IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UCB, INC., UCB BIOPHARMA SRL, HANANJA EHF and UNIVERSITY OF ICELAND,	)	
Plaintiffs,	)	C.A. No. 21-1229-JLH
v.	)	
CIPLA LIMITED and CIPLA USA INC.,	)	~~**FILED UNDER SEAL**~~
Defendants.	)	

MEMORANDUM OPINION

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Wilmington, Delaware
May 15, 2026

JENNIFER L. HALL, U.S. DISTRICT JUDGE

This is the Court's findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52(a). This patent infringement case arises out of the filing of an Abbreviated New Drug Application ("ANDA") by Defendants Cipla Limited and Cipla USA Inc. (collectively, "Cipla") with the FDA for approval to market a generic version of NAYZILAM®, a drug made and sold by UCB Inc. and UCB Biopharma SRL.

Plaintiffs UCB Inc., UCB Biopharma SRL, Hananja EHF, and University of Iceland (collectively, "UCB") allege that Cipla's ANDA submission constitutes infringement of claim 13 of U.S. Patent No. 8,217,033 and claim 10 of U.S. Patent No. 8,809,322. Cipla stipulated to infringement of those claims, but it contends that the claims are invalid as anticipated and obvious.

The Court held a four-day bench trial in October 2023.[1] The Court has reviewed the evidence presented at trial, as well as the parties' post-trial submissions and arguments at the post-trial hearing. The Court concludes that Cipla has failed to prove that the asserted claims are invalid.

I. LEGAL STANDARDS

A. Anticipation

A prior art reference anticipates a patent's claim, and is thus invalid under pre-AIA[2] 35 U.S.C. § 102, if it "discloses each and every element of the claimed invention arranged or combined in the same way as in the claim." *Monsanto Tech. LLC v. E.I. DuPont de Nemours & Co.*, 878 F.3d 1336, 1342–43 (Fed. Cir. 2018) (quoting *Blue Calypso, LLC v. Groupon, Inc.*, 815

[1] The FDA granted Nayzilam orphan drug exclusivity under 21 C.F.R. § 316.31, which prevented Cipla from entering the market until May 17, 2026.

[2] The Patent Act was amended in 2011 by the America Invents Act ("AIA"). Patent applications filed before 2013 are subject to the pre-AIA versions of 35 U.S.C. §§ 102 and 103.

F.3d 1331, 1341 (Fed. Cir. 2016)). To prove anticipation, the challenger must show that "every element and limitation of the claim was previously described in a single prior art reference, either expressly or inherently, so as to place a person of ordinary skill in possession of the invention." *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1082 (Fed. Cir. 2008). Anticipation is a question of fact. *Id.* Anticipation must be proven by clear and convincing evidence. *Whitserve, L.L.C. v. Comput. Packages, Inc.*, 694 F.3d 10, 21 (Fed. Cir. 2012).

B. Obviousness

Pre-AIA 35 U.S.C. § 103 provides that a patent "may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." Obviousness is a question of law based on underlying factual findings, including "the scope and content of the prior art," "differences between the prior art and the claims at issue," "the level of ordinary skill in the pertinent art," and "secondary considerations [such] as commercial success, long felt but unsolved needs, failure of others, etc." *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *see also KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 406 (2007).

Obviousness must be proven by clear and convincing evidence. *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 993–94 (Fed. Cir. 2009). "Generally, a party seeking to invalidate a patent as obvious must 'demonstrate by clear and convincing evidence that a skilled artisan would have had reason to combine the teaching[s] of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so.'" *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1068–69 (Fed. Cir. 2012) (quoting *Procter & Gamble*, 566 F.3d at 994).

II. FINDINGS OF FACT[3]

A. Epilepsy and Acute Repetitive Seizures

1. Epilepsy is a chronic neurological disorder characterized by chronic seizures. (D.I. 139, Ex. 1 (Statement of Uncontested Facts) ¶¶ 10–11.)[4] It is a neurological condition where a large number of a person's neurons misfire, resulting in recurrent seizures as well as altered behavior and perception. (Tr. (Klein) 414.)[5]

2. Patients with epilepsy experience seizures of varying length and degree. (*Id.*; Tr. (Privitera) 781; DTX-2362 at 85298.)

3. Following a seizure, many patients experience a postictal state, during which they may be unresponsive, uncooperative, or asleep. (Tr. (Klein) 430–31; Tr. (Privitera) 781–82.) The length of the postictal state can vary from minutes to hours. (Tr. (Klein) 430.)

4. Epilepsy is typically diagnosed after experiencing either two or more unprovoked seizures, or one unprovoked seizure with a high risk of additional seizures. (D.I. 139, Ex. 1 ¶ 11.)

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[3] The following are the Court's findings of fact. The Court recites only the facts necessary for the Court's legal conclusions; this is not a comprehensive recitation of all evidence presented at trial. In determining the credibility of the witnesses, the Court has taken into account the rationality and internal consistency of the witnesses' testimony, the extent of detail and coherent nature of the testimony, the manner of testifying by the witnesses, and the degree to which the subject testimony is consistent or inconsistent with other evidence in the case. The Court has also drawn such reasonable inferences from the credible direct and circumstantial evidence as is permitted by reason and common sense.

The Court's decision to cite and credit certain witnesses' testimony but not others does not mean that the Court ignored or failed to consider all of the testimony. The Court has considered all of the evidence in the trial record in making its findings.

Unless otherwise specified, the Court's findings reflect the state of the art as of the priority date of the patents-in-suit.

[4] The Court's Pretrial Order provides that the parties' joint statement of uncontested facts "will become part of the evidentiary record in this case" and "require no proof at trial." (D.I. 140 ¶ 28.)

[5] The trial transcript is cited as "Tr."

5. Patients with epilepsy may be prescribed an anti-seizure medication ("ASM"), which is used to prevent chronic seizure recurrence. (*Id.* ¶ 12.)

6. Despite the availability of ASMs, some patients with epilepsy still experience uncontrolled or poorly controlled seizures. (*Id.* ¶ 13.) Around one-third of epilepsy patients have epilepsy that is not adequately controlled by currently available antiseizure medications. (Tr. (Klein) 414–15.)

7. Some patients with epilepsy also experience seizures that occur in clusters, meaning that they experience multiple seizures over a short period of time. (D.I. 139, Ex. 1 ¶ 13.)

8. The phenomenon of multiple seizures over a short period of time is known as "acute repetitive seizures" ("ARS"). (*Id.* ¶ 14.)

9. Although there is no agreed-upon clinical definition for ARS, defining features of ARS include (1) the occurrence of multiple seizures within a defined period (2) despite optimal/maximal therapy with ASMs, (3) a seizure pattern distinguishable from a patient's normal pattern with respect to type, duration, frequency, and/or severity, (4) onset clearly distinguishable (by patient, caregiver, or healthcare professional) from the patient's typical seizures, and (5) recovery between seizures. (*Id.* ¶ 15.)

10. ARS is most commonly defined as two or more seizures in close succession over a short period of time, typically 24–48 hours. (*Id.* ¶ 16.)

11. For most ARS patients, the timing of seizures within a cluster is often unpredictable. (Tr. (Klein) 498–499, 501.)

12. For a patient experiencing ARS, 24% of subsequent seizures occur within two hours of the first, 37% occur within three hours of the first, and 65% occur within six hours of the first. (Tr. (Klein) 495–99; DTX-2375 at 85424.)

13. ARS patients and their caregivers report that ARS has a significant negative effect on their quality of life. (Tr. (Klein) 419; DTX-2514 at 95392.)

14. ARS patients report feeling exhausted, confused, slow-thinking, stressed, depressed, helpless, and scared as a result of their condition. (Tr. (Klein) 419; DTX-2514 at 95392.)

15. ARS negatively affects patients' economic circumstances, due to both the expense of hospitalization for seizure clusters and greater difficulty in maintaining employment. (Tr. (Klein) 419–20; Tr. (Privitera) 839–40; DTX-2514 at 95392–93.)

16. Patients with ARS have an increased risk of injury, hospitalization, and death and a decreased likelihood of entering seizure remission compared to other epilepsy patients. (Tr. (Klein) 418, 420–21; Tr. (Privitera) 838–39; DTX-2514 at 95392.)

17. Relative to other epilepsy patients, ARS patients have an increased risk of entering status epilepticus, a condition that is characterized by five minutes of other uninterrupted seizure activity or recurrent seizure activity without interim recovery of consciousness and which carries a significant mortality and morbidity risk. (Tr. (Klein) 418, 420–21; Tr. (Privitera) 776–77, 838–39; DTX-2514 at 95392.)

18. Given the risks associated with ARS, ARS should be treated promptly and efficiently to prevent future seizures. (Tr. (Klein) 421–22, 428–29, 432–34; PTX-1197.001.)

B. ARS Treatments, Compounds, and Drugs

19. Since the 1980s, researchers have investigated a variety of at-home rescue treatments for ARS, including treatments administered via oral, rectal, nasal, and buccal routes. (Tr. (Klein) 428–29, 431–32, 435, 439–41, 512–12; Tr. (Privitera) 784–85, 837–38; PTX-1194.0001; PTX-1197.0001; PTX-1359.0001–02; PTX-1366.0003; DTX-2549 at 671796.)

20. Although patients can be treated with IV-administered medication, this can only be done in a hospital setting or by other medically-trained personnel, such as EMTs. (Tr. (Klein) 421–22, 427, 428–29; PTX-1148.0001; PTX-1197.0001.)

1. Benzodiazepines

21. Benzodiazepines are a class of compounds that have long been targeted for treating acute seizure emergencies. (D.I. 139, Ex. 1 ¶ 17.)

22. Benzodiazepines increase the activity of GABA (gamma-aminobutyric acid) receptors in neurons. This increase in GABA activity reduces the neuron's excitability, thereby stopping and preventing seizure activity. (*Id.* ¶ 18.)

23. Benzodiazepines used for treating acute seizure emergencies include lorazepam, diazepam, clonazepam, and midazolam. (*Id.* ¶ 20.) Midazolam, diazepam, and lorazepam were available in injectable formulations before January 19, 2007. (*Id.* ¶ 19.)

24. Prior to 1997, the only FDA-approved formulations comprising lorazepam, diazepam, midazolam, or clonazepam were approved for oral administration or administration by injection. (*Id.* ¶ 21.)

25. In 1997, the FDA approved DIASTAT® ("Diastat"), which is indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (*i.e.*, seizure clusters, ARS) that are distinct from a patient's usual seizure pattern. (*Id.* ¶ 22.)

26. Diastat is a diazepam formulation for rectal administration. (*Id.* ¶ 24.)

27. Diastat was the first FDA-approved treatment indicated for ARS that could be administered by non-medical personnel. (*Id.* ¶ 23.)

28. Despite decades of effort, prior to 2007 there were no intranasal benzodiazepine formulations that were FDA-approved to treat ARS patients in the United States. (Tr. (Klein) 422,

425–26, 456–71; Tr. (Privitera) 834; PTX-1020; PTX-1026; PTX-1058 at "Results" Row 141; PTX-1062; PTX-1264; PTX-1362.0003; PTX-1370; DTX-2252.)

29. Prior to 2007, some physicians prescribed intravenous midazolam solution administered intranasally to treat ARS. (D.I. 139, Ex 1 ¶ 25.)

2. NAYZILAM®

30. UCB Inc. is the holder of New Drug Application No. 211321 for NAYZILAM® ("Nayzilam"), which was approved by the FDA on May 17, 2019. (*Id.* ¶¶ 26, 27.)

31. Nayzilam is indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (*i.e.*, seizure clusters, ARS) that are distinct from a patient's usual seizure pattern in patients with epilepsy 12 years of age and older. (*Id.* ¶ 28.)

32. The active pharmaceutical ingredient in Nayzilam is midazolam. (*Id.* ¶ 29.)

33. Nayzilam is available in a single-dose nasal spray unit containing 5 mg midazolam in a 100 µL (0.1 mL) solution. (*Id.* ¶ 30.)

34. The Nayzilam single-dose spray device can be administered by a patient during an early phase of a seizure or by caretakers during a seizure. (Tr. (Klein) 423–25; JTX-3005.0004, .0030–31.)

35. The composition of Nayzilam is 5 mg midazolam, 53.17 mg methoxypolyethylene glycol 350, 18.45 polyethylene glycol 400, 6.51 mg propylene glycol, 7.60 mg ethanol, and 17.78 mg purified water. (D.I. 139, Ex. 1 ¶ 31.)

36. The Nayzilam prescribing information states that an initial dose of one spray (5 mg) should be administered into one nostril and a second dose of one additional spray (5 mg) into the opposite nostril may be administered after 10 minutes if the patient has not responded to the initial dose. (*Id.* ¶ 32.)

37. The Nayzilam prescribing information states that Nayzilam has a pH range of approximately 5 to 9. (*Id.* ¶ 33.)

38. Nayzilam was the first FDA-approved intranasal medication for the treatment of ARS. (Tr. (Klein) 422.)

39. The FDA granted Nayzilam orphan drug exclusivity under 21 C.F.R. § 316.31, which expires on May 17, 2026. (D.I. 139, Ex. 1 ¶ 34.)

3. VALTOCO®

40. VALTOCO® ("Valtoco") is indicated for the treatment of intermittent, stereotypic episodes of frequent seizure activity (*i.e.*, seizure clusters, ARS) that are distinct from a patient's usual seizure pattern in patients with epilepsy 6 years of age and older. (*Id.* ¶ 35.)

41. Valtoco is a diazepam formulation for intranasal administration, approved by the FDA in January 2020. (*Id.* ¶ 36.)

42. Valtoco is comprised of diazepam, benzyl alcohol, dehydrated alcohol, n-dodecyl beta-D-maltoside, and vitamin E. (*Id.* ¶ 37.)

C. Patents-in-Suit and Asserted Claims

43. The patents-in-suit are U.S. Patent No. 8,217,033 (JTX-3004) (the "'033 patent") and U.S. Patent No. 8,809,322 (JTX-3003) (the "'322 patent"). (*Id.* ¶ 38.)

44. The patents-in-suit list Sveinbjorn Gizurarson as the inventor. (*Id.* ¶ 39.)

45. The priority date for the patents-in-suit is January 19, 2007. (*Id.* ¶ 40.)

46. Plaintiff UCB Biopharma SRL is the exclusive licensee of the patents-in-suit and currently licenses all substantial rights to the patents-in-suit. (*Id.* ¶¶ 41–42.) Plaintiffs Hananja and UI are assignees and co-owners of the patents-in-suit. (*Id.* ¶ 43.)

47. The patents-in-suit are listed in connection with Nayzilam in the Orange Book. (*Id.* ¶ 44.) The Orange Book lists the expiration date of the patents-in-suit as January 18, 2028. (*Id.* ¶ 45.)

48. Nayzilam is an embodiment of each of the asserted claims. (*Id.* ¶ 47.)

49. The specifications of the '033 patent and the '322 patent are substantively identical. (*Id.* ¶ 46.)

50. The shared specification of the patents-in-suit discloses drug formulations used for nasal administration, which contain methoxypolyethylene glycol (aka "mPEG," an alkoxypolyethylene glycol) with different concentrations of therapeutic agents, including midazolam. ('322 patent at 19:4–20:5; '033 patent at 19:4–20:5; Tr. (Smyth) 615–616.)

51. As of the priority date, mPEG had never been used in an intranasal formulation. The patents-in-suit are the first public disclosure of the use of mPEG in an intranasal formulation. The patents-in-suit are the first public disclosure of the use of mPEG in an intranasal formulation containing midazolam. (*Id.* (all citations).)

52. The shared specification provides examples of liquid intranasal formulations containing mPEG and midazolam within the scope of the asserted claims. ('322 patent at 19:4–20:5; '033 patent at 19:4–20:5.)

53. The shared specification informs the POSA that intranasal formulations containing mPEG are effective at solubilizing midazolam at high levels, with a favorable effect on sprayability relative to other solvents such as PEG. ('322 patent at 3:29–45, 7:12–21; '033 patent at 3:29–45, 7:12–21.)

54. The shared specification explains that the patents-in-suit represent an advance over the prior art because the invention is rapidly absorbed, can be administered by non-medical

personnel, can be delivered via a commercially available nasal spraying device, and avoids unwanted side-effects. ('322 patent at 1:23–46, 16:11–20; '033 patent at 1:23–46, 16:11–20.) The specification explains:

> The invention is based, in part, upon the discovery that the inclusion of one or more alkoxy-polyethylene glycols in a formulation provides certain advantages when the resulting composition is to be applied, for example, to a mucosal surface. For example, it has been discovered that when alkoxy-polyethylene glycol is used in such formulations, the therapeutic agent can be still be solubilized (which is especially useful for poorly soluble therapeutic agents) but the resulting formulations are less viscous and cause less irritation to mucosal membranes because the amount of other potentially viscous and irritable excipients, for example, polyethylene glycol or propylene glucol, can be reduced or eliminated altogether. As a result, the lower viscosity formulations, when converted into droplets, for example, by a nasal sprayer during intranasal delivery, can produce a spray pattern optimized for delivering the therapeutic agent to the mucosal membrane. In addition, formulations containing alkoxy-polyethylene glycols create less irritation (burning sensation) when applied to a mucosal surface, for example, a nasal membrane following nasal administration. In addition, when administered intranasally, the compositions of the invention minimize undesirable after taste (for example, a petroleum-like after taste) that can be associated with certain other excipients.

('322 patent at 3:29–51; '033 patent at 3:29–51.)

1. The '033 Patent

55. The '033 patent is entitled "Methods and Compositions for the Delivery of a Therapeutic Agent." It issued on July 10, 2012, from U.S. Patent Application No. 12/469,448, filed on May 20, 2009, and is a continuation of U.S. Patent Application No. 12/016,724, filed on January 18, 2008. The '033 patent further claims priority to Icelandic Patent Application No. 8593/2007, filed on January 19, 2007. (D.I. 139, Ex. 1 ¶ 48.)

56. Plaintiffs assert Claim 13 of the '033 patent.

57. Claim 1 of the '033 patent recites the following:

> A liquid pharmaceutical composition formulated for intranasal administration, comprising: (i) midazolam or a pharmaceutically [acceptable] salt thereof; and (ii) a methoxy-polyethylene glycol selected from the group consisting of methoxy-polyethylene glycol 350 and methoxy-polyethylene glycol 550.

58. Claim 2 of the ’033 patent recites the following:

> The pharmaceutical composition of claim 1, further comprising propylene glycol.

59. Claim 3 of the ’033 patent recites the following:

> The pharmaceutical composition of claim 2, further comprising water.

60. Claim 5 of the ’033 patent recites the following:

> The pharmaceutical composition of claim 3, wherein the methoxy-polyethylene glycol is methoxy-polyethylene glycol 350.

61. Claim 7 of the ’033 patent recites the following:

> The pharmaceutical composition of claim 5, further comprising polyethylene glycol.

62. Claim 10 of the ’033 patent recites the following:

> The pharmaceutical composition of claim 7, wherein the polyethylene glycol is polyethylene glycol 400.

63. Claim 13 of the ’033 patent recites the following:

> The pharmaceutical composition of claim 10, wherein the midazolam is present in a concentration from 0.001% (w/v) to 20% (w/v).

2. The ’322 Patent

64. The ’322 patent is entitled “Methods and Compositions for the Delivery of a Therapeutic Agent.” It issued on August 19, 2014, from U.S. Patent Application No. 13/446,284, filed on April 13, 2012, and is a continuation of U.S. Patent Application No. 12/016,724, filed on

January 18, 2008. The '322 patent further claims benefit and priority to Icelandic Patent Application No. 8593/2007, filed on January 19, 2007. (D.I. 139, Ex. 1 ¶ 66.)

65. Plaintiffs assert Claim 10 of the '322 patent.

66. Claim 1 of the '322 patent recites the following:

> A liquid pharmaceutical composition formulated for intranasal administration comprising:
>
> (a) a therapeutically effective amount of a therapeutic agent selected from midazolam, a pharmaceutically acceptable salt thereof or combinations thereof; and
>
> (b) a methoxy-polyethylene glycol of Formula I
>
> $H_3C—O—(CH_2CH_2O)_n—H$
>
> wherein n is a number in the range of 2 to 12.

67. Claim 10 of the '322 patent recites the following:

> The pharmaceutical composition of claim 1 wherein the therapeutic agent is midazolam.

D. Cipla's ANDA and ANDA Product

68. Cipla submitted Abbreviated New Drug Application No. 216048 ("Cipla's ANDA") to the FDA under 21 U.S.C. § 355(j) seeking FDA approval to engage in the commercial manufacture, use, or sale of a generic version of Nayzilam for the treatment of intermittent, stereotypic episodes of frequent seizure activity (*i.e.*, seizure clusters, ARS) that are distinct from a patient's usual seizure pattern in patients with epilepsy 12 years of age and older. (D.I. 139, Ex. 1 ¶ 75.)

69. By letter dated July 17, 2021, Cipla notified Plaintiffs that Cipla submitted Cipla's ANDA to the FDA under 21 U.S.C. § 355(j). (*Id.* ¶ 76.)

70. Cipla's ANDA contains a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) for the patents-in-suit. (*Id.* ¶ 77.)

71. Cipla's ANDA was tentatively approved on November 1, 2022. (*Id.* ¶ 78.)

72. Cipla's ANDA Product is a formulation for nasal administration. (*Id.* ¶ 79.)

73. The composition of Cipla's ANDA Product is 5 mg midazolam, 53.17 mg methoxypolyethylene glycol 350, 18.45 polyethylene glycol 400, 6.51 mg propylene glycol, 7.60 mg ethanol, and q.s. to 0.1 mL water for injection. (*Id.* ¶ 80.)

74. The parties have stipulated that the offer for sale, sale, use, commercial manufacture, and/or importation into the United States of Cipla's ANDA Product would constitute an act of infringement of Claim 13 of the '033 patent and Claim 10 of the '322 patent under 35 U.S.C. §§ 271(e)(2)(A) and 271(a), except as to any such claim that is found invalid. (*Id.* ¶ 83.)

E. Intranasal Formulation Development Before the 2007 Priority Date[6]

75. The parties agree that, "[f]or purposes of this case," the patents-in-suit have a priority date of January 19, 2007. (D.I. 139, Ex. 1 ¶ 40.)

76. It was known before the 2007 priority date that intranasal drug delivery has several practical benefits, including that it is non-invasive and can be administered by people without medical training. (Tr. (Wermeling) 107–09; Tr. (Smyth) 576.)

77. Intranasal drug delivery can also result in more rapid drug absorption and enhanced bioavailability compared to orally administered drugs, because intranasal drug delivery avoids gastrointestinal and hepatic metabolism. (Tr. (Wermeling) 107–09; Tr. (Smyth) 576; Tr. (Privitera) 784–86.)

[6] Given Dr. Smyth's extensive experience in drug formulation, including development of intranasal formulations specifically, the internal consistency of his testimony, the consistency of his testimony with other evidence in the record, and his demeanor testifying at trial, the Court finds Dr. Smyth's testimony particularly credible. To the extent that Dr. Smyth's testimony conflicts with the testimony of other testifying experts, the Court credits Dr. Smyth's testimony.

78. It was known before the 2007 priority date that, in developing formulations intended for intranasal administration, a formulator must consider several formulation properties, including, but not limited to, solubility, stability, pH, drug absorption, viscosity, sprayability, safety, and tolerability. (Tr. (Wermeling) 113–16; Tr. (Smyth) 576–77; Tr. (Gizurarson) 340.)

79. Solubility refers to how an active ingredient dissolves in the vehicle used for intranasal formulation. (Tr. (Smyth) 577.)

80. The nasal cavity can only retain 100–200 μL of liquid. (Tr. (Wermeling) 84–85; Tr. (Smyth) 577–78.)

81. Given the nasal cavity's volume constraints, a formulation will need to solubilize a therapeutically effective amount of a drug in 100–200 μL of liquid. (Tr. (Wermeling) 113–14; Tr. (Smyth) 577–79.)

82. Formulators must also consider the stability of an intranasal formulation, including physical stability, chemical stability, and biological stability. (Tr. (Wermeling) 113–16; Tr. (Smyth) 578–79.)

83. Formulators can alter the pH of a formulation to change drug solubility. (Tr. (Smyth) 578–79.) The pH can also affect the stability of a formulation and its excipients. (Tr. (Smyth) 579.)

84. The pH of the nasal cavity is between 5.5 and 6.5. (Tr. (Wermeling) 114; Tr. (Smyth) 578.)

85. Formulators must also consider a formulation's sprayability and its ability to be absorbed by the nasal mucosa, both of which are affected by viscosity. (Tr. (Smyth) 579–84.)

86. Nasal absorption is affected by the mucociliary clearance mechanism, through which a layer of mucus in the nasal cavity traps foreign particles and nasal cilia convey the mucus

and particles down the throat, where they are swallowed. (Tr. (Wermeling) 109–110; Tr. (Smyth) 580.)

87. With normally functioning cilia, foreign particles are removed from the nasal cavity in a matter of 10–20 minutes. (Tr. (Wermeling) 109–110; Tr. (Smyth) 580–81.)

88. Low viscosity solutions may also drain out the back of the nasal passage and into the gastrointestinal system or may drip out the front of the nose, which affects the absorption of active ingredients through the nasal mucosa. (Tr. (Ghaderi) 312–13; Tr. (Smyth) 581–82.)

89. Increasing the viscosity of a formulation can slow down the clearance of a drug from the nasal cavity. (DTX-2208 at 37; DTX-2294 at 41817:9–14; Tr. (Smyth) 581, 639, 643–44.)

90. Sprayability refers to the ability of a formulation and device in combination to form a spray. (Tr. (Smyth) 582.)

91. Several factors influence sprayability, including viscosity, surface tension, the presence of certain excipients, and the type of spraying device used. (Tr. (Gizurarson) 341–44; Tr. (Smyth) 581, 583.)

92. In formulations comprising multiple excipients, the excipients can interact in complex ways and affect the formulation's sprayability. (Tr. (Smyth) 643.)

93. Because multiple factors can affect sprayability, lowering viscosity does not always improve sprayability. For example, although ethanol has a lower viscosity than water, it does not have better sprayability. (Tr. (Gizurarson) 366.)

94. When coming up with a formulation, a formulator would prefer a formulation that can be sprayed with a nasal spraying device that has previously been approved by the FDA. (Tr. (Wermeling) 179, 271.)

95. Formulators must also consider the safety and tolerability of an intranasal formulation in humans. (Tr. (Smyth) 584–85.)

96. A safety consideration unique to intranasal formulations is the effect of the formulation on the nasal cilia, because damage to the cilia impairs a patient's immune system. (Tr. (Wermeling) 144; Tr. (Smyth) 581, 584; DTX-2294 at 41810.)

97. Excipients listed for the intranasal route in the FDA's Inactive Ingredients Database ("IID") have been tested for safety and toxicity in intranasal formulations. (Tr. (Smyth) 586–87.)

98. Tolerability, including factors such as taste and feel of a nasal spray, is important for patient acceptability. (Tr. (Smyth) 584–85.) If formulations are intolerable, patients may not use the medication and physicians may not prescribe it. (Tr. (Smyth) 585.)

99. Prior to the 2007 priority date, it was known that a formulator must balance all these factors—solubility, stability, pH, absorption, viscosity, sprayability, safety, and tolerability—through selection of excipients and devices. (Tr. (Smyth) 585.)

100. Many different classes of excipients had been used in intranasal formulations before the 2007 priority date, including stabilizing agents, pH adjusting agents, permeation enhancers, solubilizers, viscosity enhancers, preservatives, flavoring agents/sweeteners, and antioxidants. (Tr. (Wermeling) 254–57; Tr. (Smyth) 585; DTX-2294 at 41818–19.)

F. Intranasal Midazolam Formulations as of 2007

101. Although there were many efforts to develop a concentrated intranasal midazolam formulation reported in the literature before the 2007 priority date, none of this literature or the attempted formulations used or suggested the inclusion of mPEG. (Tr. (Wermeling) 246–49; Tr. (Smyth) 720; PTX-1367.0003; DTX-2048 at 36301; DTX-2294 at 41809.)

102. In 1990, Dr. Gizurarson joined Dr. Bechgaard and others in filing a patent application that resulted in Bechgaard '608, which reported intranasal benzodiazepine

formulations (the "Bechgaard Formulations"). (DTX-2134 at Cover.) The Bechgaard Formulations contained PEG-200 and glycofurol, among other optional excipients. (Tr. (Wermeling) 238–241; Tr. (Gizurarson) 385–86; DTX-2134 at 3, 18.)

103. In 1991, Lui et al. published an intranasal midazolam formulation comprising midazolam hydrochloride salt (11.1 mg/mL), methocel (1.5% w/w) (a viscosity enhancing agent), and water. (Tr. (Wermeling) 246–47; DTX-2294 at 41809.)

104. In 2001, T. Loftsson and H. Gudmundsdottir published on cyclodextrin-based intranasal midazolam formulations. (Tr. (Wermeling) 247–48, 290–91; DTX-2251 at 39998; DTX-2294 at 41809, 41823–25.) One formulation comprised midazolam base (17 mg/ml), sulfobutylether-β-cyclodextrin sodium salt (14% w/w), hydroxypropyl methylcellulose (0.1% w/w), benzalkonium chloride (0.02 % w/w), EDTA (0.1% w/w), phosphoric acid (0.43% w/w), and water (the "Loftsson Formulation"). (Tr. (Wermeling) 247–48, 290–91; DTX-2294 at 41809.)

105. In 2002, P.D. Knoester and colleagues published on an intranasal midazolam formulation (the "Knoester Formulation"). (DTX-2048 at 36300; PTX-1367.0002.) The Knoester Formulation comprised the midazolam hydrochloride salt (3.090 g), propylene glycol (25.90 g), benzyl alcohol (1.046 g), and water (up to 100 mL). (Tr. (Wermeling) 248–49; Tr. (Smyth) 720; DTX-2048 at 36301; PTX-1367.0003.)

106. In 2004, Dr. Wermeling published on a non-aqueous formulation (the "Wermeling Formulation") comprising 25 mg midazolam base, 0.18 mL PEG-400, 0.1 mg butylated hydroxytoluene, 1 mg saccharin powder, and q.s. to 1 mL propylene glycol. (Tr. (Wermeling) 262–63; DTX-2208 at 61, 85.)

107. In 2005, Dr. Merkus published on intranasal midazolam formulations. (DTX-2294 ("Merkus '893") at Cover.) Dr. Merkus focused on aqueous formulations comprising a midazolam

salt, as well as other known intranasally administered excipients such as propylene glycol, water, and PEG. (Tr. (Wermeling) 140; Tr. (Smyth) 637–38; DTX-2294 at 41818–19.)

108. One of the exemplary formulations in Merkus '893 comprises midazolam hydrochloride (corresponding to 35–75 mg/mL midazolam), propylene glycol (5–50% v/v), glycerol (5–50% v/v), polyethylene glycol (5–50% v/v), povidone (1–20% w/v), and water (the "Merkus Formulation"). (Tr. (Wermeling) 154; DTX-2294 at 41819.)

109. Midazolam base has poor solubility in water. (Tr. (Wermeling) 252; Tr. (Smyth) 636–37; DTX-2251 at 39998.)

110. By using midazolam in its salt form at a low pH, Dr. Merkus was able to solubilize high concentrations of midazolam in water. (DTX-2294 at 41817–18; Tr. (Smyth) 649.)

G. Dr. Gizurarson's Invention Using mPEG to Formulate Intranasal Midazolam

111. Dr. Gizurarson first began formulating intranasal midazolam compositions to treat epileptic seizures in 1987 with the company Novo Nordisk. (Tr. (Gizurarson) 334–35, 388.) From 1991 to 2005, he continued his research for a company called Lyfjathroun. (Tr. (Gizurarson) 336.)

112. Dr. Gizurarson worked to overcome challenges in solubilizing sufficient quantities of midazolam. (Tr. (Gizurarson) 334–337, 339–40.) He explored many excipients over nearly two decades. (Tr. (Gizurarson) 334–337.) He focused on formulations comprising PEG, particularly PEG-200, and single-chain ethylene glycols like tetra ethylene glycol. (*Id.* at 335–37.)

113. Dr. Gizurarson conceived of the idea of using mPEG in a midazolam formulation around May 2006. (Tr. (Gizurarson) 337.)

114. Prior to 2006, Dr. Gizurarson was unaware of the existence of mPEG and had not worked with mPEG. (Tr. (Gizurarson) 335, 338.)

115. Dr. Gizurarson performed solubility studies using mPEG with different benzodiazepines, and also explored the sprayability and bioadhesion of formulations comprising mPEG. (Tr. (Gizurarson) 345–47, 355.)

116. Dr. Gizurarson filed the Icelandic patent application leading to the patents-in-suit on January 19, 2007. (DTX-2507 at 68587; D.I. 139, Ex. 1 ¶¶ 48, 66; Tr. (Gizurarson) 361.)

117. Dr. Gizurarson sought to develop a commercial product in collaboration with a pharmaceutical company. (Tr. (Gizurarson) 372–74, 388.) He delivered a confidential presentation to ITI advocating for his invention in November 2007. (Tr. (Gizurarson) 373–74; Lusty 326–27; DTX-2456.)

118. Dr. Gizurarson signed a licensing and collaboration agreement with ITI in September 2007. (DTX-2417 at 33960–78.)

H. Person of Ordinary Skill in the Art

119. The person of ordinary skill in the art ("POSA") would have had a doctorate in disciplines relating to pharmaceutical development such as pharmacy, pharmacology, pharmaceutics, chemistry, drug delivery, engineering, medicine, or a related discipline. (D.I. 139, Ex. 1 ¶ 84; Tr. (Smyth) 591; Tr. (Wermeling) 104–05.) The POSA would also have had at least two years of practical experience in the field of pharmaceutical formulation development. (*Id.* (all citations).) The POSA alternatively may have a lower degree with more years of experience. (*Id.* (all citations).)

I. Scope and Content of the Prior Art

1. Cipla's Anticipation and Obviousness References

120. Cipla asserts that the asserted claims are anticipated by a reference referred to by the parties as Wermeling '359. Cipla asserts that the asserted claims are obvious in view of Wermeling '359 and a reference referred to by the parties as Carbowax.

a. Wermeling ’359 (DTX 2208)

121. U.S. Patent Application Publication No. 2004/0176359 (“Wermeling ’359”), entitled “Intranasal Benzodiazepine Compositions,” published on September 9, 2004. (D.I. 139, Ex. 1 ¶ 86.) Wermeling ’359 is prior art to the patents-in-suit.

122. Wermeling ’359 discloses intranasal formulations comprising a benzodiazepine and a nasal carrier, including the Wermeling Formulation. (DTX-2208 at Cover.)

123. Although Wermeling ’359 states that the nasal carrier may comprise aqueous or non-aqueous diluents, it expresses a preference that non-aqueous diluents used in the nasal carrier be “polyhydroxy alcohols such as propylene glycol, polyethylene glycol, [and] glycerol.” (DTX-2208 at [0030]; Tr. (Wermeling) 264; Tr. (Smyth) 595.)

124. An alcohol is any compound that has a hydroxy group (-OH) bonded covalently to a saturated carbon. (Tr. (Wermeling) 265–66; Tr. (Smyth) 595.) A polyhydroxy alcohol is an alcohol with more than one hydroxy (-OH) group. (Tr. (Wermeling) 265–66; Tr. (Smyth) 595.)

125. Wermeling ’359 discloses one exemplary formulation: the Wermeling Formulation. (Tr. (Wermeling) 262; Tr. (Smyth) 636.) The Wermeling Formulation is comprised of roughly 80% w/w propylene glycol. (Tr. (Wermeling) 263; Tr. (Smyth) 637; DTX-2208 at 85.) It does not comprise water. (Tr. (Wermeling) 263–64; Tr. (Smyth) 636.)

126. Wermeling ’359 discusses the administration of the Wermeling Formulation to healthy volunteers. (DTX-2208 at [0071]–[0109].)

127. The Wermeling Formulation was “well tolerated” in healthy volunteers. (DTX-2208 at [0071], [0078], [0098]; Tr. (Wermeling) 91.)

128. Wermeling ’359 discloses other exemplary excipients for intranasal midazolam formulations, including aqueous diluents such as saline and dextrose, and glycerol, a non-aqueous diluent. (Tr. (Wermeling) 264–65; DTX-2208 at [0030].)

129. Wermeling ’359 does not mention mPEG by name or structure. (Tr. (Wermeling) 261 (admitting that “mPEG” appeared “nowhere” in Wermeling ’359); Tr. (Smyth) 594; DTX-2208.)

130. Wermeling ’359 does not discuss the use of PEG derivatives in an intranasal midazolam formulation. (Tr. (Smyth) 611–12, 616; DTX-2208.)

131. Wermeling ’359 does not disclose any exemplary formulations comprising midazolam and water. (Tr. (Smyth) 612; DTX-2208.)

132. Wermeling ’359 discloses embodiments comprising “one or more agents that increase viscosity.” (DTX-2208 at [0037]; Tr. (Smyth) 639.)

133. Wermeling ’359 discloses embodiments where “the intranasal delivery device may be modified, for example, by increasing the size of the discharge orifice . . . in order to accommodate higher viscosity compositions.” (DTX-2208 at [0047].)

134. According to Dr. Wermeling, the Wermeling Formulation required the use of a modified version of a commercially available spraying device. (Tr. (Wermeling) 86, 179, 184–85.) This was because when the solvent system of the Wermeling Formulation was placed in a nasal sprayer, it formed a “jet” like a “squirt gun” instead of the desirable “plume.” (Tr. (Wermeling) 86.) Dr. Wermeling testified that use of a modified spraying device is not optimal for various reasons, including that it would trigger additional review by the FDA. (Tr. (Wermeling) 179, 271.)

b. Carbowax (DTX-2022)

135. Dow Chemical Company, “CARBOWAX™ and CARBOWAX™ SENTRY™: Polyethylene Glycols and Methoxypolyethylene Glycols” (“Carbowax”) is a marketing brochure published by the Dow Chemical Company in March 2006. (D.I. 139, Ex. 1 ¶ 88; DTX-2022.) Carbowax is prior art to the patents-in-suit.

136. Defendants' expert, Dr. Wermeling, was not familiar with Carbowax before this litigation. (Tr. (Wermeling) 213.)

137. Dow (or its subsidiaries) has sold PEG and mPEG since 1940. (Tr. (Wermeling) 219; Tr. (Smyth) 617–18; DTX-2022 at 36038.)

138. Carbowax describes thirteen different grades of PEG and three different grades of mPEG. (DTX-2022 at 36038.) A "grade" of PEG or mPEG refers to the average molecular weight of the polymers in the mixture. (*Id.*)

139. Carbowax refers to the thirteen Carbowax PEG and three Carbowax mPEG products as comprising the Dow "family of CARBOWAX products." (*Id.*) Otherwise, Carbowax does not refer to PEG and mPEG as belonging to the same "family." (*Id.*; Tr. (Wermeling) 227; Tr. (Smyth) 601–602.)

140. Carbowax does not discuss the use of mPEG as a pharmaceutical excipient. (DTX-2022 at 36043–44; Tr. (Wermeling) 221–23; Tr. (Smyth) 599–600.)

141. The only pharmaceutical use for mPEG discussed in Carbowax is as a chemical intermediate. (DTX-2022 at 36044; Tr. (Wermeling) 223; Tr. (Smyth) 600.)

142. Carbowax discloses numerous non-pharmaceutical uses for mPEG, such as in adhesives, household products, printing and inks, and mandrel releases. (DTX-2022 at 36048–51; Tr. (Wermeling) 224–25; Tr. (Smyth) 600–01.)

143. Under the heading "Liquid medications"—which discusses liquid-oral dose medications, nose and ear drops, and spray-on medications—Carbowax refers only to "CARBOWAX SENTRY liquid PEGs," not mPEG. (DTX-2022 at 36044; Tr. (Wermeling) 222.)

144. Carbowax does not disclose any exemplary pharmaceutical formulations comprising PEG or mPEG. (DTX-2022.)

145. Carbowax does not disclose intranasal formulations comprising midazolam. (*Id.*) Nor does it disclose the solubility of midazolam, or any drug, in mPEG. (*Id.*; Tr. (Wermeling) 231.)

146. Carbowax discloses that the viscosities of PEG-200 and PEG-300 are lower than that of PEG-400. It discloses that the viscosity of PEG-200 is 4.3 cSt at 100°C and the viscosity of PEG 300 is 5.8 cSt at 100°C. (DTX-2022 at 36053.) Carbowax discloses that the viscosity of mPEG-350 is 3.9 cSt at 100°C. (DTX-2022 at 36053–54.)

147. Carbowax does not disclose any information regarding the safety of mPEG-350 for intranasal administration. (Tr. (Wermeling) 232, 287–88.) Nor does it indicate whether mPEG would be tolerable or non-irritating when administered intranasally. (DTX-2022; Tr. (Wermeling) 232; Tr. (Smyth) 625, 627.)

2. Other Prior Art Presented at Trial

a. Bechgaard '608 (DTX-2134)

148. Bechgaard '608 is a patent relating to intranasal formulations comprising glycofurol, which is different from mPEG. (DTX-2134 at 3; Tr. (Wermeling) 240; Tr. (Smyth) 624–25.)

149. Bechgaard '608 does not mention mPEG by name or structure. (DTX-2134; Tr. (Wermeling) 239–40; Tr. (Smyth) 624.)

150. The patent examiner considered Bechgaard '608 during prosecution of the patents-in-suit. (JTX-3003.0002; JTX-3004.0002; Tr. (Smyth) 587–88.)

151. Bechgaard '608 states that "[t]he n-glycofurols of the formula I are considered to be a pharmaceutically acceptable carrier, especially a pharmaceutically acceptable carrier for nasal administration." (DTX-2134 at 8.)

152. Bechgaard ’608 discloses multiple potential solubilizers for use in intranasal formulations, including ethanol, benzyl alcohol, acetic acid, nitric acid, nitrate, oxalic acid, and phosphoric acid. (DTX-2134 at Fig. 10; Tr. (Wermeling) 242–43.)

b. Knoester 2002 (PTX-1354) and Knoester 2002b (PTX-1367)

153. Knoester 2002 and Knoester 2002b are articles reporting on the Knoester Formulation. (PTX-1354; PTX-1367.)

154. Knoester 2002b reports that the Knoester Formulation was “reasonably well tolerated.” (PTX-1367.0006; Tr. (Wermeling) 143–44.)

155. Neither Knoester 2002 nor Knoester 2002b discloses formulations comprising PEG, or PEG-400 specifically. (PTX-1354; PTX-1367.)

156. Neither Knoester 2002 nor Knoester 2002b discloses formulations comprising mPEG, or mPEG-350 specifically. (*Id.* (both citations); Tr. (Wermeling) 248.)

157. The Knoester Formulation has been made by compounding pharmacies in the Netherlands but is not approved by any regulatory authority in the Netherlands or United States. (Tr. (Klein) 469.) The Knoester Formulation has never been available to patients in the United States. (*Id.*; Tr. (Privitera) 848.)

c. Merkus ’893 (DTX-2294)

158. International Publication No. WO 2005/067893 A2 (“Merkus ’893”) published on July 28, 2005. (D.I. 139, Ex. 1 ¶ 87.)

159. Merkus ’893 was a patent application for intranasal midazolam formulations. (DTX-2294 at Title, 41804–5.)

160. The patent examiner considered and cited Merkus ’893 during prosecution of the patents-in-suit. (JTX-3003.0003–.0004; Tr. (Smyth) 587–89.)

161. Merkus ’893 states that the “aqueous solubility of the midazolam base at neutral pH is too low to prepare suitable midazolam formulations and for this purpose midazolam salts (e.g., hydrochloride) have to be used.” (DTX-2294 at 41818.) Merkus ’893 guides the POSA to use midazolam salts rather than midazolam base. (Tr. (Smyth) 709; Tr. (Wermeling) 115.)

162. Merkus ’893 discloses intranasal midazolam formulations comprising a midazolam salt, propylene glycol, water, and PEG. (DTX-2294 at 41818–19; Tr. (Wermeling) 253–55.) It also discloses additional solubilizers, including glycerol and povidone. (*Id.* (both citations).)

163. Merkus ’893 explains that propylene glycol is an attractive solubilizer because it does not have a strong adverse effect on ciliary movement. (DTX-2294 at 41815.) Merkus ’893 suggests a preference for formulations comprising propylene glycol, including in concentrations up to 90% v/v. (*Id.* at 41814–15.)

164. Merkus ’893 states that its compositions may comprise “viscosity enhancing agents” which can “enhance the delivery of the midazolam.” (DTX-2294 at 41817; Tr. (Wermeling) 259–260.)

165. Merkus ’893 states that “suitable devices” for spray delivery of its formulations (comprising PEG and propylene glycol) were already commercially available and did not discuss any need for a modified device. (DTX-2294 at 41822; Tr. (Wermeling) 260; Tr. (Smyth) 644.)

166. Merkus ’893 does not disclose mPEG, by name or structure. (DTX-2294; Tr. (Wermeling) 288–89.)

167. Merkus ’893 states that “there are no adverse effects or disadvantages associated with a composition having a [low] pH.” (DTX-2294 at 41817.)

d. Wermeling 2006 (DTX-2251)

168. Wermeling 2006 describes a study that administered the Wermeling Formulation to twelve healthy volunteers. (DTX-2251 at 39993.)

169. Wermeling 2006 also discusses studies of the Knoester Formulation and the Loftsson Formulation. Wermeling 2006 suggests that any nasal irritation caused by these formulations resulted from midazolam. (Tr. (Wermeling) 92, 290–91; DTX-2251 at 39998.)

170. Wermeling 2006 does not suggest that propylene glycol causes nasal irritation. (Tr. (Wermeling) 92, 290–91; DTX-2251 at 39998.)

171. Wermeling 2006 does not discuss mPEG, by name or structure. (Tr. (Wermeling) 290; DTX-2251.)

e. Tracy '672 (DTX-2211)

172. United States Patent Application Publication US 2004/0247672 ("Tracy '672") published on December 9, 2004. (DTX-2211 at Cover.)

173. Tracy '672 is entitled, "Injectable Sustained Release Compositions." It generally discloses injectable, polymer-paste, sustained-release formulations. (DTX-2211 at Title, [0006], [0046]; Tr. (Wermeling) 233–34; Tr. (Smyth) 620–21.)

174. Multiple paragraphs in Tracy '672 contain laundry lists of possible excipients and embodiments. Although Tracy '672 purports to disclose an advance in the form of an injectable polymer paste, it also contains a paragraph with a laundry list of "almost all of the routes of administration that you would use to deliver medications." (Tr. (Smyth) 621–22.) It lists potential administration via "injection, implantation (*e.g.*, subcutaneously, intramuscularly, intraperitoneally, intracranially, and intradermally), administration to mucosal membranes (*e.g.*, intranasally, intravaginally, intrapulmonary, buccally or by means of a suppository), topically, or in situ delivery (*e.g.*, by enema or aerosol spray)." (DTX-2211 at [0088].) That is the only paragraph that mentions intranasal administration.

175. mPEG is mentioned in Tracy '672 as one of dozens of potential excipients—including polyethylene glycol polymers, surfactants, organic solvents, and aqueous solvents—

under the heading "Viscosity Reducing Agents." (DTX-2211 at [0050]–[0055]; Tr. (Wermeling) 234–36; Tr. (Smyth) 622–24.)

176. In one of the paragraphs under the heading "Viscosity Reducing Agents," Tracy '672 states as follows:

> Polyethylene glycol polymers (PEG) are liquid and solid polymers of the general formula $H(OCH_2CH_2)_nOH$, where n is greater than or equal to 4. In general, each PEG is followed by a number which corresponds to its average molecular weight. For example, PEG200 has an average value of n of 4 with a molecular weight range between 190 and 210, PEG400 has an average value of n between 8.2 and 9.1 with a molecular weight range between 380-420, PEG600 has an average value of n between 12.5 and 13.9 with a molecular weight range between 570 and 630. In a particular embodiment, the PEG is a liquid at room temperature. For example, the PEG can be PEG200, PEG400 or MPEG350 (monomethoxy PEG) which are all liquids at room temperature.

(DTX-2211 at [0052].)

177. Tracy '672 does not disclose any exemplary intranasal pharmaceutical formulations, nor does it disclose any exemplary formulations comprising mPEG. (DTX-2211.)

f. USP 2006 (DTX-2078)

178. The United States Pharmacopeia, published in 2006 ("USP 2006"), provides general information on pharmaceutical excipients, such as structures, properties, and test methods. (DTX-2078; Tr. (Smyth) 604.)

179. USP 2006 has different entries for Polyethylene Glycol and Polyethylene Glycol Monomethyl Ether (mPEG). USP 2006 repeatedly distinguishes the uses of PEG from those of mPEG. (DTX-2078 at 36778–86; Tr. (Smyth) 604–06.)

180. USP 2006 does not indicate whether mPEG was ever used in, or could be used in, intranasal formulations. (DTX-2078.)

g. Handbook of Pharmaceutical Excipients (PTX-1090)

181. The version Handbook of Pharmaceutical Excipients published in 2006 (the "Handbook") was widely used by formulators before the priority date. (PTX-1090.0001, .0004; Tr. (Wermeling) 237; Tr. (Smyth) 603.) The Handbook describes the physical properties and uses of pharmaceutical excipients. (PTX-1090.0017–22; Tr. (Smyth) 603.)

182. The Handbook contains a chapter on PEG, but does not reference mPEG at all. (PTX-1090.0017–22; Tr. (Wermeling) 237–38; Tr. (Smyth) 603.)

h. IID (DTX-2583)

183. The IID is published by the FDA and includes information on excipients that have been used in FDA-approved products, including the specific routes of administration for which they have been used. (DTX-2583; Tr. (Wermeling) 193.)

184. Before January 2007, mPEG (specifically mPEG-350) was listed only once in the IID—in connection with a topical gel product. (DTX-2583; Tr. (Wermeling) 193; Tr. (Smyth) 618–19.)

185. Before January 2007, mPEG was not listed in connection with any intranasal formulations. (DTX-2583; Tr. (Smyth) 619; Tr. (Mittal) 555–56.)

186. Before January 2007, there were over 100 entries for PEG in the IID, including for topical, oral, vaginal, transdermal, rectal, subcutaneous, ophthalmic, nasal, intravenous, intramuscular, inhalation, and dental administration. (DTX-2583.)

J. Wermeling '359 Does Not Disclose Each Element of the Asserted Claims

187. Cipla argues that the asserted claims are invalid under pre-AIA 35 U.S.C. § 102 because they are anticipated by Wermeling '359.[7] The Court finds that Wermeling '359 does not disclose each of the elements of either asserted claim. (Tr. (Smyth) 593–612.)

1. Wermeling '359 Does Not Disclose mPEG

188. Both of the asserted claims require methoxy polyethylene glycol, otherwise known as mPEG. ('033 patent at cl. 13; '322 patent at cl. 10.)

189. Wermeling '359 does not expressly disclose mPEG. (Tr. (Smyth) 594; DTX-2208.)

190. Wermeling '359 does not inherently disclose mPEG. (Tr. (Smyth) 594–612.) The POSA would not generally understand a reference to PEG to include mPEG. (Tr. (Smyth) 595, 607–12, 619.) The POSA would not understand the reference to PEG in Wermeling '359 to include or encompass mPEG. (Tr. (Smyth) 595, 607–12.)

191. PEG and mPEG are not the same thing. (Tr. (Wermeling) 210–11; Tr. (Smyth) 595–99.)

192. PEG and mPEG have different chemical structures. (Tr. (Wermeling) 210–11; Tr. (Smyth) 595–99; DTX-2022 at 36038.)

193. PEG is a polyhydroxy alcohol, with two terminal hydroxy groups. (Tr. (Smyth) 596.)

[7] Although Cipla's post-trial briefs argue that the claims are invalid for "anticipation" under pre-AIA 35 U.S.C. § 102, Cipla specified in the Pre-trial Order that it is alleging invalidity under 35 U.S.C. § 102(b). (D.I. 139, Ex. 3 ¶ 60.) Both sides agree that, to prove invalidity under § 102, Cipla must demonstrate that each and every limitation is present (either expressly or inherently) in a single reference.

194. mPEG is not a polyhydroxy alcohol. It has a hydroxy group on one end of the carbon backbone and a methoxy group on the other end. (Tr. (Smyth) 597; Tr. (Wermeling) 266; DTX-2022 at 36038.)

195. Although mPEG is sometimes referred to as a PEG derivative, mPEG is not derived from PEG; i.e., "PEG is a different synthesis method from mPEG." (Tr. (Smyth) 608–09.)

196. The Chemical Abstract Service assigns numbers ("CAS Registry Numbers") to chemicals, which are used by the industry to differentiate between chemical entities. (Tr. (Smyth) 598.) PEG and mPEG have different CAS Registry Numbers. (Tr. (Wermeling) 210–11; Tr. (Smyth) 598; PTX-1090.0017; DTX-2583.)

197. General pharmaceutical compendia used by formulators, such as the Handbook and USP 2006, distinguished between PEG and mPEG. (Tr. (Smyth) 603–06; Tr. (Wermeling) 237–38; DTX-2078 at 36778–86; PTX-1090.0017–22.) There is no suggestion in the compendia that a reference to PEG includes or encompasses mPEG. Carbowax does not evidence that the POSA would have understood PEG to include or encompass mPEG. (DTX-2022; Tr. (Smyth) 599–602.)

198. Cipla asserts that Tracy '672 is evidence that the POSA would understand that the term PEG, as used in the art (including in Wermeling '359), would include mPEG. The Court does not so find. The Court finds that any suggestion in Tracy '672 that "MPEG350" falls under the category of "PEG" does not reflect how the POSA would have generally understood the term "PEG" as of the priority date. (Tr. (Smyth) 620.) The Court finds other record evidence more persuasive than Tracy '672 as to how a POSA would understand what Wermeling '359 disclosed (expressly or inherently) when it referred to PEG. (Tr. (Smyth) 597–99, 602–07, 620–24; DTX-2078 at 36778–86; PTX-1090.0017–22; DTX-2583.)

2. Wermeling ’359 Does Not Disclose the Combination of Midazolam, mPEG-350, PEG-400, Propylene Glycol, and Water

199. Wermeling ’359 does not disclose the combination of mPEG-350, PEG-400, propylene glycol, and water, as recited in Claim 13 of the ’033 patent. (Tr. (Smyth) 594, 606–12.)

200. Even if PEG were understood to encompass mPEG and other PEG derivatives (and it does not), Wermeling ’359 still would not disclose the combination of excipients in Claim 13 of the ’033 patent. (Tr. (Smyth) 594, 606–12.)

201. Wermeling ’359’s general disclosure of “aqueous and/or non-aqueous diluents” would have encompassed hundreds of potential combinations of excipients. The POSA would not have immediately envisioned the combination of mPEG-350, PEG-400, propylene glycol, and water from this disclosure. (Tr. (Smyth) 610–12.)

202. Wermeling ’359 did not combine PEG, propylene glycol, and water in any formulation, let alone mPEG-350, PEG-400, propylene glycol and water. (Tr. (Wermeling) 205–06; Tr. (Smyth) 610–12; DTX-2208.)

K. The POSA Would Not Have Been Motivated, With a Reasonable Expectation of Success, to Arrive at the Claimed Invention

1. The POSA Would Not Have Been Motivated to Use mPEG in an Intranasal Midazolam Formulation with a Reasonable Expectation of Success.

203. The POSA would not have been motivated to use mPEG in an intranasal midazolam formulation because mPEG was not a known excipient for intranasal formulations, and it had not been used, marketed, or even suggested for use in an intranasal formulation. (Tr. (Smyth) 613, 615–25.) Nor would the POSA have known how mPEG would affect factors such as solubility of midazolam, permeability through the nasal mucosa, sprayability, or safety and tolerability for nasal administration. (*Id.*)

a. mPEG Had Never Been Used or Suggested for Any Intranasal Formulation

204. Although it had been commercially available from Dow since the 1940s, mPEG was not a known excipient for intranasal formulations prior to 2007. (Tr. (Wermeling) 211, 219, 297–98; Tr. (Smyth) 615–22, 650; DTX-2022 at 36038.)

205. Before 2007, mPEG had not been used in an intranasal formulation. (Tr. (Wermeling) 211, 297–98; Tr. (Smyth) 615–20.)

206. Before 2007, mPEG had not been marketed for use in an intranasal formulation. (Tr. (Wermeling) 211; Tr. (Smyth) 615–20; DTX-2022 at 36044.)

207. Before 2007, no reference suggested the use of mPEG in intranasal formulations. (Tr. (Smyth) 615–22.) Although Tracy '672 refers to the use of mPEG as one pharmaceutical excipient in a laundry list of excipients that might be used in a pharmaceutical composition as a viscosity reducing agent, a POSA would not understand Tracy '672 to disclose or suggest the use of mPEG for an intranasal formulation, especially since Tracy '672 generally relates to injectable sustained release injections. (Tr. (Smyth) 620–24; DTX-2211 at [0050]–[0056], [0088].)

208. Prior to this litigation, Cipla internally described mPEG as a "novel" and "special" excipient. (PTX-1229.0005; PTX-1220; Tr. (Mittal) 555–56; Tr. (Smyth) 680–82.)

b. The POSA Would Not Have Had a Reasonable Expectation that mPEG was Suitable for Use in an Intranasal Formulation

209. Before 2007, the POSA would not have known whether mPEG was tolerable for use in an intranasal formulation. (Tr. (Smyth) 625–27.)

210. Before 2007, the POSA would not have known whether mPEG was safe for use in an intranasal formulation. (Tr. (Smyth) 625–35; PTX-1069.0001; PTX-1073.0009–10; DTX-2586 at 144–46.)

211. Before 2007, no reference indicated how mPEG would affect the nasal cilia. (Tr. (Smyth) 628–29.)

212. Before 2007, no reference disclosed pharmacokinetic data for an intranasal formulation comprising mPEG-350. (Tr. (Wermeling) 213.)

c. The POSA Would Not Have Had a Reasonable Expectation that mPEG Was Suitable for Use in an Intranasal Midazolam Formulation

213. The POSA would have considered at least efficacy, safety, stability, and tolerability to be requirements for a successful intranasal midazolam formulation. (Tr. (Wermeling) 113–14; Tr. (Smyth) 576–79, 584–85, 625–26.)

214. To achieve efficacy, the POSA would have needed to understand the effect of the chosen excipients on factors such as the solubility of midazolam, viscosity, and sprayability of an intranasal midazolam formulation, and the permeability of the formulation through the nasal mucosa. (Tr. (Smyth) 576–84.)

215. Before 2007, the POSA would not have known how well mPEG could solubilize midazolam. (Tr. (Smyth) 625–26, 647.) The prior art did not disclose the solubility of midazolam in mPEG. (Tr. (Wermeling) 211, 231, 287; Tr. (Smyth) 625–26.)

216. Before 2007, the POSA would not have known how mPEG would affect the sprayability of an intranasal midazolam formulation. (Tr. (Smyth) 625–27.) Before 2007, no prior art reference provided data on the spray plume of formulations comprising mPEG-350. (Tr. (Wermeling) 213, 231–32.)

217. Before 2007, the POSA would not have known how mPEG would affect the permeability of midazolam through the nasal mucosa. (Tr. (Wermeling) 213; Tr. (Smyth) 625–26.)

218. Before 2007, the POSA would not have known how mPEG would affect the stability of an intranasal midazolam formulation. (Tr. (Smyth) 625–26, 645–46.)

d. The Sparse Use of mPEG in Topical Products Would Not Have Motivated the POSA to Use mPEG in an Intranasal Formulation With a Reasonable Expectation of Success

219. Before 2007, mPEG had been used in only one FDA-approved product, a topical gel. (Tr. (Wermeling) 193; Tr. (Smyth) 617–19; DTX-2583.)

220. The use of mPEG-350 in topical formulations did not inform whether mPEG was safe for use in intranasal formulations, at least because there are different safety requirements for topical formulations than intranasal formulations and the skin and nasal mucosa are different tissues. (Tr. (Smyth) 627–35; PTX-1069.0001; PTX-1073.0009–10; DTX-2586 at 144–46.)

221. There are additional unique formulation development considerations for intranasal formulations that are not considerations for topical formulations, including the limitations on the volume of the formulation, which requires highly concentrated formulations, and the effect of the mucociliary clearance mechanism, which can affect drug absorption. (Tr. (Smyth) 578–84, 627–29; Tr. (Wermeling) 113–14.)

222. The FDA determined that, for safety evaluation purposes, mPEG's prior use in topical products was "not relevant" to the use of mPEG in an intranasal formulation. (Tr. (Smyth) 631–33; DTX-2586 at 145–46.) Because the FDA determined that mPEG was a "novel excipient" for intranasal use, the FDA required two-week toxicity studies of mPEG in two species before intranasal formulations comprising mPEG could progress to clinical trials. (Tr. (Smyth) 631–35; DTX-2586 at 144–46; PTX-1073.0009.)

223. In June 2007, Dr. Fisher discussed safety concerns regarding mPEG with the inventor, Dr. Gizurarson, noting that there was no published toxicity data for intranasal use of mPEG. (Tr. (Smyth) 629–31; PTX-1069.) Dr. Fisher expressed particular concerns regarding the

"exposure of the nasal mucosa surface" to mPEG and potential toxicity from enzymatic conversion of mPEG to other compounds. (Tr. (Smyth) 629–31; PTX-1069.0001–02.)

e. Carbowax Would Not Have Led the POSA to Use mPEG in an Intranasal Formulation

224. Carbowax would not have suggested to the POSA to use mPEG in an intranasal formulation. (Tr. (Smyth) 599–602, 619–20; DTX-2022 at 36043–44, 36050–51.)

225. While use of PEG in an intranasal formulation was known in the art as of the priority date, Carbowax refers to PEG and mPEG as different compounds with different structures, properties, and uses. (Tr. (Wermeling) 219–25; Tr. (Smyth) 599–602, 619–20; DTX-2022 at 36038, 36041, 36043–44, 36050–51.)

226. Carbowax describes a wide variety of pharmaceutical uses for PEG, including in liquid medications such as nose and ear drops. (DTX-2022 at 36043–44; Tr. (Wermeling) 221–22; Tr. (Smyth) 599–600, 619–20.) The only pharmaceutical use for mPEG disclosed in Carbowax is as a chemical intermediate. (DTX-2022 at 36043–44; Tr. (Wermeling) 221–23; Tr. (Smyth) 599–600.)

2. The POSA Would Not Have Been Motivated, With a Reasonable Expectation of Success, to Use mPEG to Reduce the Viscosity of the Wermeling Formulation

227. Wermeling '359 did not suggest that the viscosity of the Wermeling Formulation (or any other formulation) was too high. (Tr. (Smyth) 639, 641; Tr. (Wermeling) 269; DTX-2208.) Indeed, its only discussion of agents that affect viscosity are viscosity increasing agents—such as methylcellulose and carboxymethylcellulose sodium—to promote nasal absorption. (DTX-2208 at [0037]; Tr. (Wermeling) 269; Tr. (Smyth) 639.)

228. Although Dr. Wermeling himself testified that the POSA would have been motivated to reduce the viscosity of the Wermeling Formulation (as disclosed in Wermeling '359)

so that it could be used with an unmodified spraying device, Wermeling '359 did not state that the use of a modified device was problematic. (Tr. (Smyth) 639, 641; DTX-2208.) Dr. Wermeling did not attempt to reformulate the Wermeling Formulation to be delivered through an unmodified device. (Tr. (Wermeling) 286–87.)

229. Even if the POSA were motivated to modify the Wermeling Formulation to lower its viscosity to allow the use of a standard commercial device, the POSA would not have been motivated to use mPEG to do so. (Tr. (Smyth) 637–46.)

230. The POSA would not have expected that adding mPEG to the Wermeling Formulation would result in a viscosity compatible with standard commercial devices. (Tr. (Smyth) 639–42.) If anything, the POSA would have expected that non-aqueous formulations comprising mPEG would still require device modification. (Tr. (Smyth) 639–42.)

231. mPEG-350's viscosity is similar to propylene glycol and lower viscosity PEGs, such as PEG-200, which fall within the "higher viscosity" formulations discussed in Wermeling '359. (Tr. (Smyth) 639–42, 647; DTX-2022 at 36052–53.) The POSA would therefore have expected that substituting mPEG into the Wermeling Formulation would not markedly lower viscosity. (Tr. (Smyth) 639–42.)

232. If the POSA were motivated to modify the viscosity of the Wermeling Formulation and were willing to consider excipients not used in intranasal formulations to do so, there would have been a large number of excipients in the pharmaceutical arts to consider. (Tr. (Smyth) 641–42, 650.)

3. The POSA Would Not Have Been Motivated, with a Reasonable Expectation of Success, to Use mPEG and Water to Improve the Tolerability of the Wermeling Formulation

233. The POSA would not have been motivated to improve the tolerability of the Wermeling Formulation. (Tr. (Smyth) 646–50.) No prior art suggested that the Wermeling

Formulation was intolerable. (DTX-2208 at [0071], [0078], [0098]; Tr. (Wermeling) 91–92; Tr. (Smyth) 646–50.)

234. Even if the POSA were motivated to reduce the amount of propylene glycol to improve tolerability, the POSA would not have been motivated to use mPEG-350 instead. The POSA would not have known whether mPEG would be a tolerable excipient in an intranasal formulation. (Tr. (Smyth) 625, 627, 646–47.)

235. The POSA would not have known whether mPEG could solubilize midazolam as well as propylene glycol, which was known to be an excellent solubilizer. Before 2007, nothing was known about mPEG's ability to solubilize midazolam. (Tr. (Smyth) 647; Tr. (Wermeling) 257.)

236. Because midazolam base has poor solubility in water, the POSA would have been concerned that adding water to the Wermeling Formulation would negatively affect the stability of the formulation and could cause midazolam to precipitate. (Tr. (Wermeling) 252; Tr. (Smyth) 636–37, 648–49; DTX-2294 at 41818.)

237. Thus, the POSA would not have been motivated to add mPEG and water to a formulation with midazolam base. (Tr. (Smyth) 636–37, 648–49.)

4. mPEG Was Not Interchangeable with PEG

238. PEG and mPEG were not known to be interchangeable in the art as of the priority date. (Tr. (Smyth) 596–607.)

239. Because PEG and mPEG have different chemical structures, they also have different physical and chemical properties such as melting point, freezing point, viscosity, and chemical reactivity. (Tr. (Smyth) 594–95, 597; Tr. (Lusty) 325.)

240. As a result, they also had different pharmaceutical uses prior to 2007. (Tr. (Smyth) 597–98; DTX-2022 at 36043–44; DTX-2078 at 36778–81.)

241. Before 2007, PEG had been used as a solubilizer in a number of liquid formulations and had been used as an active ingredient in laxatives. (Tr. (Smyth) 597; DTX-2022 at 36044–45.)

242. Before 2007, mPEG had been used as a chemical intermediate, and in four topical products: one gel, one vaginal lubricant, and two bar soaps. (Tr. (Wermeling) 194–95, 223; Tr. (Smyth) 597–98, 617–18; DTX-2022 at 36044–45.) Of the four topical products, only the gel was FDA-approved. (Tr. (Smyth) 617–19; DTX-2583.)

243. The POSA would not have been able to predict the effect of substituting mPEG for PEG in an intranasal midazolam formulation. (Tr. (Smyth) 645–46, 650.)

244. Before 2007, PEG and mPEG were distinguished and treated differently in the art. (Tr. (Smyth) 594–95, 606–07; Tr. (Wermeling) 220–21; DTX-2022 at 36038.) PEG and mPEG have different CAS Registry Numbers. (Tr. (Wermeling) 210–11; Tr. (Smyth) 598; PTX-1090.0017; DTX-2583.) General pharmaceutical compendia used by formulators, such as the Handbook and USP 2006, distinguished between PEG and mPEG. (Tr. (Smyth) 603–06; Tr. (Wermeling) 237–38; DTX-2078 at 36778–86; PTX-1090.0017–22.)

245. Wermeling ’359 did not suggest that PEG is interchangeable with mPEG. It described PEG as a “polyhydroxy alcohol.” mPEG is not a polyhydroxy alcohol. (DTX-2022 at [0030]; Tr. (Wermeling) 264–65; Tr. (Smyth) 616–17.)

L. Facts that (UCB says) are Relevant to Objective Indicia of Non-Obviousness

246. As of January 2007, the industry recognized a need for an ARS treatment that could be administered by non-medical personnel (i.e., a “rescue treatment” or an “at-home treatment”) and particularly recognized the need for an intranasal treatment for ARS. (Tr. (Klein) 425, 439–41; PTX-1109.0001; PTX-1197.0001; PTX-1366.0001; PTX-1148.0001.)

247. As early as the 1960s, the industry recognized that ARS should be promptly treated because of the risks inherent to any seizure and because of the risk of status epilepticus. (Tr. (Klein) 425, 427; Tr. (Privitera) 837–38; PTX-1148.001.) Through the 1980s, the industry continued to recognize that ARS should be treated quickly with a medication that did not require administration by trained medical professionals. (Tr. (Klein) 428–29; PTX-1109.0001; PTX-1366.0003.)

248. Beginning as early as the 1990s, the industry recognized that intranasal benzodiazepines would be an advantageous ARS rescue medication. (Tr. (Wermeling) 202–03; Tr. (Klein) 438–40; PTX-1109.0001; PTX-1366.0003.)

249. In 1997, Diastat, a rectal gel formulation of diazepam, became the first FDA-approved rescue product for the treatment of ARS, and remained the only FDA-approved rescue product available prior to 2007. (Tr. (Klein) 425, 436; Tr. (Privitera) 843–44; DTX-2327 at 82761.) In order to administer Diastat, a caretaker was required to turn the patient on their side, lower their pants or skirt to bare their buttocks, separate the buttocks to access the rectum, insert and plunge the syringe, and close the buttocks together to prevent leakage. (Tr. (Wermeling) 119; Tr. (Klein) 436–38.) Caregivers and most patients, especially older children and adults, found administration of Diastat embarrassing and socially unacceptable and therefore were reluctant to use it. (Tr. (Wermeling) 119; Tr. (Klein) 436–41, 449–50, 452–53; Tr. (Privitera) 844–45; PTX-1109.0001; PTX-1366.0001–03; PTX-1183.0005.)

250. Prior to 2007, some patients were prescribed off-label uses of benzodiazepines, such as oral lorazepam, or intranasal administration of an intravenous midazolam formulation. (Tr. (Wermeling) 120–21; Tr. (Klein) 425–26, 441.)

251. Orally administered benzodiazepines (including buccal and sublingual formulations) were not ideal as at-home rescue treatments for ARS, at least because of limitations in their route of administration and their time to peak plasma levels. (Tr. (Klein) 425–26, 430–31, 493, 511, Tr. (Privitera) 785, 840–42; PTX-1194.0001; PTX-1197.0001; DTX-2536 at 85198.) Oral medications require the patient's cooperation for administration and therefore cannot be administered while a patient is actively seizing or in a postictal state in which a patient experiences unconsciousness or substantial cognitive impairment. (Tr. (Klein) 430–32, 511; Tr. (Privitera) 785, 842; PTX-1194.0001.) If oral medication is administered to the patient during a seizure or postictal state, there is a risk the medication will be inhaled. (Tr. (Klein) 430–32; Tr. (Privitera) 785; DTX-2549 at 671797; PTX-1194.0001.) Orally administered drugs, including benzodiazepines, are absorbed more slowly than other routes of administration. (Tr. (Klein) 430–32; Tr. (Privitera) 785; DTX-2549 at 671797; PTX-1194.0001.) Orally administered lorazepam may not reach peak plasma levels for up to three hours following administration. (Tr. (Klein) 430–31; Tr. (Privitera) 795–96; DTX-2356 at 85203.)

252. Intranasal administration of the IV midazolam formulation was known since the 1980s but it had drawbacks. (Tr. (Klein) 441–46, 451–52; PTX-1369.0013–15; DTX-2326 at 82755; DTX-2251 at 39993.) The IV midazolam formulation was not convenient for intranasal administration. (Tr. (Wermeling) 120; Tr. (Klein) 441–46; DTX-2326 at 82755; DTX-2251 at 39993.) To administer intranasally, the IV midazolam formulation was administered either via a dropper or through an atomizer obtained from a compounding pharmacy. (Tr. (Wermeling) 82; Tr. (Privitera) 797, 835–36.) Intranasal administration of IV midazolam led to unpredictable absorption and unpredictable effectiveness. (Tr. (Klein) 441–42.) The IV midazolam solution has a concentration of 5 mg/mL midazolam, and therefore requires the administration of 1 mL solution

intranasally to achieve a therapeutic dose of midazolam. (Tr. (Wermeling) 119–20; Tr. (Klein) 441–42.) Administering 1mL of solution is too large for the nasal cavity, resulting in the formulation leaking out of the patient's nose or being swallowed and causing discomfort to the patient. (Tr. (Klein) 441–45; Tr. (Wermeling) 120; DTX-2326 at 82755; DTX-2251 at 39993.) If a patient were administered the IV midazolam solution intranasally during a seizure and inhaled the excess solution, it could cause pneumonia. (Tr. (Klein) 442–43.) The FDA concluded that intranasal administration of IV midazolam could lead to dosing errors. (Tr. (Klein) 448–50, PTX-1372.0012–14, .0060.) Intranasal administration of IV midazolam was not a widely used treatment for ARS prior to 2007. (Wermeling 83; Tr. (Klein) 443; Tr. (Privitera) 846.)

253. In 2008, the FDA granted fast-track status to Nayzilam. (Tr. (Klein) 448–49; Tr. (Picciolo-Lehrke) 730; Tr. (Privitera) 857; PTX-1372.0020.)

254. No new FDA-approved treatment options for ARS became available between 2007 and Nayzilam's approval in 2019. (Tr. (Klein) 426, 446–49; Tr. (Privitera) 850–51; PTX-1361.0005–6; PTX-1121.0002; PTX-1372.0002, .0013–14.) Nayzilam was the first FDA-approved intranasal benzodiazepine indicated for the treatment of ARS. (Tr. (Klein) 431, 472–75; Tr. (Privitera) 834.) Nayzilam provided a safe and effective rescue treatment for ARS that patients or their caregivers could administer. (Tr. (Klein) 422–23, 474–75; DTX-2515 at 95437.) Nayzilam is the best rescue treatment option for many patients with ARS, particularly patients whose second seizure follows soon after the first. (Tr. (Klein) 433–34, 478–79; Tr. (Privitera) 834–35, 837.) Valtoco was approved in 2020. (Tr. (Klein) 478, 480.)

255. Nayzilam has received some recognition and praise in the industry. (Tr. (Klein) 480–82; Tr. (Smyth) 679–82.) Dr. Jacqueline French—a well-respected epileptologist, past president of the American Epilepsy Society, chief medical and innovation officer of the Epilepsy

Foundation of American, and professor of neurology at NYU Langhorne Health—praised Nayzilam, describing it as a "game changer" based on its formulation and intranasal method of delivery. (PTX-1364.0045; Tr. (Klein) 480–81; Tr. (Privitera) 854–55.) Prior to this litigation, Cipla publicly praised Nayzilam. (Tr. (Klein) 481–82.) Cipla recognized that Nayzilam "resulted in rapid and sustained seizure control in patients with [seizure clusters]," that Nayzilam "had an acceptable safety profile," and that Nayzilam could "potentially provide a solution for the critical unmet clinical need of acute treatment of [ARS] in an outpatient setting." (PTX-1183.0007.)

256. Beginning in 2018, Cipla spent three years attempting to design around the Nayzilam composition by developing and testing intranasal midazolam formulations without mPEG. (PTX-1210; Tr. (Mittal) 547–48; Tr. (Smyth) 667–79; D.I. 139, Ex. 1 ¶¶ 31, 80.) Cipla tried dozens of different formulations as an alternative to Nayzilam's formulation, using at least 25 different excipients. (PTX-1211; PTX-1216.0004–05; PTX-1031.0001–03; PTX-1032.0001–02; Tr. (Gandhi) 538; Tr. (Smyth) 667–72.) Ultimately, Cipla did not seek FDA approval of any formulation that did not include mPEG. (Tr. (Smyth) 667–68, 670–72, 677, 679.) This was at least partially because an intranasal midazolam formulation without mPEG would have required the inclusion of hydrochloric acid, which would have resulted in conversion of some of the midazolam into the salt form and would have prevented Cipla from using the ANDA (generic) pathway for FDA approval. (Tr. (Ghandi) 541–43; Tr. (Smyth) 674–75.)

257. Between 2007 and 2019, the patents-in-suit were licensed by four companies. (Tr. (Smyth) 657.) These include ITI, Upsher-Smith Laboratories, Proximagen, LLC, and UCB. (Tr. (Smyth) 657–61; DTX-2417 at NAYZILAM_00033958–78 (September 12, 2007 Exclusive Patent License Agreement between Hananja and ITI); DTX-2416 (June 21, 2010 Exclusive License Agreement between Ikano (f/k/a ITI) and USL); DTX-2414 at NAYZILAM_00033807 (reflecting

2017 assignment of license from USL to Proximagen); DTX-2409 (April 18, 2018 Asset Purchase Agreement between UCB and Proximagen); DTX-2415 (April 18, 2018 License and Asset Purchase Agreement between Ikano (f/k/a ITI) and UCB).) As of 2006, ITI had rights to other intranasal benzodiazepine formulations, including the Wermeling Formulation and the ITI Intranasal Lorazepam formulation, both of which were in clinical studies for the treatment of seizures. (Tr. (Wermeling) 208; Tr. (Smyth) 662–63.)

258. UCB sought to acquire an ARS rescue medication that was an alternative to Diastat. (Tr. (Picciolo-Lehrke) 726–27.) UCB valued Nayzilam over Valtoco because Nayzilam was the better choice for ARS patients as demonstrated by its superior pharmacokinetic profile, including its faster onset of action and recovery time. (Tr. (Picciolo-Lehrke) 724.) UCB would have purchased the rights to Nayzilam even if Nayzilam was second to market. (Tr. (Picciolo-Lehrke) 756–57.)

III. FINDINGS OF FACT REGARDING ANTICIPATION

Anticipation is a question of fact. Cipla contends that the asserted claims are anticipated[8] by Wermeling '359 "because it expressly discloses intranasal midazolam formulations comprising PEG-400, propylene glycol, and water, and because a POSA would have understood the disclosure of 'polyethylene glycol' to include mPEG-350." (D.I. 172, Cipla's Post-Trial Br., at 3.)[9] UCB responds that Wermeling '359 does not expressly or inherently disclose mPEG, and that even if it did, Wermeling '359 does not disclose the combination of elements as arranged in the claims. (D.I. 170, UCB's Post-Trial Br., at 5, 8.) I agree with UCB.

[8] *See* n.77, *supra*.

[9] Cipla's Reply Brief did not respond to UCB's arguments as to why the asserted claims were not anticipated. Cipla's Reply Brief did not substantively address anticipation at all.

As discussed above, the Court finds that Wermeling '359 does not disclose mPEG or mPEG-350, either expressly or inherently. Because Cipla has failed to prove by clear and convincing evidence that Wermeling '359 discloses mPEG or mPEG-350, Cipla has not established that the asserted claims are invalid as anticipated.

IV. CONCLUSIONS OF LAW REGARDING OBVIOUSNESS

Obviousness is a question of law. Cipla contends that the asserted claims are obvious based on the combination of Wermeling '359 and Carbowax. Cipla asserts that the POSA would have been motivated to reduce the viscosity of the Wermeling Formulation (as described in Wermeling '359) and would have tried including the excipient mPEG-350 (as described in Carbowax) in the formulation. Cipla also asserts that the POSA would have been motivated to substitute propylene glycol in the Wermeling Formulation with mPEG-350 and water to improve tolerability. And Cipla contends that the POSA would have had a reasonable expectation of success. I disagree with Cipla.

"In this case, the patent claims a new composition or formulation to deliver an FDA-approved active ingredient. Thus, the claimed invention is not obvious if a person of ordinary skill would not select and combine the prior art references to reach the claimed composition or formulation." *Unigene Lab'ys, Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1361 (Fed Cir. 2011) (citation omitted).

The Court finds that the POSA would not have been motivated to select mPEG, or mPEG-350 specifically, as described in Carbowax, as an excipient for use in an intranasal formulation of midazolam. There was no suggestion in Carbowax or elsewhere in the art that mPEG would be useful or suitable as an excipient in an intranasal formulation. Cipla's contention otherwise is pure hindsight.

In reaching this conclusion, I reject Cipla's specific assertion that the POSA would have been motivated to modify the formulation disclosed in Wermeling '359 by using the mPEG disclosed in Carbowax in order to (1) reduce the viscosity of the Wermeling Formulation so that it could be delivered through a standard device, and (2) improve tolerability. Even if the Court thought Cipla had proven that the POSA would have been motivated to modify the Wermeling Formulation in the ways that Cipla says (and the Court does not think that has been proven), the Court is wholly unpersuaded that mPEG (as described in Carbowax) would have been an obvious choice, given that its suitability for any nasal formulation was unknown and there was little to no information in the art suggesting that mPEG or mPEG-350 would help a POSA achieve a lower viscosity intranasal formulation or that a formulation containing mPEG would be suitable for administration with a standard device.[10]

Nor has Cipla established by clear and convincing evidence that a POSA would have had a reasonable expectation of success in using mPEG, or specifically mPEG-350, in an intranasal midazolam formulation. Again, mPEG had never been used in an intranasal formulation before.

[10] In support of its obviousness argument, Cipla cites *Almirall, LLC v. Amneal Pharmaceuticals LLC*, 28 F.4th 265, 271, 273–76 (Fed Cir. 2022). (D.I. 172 at 11.) In *Almirall*, the Federal Circuit affirmed the PTAB's holding that claims directed to a topical dapsone composition using a certain gelling agent were invalid as obvious because it was "simply a case of substituting one known gelling agent for another" and the agents "were known for use in topical compositions with water insoluble drugs." *Almirall*, 28 F.4th at 273–74. *Almirall* is inapposite because the Court has found that PEG and mPEG are not interchangeable and mPEG was not known for use in intranasal formulations.

Cipla also relies on *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1365–67 (Fed. Cir. 2007). (D.I. 172 at 12–13.) That case held that it was obvious to make a tablet containing a particular salt form of a known active ingredient by employing an FDA-approved anion known to be useful for making a pharmaceutically acceptable salt, where the POSA would have expected success with that particular anion due to its known chemical characteristics. *Id.* *Pfizer* is distinguishable from the situation here for many reasons, including because the FDA had never approved a nasal formulation containing mPEG, and because a POSA would not have reasonably expected success in using mPEG in a nasal formulation.

It had been available since the 1940s yet had only been used in one FDA-approved product—a topical gel. As of the priority date, it was not reasonably known whether midazolam would be sufficiently soluble in mPEG, or mPEG-350 specifically, or that using mPEG in an intranasal midazolam formulation would be stable, safe, sprayable, and tolerable. And, although Cipla asserts that the POSA would have been motivated to use mPEG in order to arrive at a midazolam formulation that could be administered using a standard nasal spraying device, the Court finds that the POSA would not have had a reasonable expectation that the inclusion of mPEG would achieve that result.

The parties spill a lot of ink discussing the import of evidence that they contend is (or isn't) relevant to secondary considerations of non-obviousness. The law requires the Court to consider that evidence, and I have. Even assuming that there is a nexus between the asserted claims and the FDA-approved Nayzilam product, the evidence offered for secondary considerations isn't particularly probative of non-obviousness under the circumstances here.[11] And that evidence certainly doesn't help Cipla meet its burden to prove by clear and convincing evidence that the asserted claims are obvious.

Cipla has not established by clear and convincing evidence that the asserted claims are invalid for obviousness.

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[11] For example, UCB argues that Cipla's decision to "copy" the claimed formulation after it tried to design around supports a conclusion of non-obviousness. The Court does not find that evidence particularly probative of non-obviousness where, as here, Cipla copied because potential alternative formulations would have taken it off the generic pathway for FDA approval.

The Court also recognizes that there is significant evidence of a long-felt need for an FDA-approved, commercially available nasal formulation of midazolam, but the Court gives limited weight to that fact for purposes of its non-obviousness determination. The evidence at trial revealed that there were multiple publications describing intranasal midazolam formulations before the priority date. And there are lots of business and financial reasons why a pharmaceutical company may or may not choose to further develop a particular project or pursue FDA approval for a particular formulation.

V. CONCLUSION

For the reasons above, the Court concludes that Cipla has failed to prove that the asserted claims are invalid.

The parties are ordered to meet and confer and submit a proposed final judgment consistent with this Memorandum Opinion on or before May 22, 2026.

The parties filed their post-trial briefs under seal. Accordingly, I'm issuing this Memorandum Opinion under seal in the unlikely event that it discusses any evidence that was admitted at trial under seal. To the extent that either side seeks to have any portion of this Memorandum Opinion redacted, the parties shall jointly submit a proposed redacted version no later than May 18, 2026, for review by the undersigned, along with a motion supported by a declaration that includes a detailed explanation as to why disclosure of any proposed redacted material would "work a clearly defined and serious injury to the party seeking closure." *See In re Avandia Mktg., Sales Pracs. & Prods. Liab. Litig.*, 924 F.3d 662, 672 (3d Cir. 2019) (quoting *Miller v. Ind. Hosp.*, 16 F.3d 549, 551 (3d Cir. 1994) (internal quotation marks omitted)). The Court intends to issue a public version of this Memorandum Opinion no later than May 19, 2026.