

NOT FOR PUBLICATION

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CAMDEN VICINAGE

JANSSEN PHARMACEUTICALS,
INC. *et al.*

Plaintiffs,

v.

ALKEM LABORATORIES, LTD. *et al.*

Defendants.

HONORABLE KAREN M. WILLIAMS

Civil Action
No. 1:23-cv-2939 (KMW-SAK)

**OPINION
FILED UNDER SEAL**

This Opinion constitutes the Court's findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52.

I. INTRODUCTION

Plaintiffs Janssen Pharmaceuticals, Inc. and Janssen Pharmaceutica NV (collectively "Plaintiffs" or "Janssen") bring this suit for patent infringement against Defendant Sandoz, Inc.¹ ("Defendant" or "Sandoz"). Plaintiffs own U.S. Patent No. 10,869,844 ("844 Patent"), United States Patent No. 11,311,500 ("500 Patent"), United States Patent No. 11,173,134 ("134 Patent")², and United States Patent No. 11,446,260 ("260 Patent" or the "Basstanie Patent") (collectively "Patents-in-Suit"), which are listed in the Orange Book as covering Spravato®, an intranasal ("IN") administration of ketamine to treat depression. (Joint Pre-Trial Order, "PTO" ¶¶ 25, 26, 30) (ECF No. 291). The Complaint alleges that Defendants have infringed the Patents-in-Suit by filing

¹ Plaintiffs initially brought this action against additional Defendants Hikma Pharmaceuticals USA Inc, and Alkem Laboratories Ltd. However, both Defendants subsequently entered into confidential stipulations with Plaintiff and did not participate in the trial. (See Pre-Trial Order at p. 1).

² The 844 Patent, 134 Patent, and 500 Patent collectively constitute what may be referred to as the "Caers Patents"

Abbreviated New Drug Application (“ANDA”) No. 215418 with the United States Food and Drug Administration (“FDA”).

The Court held a five (5) day bench trial beginning on February 2, 2026, and concluding on February 6, 2026. The parties completed post-trial briefing, including proposed findings of fact and conclusions of law, in June 2026.

II. JURISDICTION

This Court has subject matter jurisdiction over this action, including all claims and counterclaims asserted herein, pursuant to 28 U.S.C. § 1331 and 1338(a). Venue is proper pursuant to 28 U.S.C. §§ 1391 and 1400(b).

III. THE PARTIES

Plaintiff Janssen Pharmaceuticals, Inc. (“JPI”) is a corporation organized and existing under the laws of the Commonwealth of Pennsylvania, having its principal place of business in Titusville, New Jersey. (FPO ¶ 1). Plaintiff Janssen Pharmaceutica NV (“JPNV”) is a corporation organized and existing under the laws of Belgium, having its principal place of business in Beerse, Belgium. (FPO ¶ 2).

Defendant Sandoz, Inc. (“Sandoz”) is a corporation organized and existing under the laws of Delaware with a place of business in Princeton, New Jersey. (FPO ¶ 3).

IV. ISSUES FOR TRIAL

1. Has Defendant proven by clear and convincing evidence that claims 4, 16, 23, and 29 of the 844 patent, claim 10 of the 134 patent, claims 6, 16, and 18 of the 500 patent, and/or claims 22 and 36 of the 260 patent are invalid as obvious pursuant to 35 U.S.C. § 103?

2. Has Defendant proven by clear and convincing evidence that the Caers Patents are invalid for lack of written description pursuant to 35 U.S.C. § 112?
3. Has Defendant proven by clear and convincing evidence that the Basstanie Patent is invalid for lack of written description pursuant to 35 U.S.C. § 112?

V. DISCUSSION

The findings of fact herein are based on the Court's observations and credibility determinations of the witnesses who testified at trial and a thorough review of the evidence admitted at trial. While the Court has reviewed all of the evidence presented, given the length of the trial record, the Court includes references only to the evidence most pertinent to its analysis. For the reasons set forth below, the Court finds that (1) the Patents-in-Suit are not invalid as obvious, (2) the Caers Patents are not invalid for lack of written description, and (3) the Basstanie Patent is not invalid for lack of written description.

A. Background of the Case

The present action is for patent infringement and is brought pursuant to the Hatch-Waxman Act, *See* 21 U.S.C. § 355(j). Plaintiffs are the current owners of the Patents-in-Suit. (PTO ¶¶ 30-31). Pursuant to 21 U.S.C. § 355(b)(1), the Patents-in-Suit are listed in the United States Food and Drug Administration publication titled *Approved Drug Products with Therapeutic Equivalence Evaluations* (“the Orange Book”) as covering Spravato®. (PTO ¶¶ 25-26).

Plaintiff JPI is the holder of the New Drug Application (“NDA”) N211243, approved on March 5, 2019, for intranasal esketamine hydrochloride, which is prescribed and sold under the trademark Spravato® for the treatment of treatment resistant depression (“TRD”) and major depressive disorder with suicidal ideation (“MDD-SI”). (PTO ¶ 31).

The present action arises from Sandoz’s submission of ANDA No. 215418 seeking

approval to engage in the commercial manufacture, use, sale, offer for sale in, and/or importation into the United States of generic esketamine³ nasal spray products prior to the expiration of the Patents-in-Suit. (PTO ¶ 32).

Defendants counterclaim for a declaratory judgment that the Patents-in-Suit are invalid as obvious or, alternatively, that they are invalid for lack of written description. (See Counterclaims II, IV, VI, VIII). The parties agreed to ten representative claims for trial: claims 4, 16, 23, and 29 of the 844 Patent, claim 10 of the 134 Patent, claims 6, 16, and 18 of the 500 Patent, and claims 22 and 36 of the 260 Patent. (PTO ¶¶ 54-57). The Court's determination concerning each representative claim will resolve Sandoz's invalidity challenge to the corresponding representative claims. (PTO ¶¶ 52-53).

B. Background of the Invention

The claimed dosages and formulation in the Patents-in-Suit cover Plaintiff's product Spravato®, which uses esketamine administered intranasally to treat Major Depressive Disorder (MDD), Major Depressive Disorder with Suicidal Ideation (MDD-SI) and Treatment Resistant Depression (TRD). (PTO ¶¶ 46-48). The Caers Patents share a common specification and are directed, among other things, to dosing regimens for treating patients with MDD, TRD, or MDD-SI. (CITE) The Caers Patents specify dosing and frequency for an induction phase for initial treatment as well as a reduced dosing and frequency schedule for a maintenance phase for long term treatment. (See Tr. 748:6-749:1 (Papakostas)). The Basstanie Patent specification discloses intranasal esketamine formulations, reciting specific esketamine concentrations, inactive

³ The 260 Patent defines "S-ketamine," "S-ketamine hydrochloride," and "esketamine" as referring to the S-enantiomer of ketamine in its corresponding hydrochloride-salt form. (JTX-4 at 3:63-4:4). When discussing concentration, however, the patent sometimes distinguishes the amount of S-ketamine hydrochloride from the equivalent amount of S-ketamine. For example, it describes 161.4 mg/mL of S-ketamine hydrochloride as "S-ketamine eq. 140 mg/mL." (JTX-4 at 12:16-22). Because the parties and witnesses otherwise use "esketamine" and "S-ketamine" interchangeably, the Court mirrors the terminology used in the relevant testimony or source.

ingredients, and pH values used in those formulations. (JTX-4 at 3:43-45, 4:59-5:3, 5:51-59, 6:36-48, 7:60-67, 10:13-20, 12:17-22; Tr. 425:12-426:4, 504:9-23, 507:1-5, 508:16-23)⁴. The specification also discloses administering the formulations in clusters of between 2 and up to 8 consecutive sprays within 1 to about 60 minutes. (JTX-4 at 10:36-44, 11:39-48; Tr. 426:22-427:5, 507:11-508:3). Plaintiffs contend that collectively, the asserted Patents-in-Suit claim the core innovations embodied in Spravato®. (See Tr. 853:14-25 (Giakas), 50:13-553:3 (Little)). Spravato® was approved by the FDA on March 5, 2019. (PTO ¶ 31).

C. Person of Ordinary Skill in the Art

Because the asserted claims have both clinical and formulation aspects, the parties have proposed separate definitions of a person of ordinary skill in the art (“POSA”): one addressing the claims’ clinical aspects and another addressing their formulation aspects. Although the parties’ proposed definitions differ in some respects, they “do not differ in a meaningful way.” *AstraZeneca AB v. Aurobindo Pharma Ltd.*, 232 F. Supp. 3d 636, 645 (D. Del. 2017). Additionally, all the parties’ experts indicated that their opinions would not change regardless of which definition of a POSA the Court adopted. (Tr. 69:2-8 (Farber), 696:3-12 (Papakostas), 844:6-9 (Giakas), Tr. 315:12-17 (Donovan), Tr. 499:25-500:4 (Little)). Accordingly, the Court has defined both a clinical POSA and a formulation POSA consistent with both parties’ proposed definitions below.

1. Clinical POSA

At the critical time, a clinical POSA would have possessed a medical or other relevant doctoral degree and experience treating patients with MDD or TRD or designing or conducting clinical studies involving such patients. A clinical POSA also would have been familiar with the

⁴ Designated Video Deposition of Dr. Johanna Betz, Ph.D. (JTX-4)

available treatments for MDD and TRD, including their dosing, mechanisms of action, and adverse effects, and would have been capable of working as part of a multidisciplinary team that included individuals with expertise in pharmaceutical formulation and drug development.

2. Formulation POSA

At the critical time, a formulation POSA would have possessed a degree in pharmaceutical sciences, pharmaceutics, pharmacy, chemistry, chemical engineering, or a related field, together with experience commensurate with the person's education in pharmaceutical formulation or development, including knowledge relevant to formulating drugs for administration. A formulation POSA also would have been capable of working as part of a multidisciplinary team and drawing upon the knowledge and experience of team members with expertise in related fields, including clinical medicine and psychiatry.

D. Invalidity Experts

Defendants argue that the Patents-in-Suit are invalid as obvious. Alternatively, if the Court finds that the Patents-in-Suit are not obvious, Defendant argues that the Patents-in-Suit are invalid for lack of written description. In support of its invalidity arguments, Defendant proffered as an expert at trial Dr. Nuri B. Farber, M.D. ("Dr. Farber"), Dr. Maureen D. Donovan, Ph.D. ("Dr. Donovan"), Dr. James L. Mullins ("Dr. Mullins"), and Dr. Atanu Saha, Ph.D. ("Dr. Saha"). In rebuttal, Plaintiffs proffered Dr. George Papakostas, M.D. ("Dr. Papakostas"), Dr. Steven Little, Ph.D. ("Dr. Little"), Dr. William J. Giakas, M.D. ("Dr. Giakas"), and Ms. Carla Mulhern ("Ms. Mulhern").

1. Sandoz's Experts

Dr. Farber is a board certified psychiatrist, a practicing in-patient psychiatrist, clinician, and researcher. (Tr. 57:20 – 63:1-2 (Farber)). He is a professor in the Department of Psychiatry at

Washington University (WashU) in St. Louis, as well as vice chairman of education for the department and the program director for the psychiatry residency training program. (Tr. 58:22-25 (Farber)). Dr. Farber has more than 25 years of research experience involving NMDA antagonists, including ketamine, and has studied the effects of these agents since the early 1990s. (Tr. 59:19-25, 63:25-64:2 (Farber)). Dr. Farber was accepted by the Court, without objection, as an expert in the fields of clinical and research psychiatry, including the diagnosis, treatment, and management of major depressive disorder, which includes TRD, with specialized expertise in pharmacology including that of NMDA antagonists such as ketamine and esketamine, as well as other interventional treatments such as ECT. (Tr. 65:15-23).

Dr. Maureen D. Donovan is a professor at the University of Iowa College of Pharmacy and a faculty member in the Department of Pharmaceutical Sciences and Experimental Therapeutics. (Tr. 310:2-5 (Donovan)). She holds a Ph.D. in pharmaceutics and has more than 40 years of experience in education and research related to drug formulations and delivery system design, including intranasal drug delivery. (Tr. 310:8-14, 310:18-311:1 (Donovan)). Dr. Donovan was accepted by the Court, without objection, as an expert in the field of pharmaceutical formulation, with particular experience in the design and formulation of drugs for intranasal delivery. (Tr. 313:1-3 (Donovan)).

Dr. Atanu Saha ("Dr. Saha") is a Managing Director at the economic consulting firm Kroll, LLC, and holds a Ph.D. in Applied Economics. (Tr. 949:14-19 (Saha)). He has worked in economic research and consulting for approximately thirty (30) years and has authored more than fifty (50) peer-reviewed journal articles on a range of topics, including pharmaceutical economics. (Tr. 949:20-950:1 (Saha)). Dr. Saha was qualified without objection as an expert witness in pharmaceutical economics. (Tr. 950:2-5 (Saha)).

i. Dr. Mullins

Dr. Mullins is Dean Emeritus of Libraries, Norton Professor Emeritus, and the founder of Prior Art Documentation Librarian Services, LLC. (Tr. 456:2-5, 457:2-8 (Mullins)). He previously served as Associate Director of the MIT libraries, and was the University Librarian and Director at Villanova University. (Tr. 456:5-10 (Mullins)). Dr. Mullins has extensive knowledge of the processes associated with cataloging dissertations and providing access to them within university systems as well as experience navigating a wide range of research portals—including university library systems, digital catalogs, and print indexes—to locate bibliographic information about dissertations, and is familiar with the significance of initial cataloging records and how they reflect an item's availability and accessibility across those portals.. (Tr. 456:16-457:1, 457:9-25 (Mullins)). Sandoz proffered Dr. Mullins as “an expert in library and information sciences, the organization of materials and cataloging, including doctoral dissertations granted by universities.” (Tr. 458:10-12 (Mullins)).

Janssen objected to Dr. Mullins testifying because Sandoz did not identify him in their initial disclosures, timely serve an expert report from him, offer him for deposition during expert discovery, or include him on their timely exchanged trial-witness list. (Tr. 432:22-433:24, 435:22-23). Although Defendants produced Dr. Mullins's declaration shortly after the expert-report deadline, Plaintiffs argued that the declaration was hearsay and did not satisfy Rule 26 because, among other things, it omitted a list of the cases in which he had testified as an expert during the preceding four years (Tr. 441:17-442:15). Plaintiffs further asserted that they did not understand Dr. Mullins to be a testifying expert because Defendants' other experts did not rely on his declaration but instead treated Bitter as prior art based on counsel's instructions. (Tr. 442:1-15). Plaintiffs therefore requested that Dr. Mullins be precluded from testifying or, alternatively, that

his testimony be strictly limited to the opinions contained in his declaration. (Tr. 433:19-24).

Sandoz responded that Plaintiffs had known about Dr. Mullins and the substance of his opinions since May 2025, when they received his declaration shortly after the expert-report deadline. (Tr. 434:10-16). Sandoz maintained that the declaration identified Dr. Mullins as an expert, set forth his opinions, and stated that he was available for cross-examination. (*Id.*) It further argued that Plaintiffs had months to request Dr. Mullins' deposition, seek to strike the declaration, or raise any alleged deficiencies, but did not do so. (Tr. 435:2-4, 438:10-14, 441:4-9) After Plaintiffs moved in limine to exclude the declaration as hearsay, Defendants added Dr. Mullins to their trial-witness list so that he could testify in person. (Tr. 441:1-4). As such, Sandoz contended that any prejudice to Janssen resulted from their own inaction and did not justify the exclusion of his testimony. (Tr. 441:5-13).

The Court observed that Rule 26(a)(2) requires a party to disclose the identity of an expert and the expert's written report within the period established by the Court. (Tr. 444:21-24). Under Rule 37(c)(1), a party that fails to comply may not use the witness or information at trial unless the failure was substantially justified or harmless, and the noncompliant party bears the burden of making that showing. (Tr. 445:1-4, 446:2-5). In assessing harmlessness, the Court considered the prejudice or surprise to the opposing party, the ability to cure any prejudice, the likelihood of disrupting trial, and whether the nondisclosure resulted from bad faith or willfulness, as well as the importance of the evidence. (Tr. 445:16-446:2). The Court found no indication of bad faith or willfulness and regarded the prejudice-or-surprise factor as neutral, but concluded that Sandoz faced a substantial burden to establish harmlessness because curing the violation could disrupt the ongoing trial. (Tr. 446:6-15). As such, the Court directed the parties to focus principally on whether the untimely disclosure was substantially justified and on the importance of Dr. Mullins's

testimony. (Tr. 446:16-19).

Sandoz argued that the late production resulted from an inadvertent omission rather than an intentional failure to comply with the expert-disclosure schedule. (Tr. 448:11-21). Sandoz further maintained that Dr. Donovan's timely served report expressly cited and relied on the Mullins declaration, placing Plaintiffs on notice of both its existence and its relevance. (Tr. 448:15-17). Sandoz argued that the prompt production of the declaration afforded Plaintiffs ample time to seek a deposition and cure any resulting prejudice. (Tr. 449:4-8). Sandoz also characterized Dr. Mullins's testimony as important to its case. (Tr. 448:5-8).

Janssen responded that Dr. Donovan had not meaningfully relied on Dr. Mullins's library-science opinions, but had instead relied on counsel's representation that Bitter qualified as prior art. (Tr. 450:17-22). Nevertheless, Janssen acknowledged that the testimony was important because Sandoz bore the burden of establishing that Bitter was publicly accessible and therefore qualified as prior art, and both Dr. Farber and Dr. Donovan relied on Bitter in forming their obviousness opinions. (Tr. 451: 1-7). As such, Janssen argued that, if Dr. Mullins were permitted to testify, his testimony should be confined strictly to the opinions disclosed in his declaration. (Tr. 452:2-5).

The Court permitted Dr. Mullins to testify but limited his testimony strictly to the contents of his declaration as a means of curing potential prejudice. (Tr. 452:8-9). The Court explained that, because the case was being tried to the bench, it could assess Dr. Mullins's testimony under the governing legal standards for public accessibility and determine what weight, if any, the testimony should receive. (Tr. 452:23-453:16). The Court expressly declined, however, to hold that Dr. Mullins's declaration satisfied Rule 26(a)(2)(B), noting that it omitted information required in a proper expert report. (Tr. 453:3-10). Thus, the Court admitted the testimony because it could

compartmentalize its limited purpose and later determine whether it established that Bitter was publicly available, not because Sandoz had complied fully with the expert-disclosure requirements. (Tr. 453: 10-16).

Now, Janssen seeks to have Dr. Mullins's testimony stricken. (See Pl.'s PTB at p. 45-46). Sandoz argues that there was no prejudice to Janssen because they knew Dr. Mullins would be at trial, were prepared to cross examine him, and indeed did cross examine Dr. Mullins at trial. (See Def.'s Reply at p. 21-22).

The Court will not strike Dr. Mullins' testimony. The Court agrees with Defendant that any prejudice caused by not being able to depose Dr. Mullins was cured by Janssen's ability to cross examine him during trial. Further, Sandoz demonstrated that it was not acting willfully or in bad faith because it disclosed Dr. Mullins' declaration as soon as it discovered it had been inadvertently excluded. *Withrow v. Spears*, 967 F. Supp. 2d 982, 1006 (D. Del. 2013) ("Willfulness or bad faith has not been found, however, where a party's actions have amounted to a mere "[l]ack of diligence.") (quoting *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 792 (3d Cir. 1994)). The only disruption to trial was to hear the parties arguments regarding whether to allow Dr. Mullins to testify.

Accordingly, the Court will accept Dr. Mullins' testimony as an expert in library and information sciences, the organization of materials and cataloging, including doctoral dissertations granted by universities.

2. Janssen's Experts

Dr. George I. Papakostas, M.D. ("Dr. Papakostas") is a board-certified patient care psychiatrist who works at Massachusetts General Hospital (Tr. 689:3-16 (Papakostas)). Dr. Papakostas treats patients with TRD, MDD, and MDD-SI. (Tr. 692:10-23 (Papakostas)). He is also

a Professor of Psychiatry at Harvard Medical school. (Tr. 689: 10-12 (Papakostas)). Dr. Papakostas has more than 25 years of experience conducting research and clinical trials involving MDD and TRD, including studies related to ketamine and has published papers on both ketamine and esketamine. (Tr. 690:14-691:6). Dr. Papakostas was accepted by the Court, without objection, as an expert in psychiatry, clinical research, and the treatment of patients with major depressive disorders, or MDD, including treatment-resistant depression and major depressive disorder with suicidal ideation. (Tr. 693:4-11 (Papakostas)).

Dr. Steven Little ("Dr. Little") holds a Ph.D. from MIT in pharmaceutical formulation and has experience formulating and characterizing a wide range of dosage forms across various diseases and routes of administration, including IN dosage forms and sinus delivery. (Tr. 495:21-496:1, 496:11-15, 497:11-15 (Little)). He currently is a professor at the University of Pittsburgh, where he has worked with pharmaceutical companies to develop or advise on product formulations. (Tr. 496:3-15 (Little)). Dr. Little was qualified without objection as an expert witness in pharmaceutical sciences, pharmaceutical formulations, and drug delivery. (Tr. 499:2-6 (Little)).

Dr. William John Giakas ("Dr. Giakas") is board certified in psychiatry, forensic psychiatry, and geriatric psychiatry. (Tr. 828:20-829:8 (Giakas)). He has more than thirty years of clinical experience, including substantial experience treating patients with MDD and TRD, and has prescribed Spravato®. (Tr. 828: 15-19, 830:11, 833: 11-13 (Giakas)). Dr. Giakas has participated in clinical studies, including pharmaceutical-company trials, and has taught medical students, nurse practitioners, and other physicians. (Tr. 829: 15-830:7 (Giakas)). Sandoz objected to Dr. Giakas's qualification as an expert because he lacked specialized research experience concerning ketamine and esketamine, including any involvement in related clinical trials. (Tr. 834:15-23 (Giakas)). Sandoz also argued that his proposed testimony concerning Spravato® and

objective indicia exceeded the scope of his expert report. (Tr. 838:14-16 (Giakas)). However, the Court permitted Dr. Giakas to testify regarding his clinical experience prescribing Spravato®, treating relevant patient populations, teaching medical professionals, and participating in clinical trials to the extent those experiences related to the patents and evidence presented at trial. (Tr. 838:17-25 (Giakas)).

Carla S. Mulhern (“Ms. Mulhern”) is an economist with a master’s degree in economics from the London School of Economics and Political Science. (Tr. 885:21-886:1 (Mulhern)). Ms. Mulhern is Partner and Senior Advisor at Analysis Group, an economic and financial consulting firm where she provides economic and financial analysis for economic issues arising in litigation, primarily in patent matters. (Tr. 886:14-887:6 (Mulhern)). Ms. Mulhern was qualified, without objection, as an expert in economic analysis of intellectual property. (Tr. 888:9-13 (Mulhern)).

E. Obviousness

In order for a patent to issue, the claims may not be obvious to a Person of Ordinary Skill in the Art (“POSA”) in light of the prior art. 35 U.S.C.A. § 103; *Titan Tire Corp. v. Case New Holland, Inc.*, 566 F.3d 1372, 1380 (Fed. Cir. 2009). Prior art is defined by 35 U.S.C. § 102. Under § 102, prior art consists of any disclosure—including patents, printed publications, public uses, sales, or any other availability to the public—that predates the effective filing date of a claimed invention. *See* 35 U.S.C.A. § 102(a)(1). Additionally, patents and published applications by other inventors that were effectively filed before the claimed invention's effective filing date also constitute prior art. *See* U.S.C.A. § 102(a)(2).

Obviousness “is a question of law based on underlying findings of fact.” *In re Kubin*, 561 F.3d 1351, 1355 (Fed. Cir. 2009). It turns on four inquiries: “(1) the scope and content of prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in

the art at the time the invention was made; and (4) objective evidence of nonobviousness, if any.” *Id.* (citing *Graham v. John Deere Co. of Kan. City*, 383 U.S. 1, 17 (1966)).

Since courts must assess obviousness against the state of the art “at the time the invention was made,” *Id.*, courts must adhere to the “oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field.” *Depomed, Inc. v. Actavis Elizabeth LLC*, Civ. No. 12-1358, 2014 WL 4215435, at *26 (D.N.J. Aug. 25, 2014) (quoting *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999)). Accordingly, the Federal Circuit has regularly cautioned that a “fact finder must not allow its analysis to be distorted by hind-sight bias.” *Neptune Generics, LLC v. Eli Lilly & Co.*, 921 F.3d 1372, 1377 (Fed. Cir. 2019); *In re Kotzab*, 217 F.3d 1365, 1369 (Fed. Cir. 2000) (noting the “insidious effect” of a hindsight-driven analysis). Courts must be mindful that “[t]he inventor’s own path itself never leads to a conclusion of obviousness; that is hindsight. What matters is the path that the [POSA] would have followed, as evidenced by the pertinent prior art.” *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012).

When the challenger alleges that a patent is invalid as obvious, it is the challenger’s burden to “establish[] that a POSA would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the POSA would have had a reasonable expectation of success in doing so.” *Millennium Pharm., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1366 (Fed. Cir. 2017 (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007))). The Supreme Court has instructed courts to apply the “expansive and flexible approach” to the “obviousness question” as provided in *Graham* 383 U.S.

Patents are statutorily presumed valid and “a challenger must overcome that presumption to prevail on an invalidity defense.” *Microsoft Corp. v. I4I Ltd. P’ship*, 564 U.S. 91, 100 (2011). As

such, any party challenging patent validity, including ANDA filers asserting invalidity defenses, must prove invalidity by clear and convincing evidence. *Id.* at 95.

1. Sandoz's Obviousness Arguments

i. The Caers Claims

As a preliminary matter, Sandoz argues that Janssen did not contest the obviousness of treating MDD, TRD, and MDD-SI with S-ketamine, using adjunctive oral antidepressants, or using an aqueous formulation of S-ketamine hydrochloride. Therefore, Sandoz characterizes Janssen as having conceded that those limitations would have been obvious. Sandoz also argues that Janssen waived any contention that Sandoz's references constitute nonanalogous art because Janssen did not develop that argument in its opening brief.

a. Treating TRD, MDD, and MDD-SI with S-Ketamine

Sandoz argues that the prior art would have motivated a POSA to treat MDD, TRD, and MDD-SI with S-ketamine with a reasonable expectation of success. According to Sandoz, Charney, Singh, aan het Rot, and Mathew demonstrated ketamine's effectiveness in treating depression, while Singh and Mathew identified reasons to select S-ketamine, including its greater NMDA-receptor affinity, potential efficacy at lower doses, and possibly reduced adverse effects. Sandoz further contends that Singh expressly claimed treating TRD with S-ketamine and that Charney, Bahetwar, and Bitter described the advantages of administration, including rapid absorption, avoidance of first-pass metabolism, and ease of use. Although the prior art lacked conclusive clinical data establishing the effectiveness of S-ketamine for depression, Sandoz maintains that obviousness does not require certainty, it only requires a reasonable expectation of success and that the successful intravenous studies, combined with the known benefits of delivery, satisfied that standard.

b. Claimed Dose Amounts

Sandoz argues that the claimed intranasal doses were obvious through two independent paths. First, Sandoz argues that the claimed 56 mg and 84 mg intranasal doses fall within the dose ranges disclosed by Charney and Singh, creating a presumption that the dose limitation was obvious. Second, Sandoz argues that the doses were obvious under the standard *Graham* analysis because the prior art doses supplied a starting point that a POSA would have been motivated to optimize with a reasonable expectation of success.

The Overlapping Range Presumption

First, Sandoz argues that the dose ranges disclosed in Charney and Singh encompass the claimed 56 mg and 84 mg doses, creating a presumption of obviousness. Next, Sandoz argues that a POSA could have derived the claimed doses from prior art intravenous doses through routine optimization and straightforward conversion calculations.

Sandoz argues that Charney and Singh disclosed ketamine or S-ketamine ranges of 1–250 mg and 0.1–250 mg, respectively, which encompass the claimed doses. Sandoz contends that the overlapping ranges create a presumption that the 56 mg and 84 mg doses were obvious. Sandoz maintains that Charney also taught a POSA to increase the ketamine dose if the patient experienced an inadequate response. Because Charney also taught that S-Ketamine is approximately twice as potent as racemic ketamine, Sandoz argues that converting Charney's disclosed racemic-ketamine doses into S-Ketamine equivalents yields doses that include those recited in the claims.

Further, Sandoz argues that Janssen does not dispute that the Charney and Singh ranges encompass the claimed doses and therefore bears the burden of rebutting the resulting presumption. According to Sandoz, Janssen did not rebut the presumption through evidence that the prior art taught away from the claimed doses, that the doses produced unexpected results, or

that other secondary considerations supported nonobviousness. Sandoz further contends that Janssen did not establish the criticality of the 56 mg and 84 mg doses because the Caers specifications contain no intranasal efficacy data demonstrating that those doses produced unexpected results.

Sandoz further argues that dose amount was a result-effective variable that a POSA would have been motivated to optimize and that Janssen did not dispute that premise. Although Janssen characterizes the disclosed ranges as too broad to provide meaningful guidance, Sandoz contends that the specific example doses in Charney and Singh narrowed the relevant field of experimentation.

Graham Analysis

Additionally, Sandoz argues that the claimed dosages were obvious under the *Graham* analysis. Sandoz contends that the dosages disclosed in the prior art provided suitable starting points for routine optimization. Further, it argues that a POSA would have been motivated to determine an effective IN dose of S-Ketamine with a reasonable expectation of success. Finally, Sandoz contends that a POSA could have derived the claimed doses through straightforward conversion calculations based on the IV doses disclosed in the prior art.

According to Sandoz, Charney and Singh disclosed effective IV ketamine and S-ketamine doses for treating MDD, TRD, and MDD-SI that provided starting points from which a POSA could derive an optimize the claimed IN doses with a reasonable expectation of success. Based on the disclosures in Charney and Singh, a POSA could convert the disclosed IV doses to IN doses by accounting for patient weight, S-ketamine's greater potency, intranasal bioavailability, and the desired speed of delivery to the brain. Applying those calculations to Singh's disclosed IV doses would produce, among other values, the claimed 56 mg and 84 mg intranasal doses. Accordingly,

Sandoz contends that the claimed doses were readily derived through routine optimization with a reasonable expectation of success.

Sandoz denies that Dr. Farber worked backward from the asserted claims, maintaining that his calculations were based on the prior art. Sandoz also defends his reliance on sedation-related data, arguing that sedation and anesthesia supplied comparable endpoints for assessing the speed with which intravenous and intranasal ketamine reached the brain.

Routine Optimization

Sandoz maintains that clinician POSAs routinely optimize dosing parameters such as dose amount, frequency, and duration and that such optimization does not require an FDA-approved regimen. Sandoz also contends that Dr. Farber's prior research does not undermine that conclusion because it concerned whether extending infusion time, which is a variable not recited in the asserted claims, would prolong ketamine's response.

Induction and Maintenance Phases

Sandoz further argues that induction and maintenance phases were well-known features of depression treatment. Charney disclosed repeated dosing and maintenance therapy, Singh described acute and maintenance treatment, and aan het Rot used repeated ketamine doses modeled on ECT regimens. Sandoz also relies on Ghasemi, which compared repeated administration of ketamine with ECT, as further support for the proposition that a POSA would have considered ECT practices when designing an S-ketamine regimen.

According to Sandoz, the duration of response shown in Charney would suggest redosing approximately twice weekly, while aan het Rot and established ECT practices would motivate an induction period of approximately four weeks. In response to Janssen's contention that the ECT art did not suggest the claimed induction schedule, Sandoz relies on the Abrams ECT reference,

which described acute treatment two or three times per week for six to twelve treatments over approximately three to four weeks. Sandoz contends that once a response was achieved, a POSA would have reduced the dosing frequency to once weekly or once every other week and continued maintenance treatment as necessary, including for at least fourteen weeks.

Sandoz further argues that Charney and Singh expressly contemplated maintenance treatment with ketamine and S-ketamine, notwithstanding other references expressing uncertainty about how to sustain ketamine's antidepressant effects.

Sandoz also disputes Janssen's reliance on APA guidance recommending continuation of the same dose and frequency used during acute treatment, contending that the cited language concerns a continuation phase rather than the distinct maintenance phase required by the claims.

Remaining Formulation and Treatment Limitations

Finally, Sandoz maintains that the remaining formulation and treatment limitations were conventional. The prior art disclosed S-ketamine hydrochloride—the only ketamine salt identified in the cited art—in aqueous intranasal sprays, and a POSA would have expected that salt form to provide suitable solubility. Charney and Singh also disclosed administering ketamine or S-ketamine with conventional oral antidepressants. Sandoz accordingly argues that the claimed doses, dosing phases and frequencies, aqueous S-ketamine hydrochloride formulation, and adjunctive oral-antidepressant therapy would all have been obvious.

c. The Caers Patents as a Whole

Sandoz argues that the asserted Caers claims would have been obvious as a whole because the prior art supplied both a reason to combine its related teachings and a reasonable expectation of success. According to Sandoz, a POSA knew that MDD, TRD, and MDD-SI were serious chronic conditions; that ketamine rapidly and safely improved depressive symptoms; and that

ketamine and ECT were similar interventional treatments acting on the glutamatergic system. Those similarities would have motivated a POSA to adapt ECT's intermittent induction-and-maintenance regimen to ketamine treatment.

Sandoz further contends that a POSA would have selected S-ketamine hydrochloride because of its greater NMDA-receptor affinity, potential for lower doses and fewer side effects, established European use, and suitability for aqueous intranasal formulations. The advantages of intranasal administration over intravenous administration would then have motivated development of an intranasal regimen. Through the prior art's express teachings, routine calculations, and dose optimization, a POSA allegedly would have arrived at the claimed 56 mg and 84 mg doses, a four-week twice-weekly induction phase, and a maintenance phase using weekly or every-other-week dosing for at least fourteen weeks, with adjunctive oral antidepressants where appropriate. Sandoz therefore maintains that the combined teachings of Charney, Singh, aan het Rot, Mathew, Bahetwar, and the ordinary knowledge in the field render each asserted Caers claim obvious.

Sandoz disputes Janssen's contention that Dr. Farber analyzed only isolated claim limitations, arguing that he also testified that a POSA would have combined the prior-art teachings to create the claimed regimens with a reasonable expectation of success. Sandoz further maintains that dose amount and frequency are independent parameters for ketamine because it is administered as a bolus and can produce a sustained response after leaving the bloodstream, rather than requiring maintenance of a constant blood concentration. Sandoz therefore maintains that its element-by-element analysis, combined with Dr. Farber's testimony concerning the motivation to combine the references and the independence of relevant dosing parameters, established the obviousness of the asserted Caers claims as a whole.

ii. The 260 Patent

a. Bitter as Prior Art

As a threshold matter, Sandoz argues that the Bitter thesis qualifies as prior art because it was publicly accessible more than one year before the '260 Patent's March 15, 2013, priority date. Sandoz relies principally on a January 2012 email in which Dr. Bitter provided Janssen scientists with an allegedly public link to the thesis and stated that it had been restricted "till December" 2011. (DTX-0364-0001). Sandoz argues that Bitter was public thereafter. Sandoz also relies on Dr. Mullins's testimony that a search of the University of Basel repository using the thesis title, which contains "nasal" and "esketamine," returned a downloadable record and that the same link appeared to have been accessible in 2011. Sandoz further maintains that the asserted claims would have been obvious even if Bitter does not qualify as prior art because Drs. Farber and Donovan also relied on other references and a POSA's ordinary knowledge to support their findings.

b. Clinical Limitations

Sandoz argues that claims 22 and 36 of the 260 Patent were obvious because the prior art disclosed both their clinical and formulation limitations. Charney, Mathew, Bitter, and the '061 publication allegedly would have motivated a POSA to administer aqueous IN S-ketamine hydrochloride to treat MDD with a reasonable expectation of success.

According to Sandoz, Charney and Mathew disclosed the use of ketamine or S-ketamine hydrochloride to treat MDD, while the '061 publication disclosed ketamine or S-ketamine for treating depressive symptoms associated with bipolar disorder. Sandoz also argues that Charney, Bitter, Mathew, and the '061 publication taught the advantages of intranasal administration, thereby providing a motivation to administer intranasal S-ketamine hydrochloride with a reasonable expectation of alleviating depressive symptoms.

In response to Janssen's criticism of Sandoz's reliance on the '061 publication, Sandoz maintains that Dr. Farber principally relied on Charney and a POSA's background knowledge to establish the relevant dose range. Sandoz further contends that the known greater potency of S-ketamine justified beginning the dose analysis by halving a racemic-ketamine dose, even though the '061 publication described ketamine and S-ketamine as interchangeable.

c. Claimed Concentrations, Spray Numbers, and Administration Period

According to Sandoz, routine formulation considerations, including nasal-volume limits, delivery through both nostrils, minimizing the number of sprays, S-ketamine's solubility, and conversion between its free-base and hydrochloride forms, would have produced concentrations and spray regimens within the claims. Sandoz contends that these calculations yielded concentrations falling within claim 22's range and approximately 140 mg/mL as required by claim 36, administered in two to eight sprays over no more than an hour.

Aqueous S-Ketamine Hydrochloride

Sandoz argues that aqueous IN S-ketamine hydrochloride formulations were already disclosed in Bitter and the '061 publication and that a POSA would have selected the hydrochloride salt to improve stability, bioavailability, absorption, and water solubility. Sandoz further relies on the inclusion of S-ketamine hydrochloride in the European Pharmacopoeia as evidence that the salt was available and met established standards for use in human drug products.

Conversion Between Free Base and Hydrochloride Salt

Sandoz contends that a POSA could readily convert between the clinically desired S-ketamine free-base equivalent and the amount of S-ketamine hydrochloride used in the formulation

based on their known molecular weights. According to Sandoz, the applicable conversion factor was 0.867: a POSA would divide the desired free-base amount by 0.867 to determine the hydrochloride amount and multiply the salt amount by 0.867 to determine its free-base equivalent.

Spray Volume and Bilateral Administration

Sandoz argues that a POSA would have selected a 100-microliter spray volume because the nasal cavity is a low-volume administration site and that volume was commonly used in the prior art. Sandoz further contends that the nasal cycle would have motivated delivery through both nostrils to avoid variability in congestion, while patient-compliance considerations would have motivated minimizing the total number of sprays. In response to Janssen's contention that other IN medications use only one nostril, Sandoz argues that bilateral administration was consistent with the ketamine-specific prior art and that Janssen did not dispute that formulators consider the nasal cycle.

Solubility and Concentration

Sandoz argues that a POSA would have considered S-ketamine hydrochloride's known water solubility of approximately 200 mg/mL but formulated below that limit to prevent crystallization during manufacturing, storage, and use. Although Janssen argues that the 200 mg/mL value applies to pure water rather than a completed formulation, Sandoz responds that pure-water solubility supplies a natural starting point that a formulator could adjust through routine experimentation to account for the effects of excipients.

Sandoz also denies that Dr. Donovan selected the 55 mg and 85 mg target doses through hindsight, arguing that she applied the same methodology across the entire allegedly obvious range of 35–105 mg. According to Sandoz, applying these considerations would have produced formulations between approximately 87.5 and 141.7 mg/mL, including concentrations within

claim 22's range and approximately 140 mg/mL as required by claim 36.

Teaching Away and Alternative Formulation Approaches

Sandoz disputes Janssen's contention that the prior art discouraged concentrations above 100 mg/mL because of low or moderate bioavailability. According to Sandoz, Bitter instead encouraged higher-concentration, lower-volume formulations to reduce the swallowing associated with administering large volumes of lower-concentration solutions.

Sandoz also rejects Dr. Little's proposed use of concentrations around 100 mg/mL because that approach would require more sprays and potentially reduce patient compliance. Sandoz maintains that Dr. Donovan's approach need not have been the best or only formulation method; it need only have been a suitable option that a POSA would have pursued. Sandoz argues that a POSA would routinely adjust concentration and spray number together to deliver the desired dose and that the ability to reach the claimed combinations through those ordinary adjustments supports obviousness rather than demonstrating hindsight.

d. Claimed pH and Excipients

Sandoz further argues that the other claimed formulation features—including a pH of approximately 4.5, the specified excipients, and the omission of a preservative—were standard formulation choices disclosed in the prior art.

Sandoz argues that a POSA would have selected a pH compatible with human tissue and formulation stability. Sandoz pointed to various examples. Ketalar®, a commercially available aqueous ketamine hydrochloride product, had a pH range of 3.5–5.5; Bitter disclosed intranasal formulations with pH values between 3.1 and 6.1; and the '061 publication expressly identified approximately 4.5 as acceptable. In response to Janssen's reliance on general formulation references suggesting a pH of 5.5–7.5, Sandoz argues that the ketamine-specific evidence was

more probative and directly encompassed the claimed pH.

Sandoz further argues that formulators routinely use buffers to maintain a desired pH and pH-adjusting agents to reach that pH. According to Sandoz, the '651 patent specifically disclosed citrate as a suitable buffer and sodium hydroxide and citric acid as suitable agents for adjusting pH. Sandoz also relies on the '651 patent's disclosure of EDTA⁵ as a suitable chelating agent and notes that Janssen presented no rebuttal evidence specifically concerning EDTA. Although Bitter chose not to buffer its formulations, Sandoz maintains that Charney, the '061 publication, and the '651 patent disclosed buffers and pH-adjusting agents suitable for IN ketamine formulations.

e. Omission of Preservatives

Sandoz argues that preservatives were optional and could be omitted to avoid irritation, toxicity, or stability problems. According to Sandoz, the '061 publication described preservatives as optional, Bitter disclosed preservative-free formulations to avoid mucosal toxicity, and Dhakar taught that preservatives could irritate nasal mucosa, interfere with mucociliary clearance, and create stability, taste, or odor problems.

Sandoz further argues that a preservative would have been unnecessary where a device contained only a small number of sprays because the limited-use design reduced the opportunity for microbial contamination. Sandoz disputes Janssen's contention that the self-preserving nature of concentrated S-ketamine constituted an unexpected result, noting that several claims permit preservatives and only claim 22 requires their absence. According to Sandoz, even if there were reasons to retain a preservative, omitting one remained a known and obvious formulation option.

⁵ EDTA is ethylene diamine tetraacetic acid. (JTX-4 at 8:60–65). Dr. Donovan explained that EDTA is a chelating agent commonly used in formulations for intranasal delivery. (Donovan Invalidity Rep. ¶ 393). Because the parties refer to the compound exclusively as "EDTA," the Court does so as well.

f. The 260 Patent Claims as a Whole

Sandoz maintains that claims 22 and 36 would have been obvious as a whole over Charney combined with Bitter or the '061 publication, Mathew, Bahetwar, the '651 patent, and the ordinary knowledge of a POSA.

Sandoz argues that a POSA team comprising a clinician and a formulator would have combined the clinical determination of an effective IN S-ketamine dose with routine formulation principles to produce a compatible aqueous S-ketamine hydrochloride composition containing the claimed concentration, spray regimen, pH, and excipients.

In response to Janssen's contention that Sandoz's experts considered the limitations only individually, Sandoz argues that Drs. Farber and Donovan explained how their clinical and formulation opinions fit together and that Dr. Farber expressly addressed obviousness of the asserted claims as a whole. Sandoz further maintains that Dr. Donovan addressed the interplay among the formulation limitations by testifying that each limitation was compatible with and complementary to the others.

i. Objective Indicia

a. Nexus and Commensurateness

Sandoz argues that Janssen's evidence of objective indicia does not overcome the strong showing of obviousness because Janssen failed to establish a nexus between the asserted claims and the alleged secondary considerations. According to Sandoz, the asserted benefits largely derive from ketamine's known antidepressant properties or from unclaimed features such as FDA approval, insurance coverage, and reimbursement, and Janssen's reliance on TRD evidence is not commensurate with claims that also cover MDD.

Sandoz further argues that Janssen did not establish that the particular dosing regimens or formulation features recited in the asserted claims produced the alleged safety, efficacy, or marketplace benefits. It similarly contends that alleged benefits not required by the relevant claims, including a particular safety profile, manufacturing method, or preservative-free formulation, cannot establish nonobviousness across the full scope of those claims. According to Sandoz, even if some of Janssen's evidence possessed a nexus, the asserted objective indicia are too weak to overcome what Sandoz characterizes as a strong prima facie showing of obviousness.

b. Long-Felt but Unmet Need

Sandoz separately challenges each asserted indicium. It contends there was no long-felt unmet need because IV ketamine and other rapid treatments already existed and, in some respects, performed better than Spravato®.

According to Sandoz, IV ketamine had already addressed the asserted need for a rapid and effective depression treatment and produced faster and greater reductions in depressive symptoms than IN S-ketamine during induction. Sandoz also relies on evidence that physicians continued to use IV ketamine, allegedly more frequently than Spravato®, despite the competitive disadvantages faced by IV ketamine: unlike Spravato®, IV ketamine was not FDA-approved for treating depression, generally was not covered by insurance, and often required patients to pay out of pocket. Sandoz contends that the continued use of IV ketamine despite Spravato®'s FDA approval and access to insurance reimbursement undermines Janssen's assertion that Spravato® satisfied a previously unmet therapeutic need.

Sandoz further argues that Janssen cannot merely rely on S-ketamine's mechanism of action, antidepressant efficacy, or safety to show that the claimed inventions satisfied the asserted need. According to Sandoz, those properties are inherent in the previously known S-ketamine

molecule, and Janssen did not establish that the particular dosing regimens or formulation features recited in the claims produced those benefits. Therefore, Sandoz maintains that Janssen failed to show either that the asserted need remained unmet before the inventions, given the prior use of ketamine therapy, or that the claimed features—as distinguished from the known properties of ketamine and S-ketamine—satisfied that need.

c. Failure of Others

Sandoz maintains that there was no failure of others because Janssen did not identify any unsuccessful effort to develop the claimed IN ketamine treatment. According to Sandoz, Janssen instead relied on unsuccessful efforts to develop other NMDA antagonists without providing competent evidence concerning the nature or extent of those efforts or demonstrating that they failed because they lacked the claimed features. Sandoz further notes that Janssen identified Javelin's IN ketamine formulation as the only attempt by the relevant dates to obtain FDA approval for an IN ketamine product but did not rely on that effort as evidence of failure by others.

Sandoz also rejects Janssen's reliance on Dr. Farber's ketamine research because he was not attempting to obtain FDA approval or develop the claimed IN S-ketamine regimen. According to Sandoz, a researcher cannot have failed to accomplish an invention that he never attempted to make.

d. Unexpected Results

Sandoz contends that Janssen failed to establish unexpected results because Dr. Giakas did not compare Spravato®'s performance with the closest prior art, which Sandoz identifies as IV ketamine. According to Sandoz, the available comparative evidence showed that IV ketamine reduced depressive symptoms more rapidly and to a greater extent than IN S-ketamine during induction, undermining any contention that Spravato® produced unexpectedly superior efficacy.

Sandoz separately challenges Janssen's reliance on Spravato®'s allegedly favorable long-term safety as an unexpected result. First, Sandoz argues that Janssen did not establish the long-term safety profile that a POSA would have expected from IV ketamine. Without that prior art baseline, Sandoz contends that Janssen could not show that Spravato® represented an unexpected improvement in long-term safety. Second, Sandoz argues that Janssen did not connect Spravato®'s alleged safety advantage to the claimed dosing regimens. According to Sandoz, Janssen failed to show that the asserted safety benefit resulted from the claimed doses and dosing schedules rather than from the inherent properties of the previously known S-ketamine molecule. Finally, Sandoz argues that Spravato®'s FDA-mandated REMS program and black-box warning undermine Janssen's assertion that the claimed methods resolved ketamine's known safety concerns.

With respect to the '260 patent, Sandoz responds to Janssen's argument that the high concentration of S-ketamine rendered the formulation self-preserving, thereby eliminating the need either to use cumbersome and expensive manufacturing procedures or to add a preservative to prevent microbial contamination. As to the alleged manufacturing benefit, Sandoz argues that neither asserted claim recites a manufacturing method. It therefore contends that Janssen failed to connect the asserted ability to avoid cumbersome manufacturing procedures to the claimed inventions. Sandoz separately argues that the alleged preservative-related benefit does not establish unexpected results for claim 36 because that claim permits formulations with preservatives. Sandoz therefore contends that Janssen's evidence concerning a preservative-free formulation does not apply to claim 36.

e. Industry Skepticism and Praise

Sandoz argues that Janssen failed to establish relevant industry skepticism. Janssen relies on evidence that the industry questioned whether ketamine could be used to treat depression and

maintain its antidepressant effects without unacceptable safety problems. Sandoz responds that these concerns were directed to ketamine generally, not to the particular IN S-ketamine regimens or formulations claimed in the patents. Sandoz further argues that Janssen did not show that the claimed inventions overcame the safety concerns underlying the alleged skepticism. Thus, Sandoz maintains that Janssen failed to show either that the industry was skeptical of the particular solutions recited in the claims or that the claimed inventions overcame the alleged safety concerns.

Sandoz also rejects Janssen's reliance on the FDA's request for additional neurotoxicity data during its review of Spravato®. According to Sandoz, requesting additional safety data is part of the FDA's ordinary regulatory responsibilities and does not show that the FDA doubted the claimed inventions would work or that a POSA would have been skeptical of them. Sandoz also contends that Dr. Giakas's testimony concerning clinicians' present views of Spravato® relied on long-term, post-priority evidence and did not establish skepticism at the relevant time.

Sandoz also disputes Janssen's reliance on industry praise as evidence that the claimed inventions were not obvious. Sandoz argues that such praise is relevant only if it is directed to the features of the claimed inventions. According to Sandoz, the cited publications instead discussed the antidepressant mechanism or benefits of ketamine generally, rather than praising the particular dosing regimens or formulations recited in the patents. Sandoz also notes that one cited publication reported that IV ketamine could act faster and require fewer treatments than S-ketamine, which Sandoz characterizes as praise of the prior art rather than the claimed inventions. Finally, Sandoz discounts the FDA's prediction that Spravato® might make a life-saving difference as a tentative prediction rather than substantive praise attributable to the claimed features and argues that Janssen did not establish that the prediction proved correct.

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Finally, Sandoz disputes Janssen's commercial success evidence. It argues that Janssen's expert used inappropriate oral-drug comparators, reduced those comparators' data by 75%, relied

on new-patient share rather than total-patient share, and emphasized revenue rather than sales volume despite Spravato®'s higher price.

According to Sandoz, much of Ms. Mulhern's analysis compared Spravato® with oral antidepressants and antipsychotics even though she acknowledged that Spravato®'s closest competitors were interventional treatments. Sandoz further contends that none of the oral comparators was indicated for TRD or MDD-SI and that Janssen reduced the oral comparators' data by 75% without making a corresponding adjustment to Spravato®'s data, thereby inflating Spravato®'s apparent market share.

Sandoz also argues that relying on Spravato®'s share of new patients favored a newly introduced product when it was compared with established treatments such as ECT and transcranial magnetic stimulation ("TMS") and did not reliably demonstrate overall marketplace success. It further contends that Ms. Mulhern's reliance on revenue rather than sales volume inflated Spravato®'s apparent performance relative to IV ketamine because Spravato® was substantially more expensive.

Sandoz further contends that the continued growth of IV ketamine and Spravato®'s above-average pricing, marketing, rebates, FDA approval, insurance coverage, and reimbursement support show that any marketplace success was attributable to unclaimed commercial advantages rather than the patented invention.

Sandoz argues that the continued growth of IV ketamine is particularly probative because IV ketamine faced substantial competitive disadvantages: it lacked FDA approval, generally was not covered by insurance, and often required patients to pay out of pocket. Sandoz also maintains that Spravato®'s asserted safe, rapid, and sustained efficacy derives from inherent properties of the S-ketamine molecule rather than the claimed dosing regimens or formulations. Because

Janssen allegedly did not demonstrate that the claimed features drove Spravato®'s sales, Sandoz maintains that the commercial-success evidence is entitled to little or no weight.

2. Janssen's Obviousness Rebuttal

i. The Caers Patents

Janssen argues that Sandoz failed to establish that a POSA would have been motivated to combine the prior art teachings to achieve the claimed IN S-ketamine regimens with a reasonable expectation of success. According to Janssen, Sandoz identifies only general motivations to use ketamine to treat depression and to explore IN S-ketamine as a possible treatment. Janssen maintains that those general motivations do not establish that a POSA would have arrived at the claimed combination of specific dose amounts, frequencies, and treatment durations.

a. Treating TRD, MDD, and MDD-SI with S-Ketamine

Janssen argues that the prior art was substantially removed from the claimed long-term IN S-ketamine regimens. According to Janssen, the available clinical evidence principally concerned short-term administration of a single 0.5 mg/kg dose of IV racemic ketamine, and the prior art contained no clinical studies of IN S-ketamine for depression or any long-term ketamine treatment regimen.

Janssen characterizes Charney and Singh as early patent applications containing no new clinical data, and the Rot as an open-label study of IV racemic ketamine administered three times weekly for two weeks, and Bahetwar as a pediatric dental-sedation study. Janssen further argues that Mathew described ketamine treatment as highly experimental and premature for adoption in psychiatric practice. According to Janssen, the prior art recognized ketamine's rapid but temporary antidepressant effects but did not resolve how to transform those effects into a safe, effective, and

durable clinical treatment.

Janssen also maintains that a general interest in IN S-ketamine is insufficient to prove obviousness of the claimed regimens. Even if a POSA would have considered S-ketamine and intranasal administration as possible treatment options, Janssen argues that Sandoz still had to establish a reason to select and combine the claimed route, doses, frequencies, and durations with a reasonable expectation that the integrated regimen would succeed.

b. Claimed Dose Amounts

Janssen disputes both paths through which Sandoz contends that the claimed 56 mg and 84 mg intranasal doses were obvious. First, Janssen argues that the broad ranges disclosed by Charney and Singh do not create a presumption of obviousness under the circumstances presented. Second, Janssen argues that Dr. Farber's attempt to derive the claimed doses under a standard *Graham* analysis depended on impermissible hindsight, unsupported routine-optimization assumptions, and scientifically flawed calculations.

The Overlapping-Range Presumption

Janssen argues that the overlapping-range presumption does not arise automatically whenever a claimed value falls somewhere within a prior-art range. Instead, its application depends on the relevant inventive context, including whether a POSA would have been motivated to explore the prior art range and would have reasonably expected routine experimentation to produce a successful result. According to Janssen, Charney's range of 1–250 mg and Singh's range of 0.1–250 mg were far too broad to guide a POSA toward the claimed 56 mg and 84 mg doses. Janssen contends that those ranges encompass an unreasonably large number of potential doses and that selecting appropriate values would have required extensive and unpredictable experimentation rather than routine optimization.

Janssen further argues that Sandoz's overlapping-range theory applies, at most, to the dose-amount limitation. Because obviousness must be assessed with respect to the claimed subject matter as a whole, Janssen maintains that an overlap concerning dose amount does not render presumptively obvious the complete regimen, which also requires a particular route of administration, dosing frequency, induction duration, and maintenance schedule.

Janssen also argues that the claimed regimens constitute integrated combinations of interdependent variables falling outside the rationale underlying the presumption. Even if dose amount could generally be characterized as a result-effective variable, Janssen contends that Sandoz failed to show that a POSA would have been motivated to optimize dose amount within the claimed combination or would have expected routine experimentation to yield a successful long-term intranasal regimen.

Graham Analysis

Janssen likewise disputes Sandoz's contention that the claimed doses were obvious under a standard *Graham* analysis. According to Janssen, describing Sandoz's theory as a *Graham* analysis does not cure its dependence on the premise that the claimed doses could have been reached through routine optimization.

Janssen argues that Dr. Farber's analysis was driven by hindsight because he selected isolated disclosures from Charney and Singh that could be mapped onto the claimed 56 mg and 84 mg doses. According to Janssen, Dr. Farber began with knowledge of the claimed doses and selected particular prior art values and conversion factors that would reproduce them, rather than identifying a path that the prior art itself would have directed a POSA to follow.

Janssen also challenges the scientific validity of Dr. Farber's IV-to-IN conversions. It argues that he compared IV ketamine doses used for anesthesia in adults with IN ketamine doses

used for sedation in pediatric dental patients, notwithstanding physiological differences between adults and children and the distinct clinical objectives of anesthesia, sedation, and depression treatment. Janssen further emphasizes that Dr. Farber could not identify any prior art example in which a POSA used his particular methodology to derive a dose for any drug.

Janssen additionally argues that Dr. Farber failed to consider Charney's most specific disclosure concerning IN ketamine for depression. Charney disclosed 8–32 mg of intranasal racemic ketamine, which, under Dr. Farber's theory that S-ketamine is twice as potent, would correspond to approximately 4–16 mg of IN S-ketamine. Janssen contends that this narrower and more directly relevant disclosure would have directed a POSA toward doses substantially below the claimed 56 mg and 84 mg amounts.

Janssen further argues that Charney called for future research into a broader range of ketamine doses and administration rates, which it contends confirms that the reference did not identify an appropriate dosing regimen or provide a predictable path to the claimed doses. Moreover, Janssen maintains that Charney expressed safety concerns about administering ketamine in an outpatient setting. According to Janssen, those concerns would have led a POSA to decrease an IN dose relative to an IV dose rather than pursue the higher amounts claimed in the Caers patents.

Routine Optimization

Janssen disputes Sandoz's reliance on routine optimization to bridge the gaps between the prior art and the claimed regimens. According to Janssen, both experts described routine optimization as adjusting the dose of a known and understood drug according to patient response and established guidance. Janssen maintains that developing a novel treatment method in an uncertain field is materially different from optimizing an established regimen.

Janssen also relies on Dr. Farber's own work to argue that developing a ketamine regimen was not routine. Janssen notes that Dr. Farber had attempted to develop a clinically useful ketamine treatment, later acknowledged that he was still trying to determine how to make ketamine work effectively, and continued to identify unresolved questions concerning dose, scheduling, durability, and tolerability years after the Caers priority dates. Janssen likewise points to Dr. Papakostas's inconclusive and conflicting ketamine dose-finding results.

According to Janssen, at the critical time, the state of the art was too uncertain to support routine optimization. At the priority dates, ketamine remained a highly experimental depression treatment, and the available psychiatric data principally concerned one IV dose of racemic ketamine. The prior art had not resolved how to select an optimal dose and schedule, sustain the antidepressant response, or sufficiently reduce adverse effects for long-term treatment, and no clinical studies evaluated IN S-ketamine or the claimed long-term regimens. Janssen therefore argues that a POSA would have faced a difficult and unpredictable clinical-research program rather than a finite set of routine dosing adjustments.

Induction Phase

Janssen argues that the prior art did not suggest the claimed four-week induction phase with twice-weekly dosing. Aan het Rot administered IV racemic ketamine three times weekly for two weeks and did not recommend either reducing the frequency to twice weekly or extending ketamine treatment to four weeks. Janssen further notes that aan het Rot recommended transitioning patients to a less-invasive relapse-prevention strategy rather than continuing ketamine treatment. Janssen likewise argues that Charney did not disclose a four-week induction period. Charney referred to treatment over two to three weeks, and Janssen characterizes Dr. Farber's testimony that three weeks is "about four weeks" as conclusory and unsupported.

Janssen also disputes Sandoz's reliance on ECT as a model for the claimed induction regimen. According to Janssen, ECT is a nonpharmacological intervention involving an electrically induced seizure under anesthesia and is fundamentally different from IN administration of a psychoactive compound. Janssen further contends that the antidepressant mechanisms of both ECT and ketamine were unknown, undermining Sandoz's assertion that their allegedly similar mechanisms would have led a POSA to model an IN S-ketamine regimen on ECT.

Although aan het Rot adopted a Monday-Wednesday-Friday schedule associated with ECT, Janssen argues that it did so because both treatments required the presence of an anesthesiologist—not based on a known shared mechanism or the suitability of ECT as a model for IN treatment. Accordingly, Janssen maintains that the ECT evidence would not have motivated a POSA to administer 56 mg or 84 mg of IN S-ketamine twice weekly for four weeks with a reasonable expectation of success.

Maintenance Phase

Janssen argues that the prior art would not have motivated a POSA to use ketamine as a long-term maintenance treatment. According to Janssen, aan het Rot, Mathew, Krystal, and other evidence reflected a lack of clarity about how to sustain ketamine's antidepressant effects. The art also identified safety concerns associated with repeated or long-term ketamine use, including hypertension, cognitive impairment, neurotoxicity, psychosis, dissociation, abuse, and dependence. Janssen maintains that these unresolved efficacy and safety concerns would have discouraged a POSA from pursuing a maintenance regimen with a reasonable expectation of success.

Janssen further argues that nothing in the prior art would have motivated a POSA to reduce the dosing frequency during maintenance to once weekly or once every other week. Janssen relies

on APA guidance stating that pharmacological treatment should continue at the dose, intensity, and frequency that proved effective during the acute phase. Janssen contends that this conventional approach points away from the claimed reduction in frequency.

Janssen also disputes Sandoz's reliance on ECT maintenance practices. According to Janssen, ECT lacked established maintenance guidelines from which a POSA could derive the claimed weekly or every-other-week schedule. Janssen further maintains that the literature cited by Sandoz did not establish a specific mechanistic connection between ECT and ketamine that would justify translating an ECT maintenance schedule into an IN S-ketamine regimen.

c. The Caers Patents as a Whole

Janssen argues that Sandoz considered each limitation of the asserted claims separately but did not show why a POSA would have combined those limitations into the complete treatment regimens claimed by the Caers patents. According to Janssen, evidence that ketamine, S-ketamine, IN administration, intermittent dosing, and induction and maintenance concepts were each independently known does not establish that a POSA would have combined those features in the particular manner required by the claims with a reasonable expectation of success.

Janssen emphasizes that dose amount, route of administration, dosing frequency, and treatment duration are interdependent variables. Altering one parameter may affect the safety and efficacy of the others, making development of the claimed combination substantially more complicated than selecting any individual limitation. Janssen contends that Dr. Farber addressed only whether a POSA could arrive at individual elements through optimization and did not adequately explain why a POSA would have combined all of them into the claimed regimen with a reasonable expectation of success.

Janssen further argues that a general desire to develop an IN S-ketamine treatment is

insufficient to establish obviousness of the claimed inventions. The claims require integrated regimens combining particular dose amounts, frequencies, and durations, and Janssen maintains that Sandoz presented no reliable evidence that a POSA would have selected and combined those components as claimed. As such, Janssen contends that Sandoz failed to prove the obviousness of any asserted Caers claim as a whole by clear and convincing evidence.

ii. The 260 Patent

a. Bitter as Prior Art

Janssen argues that Sandoz failed to prove by clear and convincing evidence that the Bitter thesis was publicly accessible more than one year before the '260 patent's March 15, 2013, priority date. According to Janssen, the fact that Dr. Bitter emailed a link to certain Janssen scientists does not establish that a POSA exercising reasonable diligence could have located and accessed the thesis at the relevant time.

While Janssen also challenges Sandoz's reliance on Dr. Mullins based on allegations of improper disclosure, the Court has already considered these arguments *supra* and accepted Dr. Mullins testimony. However, Janssen argues that even if Dr. Mullins's testimony is considered, it does not establish public accessibility. Janssen contends that Dr. Mullins's 2025 search relied on knowledge of Dr. Bitter's name, the thesis title, and the University of Basel's repository, rather than demonstrating that a POSA conducting a subject-matter search in 2012 could have located the thesis. Janssen further maintains that the foreign-language record on which Dr. Mullins relied was not accompanied by a certified translation and allegedly indicated that access to the thesis had been blocked. According to Janssen, Sandoz therefore failed to establish that Bitter qualifies as prior art by clear and convincing evidence.

b. Clinical Limitations

Janssen relies principally on its objections to the clinical-dose theories advanced against the Caers patents. It argues that the prior art did not provide a predictable basis for identifying a therapeutically effective IN S-ketamine dose and that Dr. Farber's dose calculations were scientifically flawed and infected by hindsight.

Janssen further argues that the '061 publication does not cure those deficiencies. According to Janssen, the publication concerned a single young child with bipolar disorder and treated ketamine, S-ketamine, and R-ketamine as interchangeable for dosing purposes. Janssen contends that Dr. Farber ignored that teaching when he assumed that an S-ketamine dose should be one-half of a racemic-ketamine dose because of S-ketamine's greater potency.

Janssen also emphasizes that Dr. Donovan offered no independent clinical opinion concerning the therapeutically effective dose. Instead, she accepted Dr. Farber's allegedly flawed 35–105 mg range as the clinical starting point for her concentration and spray calculations. Therefore, Janssen maintains that any defects in Dr. Farber's dose analysis necessarily undermine Dr. Donovan's downstream formulation analysis.

c. Claimed Concentrations, Spray Numbers, and Administration Period

Janssen argues that Sandoz failed to establish that a POSA would have been motivated to select the claimed concentration and spray-number combinations. According to Janssen, Dr. Donovan made a series of discretionary assumptions that could be adjusted to produce the claimed values, thereby showing only that a POSA *could* have reached the claimed formulations—not that a POSA *would* have selected them with a reasonable expectation of success.

Selection of Targeted Doses

Janssen argues that Dr. Donovan selected 55 mg and 85 mg from Dr. Farber's asserted 35–105 mg range without adequately explaining why a POSA would have focused on those particular doses absent hindsight. Although Sandoz responds that Dr. Donovan's methodology could be applied throughout the dose range, Janssen's position is that, without an explanation for selecting the particular inputs, her examples demonstrate only how the claimed concentrations could be reverse engineered, not why a POSA would have selected them.

Spray Volume and Bilateral Administration

Janssen challenges Dr. Donovan's assumption that each spray would contain 100 microliters. According to Janssen, selecting a different spray volume would have produced a different concentration, and Sandoz did not establish why a POSA necessarily would have selected the assumed volume when developing the claimed formulation. Janssen contends that merely identifying 100 microliters as one available or commonly used spray volume establishes only that a POSA could have selected it, not that the prior art would have motivated that choice when developing the claimed formulation.

Janssen likewise disputes Dr. Donovan's reliance on the nasal cycle to justify dividing the dose evenly between both nostrils. It contends that numerous intranasal medicines are administered through only one nostril and that the existence of the nasal cycle does not establish that a POSA would have selected bilateral administration for S-ketamine. According to Janssen, Dr. Donovan identified bilateral administration as another technically available choice without adequately explaining why a POSA would have selected it over single-nostril administration. Because spray volume and bilateral administration directly affected the resulting concentration and number of sprays, Janssen argues that Dr. Donovan's unexplained selection of those inputs allowed her to

reconstruct the claimed combinations through hindsight rather than demonstrate that a POSA would have been motivated to arrive at them.

Solubility and Concentration

Janssen argues that Dr. Donovan improperly treated 200 mg/mL as the relevant solubility limit because that value concerned S-ketamine hydrochloride in pure water. The claimed formulations contain excipients that may alter solubility. Janssen therefore maintains that pure-water solubility did not establish the concentration a POSA would have selected for the completed formulations.

Additionally, Janssen argues that Sandoz did not establish why a POSA would have selected four sprays for the 55 mg dose and six sprays for the 85 mg dose. According to Janssen, Dr. Donovan selected different spray numbers that caused both doses to yield concentrations near the claimed 140 mg/mL value: delivering 55 mg in four 0.1 mL sprays yielded 137.5 mg/mL, while delivering 85 mg in six sprays yielded approximately 141.7 mg/mL. Because different permissible spray numbers would have produced materially different concentrations, Janssen maintains that Dr. Donovan's methodology establishes only that a POSA could generate concentrations near the claimed value from different total doses by changing the number of sprays. Janssen contends that Dr. Donovan did not sufficiently explain why a POSA would have been motivated to choose those particular combinations of dose, spray number, and concentration. In Janssen's view, the calculations demonstrate that a formulator could reconstruct the claimed concentration after knowing it, not that a POSA would have been motivated to select the claimed concentration and spray combinations.

Teaching Away and Alternative Formulation Approaches

Janssen argues that the prior art consistently used IN ketamine or S-ketamine

concentrations at or below 100 mg/mL and would have discouraged a POSA from selecting the higher concentrations claimed by the 260 Patent. According to Janssen, Bitter reported that increasing IN concentrations resulted in generally low or moderate bioavailability, meaning that less of the administered drug entered the bloodstream. Janssen maintains that a POSA would have preferred the greater bioavailability associated with concentrations at or below 100 mg/mL.

Janssen rejects Sandoz's contention that Bitter encouraged concentrations exceeding 100 mg/mL. It argues that the allegedly higher concentration actually evaluated in Bitter was 100 mg/mL, which is still below the concentrations required by claims 22 and 36. Janssen maintains that Bitter's reported bioavailability concerns either teach away from the claimed concentrations or, at minimum, provide substantial evidence pointing away from them.

Janssen also disputes Sandoz's contention that minimizing the number of sprays would have motivated a POSA to increase concentration. According to Janssen, Dr. Donovan offered no scientific evidence that patient compliance would present a meaningful problem for an IN treatment involving only two to eight sprays administered in less than an hour. Janssen further argues that Dr. Donovan did not balance any asserted compliance benefit from fewer sprays against the bioavailability concerns created by higher concentrations.

Although Sandoz argues that Dr. Donovan's approach need only have been a suitable option, Janssen responds that a suitable option does not establish obviousness if the prior art taught away from it. Janssen further maintains that technical suitability alone is insufficient because Sandoz still had to establish a reason why a POSA would have selected the claimed concentrations and combined them with the remaining limitations.

Routine Optimization

Janssen argues that Sandoz failed to establish that the claimed concentration and spray-

number combinations would have resulted from routine optimization. According to Janssen, Dr. Donovan disavowed that characterization on cross-examination by testifying that she did not believe she had described her analysis as routine optimization.

Janssen further contends that Sandoz's references to "reasonable concentrations," a "reasonable formulation rationale," and values that "could be administered" establish only technical feasibility. According to Janssen, proof that a POSA reasonably *could* have prepared a formulation does not establish that a POSA *would* have been motivated to select the claimed concentration and spray regimen.

Janssen also argues that Dr. Donovan did not address the interplay between concentration and other formulation variables, including pH and excipients, even though she acknowledged that a POSA should consider that interplay when developing an intranasal formulation. Therefore, Janssen maintains that Sandoz did not establish that routine experimentation would predictably produce the claimed combination.

d. Claimed pH and Excipients

Janssen argues that Sandoz failed to establish why a POSA would have selected the pH of approximately 4.5 required by claim 36. According to Janssen, Allen taught that a nasal solution should have a pH between 5.5 and 7.5, while Aulton stated that a pH of 6.8 was necessary because nasal mucus has limited buffering capacity. Janssen maintains that these intranasal-formulation teachings pointed away from the claimed pH.

Janssen disputes Sandoz's characterization of its lower-pH evidence as more probative because it was ketamine-specific. Janssen notes that Ketalar® was an intravenous or intramuscular product, not an intranasal formulation, and that the '061 publication broadly contemplated numerous routes of administration. According to Janssen, Sandoz did not explain why those

references would have been more pertinent to a POSA developing an IN formulation than references directed specifically to nasal products.

Janssen also argues that the prior art discouraged using the buffers required by claim 36. It relies principally on Bitter's statement that buffering nasal formulations "has to be avoided." According to Janssen, this language does not merely present a choice to omit buffers but affirmatively directs a POSA away from including them in an IN S-ketamine formulation.

Janssen maintains that Sandoz's identification of citrate, citric acid, and sodium hydroxide as technically available formulation ingredients does not establish why a POSA would have selected those ingredients in the claimed combination. In Janssen's view, proof that the ingredients were known and could perform their stated functions is insufficient without evidence as to motivation to use them in the claimed IN formulation.

e. Omission of Preservatives

Janssen argues that Sandoz failed to identify a persuasive reason why a POSA would have removed preservatives from the formulation of claim 22. According to Janssen, omitting a preservative may require burdensome manufacturing protections, including aseptic processing, to prevent microbial contamination.

Janssen further contends that the inventors unexpectedly discovered that high-concentration S-ketamine formulations were self-preserving, thereby permitting omission of a preservative. It argues that Dr. Donovan did not rebut that evidence or establish that a POSA would have expected a high-concentration formulation to remain adequately protected without a preservative.

Janssen also challenges the credibility of Dr. Donovan's opinion. It notes that, in prior litigation, she opined that including a preservative in a single-use intranasal formulation was

obvious when that position favored the party that retained her. Janssen argues that her contrary testimony in this case does not constitute clear and convincing evidence that a POSA would have omitted preservatives.

f. The 260 Patent Claims as a Whole

Janssen argues that Sandoz divided its obviousness case between the clinical and formulation limitations without establishing why a POSA would have combined them into the complete inventions claimed by the 260 Patent. Dr. Farber limited his substantive analysis to the clinical aspects, while Dr. Donovan limited hers to the formulation elements, including concentration, spray number, pH, excipients, and preservatives. According to Janssen, neither expert independently analyzed a complete claim.

Janssen further argues that Dr. Donovan failed to consider the interplay among even the formulation limitations. Although Sandoz asserts that the individual elements were compatible and complementary, Janssen maintains that identifying general considerations applicable to each element does not establish that a POSA would have selected their particular combination with a reasonable expectation of success.

Janssen also challenges Sandoz's reliance on Dr. Farber's ultimate claim-as-a-whole opinion. According to Janssen, Dr. Farber testified before Dr. Donovan, admitted that he did not offer an opinion concerning the formulation limitations, and agreed that the claims were obvious as a whole only after being asked to assume that Dr. Donovan later would establish the formulation limitations as obvious. Therefore, Janssen characterizes his claim-as-a-whole conclusion as unsupported and insufficient to satisfy Sandoz's clear and convincing burden.

Janssen maintains that Sandoz's conclusion that the claims were obvious because the prior art disclosed or rendered obvious each individual limitation repeats the same piecemeal error.

Evidence that each clinical and formulation feature was independently known, Janssen argues, does not establish that a POSA would have combined those features into the particular methods required by claims 22 and 36. Accordingly, Janssen contends that Sandoz failed to prove either asserted '260 patent claim obvious as a whole.

iii. Objective Indicia

Janssen argues that the objective indicia strongly support the nonobviousness of the asserted claims. According to Janssen, objective indicia constitute independent evidence of nonobviousness and are particularly important here because they guard against evaluating the claimed combinations with hindsight.

i. Nexus and Commensurateness

Janssen argues that Spravato® embodies the asserted claims because its formulation and labeled dosing regimens satisfy the claims' requirements. Janssen further contends that those claimed features are responsible for Spravato®'s combination of safety and rapid, sustained antidepressant efficacy, particularly in patients who did not respond to other treatments. According to Janssen, this connection permits Spravato®'s clinical and commercial achievements to be treated as evidence of the claimed inventions' nonobviousness.

Janssen rejects Sandoz's argument that these benefits merely reflect the previously known properties of ketamine or S-ketamine. According to Janssen, the relevant benefit is not simply rapid antidepressant activity, but the combination of safety, rapid efficacy, and sustained efficacy achieved by practicing the asserted claims. Janssen contends that no other form of ketamine had demonstrated that same combination of benefits and that Spravato® obtained FDA approval and achieved commercial success because the claimed inventions established its safety and efficacy.

Janssen further argues that nexus need not be limited to an individual claim feature that

was itself unknown in the prior art. Because the asserted claims recite combinations of elements, Janssen maintains that the claimed combinations as a whole may provide the necessary nexus, even if some individual elements or properties were previously known. Janssen also disputes Sandoz's contention that evidence concerning TRD is not commensurate with claims that cover MDD. According to Janssen, TRD is a subset of MDD, making the evidence concerning TRD relevant to claims directed more broadly to MDD.

Finally, Janssen challenges Dr. Farber's reliance on pre-Spravato® ketamine research and a retrospective comparison of IV ketamine and Spravato®. Janssen argues that the study did not permit a reliable comparison between the treatments and did not address long-term use. Accordingly, Janssen maintains that the study does not sever the connection between the asserted claims and Spravato®'s demonstrated clinical benefits.

ii. Long-Felt but Unmet Need

Janssen contends that there was a long-felt but unmet need for a safe treatment for TRD and MDD that could provide both rapid and sustained efficacy through a novel mechanism of action. According to Janssen, this need was widely recognized in the scientific literature and by POSAs at the time of the inventions.

Janssen relies on literature stating that TRD remained a significant clinical problem despite decades of research. It also cites Dr. Farber's own acknowledgment in a submission to the FDA that treatment options for TRD remained limited and that the need for medication providing both rapid and long-lasting relief was widely recognized. Janssen further relies on the FDA's description of TRD as a severe unmet need and its decision to grant Spravato® breakthrough-therapy designation based on preliminary evidence that the drug was likely to be more effective than existing treatments.

According to Janssen, multiple clinical trials and subsequent clinical experience demonstrate that Spravato®, through the claimed formulation and dosing regimens, met that need for many patients. Janssen maintains that later-developed evidence may be considered in determining whether the claimed inventions ultimately satisfied a need that existed at the time of invention.

Janssen rejects Sandoz's contention that IV ketamine and other treatments had already satisfied the asserted need. Janssen emphasizes that contemporaneous sources continued to describe the need as unmet despite the availability of those treatments. It also challenges Sandoz's reliance on a retrospective study comparing IV ketamine with Spravato®. According to Janssen, that study was neither randomized nor standardized, did not control for selection bias, involved material differences between the treatment groups, and expressly acknowledged that the sample may have been skewed. Janssen further notes that the study did not address long-term treatment. It therefore maintains that the study does not show that IV ketamine had already satisfied the need for a treatment providing both rapid and lasting relief.

iii. Failure of Others

Janssen argues that the failure of others to develop a safe, rapid, and sustained treatment for TRD and MDD supports nonobviousness. According to Janssen, numerous researchers and companies attempted to develop ketamine-based treatments or other NMDA-receptor modulators for depression, but none achieved Spravato®'s success.

Janssen relies on evidence that several companies attempted to develop related compounds for treating depression but failed to obtain FDA approval. It also points to Dr. Farber's decades of research into extending ketamine's antidepressant effects. According to Janssen, those efforts are relevant because the researchers shared the central goal of creating a depression treatment that

worked safely, rapidly, and durably, even if they did not attempt to reproduce every limitation of the asserted claims.

Janssen rejects Sandoz's contention that failures involving compounds other than S-ketamine are irrelevant. It argues that unsuccessful efforts involving drugs in the same therapeutic class may support nonobviousness when those efforts were directed toward the same clinical objective. Janssen further maintains that failure to obtain FDA approval is an appropriate measure of whether those efforts produced a clinically viable treatment.

iv. Unexpected Results

Janssen contends that the asserted inventions produced unexpected results with respect to both the 260 Patent and the Caers Patents.

As to the Caers Patents, Janssen argues that the claimed IN S-ketamine dosing regimens produced an unexpectedly favorable safety profile suitable for long-term treatment. In particular, Janssen maintains that S-ketamine unexpectedly was not associated with the neurotoxicity concerns attributed to racemic ketamine. According to Janssen, this safety result supports nonobviousness even though it was not fully recognized until after the patents' priority dates.

Janssen rebuts Sandoz's contention that Spravato® did not produce unexpectedly superior antidepressant efficacy because IV ketamine produced faster and greater symptom relief during induction. Janssen responds that its unexpected-results argument concerns Spravato®'s safety during long-term use, whereas the study compared only the treatments' short-term efficacy during induction. Because the study addresses a different alleged result, Janssen maintains that it does not rebut the evidence of Spravato®'s unexpectedly favorable long-term safety.

Janssen disputes Sandoz's argument that Dr. Giakas failed to compare Spravato®'s safety results with the closest prior art. Although Dr. Giakas did not designate a single reference as the

closest prior art, Janssen argues that he evaluated the results against all of the prior art Dr. Farber identified. Further, Janssen notes that Dr. Farber himself could not identify a single closest reference. Accordingly, Janssen maintains that the unexpected results evidence remains probative because Dr. Giakas compared Spravato®'s safety results with the relevant prior art, even though he did not identify one reference as the closest.

With respect to the '260 Patent, Janssen argues that the inventors unexpectedly discovered that S-ketamine at the claimed high concentrations is self-preserving. According to Janssen, the concentration itself prevents microbial contamination, allowing the formulation to be produced without adding a preservative or employing cumbersome and expensive manufacturing procedures that otherwise might be necessary to prevent contamination. Janssen maintains that this practical benefit was unexpected and is tied directly to the concentration required by the claimed invention.

v. Industry Skepticism and Praise

Janssen argues that widespread skepticism about whether ketamine could be developed into a useful long-term treatment for depression supports nonobviousness. According to Janssen, the scientific literature, Dr. Farber, and the FDA expressed concerns about the absence of long-term data and the safety risks associated with using ketamine to treat depression. Janssen specifically relies on the FDA's concerns about the potential neurotoxicity of esketamine.

Janssen maintains that this skepticism was overcome when Spravato®, used according to the asserted claims, proved sufficiently safe and effective for long-term treatment and achieved widespread clinical use. It rejects Sandoz's contention that Spravato®'s black-box warning and FDA-mandated REMS program show that the claimed inventions did not resolve the relevant concerns. According to Janssen, black-box warnings are not unusual for psychiatric medications, and the REMS program mitigates the identified risks by requiring administration under medical

supervision. Janssen therefore argues that those safeguards do not negate the evidence that Spravato® overcame skepticism about whether ketamine could become a safe and useful long-term treatment.

As to industry praise, Janssen argues that the praise received by Spravato® supports the nonobviousness of the asserted claims. It relies on scientific literature describing esketamine nasal spray as the greatest pharmacological advance in treating major depression in fifty years, as well as the FDA's statement that Spravato® could make a life-saving difference for patients. According to Janssen, that praise was directed to the distinctive combination of clinical benefits enabled by the claimed inventions, including Spravato®'s safe, rapid, and sustained efficacy. Janssen maintains that the praise is connected to the asserted claims rather than merely to ketamine's previously known antidepressant activity.

Additionally, Janssen disputes Sandoz's reliance on a publication reporting that IV ketamine might act faster or require fewer treatments than S-ketamine. Janssen argues that a favorable comparison on certain measures does not erase the substantial praise directed to Spravato®. It further notes that the publication acknowledged that no prospective, randomized, head-to-head trials had compared the efficacy and safety of IV ketamine and S-ketamine for TRD or MDD with suicidal ideation.

vi. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

vii. Commercial Success

Janssen contends that Spravato® is a major commercial success and that its success is connected to the asserted claims. Janssen relies on evidence that Spravato® generated more than \$3.5 billion in cumulative sales, exceeded \$1.5 billion in annual sales, achieved blockbuster status, continued to grow rapidly, and became a significant contributor to Johnson & Johnson's growth.

According to Janssen, Spravato®'s commercial performance is attributable, at least in substantial part, to the safe, rapid, and sustained efficacy produced by the patented formulation and dosing regimens. Janssen maintains that these clinical benefits are routinely identified as reasons for the product's marketplace performance. It further argues that the patented inventions need not be the sole cause of Spravato®'s success for the evidence to receive weight.

Janssen disputes Sandoz's criticism that Ms. Mulhern improperly compared Spravato® with oral antidepressants and antipsychotics. Janssen argues that Spravato®'s commercial success is evident regardless of the market definition used. Spravato® has a 100% share of the market for drugs approved for its specific indications and, even within the broader market comprising the interventional treatments that Sandoz identifies as Spravato®'s closest competitors, Spravato®

allegedly holds the largest share at 45.2%.

Janssen further disputes Sandoz's criticism of Ms. Mulhern's use of new-patient share rather than total-patient share. According to Janssen, Sandoz did not explain why total-patient share would provide the more reliable measurement. Janssen also notes that Dr. Saha did not analyze the interventional-treatment market in his expert report or offer his own competing market-share analysis.

Janssen rejects Sandoz's argument that the continued existence of the IV-ketamine industry undermines Spravato®'s commercial success. Janssen contends that Spravato® achieved substantial success despite the availability of IV ketamine and that IV ketamine represents only approximately 0.2% of the revenue market for drugs used to treat TRD and MDD with suicidal ideation. Janssen also argues that comparing Spravato®'s sales with the revenue of the entire ketamine-clinic industry would be misleading because those clinics provide services for numerous conditions, including post-traumatic stress disorder, anxiety, and pain management.

Finally, Janssen disputes Sandoz's contention that pricing, marketing expenditures, rebates, FDA approval, insurance coverage, or reimbursement drove Spravato®'s success independently of the patented inventions. Janssen maintains that Sandoz did not adequately support those alternative explanations and that Dr. Saha offered no opinion concerning whether a nexus existed between the claimed features and commercial success. According to Janssen, the un rebutted evidence shows that the benefits enabled by the patented combinations materially contributed to Spravato®'s sales.

3. Findings as to the Scope and Content of the Prior Art

i. Bitter

As a threshold matter, the Court must address whether Sandoz proved by clear and convincing evidence that Bitter was publicly available at the critical date, March 15, 2013, such that it qualifies as prior art. The Court concludes that it did not.

Prior art is defined by 35 U.S.C. § 102. Under § 102, prior art consists of any disclosure—including patents, printed publications, public uses, sales, or any other availability to the public—that predates the effective filing date of a claimed invention. *See* 35 U.S.C.A. § 102(a)(1). Additionally, patents and published applications by other inventors that were effectively filed before the claimed invention's effective filing date also constitute prior art. *See* U.S.C.A. § 102(a)(2). ‘public accessibility’ has been called the touchstone in determining whether a reference constitutes a ‘printed publication.’” *Nobel Biocare Servs. AG v. Instradent USA, Inc.*, 903 F.3d 1365, 1375 (Fed. Cir. 2018), *as amended* (Sept. 20, 2018) (quoting *In re Hall*, 781 F.2d 897, 899 (Fed. Cir. 1986)). “A reference will be considered publicly accessible if it was disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence[] can locate it.” *Medtronic, Inc. v. Barry*, 891 F.3d 1368, 1380 (Fed. Cir. 2018) (cleaned up). “Whether a reference is publicly accessible is determined on a case-by-case basis based on the ‘facts and circumstances surrounding the reference's disclosure to members of the public.’” *In re Lister*, 583 F.3d 1307, 1311 (Fed. Cir. 2009) (quoting *In re Klopfenstein*, 380 F.3d 1345, 1350 (Fed. Cir. 2004)). The Federal Circuit has explained that “even relatively obscure documents qualify as prior art so long as the public has a means of accessing them.” *In re Enhanced Sec. Rsch., LLC*, 739 F.3d 1347, 1354 (Fed. Cir. 2014).

“Bitter” is a doctoral dissertation titled “Transmucosal Nasal Drug Delivery:

Pharmacokinetics and Pharmacodynamics of Nasally Applied Esketamine.” (DTX-23_0001; Tr. 116:22-117:3. (Farber)). It was authored by Christoph Bitter, a student attending the University of Basel in Switzerland. DTX-23_0001, 4. Sandoz contends that Bitter was publicly available and constitutes prior art. Janssen disagrees. Sandoz relies primarily on the expert testimony of Dr. Mullins to establish public accessibility.

The “first thing” Dr. Mullins did to determine whether Bitter was publicly accessible was search the title of the thesis in the University of Basel’s online catalogue in March 2025. (Tr. 461:16-461:9 (Mullins)). This search indicated that Bitter was “shelved in two locations” and included a call number, which indicated that the thesis was available at the University of Basel by print. (Tr. 461:20-462:1 (Mullins)). The parties dispute whether the untranslated German portion of the Machine-Readable Cataloging (“MARC”) screenshot shows that Bitter was blocked by the author. However, it is clear, based on an email sent by Bitter, that public access to the thesis was restricted until at least December 2011. (See DTX-0364). Therefore, the Court does not find Dr. Mullins’s testimony that Bitter was publicly available as of April 4, 2011, credible. For the same reason, the Court does not find Sandoz’s evidence regarding Dr. Mullins’ search on the Wayback Machine’s Internet Archive indicating that Bitter may have been available as of September 1, 2011, credible. (Tr. 468:5-469:23 (Mullins)). Dr. Mullins’ testimony did not even propose a theory under which the Court could conclude that Bitter became publicly available after December 2011. While Dr. Bitter’s email suggests that his thesis may have become publicly accessible at some point after December 2011, all it definitively establishes is that access to the thesis was restricted until at least December 2011. That vaguely worded single email does not establish by clear and convincing evidence that the Bitter publication was publicly accessible such that it can be considered prior art.

Therefore, the Court holds that Bitter was not prior art.

ii. Charney

Charney is a patent application published in 2007 concerning the use of ketamine to treat depression. It reports the same study and data published in Zarate 2006, in which eighteen patients received either a single 0.5 mg/kg dose of intravenous ketamine infused over forty minutes or placebo. The study showed improvement in depressive symptoms within 110 minutes that persisted for several days. (DTX-16 ¶ 129 & Fig. 2; Tr. 98:7–100:15 (Farber)).

Charney identifies intranasal administration and discloses a general intranasal ketamine dose range of approximately 1 to 250 mg, as well as a more specific range of 8 to 32 mg of racemic ketamine. (DTX-16 ¶¶ 59, 67). It also states that S-ketamine is approximately twice as potent as racemic ketamine. (*Id.* ¶ 116). Charney contemplates repeated ketamine administration over two to three weeks and states that chronic administration of intranasal ketamine may be used for maintenance treatment at frequencies ranging from daily to weekly, depending on patient response. (*Id.* ¶¶ 50, 114). However, it does not report clinical data from intranasal or repeated administration or disclose the particular induction-and-maintenance regimens claimed in the Caers patents. Instead, Charney states that future research should explore additional ketamine doses and rates of administration. (*Id.* ¶ 152).

iii. Bahetwar

Bahetwar was published in 2011 and reported a study of intranasal ketamine for moderate sedation in pediatric dental patients. (DTX-20 at 1; Tr. 249:12–15 (Papakostas)). Bahetwar explained that intranasal administration avoids first-pass metabolism, provides greater bioavailability than oral administration, and may permit rapid absorption through the nasal and olfactory pathways; the study reported an average onset time of 5.79 minutes. (DTX-20 at 1–2, 4; Tr. 131:7–132:12 (Farber)). Bahetwar did not concern depression or disclose the use of intranasal

ketamine to treat depression. (Tr. 130:5–24 (Farber)).

iv. aan het Rot

Aan het Rot was published in 2010 and reported an open-label study in which patients with TRD received six 0.5 mg/kg intravenous doses of racemic ketamine over two weeks, administered three times per week. (DTX-18 at 4; Tr. 109:13–110:14 (Farber)). The authors selected that frequency by comparison to ECT, another hospital-based treatment requiring hemodynamic monitoring and an anesthesiologist, and administered the minimum number of treatments generally required for remission with ECT. (DTX-18 at 8; Tr. 110:25–111:19 (Farber)). The study found the repeated doses generally safe and well tolerated, but four of nine responders relapsed within two weeks. (DTX-18 at 7–8). The authors concluded that their findings suggested the feasibility of repeated-dose intravenous ketamine for the acute treatment of TRD. They nevertheless cautioned about the potential cognitive effects of longer-term use and stated that repeated infusions might be used to provide rapid relief until a less-invasive relapse-prevention strategy could be implemented. (DTX-18 at 4, 8; Tr. 258:2–14 (Farber)).

v. Singh

Singh is a Janssen patent application published in 2008 concerning the treatment of TRD with S-ketamine, either alone or with another antidepressant. It identifies intranasal administration, defines S-ketamine to include its hydrochloride salt, and discloses doses ranging from approximately 0.1 to 250 mg. (DTX-17 ¶¶ 20, 32–33 & cls. 1, 7). Singh also states that S-ketamine has greater affinity for the NMDA receptor than R-ketamine, potentially permitting lower doses. (*Id.* ¶ 7).

Singh describes acute and maintenance treatment, defining maintenance treatment as longer treatment given after a patient responds to prevent recurrence, and permits adjunctive oral

antidepressants during either phase. (*Id.* ¶¶ 20, 31, 54). Its only study example is prophetic: subjects would receive 0.20 or 0.40 mg/kg of intravenous S-ketamine or placebo, with responders receiving the same treatment again on day four. (*Id.* ¶ 71). Although Singh states that skilled artisans could determine optimal doses using conventional clinical-trial methods, it reports no clinical data or results and does not disclose a specific intranasal dose or the induction-and-maintenance regimens claimed in the Caers patents. (*Id.* ¶¶ 49, 51; Tr. 712:6–14 (Papakostas)).

vi. Mathew

Mathew, published in 2012, is a review article examining the existing evidence concerning ketamine for TRD. It reported that earlier studies had found acute efficacy and safety following a single 0.5 mg/kg intravenous dose of racemic ketamine and that intravenous ketamine had reduced suicidal ideation within forty minutes in a study of thirty-three patients. (DTX-22 at 1, 9–10; Tr. 119:17–120:25 (Farber)). Mathew also noted that S-ketamine had been approved in Europe and possessed three to four times greater affinity for the NMDA receptor than R-ketamine, which the authors suggested might permit fewer side effects without altering clinical benefit. (DTX-22 at 5). The article reported intranasal bioavailability of approximately 25% to 50% and discussed intranasal ketamine use for neuropathic pain. (*Id.* at 6, 21).

Mathew also characterized ketamine therapy for depression as “highly experimental” and in its “infancy,” identifying acute neuropsychiatric side effects and uncertainties regarding continuation therapy as significant unresolved issues. (*Id.* at 12). It observed that little was known about the cognitive effects of chronic ketamine administration and discussed a study reporting memory impairments among frequent ketamine users. (*Id.* at 10). Mathew did not report a clinical study of intranasal S-ketamine for depression or identify a long-term ketamine-treatment regimen.

vii. '061 Publication

The '061 Publication, WO 2011/020061, concerns the use of ketamine to treat bipolar disorder. (DTX-153 at Abstract, ¶¶ 3, 31–32). It explains that bipolar disorder may involve depressive episodes or symptoms. (Id. at ¶ 16). The publication defines “ketamine” to include its isomers and enantiomers, as well as pharmaceutically acceptable salts such as ketamine hydrochloride. (Id. at ¶ 31). Its disclosures therefore encompass both racemic ketamine and S-ketamine.

The '061 Publication identifies intranasal administration as one of the available routes and discloses ketamine doses ranging from approximately 1 mg to 250 mg. (Id. at ¶¶ 42–44, 54, 72). With respect to formulation, it states that nasal dosage forms generally contain substantial amounts of water in addition to the active ingredient. (Id. at ¶ 72). It also provides that the disclosed ketamine compositions may contain a buffer and lists pH values between 3 and 8 in increments of 0.5, including pH 4.5. (Id. at ¶ 84). These disclosures identify possible routes, dose ranges, and formulation parameters for ketamine compositions used in treating bipolar disorder; they do not themselves identify a particular combination of intranasal concentration, dose, pH, and excipients.

viii. '651 Publication

The '651 Patent, which issued in 2009, describes pharmaceutical compositions containing NMDA-receptor modulators, a category that includes ketamine and S-ketamine. (DTX-25). It identifies nasal administration among the routes through which the disclosed compositions may be administered. (Id. at 33:5–11). The patent also provides lists of excipients that may be included in the compositions. (Id. at 33:22–32). Those lists include buffering and pH-adjusting agents, such as citrate, sodium hydroxide, and citric acid, as well as chelating agents, including EDTA. (Id. at 32:1–15). The cited disclosures present these ingredients as possible components of

pharmaceutical compositions; they do not identify a particular intranasal S-ketamine formulation combining all of them or specify the amounts in which they should be used.

4. Findings as to the Differences Between the Claims and Prior Art

i. The Caers Patents

a. Treatment of MDD, TRD, and MDD-SI with IN S-ketamine

Sandoz relies on Charney, Singh, Aan het Rot, and Mathew to establish that, at the critical date, March 15, 2013, a POSA would have known that ketamine could effectively treat depression. (Def.'s PTB at p. 16). Charney taught that IV ketamine produced rapid improvement in depressive symptoms in patients with TRD that persisted for several days despite ketamine's rapid clearance from the body. (Tr. 98:17–100:15 (Farber)). Charney also identified IN administration, and Singh claimed a method of treating TRD with intranasally administered S-ketamine. (Tr. 126:14–23 (Farber)). Aan het Rot found that repeated doses of IV ketamine were generally "safe and well tolerated," but cautioned against longer-term use, stating that "the most practical use of repeated IV ketamine infusions might be to elicit and maintain rapid relief until a less-invasive relapse prevention strategy could be implemented." (Tr. 114:3 (Farber); PTX-320_0008). Mathew, the most recent of these references, reported ketamine's acute antidepressant and antisuicidal effects but emphasized that clinical trials in MDD remained "in their infancy," that ketamine's broader clinical effectiveness had not been systematically examined, and that questions remained regarding the durability and safety of its antidepressant effects. (PTX-326_12). Mathew concluded that ketamine therapy remained a "highly experimental treatment approach for MDD" and that adoption in psychiatric practice was "premature." (*Id.*).

Taken together, the references would have provided a POSA with reason to investigate IN S-ketamine as a treatment for depression and some expectation that it could produce a rapid

antidepressant response. They did not, however, establish the broader clinical effectiveness, durability, or long term safety of IN S-ketamine in patients with MDD, TRD, or MDD-SI.

Accordingly, these references provide some support for the general treatment limitation, but they do not establish the obviousness of the claimed regimens. The Court emphasizes that the asserted claims recite integrated treatment regimens, not collections of limitations to be evaluated in isolation. Although the Court addresses the claimed doses and treatment phases separately for organizational clarity, the ultimate question is whether the prior art would have motivated a POSA to combine the claimed route, dose, frequency, duration, and induction and maintenance phases into the complete regimens recited by the claims, with a reasonable expectation of success.

b. Claimed Dose Amounts

Sandoz first contends that the dose ranges disclosed in Charney and Singh give rise to a presumption that the claimed doses of about 56 mg and about 84 mg would have been obvious. The Court disagrees.

When the prior art discloses a numerical range that overlaps the claimed range, the overlap creates a rebuttable presumption that the claimed range was obvious. Put simply, if the prior art directed a POSA to work within a range that includes the claimed value, selecting that value ordinarily is presumed obvious. *Genentech, Inc. v. Hospira, Inc.*, 946 F.3d 1333, 1341 (Fed. Cir. 2020). The patentee may rebut the presumption with evidence that the prior art taught away from the claimed value, that the claimed value produced unexpected results, or that other evidence shows a POSA would not have selected it. *E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006–08 (Fed. Cir. 2018). The presumption concerns only the overlapping numerical limitation; the challenger must still prove the obviousness of the claimed invention as a whole. 35 U.S.C. § 103.

The Federal Circuit recently examined the scope of the overlapping-range presumption in *Janssen Pharmaceuticals, Inc. v. Teva Pharmaceuticals USA, Inc.*, 141 F.4th 1367 (Fed. Cir. 2025). The presumption has generally been applied when a claim requires a feature in a specified numerical amount and the prior art teaches the same feature in an overlapping amount or range. *Id.* at 1375; *see also In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003). When applicable, the presumption shifts to the patentee only the burden of producing evidence of teaching away, unexpected results, or other considerations bearing on nonobviousness; the ultimate burden of proving obviousness remains with the challenger. *Janssen*, 141 F.4th at 1375; *E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006–07 (Fed. Cir. 2018).

The presumption is not triggered mechanically whenever a claimed number falls somewhere within a prior art range. Whether the presumption applies depends upon the factual context and the premises that justify truncating the ordinary, case-specific obviousness analysis. *Janssen*, 141 F.4th at 1376–78. Those premises are that the prior art discloses the general conditions of the claim; that a POSA would have been motivated to identify an optimum or workable value of a known, result effective variable; and that routine experimentation would have been expected to produce a successful result. *Id.* at 1377. These factual predicates substantially correspond to the traditional obviousness inquiries concerning motivation to modify the prior art and reasonable expectation of success. *Id.* at 1377–78. Although there is no categorical rule limiting the presumption to cases in which a numerical range is the only difference between the claim and the prior art, the number and interrelationship of the remaining differences bear upon whether the presumption’s underlying premises are present. *Id.* at 1376. The breadth of the prior art range and the expectations of a POSA likewise remain relevant. *Id.* at 1376–77.

Here, the factual predicates for the overlapping range presumption are not present. The

asserted claims do not merely select a dose from an established range for a known treatment. They incorporate 56 mg or 84 mg of IN S-ketamine into regimens that also specify the condition treated, route of administration, frequency, duration, and, for certain claims, induction and maintenance phases. Because the appropriate dose is interconnected with those variables, the numerical overlap does not establish that the prior art disclosed the general conditions of the claimed regimens and left only the identification of an optimum value through routine experimentation.

The breadth of the cited ranges reinforces that conclusion. Singh disclosed approximately 0.1 to 250 mg of S-ketamine, while Charney disclosed approximately 1 to 250 mg of intranasal ketamine. (Tr. 127:7–11, 238:4–14 (Farber)). Neither reference identifies 56 mg or 84 mg, or anything remotely close to those specific dosages, as preferred, nor does either reference report clinical results for those amounts. Charney's more specific disclosure instead identifies 8 to 32 mg of IN racemic ketamine for depression, corresponding under Dr. Farber's potency assumption to approximately 4 to 16 mg of S-ketamine. (PTX-287 ¶ 67; Tr. 729:22–731:25 (Papakostas)). As such, the references did not direct a POSA toward the claimed amounts as optimum or workable doses.

Dr. Farber's calculations do not supply the missing factual predicates. He combined proposed IV doses with conversion factors based on potency, intranasal bioavailability, patient weight, and, in one calculation, comparisons involving anesthesia and pediatric sedation. (Tr. 132:13–142:6, 247:8–249:22 (Farber)). Although those calculations generated 56 mg and 84 mg as possible candidates, they also generated numerous doses ranging from 28 to 168 mg. (Tr. 249:23–251:19 (Farber)). The calculations showed that the claimed amounts could be derived mathematically, but not that a POSA would have selected them or reasonably expected them to treat depression safely and effectively.

Nor did the evidence establish that identifying the claimed doses would have involved routine experimentation. At the critical dates, IN S-ketamine treatment of depression remained experimental, with no established dosing guidelines or clinical results identifying an effective range. Dr. Papakostas testified that the antidepressant dose finding was unpredictable and that his own study varying only the IV ketamine dose produced inconclusive and conflicting results. (Tr. 718:15–721:12, 724:20–725:22 (Papakostas)). Selecting the route, enantiomer, frequency, duration, and treatment phases introduced additional interdependent variables.

Accordingly, Sandoz has not established the factual premises necessary to invoke the overlapping range presumption. While the broad ranges in the prior art numerically encompass 56 mg and 84 mg, the record does not show that a POSA would have been motivated to optimize within those ranges or would have expected routine experimentation to produce the claimed doses successfully.

Therefore, the Court declines to apply the presumption. The numerical overlap and Dr. Farber's calculations remain relevant to the ordinary obviousness analysis, but they do not substitute for proof of motivation and a reasonable expectation of success.

Since the Court has declined to apply the overlapping range presumption, it must assess whether the claimed dosages were obvious based on the standard *Graham* analysis.

Many of the same facts underlying the Court's decision not to apply the overlapping-range presumption also inform its analysis under *Graham*. For example, the breadth of the disclosed ranges, the absence of guidance directing a POSA to the claimed doses, and the experimental and unpredictable state of ketamine treatment bear directly on whether a POSA would have been motivated to select 56 mg or 84 mg and would have reasonably expected those doses to succeed. Ultimately, Sandoz has not shown by clear and convincing evidence that a POSA, without

knowledge of the claimed invention, would have selected the particular starting doses, assumptions, and conversion factors used in Dr. Farber's calculations.

Although the inputs Dr. Farber chose can mathematically generate 56 mg and 84 mg, the record does not establish that the prior art would have directed a POSA to select them. Further, Dr. Farber's analysis was insufficient to dispel the concern that the claimed doses supplied the roadmap for his calculations. Dr. Farber did not establish why a POSA would have selected the particular starting doses and conversion factors that, through simple arithmetic, produced the claimed doses. Specifically, he did not identify anything in the prior art that would have led a POSA to derive IN doses for treating TRD, MDD, or MDD-SI by combining depression related IV doses with conversion factors drawn from adult anesthesia and pediatric sedation data. Nor did he explain why a POSA would have expected that approach to yield safe and effective IN esketamine doses for TRD, MDD, and MDD-SI. Accordingly, while the calculations demonstrate that the claimed doses can be produced once particular inputs are selected, they do not establish that the prior art would have motivated a POSA to select those inputs with a reasonable expectation of success.

Therefore, the Court finds that Sandoz has not established by clear and convincing evidence that the claimed doses were obvious.

c. Induction and Maintenance Phases

Sandoz established that Charney described depression as "a chronic illness requiring maintenance treatment" and reported that a single IV ketamine dose produced a rapid antidepressant response that began to diminish around day three. Mathew similarly characterized the existing evidence as demonstrating the "acute efficacy" of a single 0.5 mg/kg dose of IV ketamine. As such, Sandoz established that the prior art taught that depression is a chronic illness,

that ketamine could produce a rapid antidepressant response, and that the response is diminished after several days. Therefore, the prior art would have motivated a POSA to seek a means of sustaining ketamine's initial therapeutic effect.

Additionally, Sandoz established that the general concepts of acute and maintenance treatment were known in the prior art. Singh expressly described both "acute treatment" and "maintenance treatment," defining the latter as longer treatment given after a patient responded to earlier treatment to prevent recurrence. Charney likewise disclosed repeated ketamine administration over two to three weeks and contemplated maintenance treatment following an initial response.

However, Sandoz did not establish that the prior art taught that ketamine itself should be used during maintenance. To the contrary, Mathew, the most recent assessment of the field at the time, emphasized the limited information concerning chronic ketamine use and the unresolved safety of continuation therapy. Other prior-art disclosures, such as aan het Rot, likewise raised concerns about the effects of repeated administration and suggested using ketamine to provide rapid relief only until a less invasive relapse prevention strategy could be implemented.

Accordingly, while the prior art would have motivated a POSA to pursue some form of long term management after an initial response to ketamine, Sandoz did not establish by clear and convincing evidence that the prior art would have motivated a POSA to continue administering ketamine as a long term maintenance treatment. Nor did Sandoz sufficiently establish that the prior art supplied a reasonable expectation that doing so would remain safe and effective.

Viewed as a whole, Sandoz's proof falls short. Although Sandoz identified prior art support for certain individual features, it did not explain why a POSA would have combined the claimed dose, route, frequency, duration, and treatment phases into the integrated regimens recited by the

claims. Further, Sandoz failed to adequately account for the interdependence of those variables or establish a reasonable expectation that the resulting regimens would produce and sustain an antidepressant response. Accordingly, Sandoz has not proven by clear and convincing evidence that the Caers Patent claims would have been obvious.

ii. The '260 Patent

The representative claims of the '260 Patent require administering two to eight consecutive sprays of an IN S-ketamine hydrochloride formulation having a concentration of eq. 120 to 250 mg/mL or about eq. 140 mg/mL. Sandoz established that aqueous S-ketamine hydrochloride formulations were known and that a POSA would have had reason to investigate their use for IN treatment of depression. (Tr. 316:5–12, 316:17–318:9, 325:18–326:12 (Donovan)). Sandoz also established that spray volume, nasal capacity, solubility, bioavailability, and patient convenience were relevant considerations in developing an IN formulation. (Tr. 328:5–329:9 (Donovan)). The disputed question is whether those teachings would have led a POSA to the claimed combination of concentration and spray number. As with the Caers Patents, the question is not whether each claimed variable was separately known, but whether the prior art would have led a POSA to combine those variables in the complete methods recited by the claims.

Dr. Donovan began with Dr. Farber's proposed therapeutic range of 35 to 105 mg of IN S-ketamine and selected 55 mg and 85 mg as target doses. (Tr. 140:6–141:7 (Farber); Tr. 341:9–348:10 (Donovan)). She did not independently evaluate the therapeutic dose or explain why a POSA would have selected 55 or 85 mg from that range. (Tr. 315:21–316:12, 400:20–401:4 (Donovan)). As discussed in connection with the Caers Patents, Sandoz did not establish that the prior art would have directed a POSA to the starting doses and conversion factors underlying Dr.

Farber's range. That deficiency necessarily weakens Dr. Donovan's formulation analysis, which accepted the resulting range as its clinical premise.

Sandoz failed to establish that the prior art would direct a POSA toward the claimed concentrations. The ketamine or S-ketamine formulations identified at trial generally used concentrations of 100 mg/mL or less. (DTX-153 ¶ 121; DTX-24 ¶¶ 23, 40; DTX-20_2; DTX-37_3; Tr. 408:11–409:16, 519:22–522:12). The evidence further indicated that increasing the concentration of an IN formulation could reduce bioavailability, thereby providing a reason to remain at or below 100 mg/mL and administer additional sprays if a larger total dose were required. (Tr. 409:25–410:4, 522:23–524:17, 530:15–531:21 (Little)). Dr. Donovan did not identify a prior art reason to depart from that pattern. (Tr. 522:18–22).

Dr. Donovan's calculations do not supply the missing motivation. Her results depended on three principal assumptions: a spray volume of 0.1 mL, administration to both nostrils, and a solubility limit of 200 mg/mL. (Tr. 329:10–332:3, 335:20–337:14, 342:4–22 (Donovan)). The evidence established that each was a possible formulation choice, but not an inevitable one based on the teachings of the prior art. Other spray volumes were available, some IN medications were administered through only one nostril, and the solubility of S-ketamine could vary with the formulation's pH and excipients. (Tr. 403:6–9, 404:11–405:23, 406:22–407:23 (Donovan)).

The existence of alternative choices does not itself establish nonobviousness. Moreover, Sandoz did not identify anything in the prior art that would have led a POSA to select Dr. Donovan's particular combination of assumptions. Because those selections determined the resulting concentration and number of sprays, her calculations show only that a POSA could have reached the claimed formulation, not that a POSA would have been motivated to do so.

Even after assuming a 0.1 mL spray volume, administration to both nostrils, and a 200 mg/mL solubility limit, Dr. Donovan did not apply the same calculation method consistently to the 55 mg and 85 mg target doses. For a 55 mg target dose, she repeatedly doubled the number of sprays and halved the concentration until reaching four sprays at eq. 137.5 mg/mL. (Tr. 341:16–344:19 (Donovan)). For an 85 mg target dose, however, she selected six sprays, producing eq. 141.7 mg/mL. (Tr. 345:8–348:10 (Donovan)). Had she repeated the same doubling-and-halving process used for the 55 mg dose, the resulting concentration would have fallen outside the claims. (Tr. 529:16–530:1 (Little)). Sandoz did not identify anything in the prior art that would have directed a POSA to use one approach for the 55 mg dose and another for the 85 mg dose.

Accordingly, while Dr. Donovan's calculations establish that a POSA could produce the claimed concentrations and spray numbers after selecting particular target doses and formulation assumptions, they do not establish that the prior art would have motivated a POSA to make those selections. Nor do they explain why a POSA would have reasonably expected the resulting formulation to alleviate symptoms of depression. Indeed, Dr. Donovan acknowledged that beginning with a 35 mg dose from Dr. Farber's range would produce a concentration of approximately 100.9 mg/mL, which is outside the representative claims. (Tr. 348:18–21 (Donovan)). Therefore, Sandoz did not prove by clear and convincing evidence that the claimed concentrations and spray numbers would have been obvious.

Sandoz separately established that the '061 publication identified approximately 4.5 as a possible pH for an IN ketamine formulation. (DTX-153_27 ¶ 84; Tr. 353:9–355:7 (Donovan)). Sandoz also presented evidence that conventional pH-adjusting agents and other excipients, including citric acid, sodium hydroxide, and EDTA, were known formulation options. (DTX-25_18 (32:1–15); Tr. 356:15–358:6 (Donovan)). Finally, the prior art treated preservatives as

optional and identified reasons to omit them from some IN formulations. (DTX-153_23, _29 ¶¶ 72, 90; Tr. 358:23–360:25 (Donovan)).

However, even assuming that Sandoz established the obviousness of those individual limitations, it did not establish the claimed invention as a whole. Dr. Farber addressed the clinical dose, while Dr. Donovan addressed individual formulation variables; neither explained why a POSA would have combined the claimed dose, concentration, spray number, pH, excipients, and preservative status into the recited formulations. (Tr. 276:4–21, 393:3–24, 400:20–401:4, 545:14–17). Dr. Donovan further acknowledged that concentration, pH, and excipients interact and should be considered together, but her analysis did not address that interplay. (Tr. 418:12–19).

Accordingly, Sandoz has not proven by clear and convincing evidence that the representative claims of the '260 Patent, considered as a whole, would have been obvious.

iii. Objective Indicia

Objective indicia of nonobviousness, also referred to as secondary considerations, “must be considered in every case where present.” *Apple Inc. v. Samsung Elecs. Co., Ltd.*, 839 F.3d 1034, 1048 (Fed. Cir. 2016) (en banc). Secondary considerations or objective indicia are “not just a cumulative or confirmatory part of the obviousness calculus but constitute[] independent evidence of nonobviousness.” *Millennium*, 862 F.3d at 1367–68 (quoting *Ortho- McNeil Pharm., Inc. v. Mylan Lab’ys, Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008)). Objective indicia “are crucial in avoiding the trap of hindsight when reviewing, what otherwise seems like, a combination of known elements.” *Leo Pharm.*, 726 F.3d at 1358; *see Graham*, 383 U.S. at 36.

To be relevant to nonobviousness, objective indicia must have a “nexus” to the patent claims, *i.e.*, they must be “attributable to the inventive characteristics of the discovery as claimed in the patent.” *In re Cyclobenzaprine*, 676 F.3d at 1079 n.6 (cleaned up). A patent owner can

“prove nexus by showing that the evidence of secondary considerations is the direct result of the unique characteristics of the claimed invention.” *Volvo Penta of the Americas, LLC v. Brunswick Corp.*, 81 F.4th 1202, 1210 (Fed. Cir. 2023) (cleaned up). For inventions, such as those at issue here, that combine multiple elements, “the patent owner can show that it is the claimed combination as a whole that serves as a nexus for the objective evidence; proof of nexus is not limited to only when objective evidence is tied to the supposedly ‘new’ feature(s).” *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1330 (Fed. Cir. 2016) (citation omitted).

Spravato®, when used according to its label, practices the asserted claims of both the Caers and 260 Patents. The evidence further established that practicing those claims produces Spravato®’s distinctive clinical benefits and contributes to its commercial success and favorable reception. Therefore, the Court finds a sufficient nexus between the asserted claims and the objective indicia discussed below.

The evidence of long felt-unmet need weighs in favor of nonobviousness. Before the critical dates, there was a recognized need for a depression treatment that could act rapidly and sustain its effect over time. Although ketamine had demonstrated a rapid antidepressant response, that response was transient, and the art expressed substantial uncertainty about whether ketamine could be administered repeatedly as a safe and effective long term treatment.

Dr. Drevets testified that “there were not controlled studies that looked beyond one – one administration of racemic ketamine. Even though this had been a discovery that was reported in 2000, here we were, 12 years later, and the field was at an impasse because there was no way to extend the benefit of the discovery.” (Tr. 606:7-12 (Drevets)). Additionally, Dr. Donovan testified that at the priority date there were no other nasally administered products for treating depression anywhere in the U.S., nor did she suspect that there was any similar treatment throughout the

world. (Tr. 387: 9-13 (Donovan)).

Further, Janssen provided evidence that in July 2012 the FDA fast tracked the TRD2001 study “[g]iven the seriousness of [MDD] and the great unmet clinical need for efficacious treatments.” (PTX-1047A at p. 1). As a result of TRD2001, on September 16, 2013, the FDA approved Janssen’s request for Breakthrough Therapy Designation for the treatment of patients with TRD. (See PTX-1001). Dr. Drevets testified that this was the first psychiatric drug that had ever received breakthrough designation. (Tr. 614:12-15 (Drevets)). Accordingly, the Court is persuaded that Spravato® addressed a long felt and unmet need by providing rapid relief through an IN formulation and sustaining the response through continued treatment under the claimed dosing regimens.

The evidence concerning failure of others provides additional, though more limited, support. Researchers and pharmaceutical companies attempted to develop ketamine and other NMDA-modulating compounds into useful treatments for depression, but several of those efforts did not result in FDA approved therapies. Those failures do not involve the precise formulations and regimens claimed here, and the Court does not give them substantial independent weight. They nevertheless reinforce the evidence that converting ketamine’s short lived antidepressant response into a practical treatment was not a straightforward undertaking.

Janssen also established unexpected results connected to each patent family. With respect to the Caers Patents, the claimed regimens produced a safety profile suitable for continued treatment without the neurotoxicity that had been associated with ketamine and had concerned the FDA. With respect to the 260 Patent, the inventors discovered that concentrated S-ketamine formulations possessed antimicrobial properties that permitted omission of a preservative without sacrificing microbial control. The latter result is particularly probative because it is directly

connected to the claimed concentration and no-preservative limitations.

Spravato®'s commercial success and the praise it received also favor nonobviousness. Spravato® achieved substantial and growing sales, and publications characterized it as a significant advance in the treatment of depression. The Court recognizes that sales and praise may also reflect FDA approval, marketing, and aspects of the product not expressly claimed. The claimed formulation and dosing regimens need not, however, be the exclusive causes of that success. The evidence sufficiently connected Spravato®'s favorable reception and commercial performance to its rapid and sustained clinical benefits, which arise materially from practicing the asserted claims. Therefore, the Court gives this evidence meaningful, but not dispositive, weight.

In sum, while the strength of the individual categories varies, considered collectively, the objective indicia weigh in favor of nonobviousness and reinforce the Court's conclusion that Sandoz did not prove the asserted claims obvious by clear and convincing evidence.

F. Lack of Written Description

Whether a patent is invalid for lack of written description is a question of fact. *Allergan*, 796 F.3d at 1308. The "critical inquiry" regarding the specification's written description is "whether the patentee has provided a description that 'in a definite way identifies the claimed invention' in sufficient detail that a person of ordinary skill would understand that the inventor was in possession of it at the time of filing." *Alcon Rsch. Ltd. v. Barr Lab'ys, Inc.*, 745 F.3d 1180, 1191 (Fed. Cir. 2014) (quoting *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1352 (Fed. Cir. 2010)).

A patent is statutorily presumed valid. *See* 35 U.S.C.A. § 282(a). Further, the patent challenger bears the burden to overcome that presumption. *Id.* ("The burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity.") Thus,

when a challenger asserts invalidity based on a lack of written description, the challenger must show, “by clear and convincing evidence that the written description requirement was not met, in light of the presumption of validity.” *Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1364 (Fed. Cir. 2003).

1. Sandoz’s Lack of Written Description Arguments

Sandoz argues alternatively that if the Court finds that the Patents in Suit are not obvious, then the Patents in Suit are invalid for lack of written description. Sandoz argues that the Caers specification does not demonstrate that the inventors possessed the claimed IN route of administration, dose amounts, induction and maintenance schedules, adjunctive treatment, or treatment of MDD-SI. Sandoz contends that the 260 Patent is even more deficient because it was filed earlier and contains no human data.

More broadly, Sandoz argues that the same uncertainty and lack of data on which Janssen relies to defeat obviousness also demonstrates that the specifications contain insufficient information to show possession of the claimed inventions. Sandoz relies on Janssen’s evidence that the relevant field was complex, unpredictable, and still developing. In opposing obviousness, Janssen maintained that a POSA could not have developed the claimed regimen through routine optimization because the route of administration, dose amount, dosing frequency, and treatment duration affect one another and could not be reliably selected independently. Janssen also argued that based on the prior art a POSA could not have predicted that repeated IN S-ketamine treatment would safely and effectively treat depression. In support, Janssen cited ketamine’s cardiovascular, neurotoxic, cognitive, dissociative, and abuse related risks, particularly with repeated use. Sandoz relies on that same evidence to argue that the specifications needed to demonstrate that the claimed regimens would safely and effectively treat depression despite those known risks.

Sandoz argues that Janssen cannot rely on the absence of IN S-ketamine data to distinguish the prior art while disregarding the same alleged deficiency in its patent specifications. In Sandoz's view, if dose, frequency, duration, efficacy, and safety data were necessary for a POSA to arrive at the claimed regimens, the specifications needed comparable disclosures to demonstrate that the inventors possessed those regimens. Because neither specification allegedly contains IN efficacy or safety data or explains how the claimed regimens would address those uncertainties, Sandoz contends that the specifications fail to demonstrate possession.

Sandoz emphasizes Dr. Papakostas's criticism that the prior art lacked data, results, and a rationale supporting the use of IN S-ketamine to treat depression. It argues that the same criticism applies more forcefully to the Patents in Suit. Specifically, Sandoz contends that the Caers specification contains only IV clinical data, while the 260 Patent contains no human data at all. Neither specification allegedly provides IN S-ketamine data concerning dose, duration, frequency, efficacy, or safety. Accordingly, Sandoz maintains that, if such information was necessary for the prior art to support a reasonable expectation of success, it was also necessary for the specifications to demonstrate possession of the claimed inventions.

i. The Caers Patents

a. Intranasal Administration

Sandoz argues that the Caers specification does not demonstrate possession of the claimed IN S-ketamine regimens because it only reported studies TRD2001 and TRD2002, which only involved IV administration of ketamine to treat depression. Sandoz argues that even though the Caers specification identifies IN administration as preferred, it merely selects that route from numerous alternatives without explaining why IN administration would be suitable or how the IV studies support an IN treatment.

Similarly, Sandoz argues that the Caers specification does not connect the weight based IV doses used in TRD2001 and TRD2002 to the claimed IN doses of approximately 56 mg and 84 mg. The specification allegedly lacks information concerning relative bioavailability, does not contain a method for converting IV doses to IN doses, and provides no other rationale for selecting the claimed amounts. Sandoz also relies on the inventors' inability to explain that connection and Dr. Daly's testimony that evidence of efficacy for the 56 mg and 84 mg doses came from the later TRD2003 study, which is not disclosed in the specification.

b. Induction, Maintenance, and Dosing Frequency

Sandoz argues that the Caers specification does not demonstrate possession of an effective four week induction regimen. Although the specification recites induction and maintenance phases, Sandoz contends that it does not define those phases, explain when they should be used, or provide a rationale for the claimed durations and dosing frequencies. According to Sandoz, the disclosed clinical studies do not supply the missing support. TRD2001 focused on a participant's response after a single IV infusion of ketamine, while TRD2002 had a Day 15 primary endpoint and permitted certain patients to receive open label ketamine thereafter. Accordingly, Sandoz argues that the specification does not reflect possession of an effective regimen, but a proposed treatment schedule.

Sandoz further argues that functional unblinding reduced the ability of TRD2001 and TRD2002 to demonstrate possession of effective treatment regimens. Sandoz points to Dr. Papakostas's criticism that ketamine's dissociative effects could reveal whether participants had received ketamine or placebo, thereby potentially biasing the results. According to Sandoz, Dr. Papakostas acknowledged that TRD2001 and TRD2002 were susceptible to the same concern. As such, Sandoz maintains that the disclosed studies should receive no greater weight in the written

description analysis than comparable studies received in the obviousness analysis.

Sandoz likewise argues that neither study tested the claimed maintenance regimen. The studies did not include a formal maintenance phase, a fourteen week maintenance period, or weekly or every other week maintenance dosing. Sandoz rejects Janssen's reliance on evidence that some TRD2002 patients remained well for as long as two weeks without additional treatment, contending that this observation does not establish the effectiveness of administering maintenance doses at those intervals. According to Sandoz, that evidence would suggest that maintenance therapy was unnecessary, not demonstrate possession of an effective maintenance regimen.

Finally, Sandoz argues that the studies do not support the claimed dosing frequencies. Although TRD2001 administered two doses during one week, its primary endpoint followed the first infusion. TRD2002 permitted dosing two or three times weekly but pooled the results, preventing a POSA from determining the efficacy of either schedule. Sandoz contends that maintenance treatment and the claimed maintenance frequencies were not investigated until TRD2003, which is absent from the specification so it cannot supply written description support.

c. Adjunctive Treatment and MDD-SI

Sandoz argues that the specification's list of oral antidepressants does not demonstrate possession of adjunctive treatment because it provides no substantive explanation of how those drugs should be used with an IN S-ketamine regimen. It maintains that, if the prior art did not render adjunctive treatment obvious, the specification's allegedly less detailed disclosure cannot support that limitation.

Sandoz also contends that the specification does not demonstrate possession of a method for treating MDD-SI. TRD2001 and TRD2002 excluded patients with suicidal ideation, produced no data concerning that population, and stated that their suicidality measurements were not

applicable or generalizable to such patients. According to Sandoz, Janssen did not investigate MDD-SI until the later SUI2001 study, which is not disclosed in the specification and did not employ the induction and maintenance phases recited in certain asserted claims.

d. Janssen's Remaining Evidence of Possession

Sandoz rejects Janssen's argument that the specification demonstrates possession because it expressly recites many of the claimed doses, phases, frequencies, and other limitations. According to Sandoz, repeating claim language does not, by itself, establish that the inventors possessed the claimed combination. It characterizes Dr. Papakostas's contrary testimony as conclusory because he did not identify supporting IN clinical data or explain why a POSA would understand the recited elements to constitute safe and effective treatment regimens.

Sandoz likewise disputes Janssen's reliance on TRD2001 and TRD2002 as studies that "advanced the art." According to Sandoz, those IV studies supplied, at most, preliminary information and direction for further research. Sandoz argues that Janssen cannot demonstrate possession by selecting isolated features from the studies and combining them with claim language elsewhere in the specification when no disclosed study evaluated the claimed method as a whole. It further relies on later statements by Drs. Papakostas and Drevets indicating that additional research remained necessary, as well as the existence of TRD1001 and TRD2003, which investigated IN S-ketamine but are not described in the specification.

Sandoz contends that this piecemeal approach is particularly inconsistent with Janssen's nonobviousness position that the claimed route, dose, frequency, and duration are interconnected and must be considered as a complete regimen.

Sandoz also rejects Janssen's reliance on the specification's hypothetical formulation examples. Sandoz argues that the specification does not identify those examples as IN formulations

or indicate that they were ever prepared or tested in patients. Thus, according to Sandoz, the examples may describe possible S-ketamine formulations, but they do not demonstrate possession of the claimed methods for treating depression with particular IN doses and dosing schedules. Even if a POSA would recognize them as IN formulations, Sandoz argues that their composition would not demonstrate the safety or efficacy of the claimed long-term treatment regimens.

Finally, Sandoz notes that much of the specification concerns whether a patient's genotype affects the response to ketamine or the selection of an appropriate dose. Because none of the asserted claims requires genotyping or differentiates treatment according to genotype, Sandoz contends that this material does not support the claimed methods or fill the asserted gaps in the disclosure.

iv. The 260 Patent

a. Claimed Concentration Range

Sandoz argues that the 260 specification does not demonstrate possession of claim 22's concentration range of approximately 120–250 mg/mL or claim 36's concentration of approximately 140 mg/mL. Although claim 22 covers S-ketamine concentrations ranging from approximately 120 to 250 mg/mL, the working examples test formulations at only 126, 140, and 150 mg/mL. Thus, the specification examples do not test formulations throughout the full claimed range, particularly concentrations above 150 mg/mL. According to Sandoz, those limited examples do not establish that the inventors possessed formulations throughout the claimed range that achieve the claimed therapeutic result.

b. Concentrations Above 150 mg/mL

Sandoz emphasizes that the specification contains no data concerning concentrations above 150 mg/mL, even though claim 22 extends to approximately 250 mg/mL. It contends that this

omission is significant because Dr. Little testified that a POSA would have avoided concentrations above 100 mg/mL due to concerns about reduced bioavailability. Concentrations approaching or exceeding 200 mg/mL would also raise potential complications because they are near the solubility limit of S-ketamine hydrochloride.

Sandoz argues that Janssen cannot maintain that bioavailability concerns would have discouraged a POSA from using concentrations above 100 mg/mL for purposes of obviousness while also asserting that the specification's bare recitation of substantially higher concentrations demonstrates possession of those formulations.

c. Nature of Disclosed Examples

Sandoz argues that none of the 260 Patent's examples evaluates whether the claimed formulations deliver a therapeutically effective amount of S-ketamine to a human patient. Examples 1 and 2 provide only microbial challenge testing data at concentrations of approximately 126 and 140 mg/mL. Examples 3 through 5 use a pipette to place a 150 mg/mL formulation into the nostrils of rats or dogs and measure resulting plasma concentrations.

According to Sandoz, these studies establish only that S-ketamine entered the animals' bloodstreams. The animals were not models of depression, and the specification does not connect their plasma levels to either the pharmacokinetics of IN S-ketamine in humans or the effective treatment of depressive symptoms. The studies do not address administration by nasal spray, administration in two to eight sprays within one hour, or therapeutic efficacy in treating MDD.

Sandoz further argues that Janssen cannot rely on the later TRD1001 Phase I trial to supply the missing clinical support because that study is not disclosed in the specification. According to Sandoz, actual possession based on information outside the patent cannot satisfy the written description requirement, even if TRD1001 was completed before the application was filed.

d. Efficacy Across the Claimed Scope

Finally, Sandoz argues that the specification does not establish efficacy for all dose and concentration combinations covered by claims 22 and 36. Sandoz contends that Dr. Little offered no opinion that administering 24 mg through two sprays of a 120 mg/mL formulation, or 28 mg through two sprays of a 140 mg/mL formulation, would produce a therapeutically effective dose. Sandoz also notes that the 28 mg dose was ineffective in the only patient population in which it was tested. Sandoz contends that merely including the claimed concentrations and spray limitations in the specification does not demonstrate that those combinations would alleviate MDD symptoms.

2. Janssen's Lack of Written Description Rebuttal

As a threshold matter, Janssen disputes Sandoz's premise that its nonobviousness positions establish a lack of written description. Janssen argues that obviousness and written description present distinct inquiries: obviousness asks what a POSA would have found obvious from the prior art without the specification, whereas written description asks what the specification conveys to a POSA about the invention the inventors possessed. According to Janssen, it is entirely consistent to maintain that the prior art did not direct a POSA to the claimed combinations while the specifications expressly describe those combinations. Janssen further argues that considerations such as safety and the predictability of clinical success may affect whether a POSA would have pursued a treatment regimen for purposes of obviousness even when those considerations are not limitations that must independently be described under § 112.

Janssen also contends that Sandoz did not support its overarching inconsistency theory with affirmative expert testimony. According to Janssen, Dr. Farber offered only a generalized conditional opinion that the claims would lack written description support if they were found

nonobvious, but did not identify which particular findings supporting nonobviousness would produce that result. Janssen further argues that Dr. Farber improperly disregarded the prior art and a POSA's background knowledge when assessing written description, even though a POSA would read the specifications with knowledge of ketamine's rapid antidepressant effect and esketamine's greater potency. As such, Janssen maintains that Sandoz's generalized attorney arguments do not satisfy its burden of proving invalidity by clear and convincing evidence.

i. The Caers Patents

a. Intranasal Administration and Dosing

Janssen argues that the Caers specification demonstrates possession of the claimed route and dose limitations because it expressly describes the IN administration of 56 mg and 84 mg of S-ketamine and identifies those doses as preferred. According to Janssen, a POSA would not need to derive the claimed IN doses from the IV doses used in TRD2001 and TRD2002 because the specification supplies the IN doses directly. Therefore, Janssen contends that Sandoz improperly evaluates whether the clinical studies independently disclose every claim limitation rather than reading the specification as a whole.

Janssen further argues that the absence of clinical data using the precise claimed IN doses does not defeat written description. It maintains that experimental examples need not reproduce every feature of the claims and that completed clinical testing or an actual reduction to practice is not required. According to Janssen, TRD2001 and TRD2002 provide relevant clinical support by establishing the efficacy of esketamine and ketamine at the frequencies and durations incorporated into the claimed IN regimens.

Janssen also relies on the specification's two prophetic IN formulations. It argues that those examples show that the inventors had developed the means to administer S-ketamine intranasally

in accordance with the expressly disclosed regimens. Janssen contends that Dr. Farber failed to address these formulations and therefore did not evaluate the specification as a whole.

b. Induction, Maintenance, and Dosing Frequency

Janssen argues that TRD2001 and TRD2002 provide clinical support for the claimed induction and maintenance schedules. Janssen argues that TRD2001 supports the use of esketamine and the claimed twice-weekly induction frequency because the study showed efficacy when esketamine was administered twice during one week. Janssen further contends that TRD2002 was a controlled multidose study that administered ketamine two or three times per week for four weeks. According to Janssen, TRD2002 showed efficacy throughout that period and supports the claimed four week induction phase and twice weekly dosing schedule. Janssen disputes Sandoz's reliance on the study's Day 15 primary endpoint and the availability of optional open label treatment after that point, arguing that these features did not convert the study into a two week or uncontrolled trial.

Janssen also rejects Sandoz's functional unblinding argument. It contends that Dr. Papakostas did not rely on functional unblinding during his obviousness rebuttal and discussed the subject only when questioned by Sandoz on cross examination. According to Janssen, because Dr. Papakostas did not contend that functional unblinding rendered the claimed regimens nonobvious, his testimony on that subject creates no inconsistency with his written description opinion.

Janssen also relies on the durability of the response observed in TRD2002 to support maintenance dosing. It argues that a time to relapse analysis could not be completed because too few patients relapsed during the observation period, with some remaining well for as long as two weeks without additional treatment. According to Janssen, this evidence supports reducing the dosing frequency after induction to once weekly or once every two weeks. Janssen rejects Sandoz's

contention that the absence of relapses indicates that no maintenance phase was necessary.

c. Adjunctive Treatment and MDD-SI

Janssen argues that the specification expressly describes adjunctive treatment and the use of the claimed regimens to treat MDD-SI. According to Janssen, written description does not require separate clinical data for every expressly disclosed claim limitation, particularly where the specification identifies the claimed methods in definite and specific terms.

Janssen also contends that inventor testimony and the history of the development program corroborate the specification's disclosures. It relies on evidence that patients were receiving the claimed MDD-SI regimen by the priority date. Janssen maintains, however, that this outside evidence merely confirms possession already evident from the specification and is not being offered to supply an otherwise missing disclosure.

d. Remaining Evidence of Possession

Janssen emphasizes that the specification describes the claimed doses, phases, frequencies, adjunctive treatment, and indications almost verbatim and repeatedly identifies the claimed parameters as preferred or exemplary. Janssen disputes Sandoz's contention that a specification must always provide evidence beyond an express recitation of the claimed invention. Janssen acknowledges that merely repeating claim language does not automatically establish possession. It argues, however, that the disclosures here are sufficient because the specification repeatedly identifies the particular combinations ultimately claimed and describes them as preferred treatment regimens.

Janssen further disputes Sandoz's contention that it improperly assembles the claimed methods from isolated disclosures. According to Janssen, the specifications repeatedly identify the claimed route, doses, phases, and frequencies as parts of the disclosed treatment regimens. Janssen

maintains that its positions are consistent: the prior art did not direct a POSA to the complete claimed combinations, while the specifications expressly describe those combinations and thereby demonstrate possession.

Janssen also disputes Sandoz's contention that the specification must explain why an induction phase, maintenance phase, or particular dosing schedule is appropriate. According to Janssen, written description requires a sufficiently definite identification of the claimed invention, not a scientific explanation of why it works.

Janssen disputes Sandoz's contention that the specification's genotyping disclosures are irrelevant because the claims do not require genotyping. Janssen argues that the disclosed regimens still practice the claimed methods because the claims use the open ended term "comprising," which permits additional steps such as determining a patient's genotype. Janssen further maintains that the study results support the claims because all participants received the treatment and showed efficacy regardless of genotype. Thus, according to Janssen, organizing the results by genotype does not prevent them from supporting the claimed treatment methods.

Finally, Janssen disputes Sandoz's characterization of TRD2001 and TRD2002 as merely preliminary research. It argues that continued clinical testing does not reduce the specification's disclosure of the regimens to a wish, plan, or hypothesis. Janssen maintains that TRD2003 tested regimens already disclosed in the specification and that the law permits a patent to issue before clinical trials are completed.

e. Efficacy and Safety

Janssen argues that Sandoz's written description theory improperly assumes that the Caers claims require the claimed methods to achieve a particular degree of efficacy. According to Janssen, most of the claims require administering S-ketamine for the purpose of "treating"

depression but do not require any particular clinical outcome. For the claims reciting a “therapeutically effective amount,” Janssen argues that the specification requires only a biological or medicinal response, not a particular degree of efficacy.

Janssen maintains that, if the claims do not require a specific efficacy result, the specification need not demonstrate that result. Nevertheless, Janssen argues that any efficacy requirement is adequately supported by the prior art’s recognition of ketamine’s antidepressant activity, the specification’s express identification of the claimed regimens as treatments for depression, and the clinical data from TRD2001 and TRD2002.

Janssen separately argues that Sandoz’s safety based written description theory was raised for the first time after trial and is waived. It relies on Dr. Farber’s testimony that none of the asserted claims contains a safety requirement and contends that Sandoz presented no expert testimony addressing safety as part of its written description case. Janssen further maintains that safety may be relevant to obviousness without becoming a limitation that must be supported under written description. Alternatively, Janssen argues that the specification need not expressly discuss neurotoxicity because the asserted absence of neurotoxicity is an inherent property of esketamine. Thus, according to Janssen, an adequate description of the claimed use of esketamine necessarily encompasses that property, even if the specification does not identify it expressly.

v. The 260 Patent

a. Claimed Concentration Range

Janssen disputes Sandoz’s argument that claim 22 covers a functionally defined category of concentrations requiring representative examples throughout the entire 120–250 mg/mL range. According to Janssen, claim 22 principally defines the formulations by their structural features—S-ketamine and water at specified numerical concentrations—rather than merely by the therapeutic

result they produce. According to Janssen, claim 36 is narrower still, reciting a concentration of approximately 140 mg/mL together with a particular pH and specified excipients. Janssen argues that requiring the claimed methods to alleviate one or more symptoms of depression does not convert these structurally defined claims into a functionally defined genus. Janssen maintains that the specification need not include test results from representative concentrations throughout the claimed range.

Janssen further argues that, even if the claims were treated as a genus, the specification need not disclose representative examples spanning the entire concentration range if it adequately describes structural features common to the claimed formulations. According to Janssen, the specification provides those common features by disclosing the formulations' "recipe" and instructions for their preparation and use. Janssen contends that a POSA would recognize the claimed formulations from the structural information provided in the specification. As such, Janssen maintains that the common structural disclosure demonstrates possession of the claimed range, notwithstanding the absence of tested examples at every concentration within that range.

b. Concentrations Above 150 mg/mL

Janssen rejects Sandoz's contention that the absence of examples testing concentrations above 150 mg/mL defeats written description of claim 22's broader range. It relies on the specification's express description of the entire range and on Dr. Little's testimony that the working examples provide information relevant to concentrations higher than those directly tested.

Janssen separately argues that Sandoz improperly treats Janssen's nonobviousness position as establishing a lack of written description. According to Janssen, whether a POSA would have selected concentrations above 100 mg/mL from the prior art is distinct from whether the specification demonstrates that the inventors possessed the concentrations it expressly describes.

Janssen maintains that the prior art's alleged concerns about high concentrations do not negate the specification's express disclosure of the claimed concentrations, its description of the formulations' common components and preparation instructions, or its working examples at 126, 140, and 150 mg/mL. Janssen also relies on Dr. Little's testimony that those examples would inform a POSA about formulations at concentrations higher than those specifically tested.

c. Nature of the Disclosed Examples

Janssen argues that Sandoz improperly evaluates the 260 Patent's working examples in isolation rather than considering the specification as a whole. According to Janssen, the specification's general disclosures identify the ingredients and concentrations of the claimed formulations, provide instructions for preparing and administering them, and describe administration through clusters of two to eight IN sprays. The working examples provide additional, more limited support: the microbial challenge studies evaluate the formulations' resistance to contamination, while the animal pharmacokinetic studies show that IN administration produces measurable levels of S-ketamine in the bloodstream. Janssen maintains that no individual example must contain every claim limitation or independently demonstrate human antidepressant efficacy because working examples and actual reduction to practice are not required.

Accordingly, Janssen argues that Dr. Donovan improperly evaluated each working example in isolation and failed to consider the specification as a whole, including that disclosure elsewhere in the specification that expressly describe the limitations absent from the individual examples. In contrast, Janssen argues that Dr. Little considered the specification as a whole and reached the contrary conclusion that the specification adequately describes the claimed invention.

d. Efficacy Across the Claimed Scope

Janssen argues that the specification and a POSA's existing knowledge adequately support the requirement that the claimed methods alleviate one or more symptoms of depression. The specification states that ketamine was known to produce a rapid antidepressant effect, identifies S-ketamine as more potent than racemic ketamine, and describes administering the claimed formulations in two to eight sprays within approximately sixty minutes. Janssen also relies on Dr. Farber's opinion that S-ketamine doses between 35 mg and 110 mg would be therapeutically effective. According to Janssen, these disclosures would convey to a POSA that the claimed formulations could deliver amounts sufficient to alleviate at least one symptom of depression.

Janssen rejects Sandoz's suggestion that Dr. Papakostas denied the prior art had demonstrated ketamine's rapid antidepressant effect. According to Janssen, Dr. Papakostas agreed that ketamine produced such an effect but distinguished that fact from establishing ketamine as a broadly efficacious clinical treatment for depression. Janssen maintains that this distinction does not affect written description because the 260 Patent claims require only alleviation of one or more symptoms during a single treatment session, not durable or comprehensive clinical efficacy.

Janssen also disputes Sandoz's reliance on a post priority date study in which a treatment regimen beginning at 28 mg failed to achieve a specified clinical trial endpoint. Sandoz cites that result to support its contention that the specification did not demonstrate possession of an effective method encompassing two sprays of a 140 mg/mL formulation, which delivers 28 mg of S-ketamine. Janssen responds that the Spravato® label reporting the study postdates the patent's priority date and therefore does not establish what the specification conveyed to a POSA at the relevant time. Janssen also notes that the study involved geriatric patients who began treatment at 28 mg but could later receive 56 mg or 84 mg. Most importantly, Janssen argues that the study's

failure to show a statistically significant improvement in overall MADRS scores does not establish that 28 mg failed to alleviate any individual symptom of depression. Because the claims require only alleviation of one or more symptoms, Janssen maintains that the study does not demonstrate a lack of written description support.

3. A Finding of Nonobviousness Does Not Require a Finding of Lack of Written Description

The Court first addresses Sandoz's argument that if the Court finds that the Patents in Suit were not obvious, then it must find that the Patents in Suit lack written description. The Court disagrees.

Sandoz argues that Janssen's positions on obviousness and written description are irreconcilable. In opposing obviousness, Janssen maintained that the prior art lacked sufficient direction for a POSA to select and combine the claimed route, doses, frequencies, and treatment phases with a reasonable expectation of success. Sandoz reasons that the Patents in Suit cannot provide adequate written description support if the prior art did not.

This argument conflates two distinct inquiries. For obviousness, the question is whether the prior art would have motivated a POSA to select and combine the claimed features with a reasonable expectation of success. *Janssen*, 141 F.4th at 1374. Written description instead requires an objective inquiry into whether the specification, viewed through the eyes of a POSA, conveys with reasonable clarity that the inventors possessed the claimed invention as of the filing date. *Ariad*, 598 F.3d at 1351.

Thus, in the obviousness analysis, the POSA begins with the prior art and asks whether it would have led to the claimed combination. In the written description analysis, the POSA begins with a specification that already identifies the claimed combination and asks whether the disclosure demonstrates that the inventors possessed it. Therefore, there is no inherent inconsistency in

finding that the prior art did not direct a POSA to the claimed invention while also finding that the specification adequately describes that invention.

Here, as to the Caers Patents, the prior art did not sufficiently direct a POSA to select and combine the claimed route, doses, and dosing schedules. The specification, by contrast, identifies those features as parts of the claimed regimens and provides additional clinical and formulation disclosures supporting them.

The clinical studies disclosed in the Caers specification serve a correspondingly different function in the written description analysis than in the obviousness analysis. They are not used to derive the claimed regimen from disparate information. Instead, they provide support for particular features of a regimen that the specification has already identified. Thus, evidence that was insufficient, standing alone, to direct a POSA to the claimed combination may nevertheless corroborate the inventors' possession of that combination once the specification expressly discloses it.

Sandoz further relies on ketamine's known safety risks to argue that a POSA would not have understood the inventors of the Caers patents to possess the claimed regimens. While those risks may bear on whether a POSA would have been motivated to pursue repeated ketamine treatment with a reasonable expectation of success, the asserted claims do not require any particular safety outcome. Accordingly, to establish possession, the specification need not demonstrate that the claimed regimens eliminate those risks. Sandoz has not shown that the known safety concerns would cause a POSA to disregard the specification's express description of the claimed regimens and conclude that the inventors did not possess them.

The same distinction applies to the '260 Patent. In addressing obviousness, the Court found that Sandoz did not adequately explain why the prior art would have directed a POSA to select the

claimed concentrations and spray numbers from the available formulation options. The Court determined that different choices concerning spray volume, administration to one or both nostrils, solubility, and the number of sprays could have produced different formulations, and that Sandoz did not establish why a POSA would have selected the particular combination recited in the claims.

However, the written description inquiry does not require a POSA to make those selections from the prior art. The 260 specification expressly identifies the claimed concentrations, ingredients, number of sprays, administration period, and therapeutic purpose. It also provides working examples concerning the antimicrobial properties of the disclosed formulations and their absorption following nasal administration. Therefore, the question is not whether the prior art would have led a POSA to select the claimed combination or whether any single example independently practices every claim limitation. Rather, the question is whether the specification as a whole, including its express descriptions, working examples, and the background knowledge of a POSA, conveys that the inventors possessed the claimed methods. Accordingly, the Court's finding that the prior art did not render the claimed formulation obvious does not compel a finding that the specification lacks sufficient written description.

4. The Caers Patents do not Lack Written Description

The Court finds that Sandoz has not proven by clear and convincing evidence that the asserted claims of the Caers Patents lack written description. The shared specification expressly describes the claimed IN esketamine regimens. It also reports clinical results supporting several central features of those regimens and discloses specific IN S-ketamine formulations through which the regimens could be administered. While no single clinical study tested the complete claimed method, which reduces the weight of the clinical evidence, that limitation does not negate the specification's other disclosures. Considered as a whole, the Caers specification conveys to a

POSA that the inventors possessed the claimed methods as of the critical date.

i. The Specification Expressly Describes the Claimed Regimens

The asserted claims generally require administering approximately 56 mg or 84 mg of IN esketamine twice weekly during an induction phase of approximately four weeks, followed by a maintenance phase in which the frequency is reduced to once weekly or once every two weeks. Certain claims also require adjunctive antidepressant treatment or treatment of a patient with MDD-SI.

The specification describes the central components of these regimens in specific terms. It identifies 56 mg and 84 mg as preferred IN esketamine doses. (JTX-1 at 8:50–52, 8:62–64). It describes administering esketamine twice weekly for four weeks during an induction phase. (*Id.* at 8:48–49, 8:56). It then describes a maintenance phase in which the frequency is reduced to once weekly or once every other week. (*Id.* at 8:65–67). These disclosures appear together in the specification’s description of preferred treatment regimens, rather than as isolated values drawn from unrelated lists. (*Id.* at 7:23–9:43). Dr. Farber accordingly acknowledged that the specification describes the claimed regimens “almost verbatim.” (Tr. 287:8–10 (Farber)).

However, the presence of language substantially tracking the claims does not end the inquiry. A specification does not necessarily demonstrate possession merely by repeating the words later used in a claim. *Nuvo Pharms. (Ir). Designated Activity Co. v. Dr. Reddy’s Lab ’ys Inc.*, 923 F.3d 1368, 1380–81 (Fed. Cir. 2019). It is not enough that the specification simply say that the inventor possessed the claims, it must “*demonstrate possession.*” *Ariad Pharms*, 598 F.3d at 1352)(emphasis added). “There must be some description, such as a constructive reduction to practice, establishing that the inventor ‘was in possession of the... claimed invention, including all of the elements and limitations.,” *Nuvo Pharms*, 923 F.3d at 1380. (quoting *Univ. Of Rochester v.*

G.D. Searle & Co., 358 F.3d 916, 926 (Fed. Cir. 2004)). Simply stated, the question is whether the disclosure, viewed through the eyes of a POSA and considered as a whole, conveys that the inventors actually possessed the claimed subject matter. *Id.* at 1380.

Here, the specification does not merely state a desired result, such as treating depression with some future undescribed intranasal regimen, nor does the specification simply recite the claimed regimens in isolated or aspirational language. Further, the specification does not force a POSA to select the claimed method from a collection of disconnected possibilities or assemble the claimed combinations from unrelated lists of options scattered throughout the specification. Instead, the specification itself selects and connects the relevant parameters. It also repeatedly characterizes the claimed parameters as preferred. These selections convey substantially more than a wish to discover an effective regimen in the future. They identify the regimens that the inventors regarded as their invention.

Sandoz emphasizes that the specification does not explain how the inventors derived the claimed 56 mg and 84 mg IN doses from the IV doses used in the disclosed studies. It likewise does not provide an IV to IN conversion formula. But written description does not require the specification to reconstruct the inventors' path to the invention. *Ariad*, 598 F.3d at 1351. The relevant question is whether the specification as a whole demonstrates possession of the invention ultimately claimed. *Id.* Because the specification expressly selects 56 mg and 84 mg as preferred IN doses, a POSA would not need to derive those doses from the IV data to identify the claimed regimen.

That distinction is important. Sandoz offered its dose calculations in the obviousness analysis to show why a POSA, beginning with the prior art, would have selected the claimed doses. The Court found that Sandoz did not establish why the prior art would have led a POSA to choose

the particular inputs necessary to calculate 56 mg and 84 mg. Written description presents a different question: whether the specification conveys to a POSA that the inventors had already selected and possessed those doses.

Here, the specification expressly identifies 56 mg and 84 mg as preferred IN esketamine doses and further discloses two IN esketamine formulations. (JTX-1 at 8:50–52, 8:62–64, 32:30–45). A conversion formula might have explained how the inventors selected the claimed doses or provided additional support for their expected efficacy, but a POSA did not need such a formula to identify the doses the specification expressly selected. Accordingly, the absence of a conversion formula does not, by itself, establish that the inventors lacked possession of the disclosed IN dose amounts.

ii. The Clinical Studies Corroborate the Express Disclosures

The clinical studies reported in the specification provide additional support for the expressly described regimens. Although the studies do not constitute a clinical reduction to practice of the complete claims, they support several material aspects of those regimens.

TRD2001 was a placebo controlled study in which patients with TRD received IV esketamine at doses of 0.2 mg/kg or 0.4 mg/kg twice during a one-week period. (JTX-1 at 18:23–35, 24:44–28:45). Dr. Papakostas explained that patients receiving esketamine improved relative to those receiving placebo regardless of genotype. (Tr. 750:8–751:11 (Papakostas)). Thus, the study provides clinical support for using esketamine to treat TRD and for administering it twice within one week.

Sandoz correctly observes that TRD2001 did not test the complete claimed induction regimen. The study used IV rather than IN administration, did not administer absolute doses of 56 mg or 84 mg, lasted only one week, and measured its primary endpoint twenty four hours after the

first infusion. (Tr. 638:6–9 (Drevets)). Accordingly, TRD2001 does not independently establish possession of a four week IN regimen at the claimed doses. Nevertheless, TRD2001 provides clinical support for using esketamine to treat TRD and administering it twice within a week, while the specification separately identifies the IN route, claimed doses, and four week duration. Considered together, these disclosures contribute to the specification's overall demonstration of possession, even though TRD2001 did not itself test every limitation of the claimed induction regimen.

TRD2002 provides additional support for the repeated treatment and maintenance features of the claims. That study evaluated IV racemic ketamine administered two or three times per week over a four week treatment period. (JTX-1 at 19:37–46, 19:62–65). The reported results showed a rapid and substantial antidepressant response among patients receiving ketamine compared with those receiving placebo. (*Id.* at 28:45–30:63 & Fig. 4; Tr. 621:4–622:22 (Drevets)). The specification also reports that many responding patients retained that response during the post treatment observation period. (*Id.* at 30:64–31:8 & Fig. 5). Dr. Papakostas explained that this durability indicated that, after repeated treatment, some patients could remain well for one or two weeks without another dose. (Tr. 622:23–623:22 (Drevets), 762:3–763:5 (Papakostas)). Those results provide support for reducing the dosing frequency after the induction phase to once weekly or once every other week.

The Court recognizes the limitations identified by Sandoz. TRD2001 involved IV rather than IN esketamine and lasted only one week. TRD2002 involved IV racemic ketamine rather than IN esketamine. Its primary endpoint occurred on Day 15, and the study did not formally test the claimed maintenance regimen. Moreover, neither study individually reproduced every limitation of the asserted claims.

However, those limitations do not establish a lack of possession. Written description does not require a working example or an actual reduction to practice of every claimed embodiment. *Alcon*, 745 F.3d at 1190–91. Nor must each example independently contain every claim limitation. *Id.* Furthermore, the studies are not the sole source of support for the claims. The specification separately and expressly identifies the complete IN dosing regimens. The clinical results corroborate material components of those regimens: the antidepressant activity of esketamine, twice weekly administration, a four week course of repeated treatment, and the durability of the resulting response. When those results are considered together with the express regimen disclosures, the absence of a single clinical study testing the complete claimed method does not show by clear and convincing evidence that the inventors lacked possession.

iii. The Intranasal Formulations Further Demonstrate Possession

The specification also discloses two specific esketamine formulations intended for IN administration. (JTX-1 at 32:30–45). Those examples identify the formulation ingredients and an esketamine hydrochloride concentration of 161.4 mg/mL, equivalent to 140 mg/mL of esketamine free base. (Tr. 287:22–288:3 (Farber), 623:25–624:12, 764:18–765:9 (Papakostas)).

While these examples do not themselves provide clinical proof that the claimed IN regimens would be safe and effective, they nevertheless address an important part of Sandoz's challenge. The examples show that the inventors possessed specific IN esketamine formulations through which the expressly described dosing regimens could be administered. Thus, the specification does not merely propose converting an IV treatment into an unidentified IN product at some later date. It discloses both the claimed IN regimens and concrete formulations for practicing them.

When the specification's disclosures are considered together, it identifies the claimed IN

doses and schedules, reports clinical results supporting the use of esketamine and the claimed dosing patterns, and provides specific IN formulations capable of administering the treatment. These mutually reinforcing disclosures distinguish the Caers Patents from a specification that merely announces a desired therapeutic result without identifying how to achieve it.

iv. The Remaining Claim Limitations Are Adequately Described

The specification also provides adequate support for the claims directed to adjunctive treatment and MDD-SI. It expressly describes administering esketamine in conjunction with another antidepressant. (JTX-1 at 14:3–7). It also recognizes the relationship between depression and suicidal ideation and describes the disclosed esketamine regimens as methods for treating the relevant depressive conditions. (*Id.* at 2:50–51; Tr. 765:10–766:23 (Papakostas)). Sandoz has not shown that separate clinical data were required for each of these expressly disclosed applications.

The specification's presentation of treatment methods and study results by genotype does not undermine written description. Although the asserted claims do not require genotyping, their use of the open-ended term "comprising" permits additional steps. Therefore, a method in which the patient is first genotyped and then receives the claimed dosing regimen remains within the scope of the claims. Moreover, the reported results showed a treatment response regardless of genotype. (JTX-1 at 5:22–7:27; Tr. 749:8–751:11 (Papakostas)). Thus, the disclosed regimens were not limited to a particular genetic subgroup but instead supported their use across the broader patient population encompassed by the claims. As such, the genotyping framework does not negate the specification's description of the claimed treatment methods.

Finally, the Court need not decide whether the term "treating" imports a particular efficacy requirement. Even assuming that the asserted claims require an effective treatment, Sandoz has not carried its burden. The specification expressly presents the claimed regimens as methods of

treating depression. It reports clinical results showing antidepressant activity from repeated esketamine and ketamine administration. It also discloses specific IN formulations for administering esketamine. Viewed together, those disclosures adequately convey possession of the claimed methods even under Sandoz's proposed understanding of "treating."

Accordingly, the Court finds that Sandoz has not proven by clear and convincing evidence that the asserted claims of the Caers Patents lack adequate written description.

5. The 260 Patent does not Lack Written Description

Sandoz's written description challenge to the 260 Patent presents a closer question than its challenge to the Caers Patents. Unlike the Caers specification, the 260 specification does not contain any clinical study data in which esketamine was administered to patients with depression. That omission is relevant because the Representative Claims expressly require the administration of a therapeutically effective amount that alleviates one or more symptoms of depression. (JTX-4 at 19:54–20:3; Tr. 188:21–189:9 (Farber)). As such, the specification must convey that the inventor possessed not only the claimed formulations and methods of administration, but also a method of using them to alleviate one or more symptoms of depression. Nevertheless, considering the specification as a whole and from the perspective of a POSA, the Court finds that Sandoz has not proven by clear and convincing evidence that the Representative Claims lack adequate written description.

i. The Specification and Working Examples Describe the Claimed Formulations and Administration Methods

The Representative Claims specify the composition's ingredients and concentrations, how the composition must be administered, and the therapeutic result it must achieve. Claim 22 requires an aqueous formulation containing S-ketamine hydrochloride at a concentration between

approximately 120 and 250 mg/mL, without a preservative, administered through two to eight consecutive IN sprays within approximately sixty minutes. Claim 36 requires a concentration of approximately 140 mg/mL, a pH of approximately 4.5, and specified excipients, including citric acid, EDTA, and sodium hydroxide.

The specification expressly describes these features. It identifies aqueous S-ketamine hydrochloride formulations at the claimed concentrations. (JTX-4 at 3:43–45, 4:59–5:3, 10:36–50). It describes administering the formulation through clusters of two to eight IN sprays within approximately sixty minutes. (*Id.* at 6:36–48, 11:23–38). It also identifies the pH and excipients recited in claim 36. (*Id.* at 5:51–59, 7:60–67, 10:13–20, 12:17–22). Dr. Little described these disclosures as providing both the formulation “recipe” and the “instructions for the recipe.” (Tr. 503:14–504:23, 506:21–509:3 (Little)). While these express disclosures are not necessarily sufficient by themselves, their specificity provides substantial evidence that the inventors had selected the claimed formulations and administration parameters.

Simply stated, these disclosures are more than a statement that an effective IN esketamine formulation could be developed. They identify what the formulation contains, its concentration, how its pH may be adjusted, which excipients may be used, how many sprays may be administered, and the period within which administration occurs. A POSA would not need to derive the claimed composition and method from unrelated disclosures or select the claimed parameters from an undifferentiated collection of possibilities. The specification itself identifies the claimed combinations. Nevertheless, Sandoz contends that these express disclosures do not demonstrate possession because the working examples do not test the claimed combinations in full.

Dr. Donovan focused her written description analysis principally on whether any one of Examples 1 through 5 contained every limitation of the Representative Claims. (Tr. 378:24–385:1

(Donovan)). She identified limitations absent from individual examples, including certain concentrations and excipients, administration by nasal spray, and therapeutic efficacy in humans. Those observations are factually relevant, but they do not resolve the written description inquiry. The specification need not include a single working example that reproduces every claim limitation, and the absence of a limitation from an individual example does not negate an express disclosure elsewhere in the specification. Rather, the general disclosures and working examples must be considered together for what they collectively convey to a POSA. *Inphi Corp. v. Netlist, Inc.*, 805 F.3d 1350, 1354 (Fed. Cir. 2015) (finding that a specification “satisfies the written description requirement when “the essence of the original disclosure” conveys the necessary information—“regardless of *how* it” conveys such information.”).

Viewed in that manner, Examples 1 and 2 provide experimental support for the preservative related properties of the disclosed formulations. They report microbial challenge testing of aqueous S-ketamine hydrochloride formulations at concentrations of approximately 140 mg/mL or less and at varying pH levels. (JTX-4 at 12:10–29, 13:1–33; Tr. 379:11–380:5 (Donovan)). Dr. Little explained that the results demonstrated an antimicrobial effect attributable to the concentration of esketamine itself. (Tr. 515:21–516:20 (Little)). The examples support the preservative free feature of claim 22 and show that the inventors had made and tested formulations possessing that characteristic. Although the tested formulations did not contain every excipient required by claim 36, they tested the approximately 140 mg/mL concentration recited in that claim. Dr. Donovan did not testify that adding the expressly disclosed excipients would eliminate the observed antimicrobial property or otherwise render the claimed formulation inoperative.

Examples 3 through 5 provide complementary support for nasal delivery and systemic absorption. In those examples, S-ketamine hydrochloride formulations at approximately 150

mg/mL were introduced into the nostrils of rats and dogs, and the resulting plasma concentrations showed that esketamine entered systemic circulation. (JTX-4 at 16:40–18:51; Tr. 382:8–19, 383:5–21 (Donovan); Tr. 517:9–12 (Little)). Although the formulations were administered with a pipette rather than a nasal spray device, Dr. Little explained that a pipette was an appropriate means of conducting nasal delivery testing in small animals. (Tr. 515:21–517:8 (Little)). The studies do not establish the plasma concentration that a human would achieve through the claimed number of sprays or demonstrate therapeutic efficacy, but they confirm that formulations near the claimed concentrations can be administered nasally and deliver esketamine into the bloodstream.

Accordingly, the general disclosures and working examples make distinct but complementary contributions to the written description. The general disclosures identify the claimed formulations and administration parameters. Examples 1 and 2 experimentally support the formulations' preservative-related properties. Examples 3 through 5 support nasal delivery and systemic absorption.

On cross examination, Dr. Donovan acknowledged that her analysis did not address the broader disclosures that Dr. Little identified as describing the claimed compositions and methods. (Tr. 425:12–427:25 (Donovan); Tr. 503:14–509:7 (Little)). Therefore, while her example by example comparison establishes that no single example practices the complete claimed method, it does not demonstrate that the specification, considered as a whole, fails to convey possession. Her analysis accordingly does not satisfy Sandoz's burden to prove inadequate written description by clear and convincing evidence.

ii. The Specification Adequately Describes the Claimed Concentrations

Sandoz separately argues that the working examples do not support the full concentration range of approximately 120 to 250 mg/mL recited in claim 22. Its principal criticism is that the

working examples concern formulations at approximately 140 or 150 mg/mL, and do not test any concentration above 150 mg/mL. The Court agrees that the examples do not represent every portion of the claimed range. But the written description inquiry is not limited to the working examples, and a claim is not necessarily invalid merely because “it is broader than the specific examples disclosed.” *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1371 (Fed. Cir. 2009).

Here, the specification expressly identifies the claimed numerical range and describes aqueous S-ketamine hydrochloride formulations within that range, including possible excipients and methods of adjusting pH. (JTX-4 at 3:43–45, 4:59–5:3, 5:51–59, 7:60–67, 10:13–20, 10:36–50, 12:17–22). It further describes IN administration through two to eight sprays administered within approximately sixty minutes. (*Id.* at 6:36–48, 11:23–38). The working examples, in turn, test aqueous S-ketamine hydrochloride formulations at approximately 140 and 150 mg/mL, concentrations falling within the claimed range. Examples 3 through 5 further demonstrate IN administration of the approximately 150 mg/mL formulations. (*Id.* at 12:10–18:51). Thus, although the examples do not span the entire claimed range, they experimentally test formulations within that range that share the active ingredient, aqueous vehicle, and other features described for the claimed formulations.

Against this evidence, Sandoz advances two more specific challenges: one directed to each boundary of the claimed range. Sandoz’s upper-bound challenge concerns whether solubility problems distinguish concentrations above approximately 200 mg/mL from the disclosed and tested formulations. To that end, Sandoz points to Dr. Donovan’s testimony that solubility “may” create additional formulation complications at those higher concentrations. (Tr. 380:19–25 (Donovan)) While that testimony suggests that the upper portion of the range may not behave

identically to the tested concentrations, it does not establish that formulations within that portion could not be made or that a POSA would understand the inventors not to possess them.

Dr. Donovan characterized the issue as a possible complication, not an insurmountable barrier. Further, Dr. Little explained that solubility in a pharmaceutical formulation depends on factors such as pH and excipients and cannot be determined solely from solubility in pure water. (Tr. 514:2–515:3 (Little)). Accordingly, Sandoz established, at most, that additional formulation work might be required at the upper end of the range. It did not establish that formulations above approximately 200 mg/mL were inoperative or so materially different from the disclosed formulations that a POSA would not understand the inventors to possess them.

Sandoz's challenge to the lower boundary raises a different issue. Rather than questioning whether a formulation at approximately 120 mg/mL could be made, Sandoz questions whether such a formulation could deliver a therapeutically effective amount when administered according to the claimed parameters. Assuming a spray volume of 0.1 mL, two sprays of a 120 mg/mL formulation would deliver 24 mg of S-ketamine. (Tr. 564:23–565:1 (Little)). Dr. Little declined to opine that either 24 mg or 28 mg necessarily constituted a therapeutically effective dose. (Tr. 588:16–591:18 (Little)). But Sandoz's calculation addresses only one possible combination of concentration, spray volume, and spray number. The claims permit administration through two to eight sprays, and Sandoz did not show that a formulation at the lower boundary could not deliver a therapeutically effective amount through another permitted number of sprays.

Sandoz also relies on a later geriatric study in which a 28 mg dose failed to meet the study's primary efficacy endpoint. That study postdated the priority date and therefore could not have informed a POSA's understanding of what the specification conveyed when filed. Even if considered as later evidence bearing on the efficacy of the lower dose, the study does not establish

that no patient experienced alleviation of any depressive symptom. The study's failure to meet its primary endpoint does not establish that the 28 mg dose failed to alleviate any symptom of depression in any patient. As such, the study does not clearly and convincingly establish that, as of the priority date, a POSA would have understood the inventors not to possess a therapeutically effective method encompassing the lower boundary of the claimed range.

Although the specification does not experimentally test the entire claimed range, particularly concentrations above 150 mg/mL, the absence of such testing does not establish that a POSA would have understood the inventors not to possess the untested concentrations. The upper bound evidence does not show that the higher concentrations constitute materially different or inoperative formulations, and the lower bound evidence does not show that a formulation at approximately 120 mg/mL could not deliver a therapeutically effective amount under the claimed administration parameters.

Accordingly, Sandoz has not established by clear and convincing evidence that the untested portions of the range encompass formulations that the inventors did not possess.

iii. The Specification Supports the Claimed Therapeutic Result

Whether the specification adequately describes the claimed alleviation of depressive symptoms presents the closest question because the patent contains no human clinical study of the claimed formulations, and the working examples do not directly measure antidepressant efficacy. Therefore, the Court must determine whether the other disclosures, viewed in light of a POSA's knowledge, convey that the inventors possessed a method capable of alleviating one or more symptoms of depression.

First, the Court notes that the claimed result is limited. The Representative Claims do not require remission, a particular reduction on a clinical rating scale, efficacy in every patient, or a

durable response following repeated treatment. Rather, they require that “a therapeutically effective amount of the pharmaceutical composition [be] administered to alleviate one or more symptoms of depression.” (JTX-4 at 19:54-20:3). Simply stated, the claims require some relief from at least one symptom of depression, not complete or lasting relief from the condition.

Consistent with that limited result, Dr. Papakostas explained that the claimed methods may consist of a single treatment session. (Tr. 767:19–768:5 (Papakostas)). Therefore, evidence that esketamine could produce rapid, short term relief bears directly on whether the inventors possessed the claimed method, even if that evidence would not establish the safety or efficacy of esketamine as a long term treatment for depression.

The specification specifically discloses that ketamine had been shown to be efficacious in treating depression, particularly in patients who had not responded to existing antidepressants, and that it could produce a rapid antidepressant effect within hours. (JTX-4 at 1:29-34). It further states that S-ketamine’s greater potency could permit lower effective doses. (JTX-4 at 1:31–42). The trial evidence confirmed that a POSA knew ketamine could provide rapid, short term relief from depressive symptoms. Dr. Papakostas testified that patients receiving ketamine could “get better really quickly,” although their symptoms could return shortly thereafter. (Tr. 705:24–706:4 (Papakostas)). He distinguished that recognized rapid effect from the broader proposition that ketamine had already been established as an effective long term treatment for depression. (Tr. 796:19–798:9 (Papakostas)). That distinction is consistent with the limited therapeutic result recited in the claims.

Significantly, Dr. Farber acknowledged that, in forming his written description opinions for Sandoz, he disregarded the prior art and the knowledge a POSA would have had at the time:

Q. What I’m just asking is when you were forming your opinions on written description, did you disregard all past

information, all past literature and all art that was out there?

A. The art I was disregarding were the studies I indicated. So the ketamine IV studies, for example.

Q. So all prior art and all the knowledge that was in the literature, you disregarded that for purposes of forming your written description opinion; is that right?

A. Yes, ma'am.

(TR. 307:6-15 (Farber)). Thus, Dr. Farber evaluated the specification in isolation, rather than from the perspective of a POSA possessing the existing knowledge of the relevant art.

That methodology is inconsistent with the governing written description inquiry and materially diminishes the weight of Dr. Farber's opinion. Written description is evaluated from the perspective of a POSA, and a patentee may rely on information known in the art. *Ajinomoto Co. v. International Trade Commission*, 932 F.3d 1342, 1359 (Fed. Cir. 2019). Here, the specification expressly identifies the claimed formulations, administration methods, and therapeutic result. A POSA would have considered those disclosures against the existing ketamine studies, which provided clinical evidence that ketamine could rapidly alleviate depressive symptoms. That knowledge supplies clinical context for understanding the significance of what the specification expressly describes and helps bridge the evidentiary gap created by the absence of human testing of the claimed formulations. By excluding those studies and the knowledge they supplied, Dr. Farber failed to consider evidence central to what a POSA would have understood the specification to convey at the priority date.

Specifically, the specification links ketamine's known rapid antidepressant effect to the claimed IN S-ketamine formulations. It identifies S-ketamine as the active ingredient, describes it as ketamine's more potent enantiomer, and discloses concentrated S-ketamine formulations for IN administration. Examples 3 through 5 then show that administering formulations near the claimed

concentrations through the nasal route introduces S-ketamine into systemic circulation. (JTX-4 at 16:40–18:51; Tr. 517:9–12 (Little)). Based on those disclosures and ketamine’s known antidepressant effect, Dr. Papakostas testified that a POSA would understand that a treatment session using the disclosed formulations would alleviate one or more symptoms of depression for some period. (Tr. 768:6–769:19 (Papakostas)).

Nevertheless, Sandoz argues that the inventors’ own testimony demonstrates that they had not progressed beyond speculation because they later characterized the expected connection between the animal pharmacokinetic studies and treatment of human patients as a “hypothesis” or “hypothetical.” While that testimony confirms that human efficacy remained untested, the absence of clinical confirmation does not itself establish a lack of possession. Written description turns on what the specification objectively conveyed to a POSA at filing, considered in light of the existing art and the knowledge in the field. It does not invariably require human clinical evidence or an actual reduction to practice.

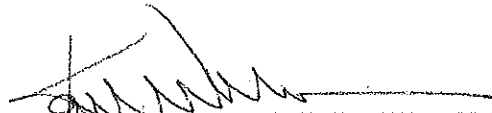
While the 260 specification does not contain human efficacy data nor does it contain a single example practicing the complete claimed methods, it expressly describes the claimed formulations and administration parameters, provides experimental support for their preservative related properties and nasal absorption, and invokes the known rapid antidepressant effect of ketamine. Considered together and from the perspective of a POSA, those disclosures adequately convey possession of the claimed methods, including their use to alleviate one or more symptoms of depression.

Therefore, Sandoz has not proven by clear and convincing evidence that any Representative Claim of the 260 Patent is invalid for lack of written description.

VI. CONCLUSION

For the reasons set forth above, the Court concludes that that Patents-in-Suit are not invalid as obvious, nor are the Patents-in-Suit invalid for lack of written description. An order reflecting the same accompanies this Opinion.

Dated: August 28, 2026



KAREN M. WILLIAMS
United States District Judge