscular injections included the deltoid, the gluteus and the thigh. Tr. 278:7–11, 280:16–21 (Wermeling); Tr. 1719:15–17 (Sinko). Although deltoid injections may be more painful than gluteal injections, *see* Tr. 398:10–12 (Wermeling), and result in a greater fluctuation in drug content, *see* Tr. 397:12–16 (Wermeling), 1604:11–1605:14 (Sinko), witnesses from both parties agreed that a patient may prefer the deltoid site for modesty reasons. Tr. 324:7–11 (Wermeling), 857:23–858:3 (Vermeulen). As one of Teva’s witnesses put it, a patient may prefer the deltoid because they would not have to “pull down [their] pants.” Tr. 1180:20–25 (Gopal). The Court acknowledges that a POSA “can be motivated to do more than one thing,” *Teva II*, 97 F.4th 915, 930 (Fed. Cir. 2024), and thus, a POSA would have been motivated to use the deltoid injection site. *See Tolmar I*, 718 F. Supp. 3d at 425 (holding a POSA “would have been motivated to develop a long-acting injectable that is administrable in the deltoid”).

ii. Reasonable Expectation of Success

As both parties’ experts acknowledged, a POSA would know that intramuscular injections are most commonly administered in either the deltoid or the gluteus. *See* Tr. 280:16–21

(Wermeling), 1719:15–17 (Sinko) (agreeing that the “two most common” sites for “intramuscular injection of drugs” are “the gluteal and the deltoid”). A POSA would have also known intramuscular administration could be used with paliperidone palmitate specifically, as the ’544 Patent discloses as much. Tr. 277:22–278:2 (Wermeling). A POSA would thus understand that paliperidone palmitate could be injected in either the gluteus or the deltoid—*i.e.*, the two injection sites were interchangeable. For these reasons, a POSA would have a reasonable expectation of success in achieving the deltoid injection site of Claim 2. *See Tolmar I*, 718 F. Supp. 3d at 425 (holding a POSA “would . . . have had a reasonable expectation of success in administering the NCT 548 injections to the deltoid”). Even though a POSA would have expected interchangeability of—and thus similar results from—the injection sites, *very favorable* results from the use of the deltoid were unexpected and are relevant to this Court’s consideration of the objective indicia of nonobviousness.

However, the obviousness of the deltoid injection site does not render Claim 2 obvious; Teva fails to establish that a POSA would be motivated to, and have an expectation of success in, achieving the claimed dosing regimen, as discussed in detail above. *See supra* § II.D.1; *see also Tolmar I*, 718 F. Supp. 3d at 425–26, 435 (holding the ’906 Patent to be nonobvious despite holding that a POSA would be motivated to use the deltoid and have a reasonable expectation of success in doing so); *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 717 (Fed. Cir. 1991) (“When analyzing a patent claim for obviousness, the claim should be considered as a whole, but the differences between the claim and the prior art need to be identified . . .”).

E. Claim 2 Presumption of Obviousness

Teva argues that the loading doses of Claim 2 fall within the range of loading dose amounts discussed in the ’548 Protocol. Specifically, Teva contends that the ’548 Protocol includes a range

of total loading doses from 200 mg-eq. (two loading doses of 100 mg-eq.) to 300 mg-eq. (two loading doses of 150 mg-eq.). *See* Tr. 321:5–10 (Wermeling). Teva argues that the 250 mg-eq. total loading doses from Claim 2 (150/100 mg-eq.), therefore, fall within the '548 Protocol's range. *See* Def. Br. at 36.²⁴

“A *prima facie* case of obviousness typically exists when the ranges of a claimed composition overlap the ranges disclosed in the prior art.” *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012) (quoting *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003)). “[S]uch overlap creates a presumption of obviousness.” *E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018). Importantly, the presumption may be rebutted “with evidence that (1) the prior art taught away from the claimed invention; (2) there were new and unexpected results relative to the prior art; or (3) there are other pertinent secondary considerations.” *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1305 (Fed. Cir. 2015) (quoting *Galderma Lab'ys, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013)). But the presumption of obviousness only applies “when the *only difference* from the prior art is a difference in the range or value of a particular variable.” *In re Kumar*, 418 F.3d 1361, 1366 (Fed Cir. 2005) (emphasis added) (citing *In re Peterson*, 315 F.3d at 1329); *see also Tris Pharma, Inc. v. Actavis Lab'ys FL, Inc.*, 503 F. Supp. 3d 183, 203 (D. Del. 2020) (“But the presumption attaches only when the range or value of a particular variable is *the difference* between the claimed invention and the prior art.” (emphasis in original, internal quotation marks and citation omitted)), *aff'd*, No. 2021-1495, 2022 WL 2525318 (Fed. Cir. July 7, 2022).

²⁴ Teva frames its argument as the total amount of the first two loading doses. *See* Def. Br. at 36. Even if Teva argued that the individual doses fell within the range disclosed in the '548 Protocol, however, the analysis in this section applies to either argument.

Here, Teva acknowledges that Claim 2 differs from the '548 Protocol because of the dosage amounts, claimed dosing sequence and requisite deltoid injections. *See* Def. Br. at 25, 38. Therefore, even considering Teva's characterization that the dosage amounts are included in the range utilized in the '548 Protocol, the presumption cannot apply because the dosage amounts are not the "only difference from the prior art." *In re Kumar*, 418 F.3d at 1366. Indeed, the specific dosing sequence of a larger initial loading dose followed by a smaller second loading dose (150/100 mg-eq.) is not taught in the prior art. *See Pharmacyclics LLC v. Alvogen Pine Brook LLC*, 556 F. Supp. 3d 377, 408 (D. Del. 2021) (holding the presumption of obviousness did not apply because "there are many differences . . . including the . . . route of administration, and number of administrations per day"), *aff'd sub nom. Pharmacyclics LLC v. Alvogen, Inc.*, No. 2021-2270, 2022 WL 16943006 (Fed. Cir. Nov. 15, 2022) (affirming district court's holding that the presumption of obviousness was not applicable where there were "additional differences between the prior art and [the] claim"). As such, the presumption is not applicable to Claim 2 and it remains Teva's burden to prove obviousness. *See Tolmar I*, 718 F. Supp. 3d 394, 429 (D. Del. 2024) ("Even if I were to agree with Tolmar's characterization of NCT 548 as disclosing ranges of paliperidone to be included in each dose, there can be no prima facie case of obviousness because the claimed method requires administration to the deltoid rather than to the gluteal muscle.").

Nonetheless, as discussed below, the Court finds that unexpected results and other pertinent secondary considerations favor nonobviousness. Thus, even if the presumption of obviousness applied, it would be rebutted by secondary considerations. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1369 (Fed. Cir. 2007) ("Evidence of unexpected results can be used to rebut a prima facie case of obviousness.").

F. Obviousness of Claims 10 and 13

The '906 Patent discloses dosing regimens for a renally impaired patient, which include loading doses of 75/75 mg-eq. and a maintenance dose of between 25 mg-eq. to 75 mg-eq. (Claim 10) or 25 mg-eq. to 50 mg-eq. (Claim 13). Teva asserts that a POSA would be motivated to apply a 50 percent reduction to each dose of the 150/150/150/150 mg-eq. regimen of the '548 Protocol for a renally-impaired patient, thus achieving the dosing regimens of claims 10 and 13. Def. Br. at 44. Contrary to Teva's assertion, however, a 50 percent reduction to the 150 mg-eq. regimen of the '548 Protocol would not achieve Claim 13. If a 50 percent reduction is applied to the 150 mg-eq. dosing regimen of the '548 Protocol, the maintenance dose would be 75 mg-eq., but Claim 13 discloses a maintenance dose of 25 mg-eq. to 50 mg-eq. PTX/DTX 1 at 33:42–47, 33:50–52. In fact, Claim 13 cannot be achieved by a 50 percent reduction to any regimen of the '548 Protocol. If a 50 percent reduction is applied to the 100 mg-eq. dosing regimen of the '548 Protocol, then the loading doses would be 50 mg-eq., not 75 mg-eq. as disclosed in Claim 13. Regardless, Teva fails to prove a motivation to reduce dosage by 50 percent to achieve either claim.

The Court acknowledges that claims 10 and 13 do not contain a specific level of renal impairment, as noted by the Federal Circuit. However, Teva's theory of motivation, as presented by its expert Dr. Wermeling at trial, was directed to mild renal impairment. Indeed, Dr. Wermeling testified that a POSA would *not* be motivated to use this medication for a patient with moderate or severe renal impairment. Tr. 332:10–15 (Wermeling) (“[P]atients with moderate to severe renal impairment are not to receive this medicine.”). Given that it is Teva's burden to prove a motivation to reach the claimed dosing regimen, the Court's analysis below addresses Teva's motivation theory regarding mild renal impairment. *See Immunex Corp. v. Sandoz, Inc.*, 964 F.3d 1049, 1067

(Fed. Cir. 2020) (explaining that although “the claims at issue do not require any therapeutic effect,” because “[t]he focus of [defendants’] motivation to combine argument remained the therapeutic benefits of the claimed invention, . . . it was not error for the district court to frame its analysis accordingly”); *Intelligent-Bio Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1368 (Fed. Cir. 2016) (noting that although the claims “do not require quantitative deblocking at all, it is central to a finding of no motivation to combine” due to petitioner’s argument). Nonetheless, the Court also finds Teva’s arguments about *any* level of renal impairment unpersuasive.

All teachings in the prior art must be considered in the obviousness determination, “including that which might lead away from the claimed invention.” *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). Indeed, “[e]vidence suggesting reasons to combine cannot be viewed in a vacuum apart from evidence suggesting reasons not to combine.” *Arctic Cat Inc. v. Bombardier Recreational Prods. Inc.*, 876 F.3d 1350, 1363 (Fed. Cir. 2017). When considering apparently conflicting references, the factfinder must weigh each reference “for its power to suggest solutions to an artisan of ordinary skill . . . consider[ing] the degree to which one reference might accurately discredit another.” *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (alterations in original) (quoting *In re Young*, 927 F.2d 588, 591 (Fed. Cir. 1991)).

At trial, Dr. Wermeling looked to the Invega ER label and a meeting abstract from 2007 (“Cleton 2007”),²⁵ which purportedly teach a 50 percent dose reduction for a patient with mild

²⁵ A. Cleton, *Effects of Renal Impairment on the Pharmacokinetic Profile of Paliperidone Extended-Release Tablets*, 81 (suppl. 1) *Clinical Pharmacology & Therapeutics* S63 (2007).

renal impairment.²⁶ Tr. 333:6–12 (Wermeling).²⁷ Notwithstanding the focus of Dr. Wermeling’s testimony, Cleton 2007 studied subjects with mild, moderate and severe renal impairment. PTX 56/DTX 84; *see also* Tr. 1586:22–1587:8 (Sinko) (explaining that Cleton 2007 included data on “three different levels of renal impairment”). Cleton 2007’s conclusion was that a lower dose “should be considered for subjects with moderate and severe renal impairment.” PTX 56/DTX 84. Dr. Sinko credibly testified that Cleton 2007, therefore, teaches *no* dose reduction for a patient with mild renal impairment. Undermining Dr. Wermeling’s theory, Dr. Sinko explained that “one of the conclusions that [Cleton 2007] came to was for mild renal impairment . . . they would not . . . need[] to reduce the dose.” Tr. 1586:14–20 (Sinko).

Weighing the prior art and the expert testimony on the subject, the Court finds Dr. Sinko’s testimony to be persuasive and credible. *See* Tr. 1586:14–20 (Sinko). Although Teva argues that Cleton 2007 is not instructive as to a dose reduction for mild renal impairment, Def. Reply Br. at 52, its argument is unconvincing in light of Dr. Sinko’s testimony.²⁸ *See Perfect Web Techs.*,

²⁶ Teva also relies on U.S. Application No. 2007/0197591 (the “’591 Application”) and the WO ’384 for the general proposition that some dose reduction may be needed for a patient with renal impairment. Def. Br. at 43–44; Tr. 328:25–330:15 (Wermeling). The Court acknowledges that the prior art would have taught a POSA that a dose reduction may be needed for a patient with renal impairment. *See KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (explaining the court should consider the “background knowledge possessed by a person having ordinary skill in the art”). However, this knowledge does not render the specific, claimed dosing regimens obvious and does not outweigh Dr. Sinko’s credible testimony that Cleton 2007 teaches no dose reduction for those with mild renal impairment.

²⁷ Dr. Wermeling explained that a patient with “moderate to severe renal impairment [is] not to receive this medicine.” Tr. 332:13–15 (Wermeling). This testimony seemingly ignores that the Invega ER label and Cleton 2007 recommend reducing the doses for patients with moderate to severe renal impairment. *See* DTX 102 at 25; PTX 56/DTX 84.

²⁸ Insofar as Teva cites to the record at all, it points to the reference itself which includes data regarding levels of paliperidone clearance for renally impaired patients. Def. Reply Br. at 52 (citing PTX 56). However, what these various levels of paliperidone clearance would suggest to a POSA regarding the dosing of paliperidone is not “easily understandable” such that expert testimony regarding the reference is not required. *See Wyers v. Master Lock Co.*, 616 F.3d 1231, 1242 (Fed. Cir. 2010). As such, the Court looks to expert testimony to explain the import of this data to the dosing of a patient with mild renal impairment, and credible testimony on that topic is provided by Dr. Sinko. *See In re Brimonidine Patent*

Inc. v. InfoUSA, Inc., 587 F.3d 1324, 1332 (Fed. Cir. 2009) (explaining how a party’s position was “merely attorney argument lacking evidentiary support”). Based on Dr. Sinko’s testimony and a review of the prior art, the Court is persuaded that a POSA “would be led in a direction divergent from the path that was taken in the claim.” *AstraZeneca AB v. Mylan Pharms. Inc.*, 19 F.4th 1325, 1337 (Fed. Cir. 2021) (internal quotation marks omitted) (quoting *Meiresonne v. Google, Inc.*, 849 F.3d 1379, 1382 (Fed. Cir. 2017)); *see also Arctic Cat Inc.*, 876 F.3d at 1360–63 (finding jury’s determination that there was no motivation was supported by substantial evidence and noting obviousness “requires consideration of all the facts” including where “the prior art . . . contain[s] one reference suggesting a combination and others critiquing or otherwise discouraging the same”). Therefore, Teva fails to meet its burden to prove a motivation to combine the references to achieve the dosing regimens for a mild renally-impaired patient.

Turning to a patient with moderate or severe renal impairment, Dr. Wermeling—Teva’s own expert witness—testified that a POSA would *not* be motivated to use this medication for a patient with moderate or severe renal impairment. Tr. 332:13–15 (Wermeling). Notwithstanding that testimony, Teva now asserts that a POSA would be motivated to use this medication for a patient with any severity of renal impairment, including moderate or severe. But even considering Teva’s revised argument, it is unpersuasive and lacks support in the record. Specifically, the label for Invega ER teaches a 75 percent dose reduction for a patient with moderate or severe renal impairment. DTX 102 at 26; *see also* Tr. 1588:1–4 (Sinko). Importantly, reducing any of the ’548 Protocol’s dosing regimens by 75 percent does not result in the claimed dosing regimens.

Litig., 643 F.3d 1366, 1376 (Fed. Cir. 2011) (“[I]t is well within a trial judge’s discretion to require expert testimony supporting technical references that are relied on to establish obviousness.”).

Teva attempts to overcome the conflicting teachings of the prior art by pointing to the label for risperidone-based LAI medication Risperdal Consta.²⁹ Teva argues that the label for Risperdal Consta teaches half-doses for a renally impaired patient. Def. Br. at 44. However, Teva did not rely on this argument at trial, and accordingly does not cite any testimony explaining how a POSA would have applied the specific numerical teachings of Risperdal Consta to paliperidone palmitate. Teva's cited testimony from Dr. Kahn does not fill this gap, *id.* (citing Tr. 98:10–17 (Kahn)), and without testimony to establish this link, Teva's argument is unavailing. *See Invitrogen Corp. v. Clontech Lab'ys, Inc.*, 429 F.3d 1052, 1068 (Fed. Cir. 2005) (“Unsubstantiated attorney argument regarding the meaning of technical evidence is no substitute for competent, substantiated expert testimony.”).³⁰ Further, the Risperdal Consta label does not change the Court's conclusion and weighing of the evidence as discussed above.

In sum, because Teva fails to prove a motivation to achieve claims 10 and 13, and obviousness requires both a motivation to combine and a reasonable expectation of success, Teva does not carry its burden to show that the claims are obvious. *See Intelligent Bio-Sys., Inc.*, 821 F.3d at 1367–68.

G. Obviousness of Claims 20 and 21

Claims 20 and 21 concern the particle size used in paliperidone palmitate. PTX/DTX 1 at 34:32–51. Initially, these claims are nonobvious because they depend from claims this Court has already found to be nonobvious. *See In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992) (“[D]ependent claims are nonobvious if the independent claims from which they depend are

²⁹ As with the Haldol Label, Janssen points out that the label for Risperdal Consta was not disclosed in the obviousness combinations in the Final Pretrial Order. Pltf. Reply Br. at 39; *see supra* n.21. Nonetheless, Teva's arguments regarding the Risperdal Consta label are unpersuasive.

³⁰ Attorney argument is particularly insufficient given that the label for Risperdal Consta explains that “patients with renal impairment were not studied” with Risperdal Consta. DTX 408 at 6.

nonobvious. . . .”); *In re Fine*, 837 F.2d 1071, 1076 (Fed. Cir. 1988); *Ortho-McNeil Pharm., Inc. v. Mylan Lab’ys, Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008). Claims 20 and 21 depend from Claim 19, which depends from claims 1, 4, 8 or 11. PTX/DTX 1 at 34:32–51. This Court has already determined that Claim 2, which is representative of claims 1 and 4, *see* FPTO at 9, is nonobvious. This Court has also determined that claims 10 and 13, which are representative of claims 8 and 11, *see id.*, are nonobvious. Therefore, because claims 2, 10 and 13 are nonobvious, dependent claims 20 and 21 are also nonobvious. *See Tolmar I*, 718 F. Supp. 3d 394, 431 (D. Del. 2024) (holding that the formulation claims of the ’906 Patent were nonobvious because the independent claims they depend from were also nonobvious); *see also In re Lemay*, 660 F. App’x 919, 927–28 (Fed. Cir. 2016). Nonetheless, the Court will address Teva’s arguments regarding claims 20 and 21.

Claims 20 and 21 disclose, among other things, a paliperidone palmitate formulation “having an average particle size (d50)³¹ of from about 1600 nm to about 900 nm.”³² PTX/DTX 1 at 34:35–37. Teva asserts that these claims are obvious in light of the ’544 Patent. Def. Br. at 48. Insofar as Teva also relies on the WO ’384 patent application, the Court notes that Teva has previously acknowledged that the WO ’384 “made no new disclosure on particle size” beyond that already found in the ’544 Patent. *See* Def. Post Trial Br. at 23. The ’544 Patent discloses an experiment in which four paliperidone palmitate formulations ranging in particle size (A, B, C and D) were “administered to four beagle dogs.” PTX 55/DTX 54 at 9:25–51. Janssen argues that

³¹ “d50” denotes that 50 percent of the particles are below the indicated size, whereas “d90,” as previously discussed, denotes that 90 percent of the particles are below the indicated size. Tr. 588:1–4 (Block); *see also* Tr. 296:6–15 (Wermeling).

³² “nm” is shorthand for “nanometer.” Tr. 272:9–12 (Wermeling).

the '544 Patent does not provide a motivation to achieve claims 20 and 21 because it teaches away from Formulation B, the only formulation with a d50 within the range of the claims. Pltf. Br. at 65.

“[A] reference that ‘teaches away’ from a given combination may negate a motivation to modify the prior art to meet the claimed invention.” *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1308 (Fed. Cir. 2006). “A reference does not teach away, however, if it merely expresses a general preference for an alternative invention but does not criticize, discredit, or otherwise discourage investigation into the invention claimed.” *Galderma Lab’ys, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013) (quoting *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009)). Rather, “[a] reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.” *Id.* (quoting *DePuy Spine, Inc.*, 567 F.3d at 1327).

“[T]he fact that there may be reasons a skilled artisan would prefer one [option] over the other does not amount to a teaching away from the lesser preferred but still workable option.” *Bayer Pharma AG v. Watson Lab’ys, Inc.*, 874 F.3d 1316, 1327 (Fed. Cir. 2017). The evidence at trial, however, demonstrated that a POSA would not have viewed Formulation B as merely unpreferred. Instead, a POSA looking at the '544 Patent as a whole would have been “discouraged from following the path set out in the reference,” here Formulation B. *AstraZeneca AB v. Mylan Pharms. Inc.*, 19 F.4th 1325, 1337 (Fed. Cir. 2021) (holding that the prior art taught away where district court held the reference “cut against the very goal a [POSA] would have been trying to achieve—a stable product”).

Indeed, Dr. Sinko credibly explained that a POSA would infer from the '544 Patent that having a d90 of less than 2,000 nm is one of the “critical components” of the '544 Patent’s

invention. Tr. 1522:24–1523:13 (Sinko). As a result, because Formulation B lacked these “critical parameters,” a POSA would be motivated by the teachings of the ’544 Patent to “exclude” and “eliminate” Formulation B. Tr. 1783:21–1785:1 (Sinko). Furthermore, the ’544 Patent states that “formulations should be stable,” but reports that only formulations C and D were subject to further studies to understand their stability. PTX 55/DTX 54 at 3:8–10, 9:33–35; Tr. 1525:8–16 (Sinko). As Dr. Sinko testified, a POSA would have understood that the choice to further study formulations C and D indicated that only those particle sizes provide certain properties that meet the requirements of the ’544 Patent. Tr. 1784:7–1785:13 (Sinko) (explaining that “within the bounds of the ’544 patent,” Formulation B would be “excluded”); *see also* Tr. 1778:21–1779:13, 1525:8–16 (Sinko); *Crocs, Inc. v. Int’l Trade Comm’n*, 598 F.3d 1294, 1308–09 (Fed. Cir. 2010) (holding the prior art taught away where the modification was “unsuitable”); *Millennium Pharms., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1366 (Fed. Cir. 2017) (holding the prior art taught away because the modification “would have been unattractive” to a POSA). In short, the ’544 Patent did not merely demonstrate a preference, but taught away from the use of Formulation B. A POSA would have been discouraged from investigating formulations having the attributes of Formulation B. *See AstraZeneca AB*, 19 F.4th at 1337–38 (finding implicit disparagement and teaching away where expert testified “that a person of ordinary skill in the art would have known that the . . . formulations were unsuitable for further experimentation, thus discouraging investigation into these formulations” (internal quotation marks omitted)); *see also Arctic Cat Inc. v. Bombardier Recreational Prods. Inc.*, 876 F.3d 1350, 1360 (Fed. Cir. 2017) (noting that teaching away “need not” be explicit).

The only testimony Teva cites to rebut this teaching away is a conclusory statement by Dr. Wermeling. Def. Br. at 50 (quoting ECF No. 167-1 ¶ 161 which in turn quotes Tr. 546:6–9

(Wermeling)).³³ However, Dr. Wermeling admitted that Formulation B was outside the range of particle size that the '544 Patent taught was “desired.” Tr. 294:2–11, 490:25–491:3, 496:2–25 (Wermeling). Dr. Wermeling’s testimony therefore fails to persuasively counter Dr. Sinko’s credible testimony and does not carry Teva’s burden. *See Apple Inc. v. MPH Techs. Oy*, 28 F.4th 254, 263 (Fed. Cir. 2022) (noting that an “expert’s contrary testimony” may be “properly disregarded as conclusory”). Thus, Teva fails to prove that claims 20 and 21 are obvious because the '544 Patent’s teaching away negates any motivation to achieve the claims.³⁴ *See AstraZeneca AB*, 19 F.4th at 1336 (holding that teaching away “on its own is sufficient to sustain” nonobviousness).

H. Objective Indicia of Nonobviousness

The Court now turns to Janssen’s arguments regarding secondary considerations of nonobviousness, which are also known as “objective indicia of nonobviousness.” *Quanergy Sys., Inc. v. Velodyne Lidar USA, Inc.*, 24 F.4th 1406, 1417 (Fed. Cir. 2022); *see also KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406–07 (2007). Objective indicia of nonobviousness are categories of evidence that are relevant to the extent they “give light to the circumstances surrounding the origin of the subject matter sought to be patented.” *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). Such evidence is important because it is used to “guard against slipping into use of hindsight . . . and to resist the temptation to read into the prior art the teachings of the invention in issue.” *Id.* at 36 (internal citation and quotation marks omitted). Here, Janssen has presented

³³ Dr. Wermeling’s cited testimony is as follows: “Q: Is there anything in the '544 patent that would tell a person of ordinary skill in the art to not use Formulation B from this table? A: There’s nothing that directs that, no.” Tr. 546:6–9 (Wermeling).

³⁴ Teva also argues that particle size is a “result-effective” variable such that a POSA would achieve the '906 Patent’s particle size by optimization. Def. Br. at 50–51. However, because the Court finds that the '544 Patent teaches away, it does not address this argument. *See Teva II*, 97 F.4th 915, 932 (Fed. Cir. 2024) (noting that where teaching away is found, a court may “deem[] it unnecessary to address optimization”).

evidence regarding long-felt but unsolved need, commercial success, unexpected results, industry praise and skepticism. *See* Pltf. Br. at 82–100.³⁵

A court need not find that all the indicia are present to determine that the objective indicia support a finding of nonobviousness. *See Graham*, 383 U.S. at 17–18. And although objective indicia of nonobviousness can be some of the most probative evidence of nonobviousness, the absence of such indicia does not tend to show obviousness. *See Medtronic Inc. v. Intermedics, Inc.*, 799 F.2d 734, 739 n.13 (Fed. Cir. 1986) (“[T]he absence of objective evidence is a neutral factor”); *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013) (noting that the presence of objective indicia of nonobviousness “can be the most probative evidence of nonobviousness”) (citation omitted).

In addressing the indicia of nonobviousness below, the Court determines whether each one relates to “claimed and novel” aspects of the patent. *Merck & Cie v. Gnosis S.P.A.*, 808 F.3d 829, 837 (Fed. Cir. 2015). This is necessary because Janssen must establish a nexus between the claimed dosing regimen for a patient and the proffered objective indicia. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1539 (Fed. Cir. 1983) (“A nexus is required between the merits of the claimed invention and the evidence offered, if that evidence is to be given substantial weight enroute to conclusion on the obviousness issue.”).

Having determined that the ’906 Patent is not obvious, the Court now also holds that the evidence of objective indicia—particularly of long-felt but unsolved need, commercial success and unexpected results—reinforces the Court’s finding of nonobviousness.

³⁵ On remand, Janssen does not advance any arguments regarding copying. Therefore, the Court will not address it herein.

1. Long-Felt But Unsolved Need

“The existence of a long-felt but unsolved need that is met by the claimed invention is . . . objective evidence of non-obviousness.” *Millennium Pharms., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1369 (Fed. Cir. 2017). As the Federal Circuit has noted, if a solution were obvious, the need likely would not have persisted. *See WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1332 (Fed. Cir. 2016). In this case, the evidence demonstrates that (1) there was a persistent need for a second-generation LAI antipsychotic that did not require oral supplementation and (2) the novel dosing features of the '906 Patent solved this need.

First, the record shows that there was a long-standing need for a second-generation LAI antipsychotic that could initiate treatment without requiring oral medication. Janssen's expert (Dr. Kohler) testified that previous treatment options forced doctors to rely on oral supplementation. Tr. 1910:7–12 (Kohler). Teva's expert (Dr. Kahn) agreed, conceding that no second-generation antipsychotics were available for monthly dosing without oral supplementation. Tr. 2410:8–17 (Kahn). Dr. Kohler also highlighted the problems caused by oral antipsychotics, such as patients not adhering to their treatment and thus suffering from “marked deterioration” and loss of independence. Tr. 1887:14–1889:20 (Kohler). Therefore, the ability to avoid oral supplementation is crucial; it ensures patients are consistently receiving their medication. Tr. 1046:4–11 (Gopal); *see also Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1380 (Fed. Cir. 2006) (finding “need for a safer . . . more effective” treatment provides basis for unmet need).

Second, the '906 Patent's novel dosing addressed this need. Dr. Kohler testified that Claim 2's dosing regimen delivers quick benefits and eliminates the need for oral supplementation. Tr. 1916:2–14 (Kohler); *see also* Tr. 1921:1–3 (Kohler) (stating that the same benefits flowed from

the dosing regimen for renally-impaired patients). As a result, patients are more likely to adhere to the medication regimen compared to previous LAI antipsychotics. *See* Tr. 1912:8–19 (Kohler). Given that the solution to the long-felt need results from the claimed and novel dosing regimens, nexus to the claimed invention is established. *See Merck & Cie*, 808 F.3d at 837. Teva counters that the lack of oral supplementation and rapid efficacy are not expressly included in the claims, but a patent can solve a long-standing need even if it does not explicitly claim the benefits of its invention. *See E.I. du Pont de Nemours & Co. v. Phillips Petroleum Co.*, 849 F.2d 1430, 1433 (Fed. Cir. 1988) (noting that courts can, when making their nonobviousness determination, consider a feature that “was not expressly included in the claims”); *see also Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1056–57 (Fed. Cir. 2016) (upholding jury finding that “a solution to the pocket dialing problem” satisfied long-felt need, even though the patent at issue did not explicitly identify the pocket dialing problem); *WBIP, LLC*, 829 F.3d at 1332 (upholding jury finding that claimed invention “solved the problem of carbon monoxide poisoning” despite claim not mentioning carbon monoxide).

Teva also argues that the ’548 Protocol had already solved this long-felt need. Def. Br. at 66. But the ’548 Protocol “is not an available product,” and thus could not have been the solution. *Millennium Pharms., Inc.*, 862 F.3d at 1369 (holding it was clear error to find that long-felt need was solved by a prior art compound that was not commercially available). In addition, it is somewhat inconsistent for Teva to argue that there was a motivation to *modify* the ’548 Protocol to meet a need for rapid efficacy and that the protocol somehow already provided for rapid efficacy. *See* Def. Br. at 28, 66; Def. Reply Br. at 67 (“[T]here was no long-felt need because that need was already met.”); *see also Adapt Pharma Operations Ltd. v. Teva Pharms. USA, Inc.*, 25 F.4th 1354, 1376 (Fed. Cir. 2022) (“[W]e fail to see how, on the one hand the [prior art] and its

known drawbacks can provide a skilled artisan with the motivation to arrive at the claimed invention and, on the other hand, satisfy an unmet need in the prior art.”).

Accordingly, the Court finds that the evidence of a long-felt but unsolved need supports its finding of nonobviousness.

2. Commercial Success

“The commercial response to an invention is significant to determinations of obviousness. . . .” *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1391 (Fed. Cir. 1988). It shows how the invention is perceived in the marketplace by those “directly interested in the product.” *Id.* As with other indicia, a finding of nexus between the claimed and novel aspect of the patent and the commercial success is required. *See Ormco Corp. v. Align Tech, Inc.*, 463 F.3d 1299, 1311–12 (Fed. Cir. 2006).

Invega Sustenna is an undisputed commercial success. Since its launch, the size and annual growth of its sales, revenue and market share have contributed to its “blockbuster status in the pharmaceutical[al] industry.” Tr. 2579:11–2580:1 (Mulhern) (net sales grew annually and exceeded one billion dollars); PTX 806B at 3, 91–92 (revenue accounted for over half of all LAI antipsychotic revenue); *id.* at 37 (market share is more than double that of its closest competitor when measured by days of treatment). As Janssen’s expert in the economic analysis of intellectual property, Carla S. Mulhern,³⁶ explained, “Invega Sustenna has achieved substantial success in the marketplace no matter how you look at it, sales or market penetration.” Tr. 2586:2–5 (Mulhern). Even Teva’s pharmaceuticals economics expert, Ivan T. Hofmann,³⁷ did not dispute this sales data

³⁶ Ms. Mulhern is a Managing Principal at Analysis Group, a global economic consulting firm. FPTO at 38–39. Her specialty is “the application of microeconomic principles to the analysis of economic issues arising in complex litigation, with a substantial focus on intellectual property matters.” *Id.*

³⁷ Mr. Hofmann is a Vice President and Managing Director at Gleason IP, an economic, accounting and financial consulting firm. FPTO at 43–45. He leads the firm’s Intellectual Property Practice. *Id.*

and acknowledged that Invega Sustenna is the top-selling LAI antipsychotic by revenue in the United States. Tr. 2741:24–2742:7, 2836:18–22 (Hofmann).

Turning to the nexus analysis, the success of Invega Sustenna is closely tied to its unique dosing features. *See Tolmar I*, 718 F. Supp. 3d 394, 430 (D. Del. 2024) (holding “that the commercial success of Janssen’s product was mainly attributable [to] the claimed dosage regimen in the ’906 patent”). Indeed, Janssen’s marketing prominently highlighted the dosing regimens. PTX 416 at 32. As Ms. Mulhern explained, this marketing indicated these features were key in distinguishing Invega Sustenna from its competitors. Tr. 2594:5–21 (Mulhern). Market research confirmed that healthcare providers saw the unique dosing regimens and the resulting benefits as major advantages. Tr. 2597:8–24 (Mulhern). Even Teva’s expert, Mr. Hofmann, did not contest that the dosing regimens’ benefits drove the demand for Invega Sustenna. Tr. 2852:17–2853:10 (Hofmann).

Teva contends that Invega Sustenna’s commercial success is instead due to its marketing strategies, including a large sales force and high spending on promotions. Def. Br. at 66–67. Janssen’s promotional spending on Invega Sustenna, however, was actually less than or equal to its competitors and less than the industry average. *See* Tr. 2665:23–2666:4 (Mulhern); PTX 806B at 9, 122–24; Tr. 2615:9–24 (Mulhern). Further, Ms. Mulhern confirmed that discounts and rebates for Invega Sustenna matched industry standards, Tr. 2615:25–2616:20 (Mulhern), and Teva’s expert conceded that he had no evidence to challenge this statement, Tr. 2848:17–22 (Hofmann). At best, Teva’s evidence suggests that Janssen’s marketing had a “marginal effect” on Invega Sustenna’s significant commercial success. *See Tolmar I*, 718 F. Supp. 3d at 430 (finding that other factors “may have had some marginal effect in the market, but not enough to negate the probative force of the huge commercial success of Invega Sustenna”). Regardless,

Janssen has provided ample evidence to demonstrate that “the commercial success of Janssen’s product was mainly attributable [to] the claimed dosing regimens in the ’906 Patent.” *Id.*; *see also Cont’l Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1273 (Fed. Cir. 1991) (noting the patented invention need not be “solely responsible for the commercial success” for nexus to be found regarding commercial success).

Accordingly, the Court finds that the evidence of commercial success supports its finding of nonobviousness.

3. Unexpected Results

When evaluating unexpected results, courts look to whether the claimed invention exhibits properties or benefits that a POSA “would have found surprising or unexpected.” *Forest Laby’s, LLC v. Sigmapharm Laby’s, LLC*, 918 F.3d 928, 937 (Fed. Cir. 2019) (quoting *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995)). This is because if something is surprising to a POSA, it would not have been obvious. *In re Soni*, 54 F.3d at 750 (“[T]hat which would have been surprising to a person of ordinary skill in a particular art would not have been obvious.”). The unexpected results inquiry focuses on a comparison between the claimed invention and the closest prior art—here, the ’548 Protocol. *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014).

Typically, the analysis compares the results obtained from the claimed invention and those obtained from the closest prior art. *Tolmar II*, No. CV 21-1784, 2024 WL 2972832, at *3 (D. Del. June 13, 2024). In this case, however, the closest prior art contains no results. Consequently, the analysis instead looks to whether “the claimed dosing regimens yielded unexpected results when compared with a POSA’s *expectations* based on the state of the prior art.” *Teva II*, 97 F.4th 915, 934 (Fed. Cir. 2024) (emphasis added). Thus, this Court must determine what a

POSA's expectations for the '548 Protocol dosing regimens were and compare those to the actual results of the claimed dosing regimens "to determine whether the claimed dosing regimen yielded results that would have been surprising to a [POSA]." *Tolmar II*, 2024 WL 2972832, at *3 (internal citations and quotation marks omitted).

As directed by the Federal Circuit, this Court must first determine what a POSA would have expected the results of the '548 Protocol to be "based on what was known in the art at the time." *Id.* (explaining that the proper inquiry is to evaluate "the expected results of NCT 548 based on what was known in the art at the time"); *see also Teva II*, 97 F.4th at 935 (noting that the "correct comparison" is "between expectations based on information available to a POSA and the claimed regimens' results"). As previously discussed, a POSA would only have known that the '548 Protocol was for a Phase III clinical trial and that Janssen would be unlikely to invest significant funds in a Phase III clinical trial without a belief that its hypothesis was correct.³⁸ *See supra* § II.C.1. Accordingly, a POSA would have understood that Janssen believed the dosing regimens were likely safe and effective. *Tolmar II*, 2024 WL 2972832, at *2 (explaining that a POSA would have "credit[ed] Janssen's hypothesis that the NCT 548 dosing regimens would be safe and effective").

A POSA's expectation must then be compared to the results of the claimed dosing regimens, which achieved rapid efficacy while maintaining a patient in the therapeutic window.

³⁸ Any purported failures in the Phase III studies that Teva points to are "irrelevant to [the unexpected results] inquiry," Def. Br. at 58, because "a POSA would not have been aware of [the '548 Protocol] results" or any failures in the Phase III studies. *Teva II*, 97 F.4th 915, 933 (Fed. Cir. 2024). In any event, the asserted randomization errors "affected only one arm of one of the failed Phase III studies." *Tolmar I*, 718 F. Supp. 3d 394, 430 (D. Del. 2024); Tr. 1168:20–1169:15 (Gopal). And any alleged needle length error is speculative because the record does not prove that using 2-inch needles to inject paliperidone palmitate into the gluteal muscle would have produced a different clinical outcome in the Phase III clinical trials, especially given that Janssen's Risperdal Consta, which uses 2-inch needle injections into the gluteal muscle, *see* PTX 283 at 30, did not achieve rapid efficacy in the same way that Invega Sustenna did, *see* Tr. 163:2–10 (Kahn); DTX 408 at 2. *See also* PFOF ¶ 72.

See Tr. 1361:18–1362:12, 1431:2–20 (Samtani) (explaining the strength of the claimed dosing regimens’ results); PTX 278A at 118–19 (demonstrating favorable drug concentration effects of the claimed dosing regimens). Specifically, the claimed dosing regimens brought patients into the therapeutic window “within a week,” and sustained them there until the maintenance doses began. Tr. 1361:18–1362:12 (Samtani). And it did so while avoiding the “intolerable side effects” that a POSA would have understood to be more likely to occur when using high loading doses. Tr. 1910:7–1911:22 (Kohler). By safely achieving this rapid and lasting efficacy, the claimed dosing regimens resulted in better treatment adherence. *See* Tr. 1910:7–1912:19 (Kohler). Importantly, improved adherence leads to significant clinical benefits for patients, especially because “nonadherence is the biggest factor of relapse in psychosis and schizophrenia.” Tr. 1887:11–1889:20 (Kohler) (noting that nonadherence can lead to loss of agency, “marked deterioration,” inability to “make decisions about what [a patient] want[s] to do,” loss of ability to “function independently” and loss of “family relationships”).

These results would have been surprising to a POSA. A POSA would have understood from the prior art that the use of higher LAI loading doses may lead to increased risk of side effects. *See* Tr. 1903:6–1905:24 (Kohler) (noting that a POSA would begin dosing of LAI antipsychotics at a lower initial dose to ensure patients did not experience extrapyramidal side effects). In light of these expectations, a POSA would have been surprised to discover that the ’906 Patent’s dosing regimens achieved “rapid onset of the therapeutic effects of the drug” without thereby producing adverse side effects in a patient. *Tolmar I*, 718 F. Supp. 3d at 430. This constitutes a dramatic difference between the ’548 Protocol’s expected results and the claimed dosing regimens—a difference that a POSA would not have foreseen. *See* Tr. 321:23–322:6 (Wermeling); *see also Tolmar I*, 718 F. Supp. 3d at 430 (“The surprising efficacy and safety of large initiation doses of

paliperidone palmitate supports Janssen’s nonobviousness argument.”); Tr. 1910:7–1912:19 (Kohler) (“[N]one of the previous long-acting injectables were able to provide all these benefits.”). The benefits of injecting these high loading doses in the deltoid in the ’906 Patent—as opposed to the gluteus in the ’548 Protocol—would have been particularly surprising to a POSA because they would have viewed the deltoid and gluteus as interchangeable “standard injection sites.” Def. Br. at 39; Tr. 278:7–11 (Wermeling), 1719:15–17 (Sinko). Contrary to this understanding, the ’906 Patent explained that deltoid injections had superior therapeutic benefits. PTX/DTX 1 at 5:2–5 (“It was also discovered that deltoid injections result in a faster rise in initial plasma concentration, facilitating a rapid attainment of potential therapeutic concentrations.”). As Judge Bryson explained in *Tolmar I*, “[w]hile ordinary artisans would have a motivation to explore the deltoid as an injection site and an expectation of interchangeability, they would not have expected the markedly superior results that the claimed dosing regimens delivered relative to the NCT 548 protocols.” 718 F. Supp. 3d at 425.

In short, the evidence at trial showed that Invega Sustenna improved patient treatment adherence through its use of high initial loading doses that rapidly achieved therapeutic concentrations of paliperidone palmitate and monthly loading doses which maintained these concentrations. *See* Tr. 1910:7–1912:19 (Kohler) (providing a detailed and persuasive analysis of the benefits of Invega Sustenna). Such a “difference between an effective and safe drug and one with significant side effects that caused many patients to discontinue treatment” has been found to “constitute an unexpected difference in kind.” *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1307 (Fed. Cir. 2015). Here too, the clinical benefits of increased adherence that result from the claimed dosing regimens demonstrate a difference in kind and establish a nexus between the asserted unexpected results and the claimed invention. *See Merck & Cie*, 808 F.3d at 837; *see also*

Tr. 1887:14–1889:20 (Kohler) (improved adherence resulting from claimed dosing regimens improves agency, “family relationships” and ability to “function independently”).³⁹

Accordingly, the Court finds that the evidence of unexpected results supports its finding of nonobviousness.

4. Industry Praise

“Evidence that the industry praised a claimed invention . . . weighs against an assertion that the same claim would have been obvious” because “[i]ndustry participants, especially competitors, are not likely to praise an obvious advance over the known art.” *WBIP, LLC*, 829 F.3d at 1334. Janssen identifies several instances of industry praise.

For example, Janssen points to an article published in the journal *Neuropsychiatric Disease*, which reviews Invega Sustenna and concludes that paliperidone palmitate is an “important treatment option.” PTX 133 at 221; Tr. 2412:9–15 (Kahn). Teva counters that the article only states that Invega Sustenna is comparable to haloperidol decanoate. Def. Br. at 62. But the article specifically touts “the importance of the initial loading doses” which provide “rapid onset of action, thereby circumventing the need for oral supplementation.” PTX 133 at 221.⁴⁰ Thus, the praise relates to the “novel dose initiation procedure,” *id.* at 205, which establishes a nexus to the “claimed invention.” *Stratoflex, Inc.*, 713 F.2d at 1539.

³⁹ Teva argues that the differences were in degree rather than in kind. But to the extent this argument compares the results of the claimed dosing regimens to Janssen’s non-prior-art internal testing, it focuses on the wrong comparison. See Def. Br. at 56–57. Unexpected results must be “different in kind and not merely in degree from *the results of the prior art.*” *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004) (emphasis added).

⁴⁰ Teva notes that Emsley—one of two authors on the article—previously received research funding from Janssen. DFOF ¶ 623 (citing PTX 133 at 221). However, Teva has not provided a sufficient basis to doubt the credibility of this peer-reviewed study. See PTX 133 at 223 (explaining the journal is an “international, peer-reviewed journal of clinical therapeutics and pharmacology”).

Janssen also points to an article in the trade publication *Psychiatric News* that praises Invega Sustenna as “more effective than oral antipsychotics at delaying incidents,” including “hospitalization, or intentional discontinuation of treatment.” PTX 131 at 1. The article explains that the “improvements seen were due in part to better adherence rates.” *Id.* at 3. As Dr. Kohler testified, “improved adherence” is a result of the ’906 Patent’s novel dosing regimens. Tr. 1910:7–1912:13 (Kohler). Teva responds that the *Psychiatric News* article merely “praises the benefits of LAIs generally.” Def. Br. at 62. Although this article initially states that “better adherence . . . is an advantage of LAIs” generally, it goes on to specifically note the 95.2 percent adherence rate for study participants receiving Invega Sustenna. PTX 131 at 3.

Accordingly, the Court finds that the evidence of industry praise supports its finding of nonobviousness.

5. Skepticism

“If industry participants or skilled artisans are skeptical about whether or how a problem could be solved or the workability of the claimed solution, it favors non-obviousness.” *WBIP, LLC*, 829 F.3d at 1335. To establish skepticism, it is enough to provide evidence that third parties were concerned or surprised by the patented claim. *Neptune Generics, LLC v. Eli Lilly & Co.*, 921 F.3d 1372, 1378 (Fed. Cir. 2019) (citing *Circuit Check Inc. v. QXQ Inc.*, 795 F.3d 1331, 1337 (Fed. Cir. 2015)).

Here, Janssen has proffered ample evidence of third-party skepticism. For instance, a group of outside experts reviewing Janssen’s proposed initial 150 mg-eq. loading dose recommended instead “starting with 100 mg-eq.” because it was “of lesser risk.” PTX 92 at 1. Similarly, the FDA recommended Janssen decrease its initial loading dose to as low as 75 mg-eq. *See* PTX 94 at PDF page 59. Meanwhile, Dr. Kohler testified that even after FDA approval,

psychiatrists remained “concerned” about the patented dosing regimens. Tr. 1907:7–1908:4 (Kohler); *see also Tolmar I*, 718 F. Supp. 3d at 429 (noting that “physicians reacted with skepticism and were reluctant to use such a high initiation dose”). In short, Janssen established that “experts in the field were skeptical” of the patented dosing claims. *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1367 (Fed. Cir. 2012) (affirming finding of skepticism because “leading experts in the field were skeptical that the counterintuitive [patented] device could work”) (internal quotation marks omitted). Given that this skepticism was aimed directly at novel aspects of the claimed dosing regimen, it has a nexus to the patented invention. *See e.g.*, Tr. 1907:7–1908:4 (Kohler) (explaining that psychiatrists were “concerned” with the “unusual” nature of the claimed unequal and decreasing dosing regimens because they were more “comfortable with” a regimen “starting with a smaller dose and then ramping up”); PTX 92 at 1 (recommending decreasing initial loading dose of the claimed dosing regimen); PTX 94 at PDF page 59 (recommending decreasing both loading doses of the claimed dosing regimen).

Accordingly, the Court finds that the evidence of skepticism supports its finding of nonobviousness.

6. Blocking Patents

Seeking to discount the evidence of long-felt need and commercial success, Teva argues that competing paliperidone palmitate products were prevented from entering the market because of blocking patents. Def. Br. at 67. Teva specifically identifies the ’556, ’843 and ’544 patents, each of which is owned by Janssen. DFOF ¶ 416. In its analysis of whether blocking patents undermine the evidence of long-felt need and commercial success, the Court focuses on the allegedly blocked space related to Invega Sustenna because that is what was commercially successful and what filled the unmet need. *See Teva II*, 97 F.4th at 936.

Evidence of long-felt need and commercial success is undermined when a blocking patent precludes “market entry by others.” *Galderma Lab’ys, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 740 (Fed. Cir. 2013) (quoting *Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005)). A patent is considered a blocking patent “where practice of a later invention would infringe the earlier patent.” *Acorda Therapeutics, Inc. v. Roxane Lab’ys, Inc.*, 903 F.3d 1310, 1337 (Fed. Cir. 2018). But “the mere existence” of blocking patents alone is not necessarily enough to undermine evidence of long-felt need and commercial success. *Id.* at 1338 (citing *Merck Sharp & Dohme Corp. v. Hospira, Inc.*, 874 F.3d 724,731 (Fed. Cir. 2017)). Instead, whether this evidence should be discounted because of a blocking patent is “a fact-specific inquiry.” *Merck Sharp & Dohme Corp.*, 874 F.3d at 731. In performing this analysis, courts look to whether competitors were deterred by the alleged blocking patents “from investing the resources needed to make, develop, and market” the later-patented invention. *Chemours Co. FC, LLC v. Daikin Indus., Ltd.*, 4 F.4th 1370, 1379 (Fed. Cir. 2021) (quoting *Acorda Therapeutics, Inc.*, 903 F.3d at 1337).⁴¹

In this case, a competitor was incentivized to and did invest the resources to develop a competing paliperidone palmitate product during the allegedly blocked period. Specifically, Teva itself filed a patent application involving preparation and purification of paliperidone palmitate in January 2008—prior to the expiration of the alleged blocking patents (2013, 2017 and 2018). PTX 813 at PDF page 9; Tr. 2840:8–20 (Hofmann). Moreover, given that drug development takes “ten years or more,” a competitor seeking to introduce an LAI paliperidone palmitate product following the expiration of the blocking patents would have necessarily begun development of such a product prior to the ’906 Patent’s December 2007 priority date. Tr. 2629:1–15 (Mulhern).

⁴¹ The inquiry into the incentives to develop the later-patented invention thus focuses on the development period leading up to the ’906 Patent’s priority date—December 2007. See *Acorda Therapeutics*, 903 F.3d at 1327 (looking to period preceding patent-at-issue’s priority date to determine effect of blocking patents).

This aligns with credible testimony presented by Janssen that there *were* indeed incentives to develop a competing LAI paliperidone palmitate product prior to the priority date, *see* Tr. 2628:3–2631:5 (Mulhern), and testimony from Teva’s own expert, Tr. 2829:4–10 (Hofmann) (“Q: . . . [T]here certainly would be an incentive to conduct R&D in paliperidone palmitate as of December 2007, right? A: Yeah.”).

Teva’s patent application involving paliperidone palmitate and Janssen’s credible testimony contradict Teva’s expert testimony that “[n]o one would have an economic motivation to try and research and discover . . . the alleged novelties of the ’906 patent” because of Janssen’s alleged “patent fortress around paliperidone palmitate for the treatment of schizophrenia.” Tr. 2752:20–24 (Hofmann). The record thus shows that the alleged blocking patents did not deter the development of LAI paliperidone palmitate products.

When considering the same patent and the same alleged blocking patents, Judge Bryson likewise found that the patent challenger “failed to show that [the three alleged blocking] patents prevented competitors from developing a competing paliperidone palmitate product before the priority date of the ’906 patent.” *Tolmar I*, 718 F. Supp. 3d at 430. For the foregoing reasons, this Court continues to credit Janssen’s evidence of commercial success and long-felt but unsolved need.

In conclusion, all of the objective indicia of nonobviousness discussed above (*see supra* §§ II.H.1–6) reinforce, but are not critical to, the Court’s previous finding of nonobviousness.

III. CONCLUSION

For the reasons set forth above, the Court finds that Defendants have failed to prove, by clear and convincing evidence, that the '906 Patent, or any claim of that patent, is invalid. An appropriate Order accompanies this Opinion.

Date: November 21, 2024



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