NOT FOR PUBLICATION

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

ADAPT PHARMA OPERATIONS LIMITED, *et al.*, Plaintiffs, v. TEVA PHARMACEUTICALS USA, INC., *et al.*, Defendants.	Case No. 2:16-cv-7721 (BRM) (JAD) **OPINION FILED TEMPORARILY UNDER SEAL** [REDACTED]

MARTINOTTI, DISTRICT JUDGE

Before the Court[1] is an Amended Complaint for Patent Infringement brought by Plaintiffs Adapt Pharma Operations Limited; Adapt Pharma, Inc.; Adapt Pharma Limited (collectively "Adapt"); and Opiant Pharmaceuticals, Inc. ("Opiant") (together with Adapt, "Plaintiffs") against Defendants Teva Pharmaceuticals USA, Inc. and Teva Pharmaceuticals Industries Ltd. (collectively, "Teva" or "Defendants"). (ECF No. 43.) This action relates to the validity of the following claims of the corresponding United States Patents held by Plaintiffs: (1) Claims 7 and 9 of United States Patent Number 9,468,747 (the "'747 Patent") (TX-0001)[2]; (2) Claim 4 of United States Patent Number 9,561,177 (the "'177 Patent") (TX-0002); (3) Claims 21, 24, and 25 of United States Patent Number 9,629,965 (the "'965 Patent") (TX-0003); and (4) Claims 2, 24, 33,

[1] On May 22, 2019, this case was reassigned to the undersigned. (ECF No. 213.)

[2] Where appropriate, the Court references trial exhibits. Such citations are preceded by a "TX." The Amended Bench Trial Exhibit List can be found at ECF No. 338.

and 38 of United States Patent Number 9,775,838 (the "'838 Patent) (TX-0004) (collectively, the "Patents-in-Suit"). The Patents-in-Suit cover the pharmaceutical formulations, methods of treatment, and devices encompassed within Plaintiffs' patented invention NARCAN® Nasal Spray ("Narcan"). (ECF No. 287.) Narcan is a branded nasal spray used to treat patients suffering from an opioid overdose. (*Id.*)

The Court held a two-week bench trial beginning on August 26, 2019, and concluding on September 6, 2019. Due to scheduling issues, testimony from the parties' experts on pharmaceutical economics was heard on October 17, 2019. The parties submitted opening post-trial briefs, and proposed findings of fact and conclusions of law on November 13, 2019. (ECF Nos. 284–87.) The parties submitted responsive post-trial briefing on December 6, 2019. (ECF Nos. 300, 302–04.) Closing arguments were held on February 26, 2020.

This Opinion constitutes the Court's findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52(a). The findings of fact are based on the Court's observations and credibility determinations of the witnesses who testified, and a thorough review of all the evidence admitted at trial. For the reasons set forth below, and for good cause shown, the Court finds that the asserted claims of the Patents-in-Suit are **INVALID**.

I. BACKGROUND

The Patents-in-Suit cover the pharmaceutical formulations, methods of treatment, and devices encompassed within Plaintiffs' patented invention Narcan, which was approved by the Food and Drug Administration ("FDA") on November 18, 2015. (ECF No. 287 ¶¶ 1–2.)[3] Narcan is a branded nasal spray used to treat patients suffering from an opioid overdose. (*Id.* ¶ 2.) Teva filed an abbreviated new drug application ("ANDA") No. 209522 seeking FDA approval to

[3] ECF No. 287 is Adapt's Post-Trial Proposed Findings of Fact and Conclusions of Law.

commercially manufacture and sell a generic version of Narcan 4mg spray. (ECF No. 241 ¶ 46.)[4] "Teva included in its ANDA . . . a certification alleging, [*inter alia*], that the claims of the [P]atents-in-[S]uit are invalid, unenforceable, and/or will not be infringed by the manufacture, use, or sale of Teva's ANDA Product." (*Id.* ¶ 47.) Narcan is the reference listed drug ("RLD")[5,6] for ANDA No. 209522. (ECF No. 287 ¶ 3.) Teva does not contest infringement of the asserted claims of the Patents-in-Suit and, therefore, the issue before the Court is whether or not the asserted claims of the Patents-in-Suit are invalid due to the legal principle of obviousness. (*See* ECF No. 241 ¶¶ 48–51; *see* TX-1018 at 2–8.)

A. Parties

Adapt is the current holder of New Drug Application ("NDA") No. 208411 under which the 4mg/spray dose of Narcan was approved. (ECF No. 241 ¶ 42.) Opiant was formerly named Lightlake Therapeutics, Inc. ("Lightlake"). (*Id.* ¶ 5.) Adapt and Opiant are the assignees of the Patents-in-Suit. (*Id.* ¶¶ 22, 28, 34, 41.) Teva is a manufacturer and distributor of generic drugs. (*Id.* ¶ 10.) As referenced above, Teva has sought FDA approval to manufacture and sell a generic 4mg/spray naloxone hydrochloride nasal spray prior to the expiration of the Patents-in-Suit. (*Id.* ¶ 46.)

[4] ECF No. 241 is the Final Pretrial Order, entered by the Honorable Joseph A. Dickson, U.S.M.J.

[5] An RLD "is a drug that a brand company submitted [to the FDA] and got approved." (Zahavi Tr. 56:5–6, ECF No. 296.) Every generic drug has a corresponding RLD. (*Id.* at 56:12–13.)

[6] Due to the voluminous nature of the written record of the trial proceedings, the Court references the transcripts as "(Witness Name) Tr." and, because often multiple witnesses testified on the same day, includes the ECF citation for clarity.

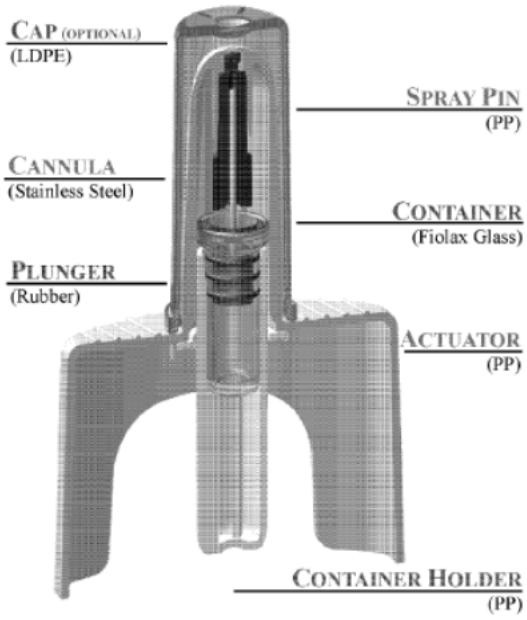
B. Naloxone and Narcan

Naloxone is used to treat opioid overdoses, including overdoses from illegal drugs such as heroin or from prescription painkillers such as oxycodone or fentanyl. Naloxone works as an "opioid antagonist," in that it quite literally reverses the effects of opioids. Naloxone, however, is not new and has been around since 1971. (Smyth Tr. 326:14–18, ECF No. 292; Illum Tr. 576:19–23, ECF No. 293; TX-3195.02.) The drug was typically administered either intravenously or intramuscularly by trained medical providers. Injection-based administration of naloxone is limited to certified medical professionals, precluding many first responders such as police officers, firefighters, and even some EMTs from providing naloxone to overdose victims in that manner. As a workaround, many first responders combined a naloxone injection device with another device called a disposable Mucosal Atomization Device ("MAD"), which converted the injection-based naloxone delivery method into an improvised nasal spray. The MAD kits had several disadvantages in that they required assembly prior to use (Smyth Tr. 329:22–330:6) and that they delivered too much fluid into the nostrils (Illum Tr. 830:2–15).

In 2012, amidst the rise of opioid overdoses, the FDA held a public meeting to discuss naloxone's role in in preventing opioid-related deaths (the "2012 FDA Meeting"). The FDA specifically mentioned that it was curious about the bioavailability of an intranasal naloxone product as compared to the existing intravenous or intramuscular products. Narcan has since been critical in preventing overdose deaths, and now possesses more than 90% of the retail naloxone market.

Narcan is the first and only FDA-approved naloxone nasal spray. Narcan is used primarily by those without medical training, such as police officers or friends and family of opioid users, when those individuals encounter someone overdosing on an opioid. Narcan has simplified the

delivery of naloxone for non-medical professionals. Narcan's naloxone formula is housed in a ready-to-use, single-use, pre-primed device that is specifically designed for nasal delivery. (Smyth Tr. 333:2–23.) The device Adapt chose, pictured below, is the Aptar UnitDose device—a well-known off-the-shelf device used for nasal delivery.



(TX-3170.07[7]; ECF No. 285 ¶ 48.)

It has been well documented that the country is in the grips of an opioid epidemic. Over two million Americans struggle with opioid addiction,[8] with approximately 130 Americans dying from opioid overdoses every day.[9] At the time of this Opinion, the country is facing the uncertainty of the coronavirus pandemic. Those who suffer from opioid addiction are particularly vulnerable

[7] TX-3170 is an email chain from Sergei Shpichuk to Limor Zahavi relating to a single dose device. (*See* ECF No. 338.) It was offered and entered into evidence on August 26, 2019.

[8] *Why Aren't More People With Opioid Use Disorder Getting Buprenorphine?*, Pew.com (July 31, 2019), https://www.pewtrusts.org/en/research-and-analysis/articles/2019/07/31/why-arent-more-people-with-opioid-use-disorder-getting-buprenorphine.

[9] *A Comprehensive Look at Drug Overdoses in the United States*, Centers for Disease Control and Prevention, https://www.cdc.gov/injury/features/prescription-drug-overdose/index.html

to infection and are likely to have a more severe case of the disease should they be infected.[10] Individuals are also finding that addiction services have been disrupted amid fears of community spread.[11] As more and more individuals are isolated in their homes, "[c]ounty coroners, law enforcement and emergency responders around the country are reporting spikes in overdose calls and deaths."[12] There are even reports that at least one police department has suspended administering naloxone due to concerns that officers would contract the virus.[13] While much is uncertain, it is clear that the coronavirus pandemic has exacerbated the opioid crisis.[14]

C. The Patents-in-Suit

The asserted claims in the Patents-in-Suit relate generally to the pharmaceutical compounds, delivery methods, and devices used with Narcan. The compound consists of about 4.4mg of naloxone hydrochloride dihydrate, between about 0.005mg and about 0.015mg of benzalkonium chloride ("BZK"), between about 0.1mg and about 0.5mg of disodium edetate ("EDTA"), between about 0.2mg and about 1.2mg of sodium chloride, and an amount of acid

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[10] Peter Grinspoon, *A tale of two epidemics: When COVID-19 and opioid addiction collide*, Harvard Medical School: Harvard Health Publishing (April 20, 2020), https://www.health.harvard.edu/blog/a-tale-of-two-epidemics-when-covid-19-and-opioid-addiction-collide-2020042019569.

[11] *Id.*

[12] Harmeet Kaur, *The opioid epidemic was already a national crisis. Covid-19 could be making things worse*, CNN.com (May 7, 2020), https://www.cnn.com/2020/05/07/health/opioid-epidemic-covid19-pandemic-trnd/index.html.

[13] Grinspoon, *supra* note 6.

[14] On May 21, 2020, the New Jersey Attorney General Gubir Grewal announced an administrative order, valid for the remainder of the coronavirus crisis, requiring physicians to prescribe naloxone to patients regularly taking higher doses of opioids. *See* Steve Janoski, *New Jersey says doctors must prescribe Narcan alongside opioids for at-risk patients*, northjersey.com (May 22, 2020), https://www.northjersey.com/story/news/new-jersey/2020/05/22/nj-doctors-must-prescribe-narcan-opioids-at-risk-patients/5236736002/.

sufficient to sustain a pH balance of 3.5–5.5 in about 100 microliters of solution. That solution is delivered into a single nostril of a patient by the Aptar UnitDose device. The specific patent claims are described in more detail below.

1. United States Patent No. 9,211,253 (the "'253 Patent")

The '253 Patent, which is not at issue in this action, was issued on December 15, 2015. (ECF No. 241 ¶ 11.) The '253 Patent was issued pursuant to a patent application filed on March 16, 2015.[15] (*Id.* ¶ 12.) The inventors of the '253 Patent are Roger Crystal and Michael Brenner Weiss. (*Id.* ¶ 14.) Lightlake, now Opiant, is the assignee of the '253 Patent. (*Id.* ¶ 15.) The '253 Patent expires on March 16, 2035. (*Id.* ¶ 13.)

2. The '747 Patent[16]

The '747 Patent was issued on October 18, 2016, and is entitled "Nasal Drug Products and Methods of Their Use." (ECF No. 241 ¶ 16.) The inventors of the '747 Patent are Roger Crystal and Michael Brenner Weiss. (*Id.* ¶ 21.) The '747 Patent was issued pursuant to an application that was a continuation-in-part of the application filed for the '253 Patent. (*Id.* ¶ 18.) Plaintiffs are asserting Claims 7 and 9 of the '747 Patent against Teva. (ECF No. 287 ¶ 4.) "Claim 9 of the '747 Patent is representative of the other asserted claims." (*Id.* ¶ 7.) Claims 7 and 9 depend from Claims 1, 2, and 3, which read:

> **[Claim 1]** A method of treatment of opioid overdose or a symptom thereof, comprising nasally administering to a patient in need thereof a dose of naloxone hydrochloride using a single-use, pre-primed device adapted for nasal delivery of a pharmaceutical formulation to a patient by one actuation of said device into one nostril of said patient, having a single reservoir comprising a

[15] March 16, 2015 is the priority date of the Patents-in-Suit.

[16] (*See* ECF No. 65-3; TX-0001.)

pharmaceutical composition which is an aqueous solution of about 100 µL[17] comprising:

about 4 mg naloxone hydrochloride or a hydrate thereof;
between about 0.2mg and about 1.2mg of an isotonicity agent;
between about 0.005 mg and about 0.015 mg of a compound which is at least one of a preservative, a cationic surfactant, and a permeation enhancer;
between about 0.1 mg and about 0.5 mg of a stabilizing agent; and
an amount of acid sufficient to achieve a pH of 3.5-5.5.

[Claim 2] The method as recited in claim 1 wherein:
the isotonicity agent is NaCl;
the preservative is benzalkonium chloride;
the stabilizing agent is disodium edetate; and
the acid is hydrochloric acid.

[Claim 3] The method of claim 2, wherein the aqueous solution comprises:
about 4.4 mg naloxone hydrochloride dihydrate;
about 0.74 mg NaCl;
about 0.01 mg benzalkonium chloride;
about 0.2mg disodium edetate; and
an amount of hydrochloric acid sufficient to achieve a pH of 3.5–5.5

(ECF No. 65-3 at *37.)[18] Lightlake, now Opiant, is the assignee of the '747 Patent. (ECF No. 241 ¶ 22.) The '747 Patent expires on March 16, 2035. (*Id.* ¶ 20.)

3. The '177 Patent[19]

The '177 Patent was issued on February 7, 2017, and is entitled "Nasal Drug Products and Methods of Their Use." (ECF No. 241 ¶ 23.) The inventors of the '177 Patent are Fintan Keegan, Robert Gerard Bell, Roger Crystal, and Michael Brenner Weiss. (*Id.* ¶ 27.) Plaintiffs are asserting Claim 4 of the '177 Patent against Teva. (ECF No. 287 ¶ 4.) Claim 4, which depends from Claim 1

[17] µL stands for microliter, which is one millionth of a liter and is numerically represented as 1×10^{-6} m.

[18] Citations preceded by an asterisk reference the page number as displayed in the ECF header.

[19] (*See* ECF No. 65-4; TX-0002.)

and generally describes the method of delivery of Narcan, reads: "the method of claim 3, wherein: the isotonicity agent is sodium chloride; the stabilizing agent is disodium edetate; and the acid is hydrochloric acid." (ECF No. 65-4 *41.) Adapt and Opiant are the assignees of the '177 Patent. (ECF No. 241 ¶ 28.) The '177 Patent expires on March 16, 2035. (*Id.* ¶ 26.)

4. The '965 Patent[20]

The '965 Patent was issued on April 25, 2017, and is entitled "Nasal Drug Products and Methods of Their Use." (ECF No. 241 ¶ 29.) The inventors of the '965 Patent are Roger Crystal and Michael Brenner Weiss. (*Id.* ¶ 33.) Plaintiffs are asserting Claims 21, 24, and 25 of the '965 Patent against Teva. (ECF No. 287 ¶ 4.) These claims cover the pre-primed single use device. Claim 21 reads: "The device as recited in claim 20, wherein: the isotonicity agent is NaCl; the preservative is benzalkonium chloride; the stabilizing agent is disodium edetate; and the acid is hydrochloric acid." (ECF No. 65-5 *37.) Claim 24 reads: "The device of claim 20, wherein the volume of said reservoir is not more than about 140 µL." (*Id.*) Claim 25 reads: "The device of claim 20, wherein about 100 µL of said aqueous solution in said reservoir is delivered to said patient in one actuation." (*Id.*) Opiant is the assignee of the '965 Patent. (ECF No. 241 ¶ 34.) The '965 Patent expires on March 16, 2035. (*Id.* ¶ 32.)

5. The '838 Patent[21]

The '838 Patent was issued on October 3, 2017, and is entitled "Nasal Drug Products and Methods of Their Use." (ECF No. 241 ¶ 35.) The inventors of the '838 Patent are Fintan Keegan, Robert Gerard Bell, Roger Crystal, and Michael Brenner Weiss. (*Id.* ¶ 40.) Plaintiffs are asserting

[20] (*See* ECF No. 65-5; TX-0003.)

[21] (*See* TX-0004.)

Claims 2, 24, 33, and 38 of the '838 Patent against Teva. (ECF No. 287 ¶ 4.) These claims cover the method of treating an opioid overdose with Narcan. Claim 1 lays out this method as follows:

> [D]elivering a 25–200 µL spray of a pharmaceutical solution from a pre-primed device into a nostril of a patient, wherein the device is adapted for nasal delivery, wherein the spray delivers between about 4 mg and about 10 mg naloxone, an isotonicity agent, and between about 0.005% and about 0.015% (w/v) of benzalkonium chloride.

(ECF No. 6-1[22] *57.) Claim 2 of the patent reads: "the method of claim 1, wherein the spray delivers about 4mg naloxone." (*Id.*) Claim 24 reads: "the method of claim 18 [wherein the patient is an opioid overdose patient or a suspected opioid overdose patient] wherein the device comprises a reservoir not more than about 140 µL in volume." (*Id.*) Claim 33 reads: "the method of claim 32, wherein: the isotonicity agent is sodium chloride; the stabilizing agent is disodium edetate; and the acid is hydrochloric acid." (*Id.*) Lastly, claim 38 reads:

> [T]he method of claim 37 [with the device comprising a reservoir, piston, and swirl chamber], wherein the device comprises a plunger that houses a container closure comprising a vial comprising an opening, a cannula, and a rubber stopper, wherein the stopper is configured to occlude the opening of the vial, and wherein the cannula is configured such that the cannula can pierce the stopper when the plunger applies sufficient force to the cannula.

(*Id.* *57–58.) Adapt and Opiant are the assignees of the '838 Patent. (ECF No. 241 ¶ 41.) The '838 Patent expires on March 16, 2035. (*Id.* ¶ 39.)

D. Procedural History

Plaintiffs filed Civil Actions Nos. 16-7221, 17-864, 17-2877, and 17-5100, which alleged various infringement claims against Defendants relating to the '253, '747, '177, and '965 Patents. (*See* ECF No. 124 at *1.) On September 11, 2017, the Court consolidated those actions into this

[22] This docket entry can be found in the matter of *Adapt Pharma Operations Ltd. v. Teva Pharmaceuticals USA, Inc.*, No. 18-9880. That matter was consolidated with this case on October 11, 2018. (ECF No. 124.)

case. (ECF No. 33.) On May 30, 2018, Plaintiffs filed Civil Action No. 18-9880 (the "9880 Action"), alleging various infringement claims against Defendants relating to the '838 Patent. (*See* ECF No. 124 at *2.) On October 11, 2018, the Court consolidated the 9880 Action with this matter. (ECF No. 124.)

On March 13, 2019, the Court held a Markman Hearing and reserved its decision. (ECF No. 188.)[23] On April 24, 2019, the Court issued its decision on claim construction. (ECF No. 200.) On May 22, 2019, this case was reassigned. (ECF No. 213.) On July 25, 2019, the Final Pretrial Order was entered by the Honorable Joseph A. Dickson, U.S.M.J. (ECF No. 241.)

On August 13, 2019, the parties submitted a letter informing the Court they had agreed to narrow the number of asserted claims and defenses asserted at trial. (ECF No. 251; TX-0069.)[24] Adapt agreed not to assert and Teva agreed not to challenge claims 2, 8, and 32 of the '747 Patent; claim 26 of the '965 Patent, and claims 3, 34, and 35 of the '838 Patent. (TX-0069.) The parties also stipulated that Narcan embodies claims 20, 21, 24, and 25 of '965 Patent, and that a person using Narcan in accordance with its instructions practices the methods in claims 1–2, 4–7, and 9 of the '747 Patent, claims 1–4 of the '177 Patent, and claims 1, 2, 18, 24, 30–33, and 37–38 of the '838 patent. (TX-0036). As a result of the stipulation, any factual and legal disputes relating to invalidity under 35 U.S.C. § 112 were nullified and the only remaining issues before the court involved obviousness under 35 U.S.C. § 103. (ECF No. 251 at 2.)

The Court held a two-week bench trial beginning on August 26, 2019, and concluding on September 6, 2019. Due to scheduling issues, testimony from the parties' experts on

[23] The transcript of this proceeding can be found at ECF No. 193.

[24] TX-0069 is the Second Stipulation to Narrow Asserted Claims and Defenses. (*See* ECF No. 338.) It was offered and admitted into evidence on September 3, 2019.

pharmaceutical economics was heard on October 17, 2019. Closing arguments were held on February 26, 2020.

II. FINDINGS OF FACT[25]

The following constitutes the Court's findings of fact pursuant to Federal Rule of Civil Procedure 52(a). The Court begins with a discussion of the witness testimony heard at trial and the Court's resulting factual findings and credibility determinations. The Court then makes finding regarding a person of ordinary skill in the art (a "POSA") before finally discussing the Court's factual findings related to the prior art relevant to this dispute.

A. Defendants' Trial Witnesses[26]

1. Limor Zahavi

Limor Zahavi testified on August 26, 2019, and offered testimony relating to Teva's development of its intranasal naloxone product. Overall, the Court found Ms. Zahavi to be a credible witness, and accorded her testimony commensurate weight.

Ms. Zahavi has worked at Teva for nearly twenty years and currently works as a "handshake leader" who "connect[s] the work" of research and development with operations. (Zahavi Tr. 52:20–25, ECF No. 296.) During the relevant time period, Ms. Zahavi was the "head of a developmental unit that was developing nasal generics" and other sterile generic products. (*Id.* 53:12–14.) Ms. Zahavi testified that Teva began development on a generic intranasal naloxone product around mid-2014. (*Id.* 53:19–54:3; 60:4–6.) To submit an ANDA for a generic intranasal

[25] To the extent any findings of fact are more appropriately categorized as conclusions of law, and vice versa, they are adopted as such.

[26] The Court notes that its credibility determinations were based, not only on a witness's response to a particular question, but also the witness's physical reaction (*i.e.* body language, facial expressions, furtive movements, shifting, squirming, folding of their arms, etc.).

naloxone product, Teva would have to show its product was bioequivalent, meaning it would have the same active pharmaceutical ingredient and the same safety and frequency profile, to an RLD. (*Id.* 55:15–56:11.) At the time Teva began development of its generic intranasal naloxone product, no branded naloxone nasal spray products had received FDA approval. (*Id.* 58:8–11.)

Ms. Zahavi then described the development process Teva and her team utilized to create their generic intranasal naloxone product. Ms. Zahavi testified that it was not uncommon for a generics company to begin development without knowing what the RLD was, noting that the generic market in the United States is highly competitive and getting a head start on other generics companies was highly desirable. (*Id.* 58:20–59:6.) Because Teva did not know the identity of the RLD, they conducted a thorough literature search to see all of the information that had been published and learn about existing art relating to intranasal naloxone formulations. (*Id.* 59:10–14; 60:7–12; 69:20–70:10.) During this time, Teva employed a competitive intelligence company to aid their search. (*Id.* 60:18–61:3.) Teva's research indicated that at least three other programs were in the process of developing an intranasal naloxone product: (1) the AntiOp program, (2) the Lightlake program, and (3) the Norwegian University program. (*Id.* 62:10–13.)

On December 8, 2014, Teva prepared a naloxone formulation based on prior art and an FDA-approved injectable naloxone product. (*Id.* 65:11–25; 66:1–2; *see also* TX-3155.04[27].) This formulation included water, naloxone, and sodium chloride. (Zahavi Tr. 66:1–2.) On the same day, Teva made a second formulation that used a 0.02% concentration of BZK as a preservative. (*Id.* 66:1–2; 66:18–67:8; TX-3155.11.) Teva selected this concentration of BZK because it was used in "each and every one of [Teva's] nasal programs, [because] it is stable and well known."

[27] TX-3155 is Teva Laboratory Book No. D-837. (*See* ECF No. 338.) It was offered and admitted into evidence on August 26, 2019. (*Id.*)

(*Id.*) On the same day, Teva prepared a third formulation that added EDTA in a concentration of 0.001%. (*Id.* 68:12–16; 68:22–69:2.) Teva utilized the Aptar UnitDose device for its formulations because it was an off-the-shelf device that was "readily available and [] cheaper than developing your own device." (*Id.* 73:25–74:6.) Teva's formulations used a 2mg dose of naloxone because that concentration had been found in the literature for injectable naloxone products that had been FDA-approved. (*Id.* 69:20–70:10; 71:20–72:6.) Upon seeing the RLD patent application, Kathryn Jones, the head of one of the competitive intelligence companies hired by Teva, e-mailed Ms. Zahavi stating, in part, "[a] puzzling issue concerning Lightlake is why they would need such a high dose [compared to] Indivior" (the "KLJ E-Mail"). (*Id.* 77:3–25, 78:17–79:21; *see also* TX-1131[28].) Ms. Zahavi testified, however, that she herself was not puzzled about the 4mg dose. (*Id.*) Ms. Zahavi noted that Teva was focusing on creating a stable formulation, rather than attempting to find the optimum dose of naloxone, because "the amount of the active ingredient, the amount of naloxone is to be selected by the brand. The generic must use the same amount." (*Id.* 70:1–18.) If the amount of naloxone was not the same, then it would not be appropriate for an ANDA application because the products would not be bioequivalent. (*Id.* 72:1–6.) Ms. Zahavi testified that after learning about the final formulation of Narcan, the only thing Teva changed about its product was the amount of naloxone. (*Id.* 80:9–13.)

On cross examination, Ms. Zahavi testified that Teva had designated the development of its intranasal naloxone to be a "red carpet" project, meaning that it was high-priority, with Teva estimating sales exceeding $100 million. (*Id.* 82:7–20; 83:16–84:4.) During development, Teva reviewed a patent issued to Dr. John Strang. Strang concluded that the optimum intranasal dose

[28] TX-1131 is described as, "Email from K. Jones to L. Zahavi, S. Fireman, M. Eliaszada, S. Shpichuk, and S. Nahum re US patent by Lightlake - when can we talk?" (*See* ECF No. 338.) It was offered and admitted into evidence on August 26, 2019. (*Id.*)

was between 0.65mg and 1.6mg of naloxone. (*Id.* 100:3–7; 100:14–23.) Ms. Zahavi testified that, prior to seeing the RLD patent, filed by Lightlake, Teva never tested a formulation that included more than 2mg of naloxone. (*Id.* 104:4–20.) After seeing the RLD patent, Teva adjusted the amount of the active ingredient, naloxone, to 4mg in their formulations. (*Id.* 112:7–18.)

2. Dr. Mark Merlin

Dr. Mark Merlin testified on August 26, 2019, and offered testimony relating to whether the claimed dose of naloxone would have been obvious to a POSA, and various objective indicia of nonobviousness. Overall, the Court found Dr. Merlin to be a credible witness, and accorded his testimony commensurate weight.

The Court accepted Dr. Merlin as an expert in the field of emergency medicine and the treatment of opioid overdoses. (Merlin Tr. 120:17–24, ECF No. 296.) Dr. Merlin is the Vice Chair of Emergency Medicine at Newark Beth Israel Medical Center, a professor of emergency medicine and emergency medical services at Rutgers New Jersey Medical School, and the chair of the New Jersey EMS Council. (*Id.* 117:19–119:12.) Dr. Merlin has trained first-responders, EMTs, paramedics, and medical students in the treatment of opioid overdoses. (*Id.* 119:13–18.) Dr. Merlin has also treated thousands of patients suffering from opioid overdoses in both hospital and non-hospital settings. (*Id.* 120:3–10.)

On direct examination, Dr. Merlin testified that prior to the priority date of the patents, it would have been obvious to a POSA that outside the hospital setting, intranasal naloxone would be the preferred method of administration and it would have been obvious to a POSA that patients might need a dose of naloxone greater than 2mg. (*Id.* 164:7–165:7.) A POSA would also recognize that a person overdosing on higher potency opioids would require a higher dose of naloxone to reverse their symptoms and that higher potency opioids were a pervasive problem prior to the

priority date of the Patents-in-Suit. (*Id.* 126:6–24; 139:21–141:16.) Dr. Merlin testified that, outside the hospital setting, the most important thing is to quickly restore breathing to a patient suffering from an opioid overdose. (*Id.* 128:1–23.) Outside a hospital setting, the individual administering naloxone is likely to have limited medical resources and training and, therefore, a POSA would want to use a higher initial dose of naloxone to ensure that a patient's symptoms of respiratory depression are reliably reversed. (*Id.* 159:22–160:1.) Moreover, a POSA would recognize significant dangers to a patient, including cardiac arrest, brain damage, and death, that would be associated with administering a lower initial dose and then having to administer a second dose. (*Id.* 165:1–7.) Dr. Merlin testified that prior to March 2015, he had personally administered more that 2mg of naloxone intranasally using a MAD kit. (*Id.* 150:10–151:3.) A POSA would also recognize that the life-saving potential of a higher initial dose of naloxone outweighed the risk of a patient suffering withdrawal symptoms. (*Id.* 162:3–15.) Dr. Merlin also testified that naloxone is a "very, very safe medication" and expressed little concern that a higher dose would render the medication unsafe. (*Id.* 160:2–7; 161:15–162:2.)

On cross examination, Dr. Merlin admitted that there was "no compelling science" that a 4mg dose of naloxone would be more effective than a 2mg dose. (*Id.* 187:23–188:5.) Dr. Merlin was also unable to point to any clinical literature that, prior to the priority date, recommended a starting dose of naloxone greater than 2mg. (*Id.* 189:16–25.) Dr. Merlin's testimony often relied on his stated personal experiences administering doses greater than 2mg, which would not have been available to a POSA before the priority date. (*Id.* 216:7–218:22.) Dr. Merlin also admitted that no prior art would have indicated to a POSA the need to administer a dose greater than 2mg or identified re-dosing as an issue that needed to be solved. (*Id.* 179:20–180:10; 203:16–19.) Although Dr. Merlin's 2010 paper discussed re-dosing, it stated that the need for a higher intranasal

dose was a possibility, rather than a requirement. (*Id.* 194:16–24.) Dr. Merlin also acknowledged that although he had not personally seen serious withdrawal symptoms, numerous reports and publications had identified such symptoms following administrations of naloxone. (*Id.* 203:24–204:18.) A POSA would also have been aware of various reports that a higher dose of naloxone increases the risk a patient will suffer acute withdrawal symptoms. (*Id.* 211:18–212:15.) Dr. Merlin conceded that groups, including the FDA and Dr. Daniel Wermeling, had noted the need for better, needle-free devices, notwithstanding the existence of Evzio and MAD kits.[29] (Merlin II Tr. 1467:2–1469:14; 1471:20–25, ECF No. 294.)

3. Dr. Roger Crystal

Dr. Roger Crystal testified as a fact witness via video deposition on August 27, 2019, and offered testimony related to the development of Narcan. Dr. Crystal is one of the named inventors of the Patents-in-Suit. Overall, the Court found Dr. Crystal to be a credible witness, and accorded his testimony commensurate weight.

Dr. Crystal was the CEO of Lightlake and later Opiant, and had final decision-making authority regarding formulation and dose of Narcan. (Crystal Tr. 294:9–14, ECF No. 292.) Dr. Crystal selected the inactive ingredients included in Narcan, including BZK and EDTA. (*Id.* 286:11–15.) Dr. Crystal testified that Lightlake had a pre-investigational new drug application ("pre-IND") meeting with the FDA to solicit feedback from the FDA on its proposed intranasal naloxone formulation (*Id.* 303:10–25.) Before the pre-IND meeting, Lightlake submitted a

[29] Dr. Merlin offered testimony relating to a 2015 article by Dr. Daniel Wermeling entitled, "Review of Naloxone Safety for Opioid Overdose: Practical Considerations for New Technology and Expanded Public Access" (the "Wermeling 2015 Article"). (*See* TX-0053.) A 2010 article written by Dr. Wermeling, entitled, "Opioid Harm Reduction Strategies: Focus on Expanded Access to Intranasal Naloxone," was also entered into evidence (the "Wermeling 2010 Article"). (*See* TX-0052.)

package to the FDA expressing concerns about the development of an intranasal naloxone product noting, "[t]here is little if any commercial incentive for developing a new nasal naloxone drug product" and that "because of its widespread use, it most likely is not patentable because its use for opioid overdose is 'obvious.'" (*Id.* 301:3–17; 302:14–20.) Dr. Crystal also stated that the FDA suggested that Lightlake consider using the Aptar UnitDose device for its intranasal naloxone product. (*Id.* 300:8–13; 306:7–13.) Dr. Crystal testified that he was aware BZK was used as a preservative for nasal formulations. (*Id.* 286:20–287:14; 294:20–295:16.) In March of 2013, Lightlake's contractor, Rechon, proposed the addition of EDTA to the formulation for increased stability. (*Id.* 311:16–313:15.)

4. Dr. Hugh Smyth

Dr. Hugh Smyth testified on August 27, 2019, and offered testimony relating to whether the claimed dose of naloxone, formulation, device, and method of administration would have been obvious to a POSA. Dr. Smyth also discussed whether there was a nexus between objective indicia of nonobviousness and the asserted claims of the Patents-in-Suit. The Court found Dr. Smyth to be highly credible and convincing and credited his testimony significantly over that of Dr. Illum. In fact, the Court concludes this testimony was the linchpin of Defendants' case and has persuaded the Court, by clear and convincing evidence, of the invalidity of the asserted claims of the Patents-in-Suit. The Court recognized Dr. Smyth as an expert in the field of pharmaceutical formulations, including nasal formulations and delivery systems. (Smyth Tr. 319:19–320:1, ECF No. 292.)

Dr. Smyth testified that prior to March 16, 2015, the priority date of the Patents-in-Suit, all elements of the claimed invention were known in the prior art and that the asserted claims of the Patents-in-Suit were obvious. (*Id.* 364:1–365:25.) He stated that the prior art referenced doses of

naloxone ranging from 0.4mg to 20mg with various routes of administration. (*Id*. 327:4–329:11.) Moreover, the Aptar UnitDose device had been used for intranasal administration prior to 2015. (*Id.* 335:17–21; 382:1–4.)

In 2012, the FDA held a public meeting to discuss the importance of naloxone in treating the rising opioid crisis and discussed its interest in improving the MAD Kit device. (*Id*. 336:11–15.) The purpose of the meeting was to encourage the industry to "develop an intranasal naloxone product that could be FDA approved." (*Id.* 336:23–25.) Expert speakers at the meeting discussed how intranasal naloxone could be improved through the use of a one-step intranasal delivery device. (*Id.* 337:15–20.) In fact, at Lightlake's own pre-IND meeting with the FDA, the agency suggested that Lightlake use the Aptar UnitDose device, the very device it ended up claiming in its patent. (*Id.* 358:4–20; TX-3092–93.)[30,31] At the general meeting, the FDA expressed concern about whether the amount of drug that gets into the bloodstream via an intranasal administration would be too low. (*Id.* 339:2–11.) The FDA also said they were not especially concerned about high exposure, because naloxone could be given in very high doses without noticeable adverse effects. (*Id.* 339:21–340:9.) Experts at the FDA meeting discussed reports showing no adverse effects in healthy individuals as high as 700 times the recommended level as well as the fact that the risks of withdrawal in an overdose situation would not keep these experts from administering naloxone to a patient. (*Id.* 340:15–343:8.)

[30] TX-3092 is an email chain from L. Basham to Roger Crystal relating to the pre-IND 114704 meeting. (*See* ECF No. 338.) It was offered and admitted into evidence on August 27, 2019. (*Id.*)

[31] TX-3093 is an email from Roger Crystal to L Basham relating to the pre-IND 114704 meeting and attachment. (*See* ECF No. 338.) It was offered and admitted into evidence on August 27, 2019. (*Id.*)

Dr. Smyth testified that a POSA looking to improve the MAD Kit would have a selected a device that delivered a volume of liquid suitable for the nose, such as the Aptar UnitDose device. (*Id.* 329:22–330:16; 335:15–336:10.) A POSA would have understood that intranasal administration would require a higher dose of naloxone because it has a lower bioavailability that intravenous or intramuscular administration; that is, less of the drug is absorbed into the bloodstream when administered intranasally. (*Id.* 338:1–400:10.) Finally, a POSA would have been motivated to use sodium chloride, hydrochloric acid, BZK, and EDTA in an intranasal naloxone formulation. (*Id.*)

Dr. Smyth concluded that the asserted claims of the Patents-in-Suit were obvious on two grounds: (1) the combination of the Strang, Kulkarni, and Djupesland references; and (2) the combination of the Davies patent application, Kerr and the Kerr formulation, and the Bahal patent. (*Id.* 365:25–366:6.)[32] As to the first combination, Dr. Smyth testified that a POSA would have been motivated to combine these references and would have had a reasonable expectation of successfully formulating an improved intranasal naloxone product. (*Id.* 383:4–18.) Indeed, Strang discussed an intranasal dose of naloxone of 4mg. (*Id.* 367:10–368:4; 368:24–371:22; 393:20–394:20.) A combination of the Strang and Djupesland references would have led a POSA to select the Aptar UnitDose device as well. (*Id.* 334:7–9; 380:18–382:9; 386:4–393:19; 410:10–411:18.) Additionally, a combination of Strang and Kulkarni would have led a POSA to use sodium chloride, hydrochloric acid, BZK, and EDTA in their intranasal naloxone formulation. (*Id.* 374:2–24; 377:20–378:19; 394:21–396:22; 397:3–7.)

As to the second combination—Davies, Kerr 2009/Kerr Formulation, and Bahal—Dr. Smyth similarly testified that a POSA would have reasonably expected to successfully

[32] A discussion of the specific details of these references can be found in section II.D.1–6., *infra*.

formulate an improved intranasal naloxone product. (*Id.* 408:11–24; 417:13–19.) The Davies reference disclosed a volume for the nasal formulation of 100 microliters, administered in a single-use, pre-primed device. (*Id.* 409:18–412:12.) A POSA would have been motivated to select the Aptar UnitDose device as the single-use device because it was readily available and easy to use. (*Id.* 414:1–12.) All told, this combination would lead a POSA to formulate an intranasal naloxone product containing sodium chloride, hydrochloric acid, BZK, and EDTA, in amounts and concentrations commensurate with the Patents-in-Suit. (*Id.* 402:20–403:7; 406:10–25; 407:20–408:10; 415:24–416:11.)

Dr. Smyth opined that a POSA would not have been taught away from using BZK, because it was a well-known and commonly used preservative for nasal products. (*Id.* 382:11–23, 422:7–9; 427:23–429:1.) Indeed, the Wyse reference was not published until June 2015 and would not have been available to a POSA at time of the priority date of the patents. (*Id.* 422:2–6.) Dr. Smyth further undercut the persuasiveness of Wyse, noting that Wyse only created a preliminary formulation with BZK and that Wyse's other preliminary results, including a conclusion that paraben preservatives were well-suited for use in nasal formulations, were undercut by more rigorous subsequent studies. (*Id.* 424:3–20; 425:7–426:4.) Additionally, Wyse used a concentration of BZK that was significantly higher than what appeared in the FDA inactive ingredient list. (*Id.* 422:17–423:7; 426:13–19.) Smyth testified that a POSA might conclude that the degradation Wyse observed was the result of the excessively high concentration of BZK. (*Id.*)

Dr. Smyth also testified that "there were not unexpected results arising from the asserted claims [of the Patents-in-Suit]" that would alter his conclusion that the asserted claims were obvious. (Smyth II Tr. 1268:5–10, ECF No. 295.) Adapt's claimed invention did not have unexpected bioavailability or stability and any differences between the prior art and the

Patents-in-Suit relating to these properties were negligible. (*Id.* 1269:11–1270:19; 1271:1–1272:3; 1275:2–1276:22.)

Dr. Smyth also testified that there was no nexus between the commercial success of Narcan and the novel aspects of the asserted claims because these aspects were known in the prior art. (*Id.* 1242:1–9.) Narcan was not unique in its ability to treat opioid overdoses, and a 4mg dose of naloxone was known in the prior art. (*Id.* 1246:15–1247:10.) Moreover, the fact that other companies failed to secure FDA-approval for their intranasal naloxone products did not indicate the "failure of others to solve the problem that the patents purport[] to solve." (*Id.* 1257:14–1258:11.) Indeed, FDA approval is not an aspect of the claims and Dr. Smyth testified that there are examples "of safe and effective community use [of] intranasal naloxone that have not received FDA approval," including the MAD Kit device. (*Id.*) Dr. Smyth also rebutted Dr. Illum's assertions that the Mundipharma formulation and Evzio were evidence of the copying of Narcan. (*Id.* 1285:3–1286:18.)

On cross examination, Dr. Smyth conceded that he arrived at his stated opinions by first analyzing the Patents-in-Suit and then looking at the prior art to see whether the prior art taught what was in the asserted claims. (Smyth Tr. 485:10–486:4.) Although Dr. Smyth stated that Davies, Strang, and Wyse "disclosed" doses greater than 2mg, he admitted that nothing in Davies suggested his formulation was ever tested. (Smyth II Tr. 1252:23–1256:9; Smyth Tr. 438:11–25.) Dr. Smyth also conceded that making a more concentrated 2mg dose of naloxone would solve the issue of excess fluid without deviating from the more widely used 2mg dose. (Smyth Tr. 444:2–23.) Dr. Smyth admitted that the prior art included several excipients other than those used in the claimed invention. (*Id.* 380:8–10; 466:6–469:18.)

5. Michael Potestio

Michael Potestio testified via video deposition as a fact witness on August 27, 2019, and offered testimony regarding the sales of Narcan in connection with the public interest market. Mr. Potestio is Adapt's Vice President of Field Operations. (Potestio Tr. 496:5–11, ECF No. 292.) Mr. Potestio leads a team that educates states, counties, law enforcement, and first responders on the opioid crisis and assists them with procuring Narcan. (*Id.* 497:10–498:5.) Overall, the Court found Mr. Potestio to be a credible witness, and accorded his testimony commensurate weight.

On direct examination, Mr. Potestio testified that at the relevant time, there were only two naloxone products approved by the FDA for use in the community setting: Narcan and Kaleo's Evzio autoinjector. (*Id.* 499:5–25.) Although there is no publicly available data, Mr. Potestio estimated that Narcan possessed around 80 percent market share in the public interest market. (*Id.* 498:8–24.) Mr. Potestio attributed Narcan's success in the public interest market to the fact that it is "an FDA-approved nasal spray, which is easy to use, with the correct dose." (*Id.* 502:22–25.) Narcan's wholesale acquisition cost ("WAC") is lower than that of Evzio's. (*Id.* 503:12–505:21.) Mr. Potestio testified that the public interest market was far more price-sensitive than the retail setting. (*Id.* 505:1–12.) Mr. Potestio's team would meet with states and their grant writers to educate them on Narcan and provide assistance with obtaining federal Department of Health and Human Services ("HHS") or Substance Abuse and Mental Health Services Administration ("SAMHSA") grants to expand access to Narcan. (*Id.* 510:24–511:25.) Mr. Potestio testified that there was initially resistance to the 4mg dose included in Narcan because stakeholders were concerned about rapid withdrawal. (*Id.* 508:9–17.)

6. Ivan Hofmann

Ivan Hofmann testified on October 17, 2019, and offered testimony relating to whether there is a nexus between objective indicia of nonobviousness and the claimed invention and discussed commercial success and third-party praise. The Court accepted Mr. Hofmann as an expert witness in pharmaceutical economics. (Hofmann Tr. 1616:10–16, ECF No. 298.) Overall, the Court found Mr. Hofmann to be a highly credible and persuasive witness, and credited his testimony over that offered by Dr. Vigil and Dr. Majumdar.

Mr. Hofmann testified that, in his opinion, Narcan's marketplace success did not provide objective evidence of nonobviousness. (*Id.* 1620:21–1621:2.) Mr. Hofmann stated Dr. Vigil and Dr. Majumdar "failed to look at what was known in the prior art" when conducting their analysis of what factors contributed to Narcan's marketplace success. (*Id.* 1619:13–1620:7.) Specifically, he disagreed with the conclusion of Dr. Vigil and Dr. Majumdar that Narcan's efficacy was a feature that was driving sales and had a nexus to the claims asserted in the Patents-in-Suit. (*Id.* 1622:25–1623:22.) Rather, Narcan's success was attributable to Adapt's expansive marketing efforts. (*Id.* 1637:22–1638:9.) Mr. Hofmann identified Adapt's patient outreach programs, marketing, assistance in grant writing efforts, and advocacy for co-prescription legislation as the driving factors that lead to increases in Narcan's sales, rather than the claimed inventions of the Patents-in-Suit. (*Id.* 1628:22–1632:18; 1637:24–1638:9.) Adapt's strategic pricing efforts played a similar role in Narcan's success. (*Id.* 1642:4–1643:7.) By keeping Narcan's WAC price low, Adapt was able to secure priority formulary placement. (*Id.*) Mr. Hofmann similarly disagreed with Dr. Vigil's conclusion that Evzio is cheaper than Narcan. (*Id.* 1643:8–1645:6.) Mr. Hofmann noted that Dr. Vigil failed to address the cost of the medication paid by the insurer, instead focusing solely on the out-of-pocket costs paid by the consumer. (*Id.*) Dr. Vigil's analysis ignored the

"behind-the-scenes payments" made by insurers, Medicare, and Medicaid, and, therefore, "[didn't] tell the whole story in terms of how pharmaceutical products are reimbursed and who is paying the cost." (*Id.*)

Mr. Hofmann also testified that there was no economic incentive for a POSA to develop a naloxone product. (*Id.* 1649:4–6.) He cited the pre-IND meeting letter Lightlake themselves had sent the FDA regarding what Lightlake perceived as the dismal economic potential of a naloxone product. (*Id.* 1649:16–1650:18.) Mr. Hofmann also rebutted Dr. Vigil's assertion of third-party praise for Narcan, and argued that the testimony of Dr. Vigil "[was] really information about things don't represent praise" of the unique features of Patents-in-Suit. (*Id.* 1656:7–13.) Rather, it related to "the ease-of-use of the Aptar [UnitDose] device or some of the other things I talked about as far as what was previously known." (*Id.*)

B. Plaintiffs' Trial Witnesses

1. Dr. Lisbeth Illum

Dr. Lisbeth Illum testified on August 28, 2019, and offered testimony relating to whether the claimed dose of naloxone, the formulation, the device, and method of administration would have been obvious to a POSA. Dr. Illum also testified on objective indicia of nonobviousness, including the failure of others, unexpected properties, and evidence of copying. The Court found Dr. Illum to be evasive at times and less credible than Dr. Smyth and the other witnesses who testified. The Court, accordingly, accorded her testimony lesser weight than that of Dr. Smyth.

Dr. Illum has served as a special professor of pharmacy at the University of Nottingham, a professor at the Royal Danish School of Pharmacy, has founded several companies in the area of drug formulation and drug delivery, and is the named inventor on about 45 patents. (Illum Tr. 564:13–566:21, ECF No. 293.) The Court recognized Dr. Illum as an expert in

transmucosal drug delivery, pharmaceutical formulation, and pharmaceutical product development and delivery systems. (*Id.* 570:7–14.)

Dr. Illum testified that it would not have been obvious to a POSA to develop a formulation of intranasal naloxone with a dose greater than 2mg prior to the priority date of the Patents-in-Suit. (*Id.* 711:6–20.) Dr. Illum specifically noted that the choice of a 4mg dose would not have been obvious. (*Id.*)

Dr. Illum testified that clinical studies conducted before the priority date of the Patents-in-Suit repeatedly concluded that a 2mg dose of naloxone, delivered intranasally with a MAD Kit, was effective at treating opioid overdoses. (*Id.* 577:25–642:3.) Dr. Illum further testified that no prior art recommended increasing the dose of naloxone. (*Id.*) Dr. Illum stated that the prior art taught away from a higher dose of naloxone due fears that patients would suffer from withdrawal and other side effects. (*Id.* 579:17–587:18.) As a result, the prior art taught to dose naloxone "low and slow" in the hospital setting; that is, to administer naloxone with a low initial dose and slowly increase the dosage over time only if necessary. (*Id.* 587:10–22.) Rather than seeking to increase the dosage of naloxone, a POSA would have sought to improve the combination of the MAD Kit and a 0.4mg intramuscular naloxone dose. (*Id.* 643:20–645:19; 695:14–697:6.) Dr. Illum testified that the Strang and Wyse references stated that a 2mg intranasal dose of naloxone was equivalent to a 0.4mg intramuscular dose and, therefore, a POSA would have selected an intranasal dose of 2mg or less. (*Id.* 646:3–711:20.)

Dr. Illum also testified that the prior art taught away from using BZK or EDTA with an intranasal naloxone product. (*Id.* 728:24–729:16.) Specifically, Wyse taught away from the use of BZK and EDTA, noting that those formulations caused naloxone to degrade. (*Id.* 671:2–680:3.) A POSA, therefore, would have been motivated to select a formulation that was either

preservative-free or used a preservative other than BZK. (*Id.* 726:12–728:22.) Dr. Illum testified that a POSA would not have found the features of the claimed invention to be obvious. (*Id.* 774:14–775:16.) This is because much of the prior art taught toward administering doses in both nostrils rather than one and the prior art included numerous devices that would have been suitable for an intranasal naloxone product in addition to the Aptar UnitDose device. (*Id.* 603:10–16; 606:15–20; 608:25–609:8; 632:22–633:6; 723:19–724:6.)

Relating to objective indicia of nonobviousness, Dr. Illum opined that the failure of other companies—including Teva, AntiOp/Indivior, Amphastar, and Mundipharma—to arrive at an intranasal dose greater than 2mg was evidence that the asserted claims of the Patents-in-Suit were nonobvious. (*Id.* 732:24–744:12.) Dr. Illum argued that the decision of Mundipharma to change their formulations to copy the dose of the Patents-in-Suit further highlighted their nonobviousness. (*Id.* 745:3–747:22.) Finally, Dr. Illum testified that Narcan showed unexpected stability and unexpectedly high bioavailability compared to the Wyse formulation, which Dr. Illum characterized as the closest prior art formulation to Narcan. (*Id.* 747:24–774:13.)

On cross examination, Dr. Illum admitted there were instances in the prior art that taught administering doses of naloxone greater than 2mg. (*Id.* 655:16–656:21.) Indeed, Illum conceded that Strang disclosed a clinical study that included intranasal doses of naloxone of 8mg and 16mg. (*Id.*) Dr. Illum further admitted that the Walley 2013 reference[33] concluded that naloxone administered intranasally via a MAD Kit required redosing approximately 50% of the time. (*Id.* 635:11–636:24.) Dr. Illum acknowledged that a low initial dose would not be successful to

[33] The Walley 2013 reference was "a community project [that involved] giving the MAD dose device kits to the community. And they were dosing the people who needed to be dosed because they had taken too much opioid[s]." (Illum Tr. 635:11–18, ECF No. 293.) It was a peer-reviewed article that appeared in the British Medical Journal. (Merlin II Tr. 1452:18–22, ECF No. 296.)

reduce the opioid overdose in some patients and that a POSA would have understood that an increased dose would have increase the clinical effects of naloxone. (*Id.* 846:7–16; 642:14–21.) Dr. Illum also conceded that she was "not an expert on naloxone or overdose." (*Id.* 837:12–24.)

Dr. Illum acknowledged that the bioavailability of intranasal naloxone was significantly lower than the bioavailability of an intravenous dose and admitted that Strang taught that 3 to 4mg of naloxone was required to be bioequivalent to a 1mg intravenous dose. (*Id.* 648:4–649:4; 656:24–657:4.) Dr. Illum also admitted that the prior art characterized the symptoms of withdrawal to be "not life-threatening" and that Walley 2013 and other prior art references did not express concerns relating to administering greater than 2mg of naloxone. (*Id.* 847:13–24; 849:23–850:16; 635:11–636:24.) Dr. Illum acknowledged that Narcan carries a warning label relating to opioid withdrawal and that there is no evidence Narcan causes fewer withdrawal symptoms compared to other naloxone products. (*Id.* 856:12–21.)

Prior to the priority date of the Patents-in-Suit, Dr. Illum testified that it was well known in the prior art that BZK could be used in nasal formulations. (*Id.* 776:20–23.) In fact, prior to Wyse, there was no prior art that concluded BZK degraded naloxone. (*Id.* 800:13–801:7.) Dr. Illum also acknowledged that the amount of BZK used by Wyse was greater than had been used in any other FDA-approved intranasal product and was 8.5 times higher than the amount of BZK in the Patents-in-Suit. (*Id.* 801:23–803:16.)

Dr. Illum admitted that the Kerr formulation included naloxone and BZK and was shown to be effective at reducing opioid overdoses. (*Id.* 804:7–805:9.) It was also known in the prior art that BZK and EDTA could be used in intranasal formulations. (*Id.* 805:23–806:6.) Dr. Illum also conceded that her opinion that other products had failed to solve the problem solved by the claim

invention was based on the fact that no other product had received FDA approval. (*Id.* 810:8–811:23.)

2. Eric Karas

Eric Karas testified on August 29, 2019, as a fact witness and offered testimony relating to Adapt's activities and the sales of Narcan. Mr. Karas is a Vice President and General Manager in the Commercial Division of Emergent BioSolutions, which acquired Adapt in late 2018. (Karas Tr. 914:16–22; 916:9–15, ECF No. 290.) Prior to its acquisition of Adapt, Mr. Karas served as the head of marketing for Adapt. (*Id.* 917:3–7.)

Mr. Karas testified that Narcan currently held 97% market share for naloxone products in the traditional retail market and estimated that it possessed approximately 75% market share in the public interest market. (*Id.* 937:3–10; 943:14–944:7.) Adapt does not engage in direct-to-consumer marketing and the advertising and promotional budget of Narcan is smaller than is typical for pharmaceutical products. (*Id.* 937:22–942:11.) Mr. Karas also offered testimony on Adapt's efforts to encourage the enactment of co-prescription legislation, wherein doctors who prescribe opioids would be required by law to also consider prescribing a naloxone product. (*Id.* 919:1–21.)

On cross examination, Mr. Karas admitted that, from the perspective of an insured patient, Narcan is more expensive than Evzio or other naloxone products. (*Id.* 936:23–937:2.) Adapt invests in two different marketing segments, targeting the retail and public interest markets. (*Id.* 969:24–970:4.) Mr. Karas admitted that co-prescription legislation has led to an increase in sales for Narcan. (*Id.* 972:10–973:5.) Adapt has also benefited from federal government purchases of Narcan through SAMHSA, an agency responsible for earmarking budget dollars to fight the opioid crisis. (*Id.* 976:14–978:10.)

3. Dr. Soumyajit Majumdar

Dr. Majumdar testified on September 3, 2019, and offered testimony relating to whether a nexus existed between objective indicia of nonobviousness and the claimed invention. The Court found Dr. Majumdar to be a less credible witness than Mr. Hofmann and accorded his testimony commensurate weight.

The Court accepted Dr. Majumdar as an expert in transmucosal pharmaceutical formulation and drug development. (Majumdar Tr. 1010:2–8, ECF No. 291.) Dr. Majumdar is the Associate Dean for Research and Graduate Programs and a Professor in the Department of Pharmaceutics and Drug Delivery at the University of Mississippi School of Pharmacy. (*Id*. 1003:9–15.) Dr. Majumdar testified about various attributes of Narcan, including its efficacy, stability, ease-of-use, and needle-free route of administration. (*Id.* 1018:24–1027:18.) Dr. Majumdar concluded that there was a nexus between the commercial success of Narcan and the claimed invention. (*Id.*)

On cross examination, Dr. Majumdar testified that he did not analyze whether the features of Narcan were known in the prior art. (*Id.* 1041:16–19.) Dr. Majumdar further testified that the ease-of-use and needle-free route of administration features were attributable to the Aptar UnitDose device (*id.* 1040:12–1041:14), and that they are not claimed in the asserted patents (*id.* 1039:23–1040:3). Dr. Majumdar admitted that the asserted claims of the Patents-in-Suit have no limitations on the efficacy of Narcan in treating an opioid overdose. (*Id.* 1039:1–1040:3; 1043:7–1047:5). Dr. Majumdar also admitted that before the priority date of the patents, a POSA would know that the excipients EDTA and BZK are listed in the *Handbook of Pharmaceutical Excipients* and would have the knowledge to select those excipients, among others, from that handbook in the formulation of a pharmaceutical compound. (*Id.* 1032:11–1037:5.) A POSA

would have been familiar with BZK as a preservative and EDTA as a stabilizing agent in pharmaceutical compounds. (*Id.* 1034:10–21; 1035:13–17; 1036:16–1037:5.) Dr. Majumdar further admitted that a POSA would have known that sodium chloride was used as a tonicity agent. (*Id.* 1031:10–15; 1032:11–14.)

4. Sergey Shpichuk

Mr. Shpichuk testified via video deposition on September 3, 2019, and offered testimony relating to Teva's development of its intranasal naloxone product. Overall, the Court found Mr. Shpichuk to be a credible witness and accorded his testimony commensurate weight.

Mr. Shpichuk was the team manager working on Teva's Naloxone HCl nasal spray. (Shpichuk Tr. 1048:20–1049:7, ECF No. 291.) Mr. Shpichuk was tasked with making a generic version of the "Reference Listed Drug," without knowing the details of that Reference Listed Drug. (*Id*. 1051:17–24.) To do so, Mr. Shpichuk testified that his team would gather all the publicly available information related to the project. (*Id*. 1051:22–1052:2.) The goal was to make the generic product equivalent to the branded product. (*Id*. 1053:2–3.) Teva also hired two competitive intelligence firms to aid their search. (*Id.* 1061:7–1062:15.)

Mr. Shpichuk acknowledged that there was an unmet need in the market for a non-injection-based Naloxone product. (*Id*. 1063:5–13.) Mr. Shpichuk's testimony established that Teva was aware of a University of Oslo Naloxone nasal spray trial that was administering five doses of 0.4mg of naloxone to patients. (*Id*. 1064:17–1066:17.) As of May of 2015, Mr. Shpichuk's team had estimated that there were three likely doses for the RLD, which were: 2mg, 1.6mg, and 0.8mg of naloxone in a 100µL spray. (*Id*. 1067:8–1068:12.) Some of the sources that Mr. Shpichuk's team relied on when coming to this estimation include some of the prior art that Teva relies on in this case. (*Id*. 1070:1–1071:15.) Mr. Shpichuk's pharmacokinetic trials included a

single-actuation 2mg dose of naloxone to one nostril. (*Id*. 1075:10–13.) Mr. Shpichuk recognized one of Teva's proposed formulations that was geared to be quantitatively and qualitatively similar to the Reference Listed Drug as containing the excipients citric acid monohydrate, sodium chloride, EDTA, benzyl alcohol, and sodium hydroxide. (*Id*. 1081:2–20.)

In October 2015, Teva obtained the new formulation from Lightlake showing a dosage of 4mg naloxone, which Mr. Shpichuk affirmed was different from what they had previously expected. (*Id*. 1085:6–21.) Teva created a second quantitatively and qualitatively similar formula for the Lightlake reference. (*Id*. 1087:3–16.) In order to gain approval for a generic drug, the generic must be bioequivalent to a branded drug. (*Id.* 1053:2–11.) When Teva began working on its generic intranasal naloxone product, there was no branded RLD on the market. (*Id.* 1051:17–24.) Mr. Shpichuk testified that differences between Teva's test results and those of the RLD could potentially be explained by differences in the populations of the studies and noted that a dosage change was only one factor that could have impacted the results. (*Id.* 1101:13–1102:5.)

5. Thomas Begres

Thomas Begres testified on September 5, 2019, and offered testimony as a fact witness relating to his experience using naloxone to treat opioid overdoses. Overall, the Court found Mr. Begres to be a credible witness, and accorded his testimony commensurate weight.

Thomas Begres is the senior director of clinical and medical affairs for Emergent BioSolutions, Inc. ("Emergent") and a firefighter and paramedic with the Scio Township Fire Department. (Begres Tr. 1147:18–23, ECF No. 295.) Mr. Begres is a licensed paramedic who started his career in the field twenty-one years ago. (*Id.* 1148:13–20.) He is also a registered nurse. (*Id.* 1149:14–22.) In his role for Emergent, Mr. Begres provides medical and clinical information

about the use of naloxone to health care providers or others in a non-commercial capacity. (*Id.* 1153:3–10.) Mr. Begres testified that he has seen the needles and vials present in non-nasal naloxone kits be stolen for IV drug use. (*Id.* 1155:17–1156:2.) Mr. Begres testified that he does not typically give naloxone to patients that are not breathing, because the therapeutic window has often closed by that point. Therefore, naloxone is intended for people who have suboptimal breathing. (*Id.* 1158:20–1159–17.) However, the ideal dose of naloxone would not wake the patient up to avoid adverse symptoms of withdrawal. (*Id.* 1160:4–16.) As a paramedic, he uses IV naloxone, because it is more immediate and precise. (*Id.* 1161:12–19.) One reason to give minimum amount of naloxone is because the paramedic may not be aware of the other illicit drugs in the patient's system, for example cocaine or an amphetamine, which could overwhelm the patient's system after the depressant effect of the opioid is reversed by the naloxone. (*Id.* 1163:4–11.) His typical starting dose is 0.4mg of IV naloxone. (*Id.* 1164:14–16.) This is also the most common dose across the U.S. amongst paramedics in his experience. (*Id.* 1164:17–21.) As of March 2015, that dose was effective about 90% of the time. (*Id.* 1165:4–9.) One of the consequences of waking a patient up with too much naloxone is that the patient may consciously refuse treatment and succumb to a later overdose. (*Id.* 1166:19–24.) Mr. Begres testified that pulmonary edema is a side effect of naloxone but has never seen it personally. (*Id.* 1172:6–24.)

When Mr. Begres first heard about Narcan, he was surprised that the dose was so high. (*Id.* 1181:10–12.) Mr. Begres testified that his concerns have subsequently lessened because, while incidents involving side effects of Narcan are underreported, he nevertheless has not seen many cases of withdrawal with the 4mg Narcan dose. (*Id.* 1182:8–20.) Mr. Begres's initial concerns were shared by EMS medical directors across the country. (*Id.* 1183:3–1185:20.) Many of these medical directors have approved the use of Narcan in the areas they oversee, but not all. (*Id.* 1185:21–25.)

As to the MAD Kit, Mr. Begres testified that it would distribute too much fluid for the nose to absorb. (*Id.* 1191:9–25.) Mr. Begres trains people to use the MAD Kit and has seen them struggle assembling it. (*Id.* 1192:23–1193:12.) He further stated that he has seen first responders in the field and even nurses in the emergency room setting have difficulty assembling the MAD device. (*Id.* 1193:13–1195:11.) Even once assembled, the MAD Kit can be difficult to administer into the patient's nose. (*Id.* 1195:16–1196:5.)

Mr. Begres expressed several concerns with the Evzio auto-injector. First, it comes with a training device, which only gives instructions in English, meaning it may be problematic for communities where English is a second language or not spoken at all. (*Id.* 1201:5–13.) The spoken portion of the instructions in the training device would not be useful to anyone hard of hearing or if it were particularly loud in the location where a patient overdosed. (*Id.* 1201:21–24.) Additionally, because the device contains a needle, it requires special packaging to dispose of the device properly. (*Id.* 1201:14–20.) Lastly, needles, even in an auto-injector, scare a large amount of the population. (*Id.* 1202:6–9.)

On cross examination, Mr. Begres testified that the initial dose was anywhere from 0.4mg to 2mg of IV naloxone. (*Id.* 1211:8–11.) He also mentioned that it was quite common to administer a second dose of naloxone. (*Id.* 1211:12–23.) At one point, Mr. Begres told Adapt's advisory board that the National Institute on Drug Abuse and the FDA were part of the creation of Narcan's clinical study and provided Adapt with information regarding the desirability of a 4mg dose. (*Id.* 1215:9–1217:13.) Mr. Begres admitted that in some situations a 4mg dose mitigates the need to administer a second dose. (*Id.* 1219:11–1220:18.) Mr. Begres agreed that a 4mg dose of Narcan achieves approximately the same amount of naloxone exposure as a 2mg intramuscular dose. (*Id.* 1224:25–1225:6.) Mr. Begres's protocol allows for a 2mg intramuscular dose.

(*Id.* 1225:7–10.) In his 20 years as a paramedic, Mr. Begres can recall about six instances of a patient experiencing withdrawal from naloxone and is not aware of any studies comparing the withdrawal symptoms from a 2mg intramuscular dose to a 4mg dose of Narcan. (*Id.* 1226:5–20.) Mr. Begres insinuated that the 4mg dose of Narcan was less safe than an IV administration. (*Id.* 1231:15–23.)

On redirect, Adapt established that the data that Mr. Begres saw comparing a 2mg intramuscular dose to a 4 mg Narcan dose was after March 2015. (*Id.* 1237:3–16.)

6. Kenneth A. Williams

Dr. Kenneth Williams testified on September 6, 2019, and offered testimony relating to whether the claimed dose of naloxone would have been obvious to a POSA and objective indicia of nonobviousness, including unmet need and skepticism. Overall, the Court found Dr. Williams to be a credible witness and accorded his testimony commensurate weight.

Dr. Williams works in the emergency department at Rhode Island Hospital and also serves as the medical director for the Rhode Island Department of Health. (Williams Tr. 1353:20–1354:5, ECF No. 294.) The Court recognized Dr. Williams as an expert in emergency medicine and the treatment of opioid overdose, including the administration of naloxone. (*Id.* 1356:22–1357:5.)

Dr. Williams testified that it would not have been obvious to a POSA to develop an intranasal naloxone product with a dose greater than 2mg, and expressed particularly skepticism that it would have been obvious to select a 4mg dose. (*Id.* 1384:22–1385:4; 1393:15–22.) He also testified that prior to the priority date, the typical dose of intranasal naloxone was 2mg or less and that such a dose was proven to be safe and effective. (*Id.* 1365:24–1366:2; 1383:13–1384:16.) Dr. Williams opined that redosing was not a significant concern because a second dose of naloxone did not put a person at risk of suffering a brain injury or death. (*Id.* 1373:7–1374:24.) An individual

would be concerned about administering a higher initial dose due to fears that patient would suffer serious withdrawal and other side effects. (*Id.* 1362:5–13.) Dr. Williams testified that higher doses correlated with a greater likelihood of serious withdrawal which would have discouraged a POSA from using a dose greater than 2mg. (*Id.* 1385:5–9; 1392:21–1393:22.) Dr. Williams indicated that he and other medical professionals were highly skeptical of Narcan's 4mg formulation when it first entered the market due to fears of increased withdrawal side effects. (*Id.* 1385:13–1388:11.) Finally, Dr. Williams testified that Narcan satisfied the unmet need of an intranasal naloxone product that was needle-free and easy to use. (*Id.* 1388:14–1389:7.)

On cross examination, Dr. Williams admitted that there is not a universal effective dose of naloxone that works to reverse opioid overdose in all patients. (*Id.* 1405:1–15.) He acknowledged that a POSA would have known that an initial 4mg dose of naloxone might not be sufficient for all patients. (*Id.* 1418:19–1419:7.) Indeed, a POSA would have understood that synthetic opioids are more potent and would require a higher dose of naloxone in order to treat an overdose. (*Id.* 1406:22–1407:1; 1427:19–23; 1428:2–16.) Dr. Williams testified that time is a critical factor when treating opioid overdoses and that a patient who stops breathing will begin to suffer brain damage within 3 to 5 minutes. (*Id.* 1411:15–21.) There have been systematic studies concerning the exact timing of when to administer a re-dose should the initial dose be inadequate. (*Id.* 1410:20–1411:3.) Dr. Williams further admitted that a POSA would understand that a lower initial dose increased the risk that a patient overdosing on a long-acting opioid would re-overdose after the naloxone in their system wore off. (*Id.* 1410:1–16.) Dr. Williams stated that the risk of severe withdrawal was less when naloxone was administered intranasally compared to intramuscular injection. (*Id.* 1420:19–21; 1432:24–1433:6; 1434:2–25.)

CONFIDENTIAL MATERIAL OMITTED

Dr. Williams also conceded that Narcan did not ameliorate the risk of withdrawal symptoms or agitation as side effects of administering naloxone. (*Id.* 1437:12–24; 1438:5–7.) Indeed, Dr. Williams does not recommend the use of Narcan within his EMS system because of the 4mg dose, has never used it on an actual patient, and admitted that ambulances in Rhode Island "carry a variety of ways of delivering naloxone, including the MAD Kit." (*Id.* 1428:21–25; 1395:6–22.)

7. Dr. Robert Vigil

Dr. Robert Vigil testified on October 17, 2019, and offered testimony relating to whether a nexus existed between objective indicia of nonobviousness and the claimed invention. Overall, the Court found Dr. Vigil to be a less credible witness than Mr. Hofmann and accorded his testimony commensurate weight. Dr. Vigil received a PhD in economics from the University of Maryland and currently works as a principal at Analysis Group, Inc, where he specializes in "applying economics and finance to matters involving intellectual property." (Vigil Tr. 1529:23–1530:15, ECF No. 298.) The Court accepted Dr. Vigil as an expert in the economics of the pharmaceutical industry and market analysis. (*Id.* 1531:25–1532:6.)

Dr. Vigil opined that Narcan had been a commercial success, that success was attributable to the benefits and features of the asserted claims of the Patents-in-Suit, and that there is substantial evidence of third-party praise for Narcan. (*Id.* 1533:3–8.) Dr. Vigil noted that since its launch in February 2016, Narcan has generated [redacted] in revenue, which Dr. Vigil characterized as "significant for the time period that it's been on the market." (*Id.* 1536:16–1538:16.) Dr. Vigil opined that Narcan's price was not responsible for its success in the public interest market, instead arguing that, if price were a driver of success, products priced lower than Narcan would have enjoyed comparable success. (*Id.* 1545:15–24; 1557:14–25.)

Dr. Vigil testified that Adapt utilized a variety of tactics to market Narcan, including direct mail and email promotion to target physicians, and print and online advertising. (*Id.* 1567:16–1569:3.) Dr. Vigil also discussed Adapt's co-prescription initiatives, which require doctors to prescribe naloxone when prescribing opioids. (*Id.* 1570:22–1571:11.) In Dr. Vigil's opinion, however, Adapt's marketing strategy and marketing tactics were not unusual within the pharmaceutical industry. (*Id.* 1572:1–15.) Dr. Vigil testified that because other companies were attempting to develop a drug to enter the community-use naloxone market, it was his conclusion that "clearly there was an economic incentive to develop such a product. Or so many companies that are doing that wouldn't be doing that." (*Id.* 1592:16–1593:5.)

On cross examination, Dr. Vigil admitted that Adapt saw an increase in Narcan sales following lobbying efforts for co-prescription legislation. (*Id.* 1611:3–1612:25.) Dr. Vigil also conceded that he relied on Dr. Majumdar's analysis for "the proposition that the four things that I mentioned [efficacy, ease-of-use, the product is needle-free, stability], were attributable to the patents." (*Id.* 1598:1–1600:10; *see also* 1579:24–1580:11.) Dr. Vigil did, however, admit that, from a legal or technical perspective, he did not know what it means to say "Narcan embodies the claims of the [P]atents-in-[S]uit." (*Id.* 1606:7–16.)

Dr. Vigil testified that the Amphastar MAD Kit had been used to treat opioid overdoses for many years prior to the formulation of Narcan. (*Id.* 1540:18–1541:2.) He also admitted that the Aptar UnitDose device was in the prior art. (*Id.* 1597:11–1598:1.) Dr. Vigil further testified that, because it lacked FDA-approval, the Amphastar MAD Kit could not be marketed for the treatment of opioid overdose and that the MAD Kit had less marketplace success than Narcan. (*Id.* 1609:10–24.) In Dr. Vigil's opinion, FDA-approval by itself cannot explain marketplace success. (*Id.* 1609:25–1610:12.) Dr. Vigil admitted, however, that he did not examine whether

Narcan would have had comparable marketplace success if it lacked FDA-approval. (*Id.* 1610:13–16.)

C. The Prior Art

The Court finds that the Patents-in-Suit are entitled to a priority date, which is the date of alleged invention, of March 16, 2015. (*See* Smyth Tr. 322:15–24, ECF No. 292; '747 Patent, TX-0001; '177 Patent, TX-0002; '965 Patent, TX-0003; '838 Patent, TX-0004.) When determining whether the asserted claims of the Patents-in-Suit are obvious, the Court, therefore, considers the prior art that would have been available to a POSA on or before that date.

1. Strang

The Strang reference ("Strang") was an international patent application published on November 22, 2012, prior to the priority date of the Patents-in-Suit, that discussed the treatment of opioid overdoses with intranasal naloxone. (Smyth Tr. 366:21–367:5, ECF No. 292; *see* TX-0054.) Strang identified various risks associated with injectable naloxone, including the requirement of trained medical personnel to administer it; the difficulty in finding a vein to administer the injection; the risk of exposure to blood-borne pathogens and diseases, including HIV, and hepatitis B and C; and needle-stick injuries. (Smyth Tr. 367:6–15; *see also* TX-0054.03.) Strang identified intranasal naloxone as a solution to these issues. (Smyth 367:6–15; *see also* TX-0054.03.) Strang recommended that intranasal naloxone would be administered by individuals without medical training, such as a family member. (Smyth Tr. 367:23–368:4.) Strang noted that the volume of the solution would have to be optimized for nasal administration and identified potential volumes of 50, 100, 150, and 200 microliters. (*Id.* 368:5–17.) Strang preferred a low volume due to the capacity of the nose and the ensuring bioavailability. (*Id.*) He also recommended the use of a single-dose unit which would be administered to a single nostril. (*Id.* 368:18–23;

TX-0054.11.) Strang references various ranges for the preferred dose of naloxone, with 0.5mg to 20mg being the broadest suggested range. (Smyth Tr. 368:24–369:10; TX-0054.06.) He also states "it can be preferred to start with an amount to 4mg" of naloxone and also discusses other starting doses. (Smyth Tr. 369:11–18; Illum Tr. 664:6–8, ECF No. 293.)

Strang also conducted pharmacokinetic studies wherein he administered intranasal naloxone to patients. (Smyth Tr. 369:20–370:17.) Strang administered intranasal doses of 8 and 16 milligrams using 400 microliters of solution. (*Id.*) Strang administered 200 microliters per nostril, achieving that dose by squirting 100 microliters into each nostril two times. (*Id.*) To achieve a dosage of 16mg, each 100-microliter spray contained 4mg of naloxone, the same concentration found in Narcan. (*Id.*) To arrive at these doses, Strang analyzed pharmacokinetic studies of naloxone administered intravenously and determined that the intranasal equivalent of a 1mg intravenous dose would be between 3 and 4 milligrams. (*Id.* 370:25–371:16.) Strang would motivate a POSA to use a 4mg intranasal dose to match the bioavailability the FDA-approved 1mg intramuscular injectable dose. (*Id.* 371:11–22.)

Strang used sodium chloride as a tonicity-adjusting agent in his formulations and recommended using hydrochloric acid to adjust the pH of the formulation to be less than or equal to 5.5. (*Id.* 372:1–17.) Strang also discusses the typical pharmaceutical excipients, known to a POSA, that could be used with intranasal formulations. (*Id.* 372:22–373:15.)

2. Kulkarni[34]

The Kulkarni reference ("Kulkarni") is a review article focusing on the formulation of nasal sprays published in 2012, prior to the priority date of the Patents-in-Suit. (Smyth Tr. 373:16–374:1,

[34] TX-3103 is the Kulkarni reference, entitled "Formulation and characterization of nasal sprays: an examination of nasal spray formulation parameters and excipients and their influence on key in vitro tests." (*See* ECF No. 338.) It was offered and admitted into evidence on August 27, 2019.

ECF No. 292.) Kulkarni discusses various inactive ingredients and preservatives common to nasal sprays. (*Id.* 374:6–11.) Kulkarni noted that the pH range for commercially available nasal spray products ranges from 3.5 to 7, and discloses the optimal range as 4.5–6.5. (*Id.* 374:15–24.)

Kulkarni also discussed various inactive ingredients commonly found in nasal spray products. (*Id.* 374:25–375:9.) There are a limited number of excipients listed in the FDA inactive ingredients guide for nasal formulations. (*Id.*) The guide is a publicly available database that lists concentrations of inactive ingredients that have been approved by the FDA. (*Id.*) Sodium chloride, BZK, hydrochloric acid and edetate disodium, which is highly similar to EDTA, are included in this guide. (*Id.* 376:11–378:19.) Kulkarni states that EDTA has been used as a chelating agent in intranasal formulations and the BZK has similarly been used as a preservative. (*Id.* 378:10–379:9, 382:12–383:17.)

3. Djupesland

The Djupesland reference ("Djupesland") is a "review article published in 2013 focusing on nasal drug delivery devices" published in Drug Delivery and Translational Research journal. (Smyth Tr. 379:14–380:1, ECF No. 292.) Djupesland discusses specific delivery devices, their characteristics, and under what conditions they should be used. (*Id.* 380:8–15.) Djupesland recommended the use of unit-dose devices, like the Aptar UnitDose device, for "indications which require sporadic administration or sporadic use." (*Id.* 380:18–22.) Intranasal naloxone is an agent that requires sporadic administration. (*Id.* 380:23–381:5.) Djupesland specifically recommends the use of a specific single-dose and a duo-dose device, and links to Aptar's website. (*Id.* 381:7–10.) Djupesland discusses an Aptar device with a reservoir of 125 microliters that delivers 100 microliters of a nasal formulation. (*Id.* 382:6–9.)

Djupesland also briefly discusses the use of BZK as a preservative in nasal formulations, noting that while initial studies indicated a risk of nasal irritation associated with the use of BZK, more recent studies have indicated it is well-tolerated for chronic use. (*Id.* 382:11–383:3.)

4. Davies

The Davies reference ("Davies") is an international patent application, filed by David Davies and published in 2000, "directed to formulations and devices containing opioid antagonists for the treatment of opioid overdose." (Smyth Tr. 398:21–399:6, ECF No. 292.) Similar to Strang, Davies discusses the difficulties associated with medically untrained individuals treating opioid overdoses with injections and discusses how these difficulties could be alleviated with the use of intranasal naloxone. (*Id.* 399:17–23.) Indeed, Davies states that with intranasal naloxone "treatment can be given quickly and effectively without the need for the first-aider to find a blood vessel and give an intravenous injection." (TX-3109.08.) Davies notes that the ideal device to administer intranasal naloxone would be a single-use pre-primed device and describes an ideal dose volume ranging between 20 and 100 microliters. (Smyth Tr. 400:11–401:16.) Davies provides a dosing range of 0.2mg to 5.0mg of naloxone to be suitable for intranasal administration. (*Id.* 402:9–12.) In terms of inactive ingredients, Davies identifies sodium chloride and BZK as being suitable for use in his intranasal naloxone formulation. (*Id.* 402:20–25.)

5. Kerr 2009 / Kerr Formulation

The Kerr 2009 reference ("Kerr 2009") is a research article published in the Journal of Addiction in 2009. (Smyth Tr. 403:12–14, ECF No. 292.) Dr. Deborah Kerr conducted a clinical trial comparing the efficacy and safety of intranasal naloxone compared to naloxone administered via intramuscular injection. (*Id.* 403:15–19.) Like the prior art of Strang and Davies, Dr. Kerr noted the benefits of intranasal naloxone, including increased access for patients, reduced risk of

needle-related injuries, and ease of use for those without medical training. (*Id.* 404:6–15.) Dr. Kerr's study compared a 2mg dose of intranasal naloxone in a 0.5ml solution, administered with a MAD Kit, to a 2mg dose of intramuscular naloxone. (*Id.* 404:23–405:7.) Dr. Kerr concluded that intranasal administration was similarly efficacious to intramuscular administration. (*Id.* 405:12–19.) She also noted that re-dosing was more frequently required when naloxone was administered intranasally. (*Id.* 405:23–406:9; TX-0029.05.) Kerr discussed the benefits of using a smaller volume of liquid with a greater concentration of naloxone for intranasal administration. (Smyth Tr. 404:16–22; TX-0029.02.)

Dr. Kerr's formulation (the "Kerr Formulation") was not disclosed in the 2009 article; however, the parties here agree that Kerr's formulation included naloxone hydrochloride 0.2%, sodium chloride, BZK 0.01%, purified water, and hydrochloric acid to adjust the pH of the solution. (*See* TX-3098.01.) In February 2011, Lightlake's Chief Science Officer Dr. David Sinclair emailed Dr. Kerr regarding her intranasal naloxone study. (Crystal Tr. 287:16–289:24, 305:4–6, ECF No. 292). Dr. Kerr responded that she had obtained the naloxone for her study from Orion Laboratories in Australia. (*Id.*) Dr. Kerr also included a copy of the quote she had received from Orion Laboratories relating to her order. (*Id.*; *see* TX-3096.02.)[35] Dr. Crystal testified that Dr. Kerr was not a consult for Opiant and did not have a formal relationship with the company. (Crystal Tr. 290:8–13.) Dr. Sinclair exchanged emails with Paul Thomas from Aptar and, in one message, stated, "we have decided to use the preservative Debby Kerr used in Australia," which was BZK. (*See* TX-3096.01.)

[35] TX-3096 is described as "Email chain from D. Sinclair to S. Sinclair et al re Nasal spray formula." (*See* ECF No. 338.) It was offered and admitted into evidence on August 27, 2019. (*Id.*)

6. Bahal

The Bahal reference ("Bahal") is a U.S. patent published in 1999 discussing stabilized injectable naloxone solutions. (Smyth Tr. 407:1–19, ECF No. 292; *see* TX-3009.01.) Bahal identified that naloxone could be unstable and discovered that adding a chelating agent, like EDTA, prevents naloxone from degrading. (Smyth Tr. 407:20–408:1.) Bahal also used hydrochloric acid as a stabilizing agent. (*Id.* 408:5–10.) Dr. Illum admitted that after reading Bahal, a POSA might be motivated to try combining EDTA and BZK. (Illum Tr. 720:18–721:1, ECF No. 293.)

7. Wyse

The Wyse reference ("Wyse") is a United States patent, filed on December 19, 2014, and published on June 25, 2015. (Illum Tr. 667:12–668:5, ECF No. 293; Smyth Tr. 421:23–422:16, ECF No. 292.) Wyse discussed intranasal naloxone formulations and methods of administration. (Smyth Tr. 421:23–422:16.) The Wyse patent used a BZK concentration of 0.125%, which is significantly higher than the level in the FDA's list of inactive ingredients. (*Id.* 422:21–423:12.) Wyse concluded that naloxone degraded significantly when it was combined with BZK. (*Id.* 423:16–19.) Wyse's preliminary study concluded that BZK was not suitable for use as a preservative with naloxone and instead recommended the use of benzyl alcohol and paraben preservatives. (*Id.* 424:3–20.) Later in the patent, Wyse noted that subsequent studies indicated methyl paraben and propylene glycol and glycerin in fact caused increased naloxone degradation. (*Id.* 425:7–426:4.)

D. A Person of Ordinary Skill in the Art

The Court finds, and there is little disagreement between the parties, that a POSA is an individual that would have had a bachelor's of science in the pharmaceutical sciences or related

disciplines, including chemistry, and would have four to five years of experience developing intranasal drug products. (Smyth Tr. 322:1–323:3, ECF No. 292; Illum Tr. 575:1–17, ECF No. 293; Merlin Tr. 122:1–12, ECF No. 296.) Such a POSA might also possess a higher level of formal education but fewer years of practical experience. (*Id.*) They would work with a team and rely in part on the knowledge of their skilled team members. (*Id.*) A POSA would be supported by a team member with a medical degree with several years of clinical experience treating opioid overdose patients in both the hospital and community settings. (*Id.*) Dr. Smyth and Dr. Illum noted that they had both reviewed the parties' POSA definitions and that their opinions regarding obviousness would not be affected if one party's definition was applied by the Court over the other's. (Smyth Tr. 322:1–14, Illum Tr. 576:1–12.)

E. Lightlake's Pre-IND Meeting with the FDA

On May 24, 2012, Lightlake had a pre-IND meeting with the FDA. (Crystal Tr. 303:10–19, ECF No. 292; Smyth Tr. 352:1–5, ECF No. 292.) Before the pre-IND meeting, Lightlake submitted a package to the FDA expressing concerns about the development of an intranasal naloxone product noting, "[t]here is little if any commercial incentive for developing a new nasal naloxone drug product" and that "because of its widespread use, it most likely is not patentable because its use for opioid overdose is 'obvious.'" (Crystal Tr. 301:3–17; 302:14–20; *see* TX-3079.14.)[36] Lightlake's package noted "[t]here is no question about the clinical viability of nasal naloxone; it is arguably the perfect antidote, and has already achieved the status of a preferred standard of care." (Crystal Tr. 301:3–302:1; TX-3079.14.)

[36] TX-3079 is a letter from Lightlake to the FDA relating to Type B pre-IND meeting information package and attachment. (*See* ECF No. 338.) It was offered and entered into evidence on August 27, 2019. (*Id.*)

During the meeting, Lightlake discussed their plans to compare a 2mg dose of intranasal naloxone with the FDA-approved 2mg intramuscular dose. (TX-3088.10.)[37] The FDA recommended that Lightlake consider a higher dose of naloxone for their proposed intranasal product. (Smyth Tr. 355:9–25; TX-3088.04.) Specifically, the FDA noted that:

> [T]he population-[pharmacokinetic] studies in the literature indicate the relative bioavailability of 2mg naloxone administered in [the intranasal] route is relatively poor in comparison to 2mg administered via the [intramuscular] route. Therefore, as you intend to use a 2mg [intramuscular] naloxone dose in the relative bioavailability study, *you may need to consider increasing the dose of your proposed product to achieve systemic exposure*.

(TX-3088.10) (emphasis added). The FDA further stated "[i]t would be acceptable if a more concentrated naloxone product, or a higher dose of naloxone was needed to achieve the targeted [pharmacokinetic] characteristics by the intranasal route." (TX-3088.04; Smyth Tr. 356:22–357:9.) Indeed, the FDA recognized, as a POSA would, that intranasal administration has a lower bioavailability and, therefore, greater concentrations are needed to achieve comparable bioavailability with an injectable dose. The FDA did not express any concerns about any side effects associated with a higher dose of naloxone. (Smyth Tr. 356:1–3, 357:6–9.)

F. Intranasal Naloxone Was Known to Be Safe and Efficacious, and Was Widely Used Prior to March 16, 2015

Naloxone was initially approved for the treatment of opioid overdoses in 1971 and has become widely used since its approval. (Smyth Tr. 326:11–15, 329:1–8, ECF No. 292; Illum Tr. 576:19–23, ECF No. 293.) Today, naloxone is commonly administered by EMTs and other first responders via intravenous injection, subcutaneous injection, intramuscular injection, and intranasal administration. (Smyth Tr. 328:7–15, 329:1–12; Illum Tr. 576:24–577:3;

[37] TX-3088 is a letter from FDA to Dr. Crystal enclosing May 24, 2012 meeting minutes. (*See* ECF No. 338.) It was offered and entered into evidence on August 27, 2019. (*Id.*)

577:24–578:21.) Indeed, it is standard practice for emergency responders to carry naloxone to reverse opioid overdoses. (*See* Wermeling 2010 Article, TX-0052.)

Prior to March 16, 2015, naloxone was known to be "an extremely safe drug" and it was known in the prior art that naloxone could be administered intranasally. (*See* Kerr 2009, TX-0029.07[38]; Smyth Tr. 340:12–343:20; Merlin Tr. 160:2–7, ECF No. 296; Illum Tr. 829:20–23.) Intranasal administration was popular with EMS responders and laypeople in the community setting because it was needle-free and therefore did not pose the dangers associated with exposed needles that injectable naloxone did. (Smyth Tr. 367:1–15.)[39] The Kerr 2009 Reference stated, in relevant part, "naloxone administered via the [intranasal] route is an effective and safe intervention for the initial management of heroin overdose." (*See* TX-0029.07; Merlin Tr. 151:24–25.)

To administer naloxone intranasally, individuals utilized a MAD Kit which consisted of a mucosal atomizer and a syringe of naloxone solution that had to be assembled prior to use. (Smyth Tr. 329:10–19.) A MAD Kit was considered the "gold standard for [administration of] intranasal naloxone." (Merlin II Tr. 1448:24–1449:2, ECF No. 294.) Indeed, prior to the priority date of the Patents-in-Suit, naloxone was most-commonly used with a MAD Kit and such use was found in emergency medical service protocols. (Merlin II Tr. 1454:1–3; Williams Tr. 1448:18–23, 1396:18–23, ECF No. 294.) Intranasal administration, however, was not limited to medical

[38] TX-0029 is the Kerr 2009 study. (*See* ECF No. 338.) It was offered and admitted into evidence on August 26, 2019. (*Id.*)

[39] "[A] series of clinical studies have demonstrated that intranasal naloxone avoids potentially dangerous needle sticks and the risk of air embolism while maintaining potency and efficacy for reversing respiratory depression due to opioid overdose." (*See* TX-3195.04.) TX-3195 is "S. Leavitt. Intranasal naloxone for at-home opioid rescue. Pract. Pain Manag. 2010." It was offered and admitted into evidence on September 6, 2019. (*Id.*)

professionals and emergency services technicians. Prior to March 16, 2015, MAD Kits were frequently used by laypeople to administer intranasal naloxone in the community setting and MAD devices were commonly distributed for such community use. (Merlin Tr. 136:3–20; Williams Tr. 1398:12–16.)

In light of the testimony given at trial and the exhibits entered into evidence, the Court finds by clear and convincing evidence, that before the priority date of the Patents-in-Suit, a POSA would have recognized the prior art indicated that naloxone was safe and efficacious when administered intranasally.

G. Aptar UnitDose Device

The Aptar UnitDose Device is an FDA-approved device that administers intranasal medications in 100 or 200 microliter volumes. (Smyth Tr. 335:17–21, ECF No. 292.) The Aptar device was commercially available prior to March 16, 2015, and was not invented by the inventors of the Patents-in-Suit. (Majumdar Tr. 1041:7–14, ECF No. 291.) Narcan is also not the first intranasal medication to use the Aptar UnitDose device. Before the priority date of the Patents-in-Suit, the Aptar device had been used with the intranasal migraine drugs Immitrex and Zomig, and also the intranasal influenza vaccine, FluMist. (Smyth Tr. 382:1–4; Illum Tr. 724:11–725:1, ECF No. 292; *see* TX-3007.08 (Djupesland).)

Prior to Narcan, intranasal naloxone was administered using a MAD Kit. The MAD Kit was FDA-approved to deliver injectable formulations intranasally. (Smyth Tr. 329:12–19.) When used to administer naloxone, the MAD Kit had numerous drawbacks which were well known to a POSA. First, the dose of naloxone delivered by the MAD Kit was an injectable dose that was converted for intranasal administration and, therefore, was not optimized for intranasal delivery. (Smyth Tr. 330:17–19).

Second, the MAD Kit delivered too much fluid into a patient's nostrils. (Illum Tr. 830:2–15.) When used to administer naloxone, the MAD Kit typically delivered a 2mg dose in 2 milliliters of solution, with 1 milliliter being delivered to each nostril. (Smyth Tr. 330:17–19; Merlin II Tr. 1450:14–18, 1451:24–1452:3, 1474:22–1475:8, ECF No. 294.) The human nostril, however, can only hold approximately 250 microliters of fluid. (Smyth Tr. 330:20–24.) Excess fluid will either drip out of the patient's nostrils or will go down their throat and into their stomach. (Illum Tr. 597:24–599:2.) The medication contained in this excess fluid is not absorbed into the blood stream in a significant amount. (*Id.*) A POSA, therefore, would have been motivated to use a device that delivered a smaller volume of liquid.

Finally, the MAD Kit also had to be assembled prior to use. (Smyth Tr. 329:22–330:6.)[40] This intermediary assembly step presented a significant impediment to use in the community setting where individuals lack medical training. (Williams Tr. 1432:2–5.) The shortcomings of the MAD Kit were discussed at the 2012 FDA Meeting, with one physician noting that the administration of naloxone "could be improved [] with a one-step affordable FDA-approved intranasal delivery device." (*See* TX-0047.117–.118[41]; Smyth Tr. 336:18–337:25.) A POSA, therefore, would have been motivated to select a device that was as easy to use as possible. (Williams Tr. 1432:2–5.)

By contrast, the Aptar UnitDose device delivers volumes of either 100 or 200 microliters, both of which are suitable for nasal delivery. (Smyth Tr. 335:17–21.) It is an off-the-shelf

[40] During his testimony, Dr. Merlin demonstrated to the Court how to assemble a MAD Kit device. (*See* Merlin Tr. 134:25–135:25, ECF No. 296.)

[41] TX-0047 is a transcript of the 2012 FDA Meeting, entitled "Role of Naloxone in Opioid Overdose Fatality Prevention, dated Thursday, April 12, 2012, from 8:30am to 5:30pm." (*See* ECF No. 338.) It was offered and admitted into evidence on August 27, 2019. (*Id.*)

commercially available product that is pre-primed and requires no assembly. (Smyth Tr. 333:2–23.) Djupesland specifically recommended the Aptar UnitDose device for indications that require sporadic use, which is how naloxone is administered. (Smyth Tr. 380:11–381:13.) Indeed, prior to March 16, 2015, AntiOp selected the Aptar UnitDose device for use with the intranasal naloxone product they were developing. (Illum Tr. 735:10–736:23; *see also* TX-0057.04, .06, .16–.23.)

In light of the testimony given at trial and the exhibits entered into evidence, the Court finds by clear and convincing evidence, that before the priority date of the Patents-in-Suit, a POSA would have recognized the limitations of the MAD Kit and been motivated to select the Aptar UnitDose device when developing an improved intranasal naloxone product for community use.

H. A POSA Would Have Thought a 4 Milligram Intranasal Dose Was Safe and Would Have Preferred a Higher Initial Dose of Naloxone in the Community Setting

Prior to March 16, 2015, naloxone was known to be "an extremely safe drug." (*See* Kerr 2009, TX-29.07; Smyth Tr. 340:12–343:20, ECF No. 292; Merlin Tr. 160:2–7, ECF No. 296; Illum Tr. 829:20–23, ECF No. 293; Williams Tr. 1432:10–19, ECF No. 294.) The prescribing information on the FDA-approved injectable form of naloxone states, in relevant part:

> An initial dose of 0.4 to 2 milligrams of naloxone hydrochloride may be administered intravenously. If the desired degree of counteraction and improvement in respiratory functions is not obtained, it may be repeated at 2-to-3-minute intervals. If no response is observed after 10 milligrams of naloxone hydrochloride has been administered, the diagnosis of narcotic-induced or partial narcotic-induced toxicity should be questioned.

(TX-3079.55; Smyth Tr. 327:4–328:6.) The prescribing information does not set an upper limit on the amount of naloxone that should be administered but notes that if the patient does not respond after 10mg, the diagnosis of opioid overdose should be reconsidered. (Smyth Tr. 327:22–328:6.)

The prior art indicated that naloxone could be administered safely in a doses of 0.5mg to 20mg. (*See* Strang, TX-0054.41[42]; Smyth Tr. 369:2–6, 402:9–12.) Among the initial doses recommended by Strang was an initial dose of 4mg. (Smyth Tr. 369:11–18.) A POSA would also have known that there was no single effective dose that would work for all patients and that an initial dose of 4mg would not be sufficient for some patients. (Williams Tr. 1405:1–15, 1418:19–1419:7.)

1. The 2012 FDA Meeting

The general purpose of the 2012 FDA Meeting was "to promote or encourage the industry to develop an intranasal naloxone product that could be FDA-approved." (Smyth Tr. 336:21–337:3, ECF No. 292.) The FDA provided attendees with insights into the regulatory approval process and discussed "what it would take to develop an intranasal form [of naloxone]." (TX-0047.14; Smyth Tr. 336:11–20.) Part of the focus of the meeting was comparing the bioavailability of an intranasal naloxone product with the already approved intravenous and intramuscular injectable products. (Smyth Tr. 338:1–400:10; TX-0047.167.) The FDA noted that, for an intranasal naloxone product, "the idea is to start off with a product that can provide exposure *at least* comparable to what's been approved." (TX-0047.172; *see also* Smyth Tr. 338:1–400:10 (emphasis added).) The FDA also noted that they were not overly concerned about the safety implications of a higher dose of naloxone because it is known to be a relatively safe drug. (TX-0047.172; Smyth Tr. 339:13–340:9.)

[42] TX-0054 is the Strang reference. (*See* ECF No. 338.) It was offered and admitted into evidence on August 27, 2019. (*Id.*)

2. Naloxone Has a Lower Bioavailability When Administered Intranasally Compared to Intramuscular or Intravenous Administration

Prior to March 2015, a POSA would have known that naloxone has a lower bioavailability when administered intranasally compared to when it is administered in an injectable dose because an intranasal dose must first be absorbed through the nasal mucosa prior to be absorbed into the bloodstream. (Smyth Tr. 344:13–345:2, ECF No. 292; Illum Tr. 648:4–649:4, ECF No. 293.) Intranasal naloxone, therefore, requires a higher dose of naloxone to achieve the same bioavailability as an intravenous dose. (Williams Tr. 1419:25–1420:7, ECF No. 294.) In Adapt's Narcan NDA, they noted that with intranasal dosing, "the appropriate dose [of naloxone] may be 2mg or 4mg to achieve equivalent effects as that observed with [a] 1mg or 2mg [intramuscular dose of] naloxone." (TX-3052.17.)

The prior art also indicated that patients who received intranasal naloxone in doses of 0.4mg to 2mg more often required redosing compared to patients who received an intramuscular dose. (Merlin Tr. 152:10–15, 154:17–22, 183:5–13, 234:12–17, ECF No. 296; *see also* Kerr 2009.) There have been no clinical studies, however, concerning the exact timing of when to administer a second dose to a patient who is not responding to a low initial dose. (Williams Tr. 1410:20–1411:3.) The time delay inherent in redosing poses significant health risks to a patient, including brain damage and death. (Merlin Tr. 160:8–16.) Adapt noted that the prior art discussed these risks in their NDA. (*See* TX-3052.16–.17.)[43] The time-related risks associated with redosing are exacerbated in the community setting where naloxone is administered by a layperson instead of a trained medical professional. (Merlin Tr. 139:2–10, 160:21–161:4.) Adapt's

[43] TX-3052 is NDA 208411 for Narcan (naloxone hydrochloride) nasal spray. (*See* ECF No. 338.) It was offered on August 28, 2019, and entered into evidence on August 29, 2019. (*Id.*)

NDA admits that, in the community setting, individuals are often unsure when to re-dose. (TX-3052.24.) Prior to March 2015, a POSA would have known that a layperson using a MAD Kit to administer a 2mg dose of intranasal naloxone had to re-dose nearly half of the time. (Illum Tr. 635:11–636:24; *see* TX-0051 (Walley 2013) (noting that 48% of cases in the study required a second 2mg dose of naloxone).)

3. A POSA Would Have Preferred a Higher Initial Dose in the Community Setting

Prior to March 2015, a POSA would have preferred a higher initial dose of naloxone in the community setting: (1) to keep treatment simple for a layperson to administer; (2) to avoid the dangers of re-dosing; and (3) because a layperson may lack training in rescue breathing and lacks the additional tools to combat opioid overdoses inherent in a hospital or EMS setting. (Merlin Tr. 159:22–160:1, 165:1–7, ECF No. 296; Merlin II Tr. 1453:9–17, 1463:4–8, 1463:23–1464:17, ECF No. 294; Williams Tr. 1416:1–1418:17, ECF No. 294; Illum Tr. 837:12–24, ECF No. 293.)

In a hospital setting, administering naloxone "low and slow" is generally preferred because of the resources and therapeutic objectives inherent in such a treatment setting. (Merlin II Tr. 1464:12–14, 1465:7–1466:1.) Physicians and nurses in a hospital setting can safely administer naloxone intravenously due to the nature of the environment. (*Id*. 1463:9–17.) However, a POSA would have understood that intranasal naloxone is more appropriate for the community setting. (*Id.* 1463:4–8.) In addition to often lacking training in rescue breathing and chest compressions, Walley 2013 found that only 33% of participants called emergency services when faced with a suspected overdose. (Williams Tr. 1416:1–1418:17; *see* TX-0051 (Walley 2013).) The emergence of more potent opioids, such as fentanyl, would also have led a POSA to prefer a higher initial dose. (Merlin Tr. 125:10–23.) Indeed, a higher dose of naloxone is required to reverse the effects

of more potent opioids. (*Id.*) Prior to 2015, 4mg intranasal doses of naloxone were administered via a MAD Kit to reverse the effects of higher potency opioids. (*Id*. 150:12–151:3.)

4. A POSA Would Have Known that the Benefits of a Higher Initial Dose Outweighed the Concerns About Withdrawal Side Effects

When treating a suspected opioid overdose, the priority is to restore breathing as quickly as possible. (Merlin Tr. 128:16–129:11, ECF No. 296.) After a patient loses respiratory function, brain damage will begin to occur within three to five minutes. (Williams Tr. 1411:15–21, ECF No. 294.) A POSA, therefore, would understand that administering a higher initial dose to ensure the restoration of breathing function, with the potential of withdrawal side effects, was preferable to administering a low initial dose and the corresponding time-related risks. (*Id.* 1466:2–9.) Adapt's own NDA even acknowledged this, stating, in relevant part,

> While it is possible to induce a rapid opioid withdrawal in tolerant patients, *this is more of an unpleasant experience and not typically life-threatening or high enough risk to off-set the benefit of naloxone use to stop symptoms of overdose*. It is also possible that additional doses may be needed to properly treat an opioid overdose situation and as such more than one administration of [n]aloxone is sometimes required.

(TX-3052.07 (emphasis added).) Administering a less than effective dose of naloxone will result in a patient suffering prolonged respiratory depression, which risks the loss of heartbeat, brain damage, and even death. (Merlin Tr. 129:8–11, 138:12–139:1, 160:11–14.) A low dose of naloxone may also fail to return some patients to consciousness. (Illum Tr. 846:7–16, ECF No. 293.)

Dr. Smyth testified that, based on the discussion at the 2012 FDA Meeting, a POSA would not have been discouraged from using a higher dose of naloxone to reverse an opioid overdose. (Smyth Tr. 343:13–23, ECF No. 292.) In a 2012 article published in the New England Journal of Medicine, Dr. Edward Boyer discussed an algorithm for treating opioid overdoses in a hospital

setting. (Merlin Tr. 141:20–144:9, TX-0017.06.) Dr. Boyer's algorithm recommended increasing intravenous doses up to a total of 15mg if the initial dose is not successful at reversing the overdose. (*Id.*) The Boyer article recommended an initial 0.5mg intravenous dose, a second dose of 2mg if the patient does not respond to the initial dose, and then a third dose of 4mg if the patient is still not responding. (Illum Tr. 834:11–13, TX-0017.06.)[44] The prior art also did not discourage or rule out a dose greater than 2mg. (Smyth II Tr. 1252:5–18.)

Indeed, Naloxone was known to be a safe medication, even when administered in higher doses. (Merlin Tr. 161:15–23; Smyth Tr. 340:12–343:20; Illum Tr. 580:3–6.) The clinical experts present at the 2012 FDA Meeting made similar statements, with Dr. Terman, a professor at the University of Washington, stating that doses of naloxone "700 times as much as the indicated dose" had been giving to healthy patients who subsequently suffered no adverse effects. (Smyth Tr. 340:12–343:20; TX-0047.59.) Dr. Merlin, discussing the research of Dr. Lewis Goldfrank whom he characterized as "probably the most highly-respected toxicologist in the world," testified that the prior art indicated that "complications attributed to naloxone . . . were erroneous or at most extremely rare." (Merlin Tr. 161:15–162:2.) Adapt's NDA stated that:

> The most common dose of [intramuscular] in most efficacy studies in the literature is approximately 2 milligrams, and in-use studies confirmed that doses of 2 milligrams or greater were typically used to control opioid overdose in subjects with mild to moderate respiratory depression. . . . Other studies with [intramuscular] naloxone demonstrate that doses up to 10 milligrams would improve efficacy with little to no increase in risk to subjects.

[44] TX-0017 is a 2012 article written by Dr. Edward Boyer, entitled "Management of Opioid Analgesic Overdose." (*See* ECF No. 338.) It was offered and admitted into evidence on August 26, 2019. (*Id.*)

(Illum Tr. 841:3–10, 838:14–24; TX-3052.23.) Indeed, Thomas Begres testified that he had administered naloxone "hundreds of times" and could "recall about six" patients who experienced withdrawal symptoms. (Begres Tr. 1226:5–16, ECF No. 295.)

The prior art indicated that withdrawal symptoms from naloxone tend to dissipate within thirty to sixty minutes because the drug has a relatively short half-life. (*See* TX-0053.08 (Wermeling 2015).)[45] The most common side effects associated with withdrawal are sweating, difficulty seeing, problems breathing, and diarrhea. (Merlin Tr. 161:9–14.) The Loimer 1994 reference tested a 1mg dose of intranasal naloxone on prisoners who were opioid addicts rather than overdose patients. (Illum Tr. 588:25–589:14.) Loimer reported withdrawal symptoms including "uncontrollable yawning, running nose, lacrimation, profuse sweating, shivering, abdominal cramps, piloerection, hand tremors, muscular twitches, restlessness, and vomiting." (*Id.* 847:13–24; TX-0032.03.)[46] Symptoms of withdrawal are often difficult to untangle from the patient's underlying toxicity. Indeed, Wermeling 2013 states "[i]t is difficult to separate out opioid overdose effects concurrent co-intoxicant effects (benzodiazepines, ethanol, etc.) from naloxone effects, from the underlying hypoxia/hypercarbia and subsequent reversal." (TX-3108.10[47]; Illum Tr. 848:21–849:12.)

[45] TX-0053 is a 2015 Wermeling article entitled, "Review of naloxone safety for opioid overdose: practical considerations for new technology and expanded public access." (*See* ECF No. 338.) It was offered on August 28, 2019 and admitted into evidence on August 29, 2019. (*Id.*)

[46] TX-0032 is the 1994 Loimer reference, entitled "Nasal administration of naloxone is as effective as the intravenous route in opiate addicts." (*See* ECF No. 338.) It was offered on August 26, 2019 and was admitted into evidence August 27, 2019. (*Id.*)

[47] TX-3108 is an exhibit described as "Daniel P. Wermeling, A Response to the Opioid Overdose Epidemic: Naloxone Nasay Spray." (*See* ECF No. 338.) It was offered on August 26, 2019 and was admitted into evidence on August 27, 2019. (*Id.*)

Withdrawal symptoms are also not unique to higher doses of naloxone and have been observed in patients receiving doses of naloxone as low as 0.4mg. (Illum Tr. 587:23–588:3, 590:8–22, 596:23–597:9.) The FDA did not require that Adapt conduct studies on whether Narcan had fewer withdrawal effects compared to other 4mg doses of naloxone, and no evidence was presented to the Court to that effect. (*Id*. 855:16–856:15.) Narcan's own label warns about the possibility of severe opioid withdrawal, with the same potential side effects listed for the 2mg and 4mg doses. (*Id*. 856:19–21; Merlin Tr. 162:16–163:8; TX-3013.01, .05–.07.)[48] Wermeling 2015 also indicated that studies comparing intranasal and intramuscular naloxone found "no major adverse events in either group" and that such adverse events were "described as mild." (TX0053.07.)

In light of the testimony given at trial and the exhibits entered into evidence, the Court finds by clear and convincing evidence, that before the priority date of the Patents-in-Suit, a POSA would have thought a 4mg intranasal dose was safe and would have preferred a higher initial dose of naloxone in the community setting.

I. The Inclusion of BZK, EDTA, Hydrochloric Acid, and Sodium Chloride

Prior to 2015, intranasal naloxone was administered via a MAD Kit which converted an injectable dose into one suitable for nasal administration. However, as discussed above, this dose was not optimized for nasal administration. (Smyth Tr. 329:22–330:6, ECF No. 292; Illum Tr. 830:2–15, ECF No. 293.) A POSA who was developing an intranasal naloxone product would, therefore, have been motivated to optimize their formulation for nasal delivery. (Smyth Tr. 329:22–330:6.) Strang noted that "[t]ypical pharmaceutical excipients used in

[48] TX-3013 is described as "Revised Narcan (Naloxone Hydrochloride) Nasal Spray Prescribing Information." (*See* ECF No. 338.) It was offered and admitted into evidence on August 26, 2019. (*Id*.)

intranasal formulations are known to the skilled person and can be used for the formulations according to the present invention." (TX-0054.34; Smyth Tr. 372:22–373:15.) A POSA would know that "intranasal formulations generally have certain characteristics to make them acceptable and tolerable in the nose, things like the tonicity and pH." (Smyth Tr. 345:16–18.)

Tonicity measures the "saltiness or the strength of the solution." (*Id.* 345:19–346:23.) Intranasal formulations seek to match the tonicity of the medication with that of the nose. (*Id.*) If these values are not similar it can cause nasal irritation. (*Id.*) Intranasal products are known to be "isotonic or slightly hypertonic" and often require a tonicity agent. (*Id.*) Prior to the priority date of the Patents-in-Suit, sodium chloride was a known tonicity agent and was listed in the Handbook of Pharmaceutical Excipients. (Majumdar Tr. 1031:10–15, ECF No. 291.) The Court finds, therefore, that a POSA would have used sodium chloride as a tonicity agent in a nasal formulation.

Similarly, an intranasal formulation with an unbalanced pH can cause nasal irritation. (Smyth Tr. 347:1–6.) The typical pH of an intranasal product ranges from 3.5–7 on a scale of 1 to 14. (*Id.* 347: 12–17.) The pH of an intranasal product is commonly adjusted and can be optimized with repeated experimentation. (*Id.* 347:18–21.) The Court finds, therefore, that a POSA would have used hydrochloric acid to adjust the pH of a nasal formulation.

Preservatives are commonly used in intranasal formulations and prior to the priority date of the Patents-in-Suit, it was regular practice to optimize the amount of preservatives for intranasal use. (*Id.* 348:22–349:2; Illum Tr. 807:4–25.) Before March 2015, BZK was commonly used as a preservative and had been used in over 200 intranasal products. (Smyth Tr. 382:11–383:3; Illum Tr. 776:20–23, 777:5–8; Majumdar Tr. 1034:17–21.) Limor Zahavi testified that Teva used BZK in "each and every one of [its] nasal programs, [because] it is stable and well known."

(Zahavi Tr. 66:18–23, ECF No. 296.) The Court finds, therefore, that a POSA would have been motivated to select and use BZK as a preservative for an intranasal naloxone formulation.

Prior to March 2015, it was known in the prior art that naloxone was subject to degradation in the form of oxidation. (Smyth Tr. 349:8–13.) It was common to stabilize naloxone with a chelating agent. (*Id.* 349:14–350:12.) Chelating agents slow the oxidation of naloxone. (*Id.* 350:1–7.) EDTA was a known stabilizer in pharmaceutical formulations prior to the priority date of the Patents-in-Suit and was listed in the Handbook of Pharmaceutical Excipients as a chelating agent. (Illum Tr. 805:10–17; Majumdar 1035:14–17.) In fact, EDTA was also a known stabilizer for naloxone formulations. (*Id.*; *see also* Smyth Tr. 378:9–19.) It was also known that EDTA could be used with BZK in intranasal formulations to increase their preservative effects. (Illum Tr. 805:23–806:6; Smyth Tr. 378:9–19, 430:25–431:20.) The Court finds, therefore, that a POSA would have been motivated to select and use EDTA as a stabilizing agent for an intranasal naloxone formulation.

In light of the testimony given at trial and the exhibits entered into evidence, the Court finds by clear and convincing evidence, that before the priority date of the Patents-in-Suit, a POSA would have optimized naloxone for intranasal administration and found it obvious to use sodium chloride, hydrochloric acid, BZK, and EDTA.

J. The Prior Art Renders the Asserted Claims of the Patents-in-Suit Obvious

For economy, the Court incorporates by reference the detailed descriptions of the prior art it described in section II.E., *supra*. For the reasons described below, the Court finds, by clear and convincing evidence, that the asserted claims of the Patents-in-Suit are rendered obvious by the prior art.

1. The Strang / Kulkarni / Djupesland Combination

The Court finds the asserted claims of the Patents-in-Suit are obvious in light of the Strang / Kulkarni / Djupesland combination.

Strang discloses an intranasal form of naloxone formulated for the treatment of opioid overdoses. (Smyth Tr. 367:4–5, 385:4–21, ECF No. 292; TX-0054.02, .13.) He describes a need "for naloxone dosage form which can easily be administered to drug addicts suffering from overdosing by medically untrained subjects, e.g., by family members or other careers." (Smyth Tr. 367:18–22; TX-0054.04, .56.) He recommended a multi-directional nasal spray as the preferred form of the intranasal dosage. (TX-0054.34.) Strang stated "[p]referably, the dosing unit of the intranasal dosage form as claimed herein is administered to a single nostril. Thus, preferably, the above-mentioned amount of naloxone or a pharmaceutically acceptable salt thereof is provided by administration to one nostril." (TX-0054.07; Smyth Tr. 386:4–23.)

Djupesland states that drugs "intended for single administration or sporadic use and where tight control of the dose and formulation is of particular importance, single-dose or duo-dose spray devices are preferred (www.aptar.com)." (Smyth Tr. 386:4–388:7; TX-3007.07.) Djupesland also notes that these preferred devices could be operated with one hand. (Smyth Tr. 386:4–388:7; TX-3007.08.)

Strang noted that the volume of liquid delivered to the nostril should be less than 250 microliters and specifically preferred volumes of 50, 100, 150, and 200 microliters. (Smyth Tr. 386:4–388:7; TX-0054.07.) The device described by Djupesland is filled with 125 microliters of solution and administers a dose consisting of 100 microliters of fluid, which is delivered in a single actuation. (Smyth Tr. 386:4–388:7; TX-3007.08.)

A confidence interval is a measure of the "margin of error or the reliability of a particular device." (Smyth Tr. 390:10–18.) A confidence interval of plus or minus 2.5% per actuation, which is found in the Patents-in-Suit, is "an inherent feature of the Aptar UnitDose device." (*Id.* 390:10–393:19.) The structural features of the Aptar UnitDose, including a reservoir, piston, and swirl chamber, are features of the device discussed by Djupesland. (*Id.* 388:8–390:10.)

Strang states that "[i]t can be preferred to start with an amount equivalent to 4mg" of naloxone. (*Id.* 369:11–18, 393:20–394:20; Illum Tr. 664:6–8, ECF No. 293; TX-0054.30.) Strang estimated that an intranasal dose of 3mg to 4mg would be bioequivalent to the FDA-approved 1mg injectable dose. (Smyth Tr. 393:20–394:20; TX-0054.49.) The Court finds that a POSA would be motivated to select a 4mg intranasal dose of naloxone to match the bioavailability of the 1mg injectable dose.

As to the tonicity agent, Strang describes a solution that has "[sodium chloride] in purified water at a concentration of about 1.0% weight/volume, most preferably [sodium chloride] in purified water at concentration of about 0.9% weight/volume." (Smyth Tr. 394:21–395:23; TX-0054.10.) The Court finds that a POSA could arrive at the range of sodium chloride claimed by the Patents-in-Suit through routine optimization. (Smyth Tr. 394:21–395:23.)

As to the pH of the formulation, Strang prefers a pH that is less than or equal to 5.5, and Strang and Kulkarni specifically discuss using hydrochloric acid as an agent. (Smyth Tr. 395:24–396:22; TX-0054.10; TX-3103.04.)

As to the use of BZK as a preservative, Strang generally describes typical pharmaceutical excipients used in intranasal formulations. (Smyth 372:22–373:15; TX-0054.34.) Kulkarni discusses specific preservatives that can be used to stabilize a nasal formulation in more detail and discloses a range of BZK with an upper limit of 0.119%. (Smyth Tr. 397:3–11.) The Court finds

that a POSA could arrive at the range of BZK claimed by the Patents-in-Suit through routine optimization. (*Id.*)

As to the use of EDTA, Kulkarni states a concentration of 0.5% of EDTA and describes using hydrochloric acid to adjust the pH of the formulation. (Smyth Tr. 397:12–25; TX-3103.04.) As with the other pharmaceutical excipients, the Court finds a POSA could arrive at the range of EDTA claimed in the Patents-in-Suit through routine optimization.

In light of the prior art, Court finds, by clear and convincing evidence that a POSA would have been motivated to combine Strang, Djupesland, and Kulkarni and would have had a reasonable expectation of success in arriving at an improved intranasal naloxone product. (Smyth Tr. 383:4–9.)

2. The Davies / Kerr 2009 / Kerr Formulation / Bahal Combination

Alternatively, the Court finds the asserted claims of the Patents-in-Suit are obvious in light of the Davies / Kerr 2009, Kerr Formulation / Bahal combination.

Davies discusses formulations and devices that can be used to treat opioid overdoses and states that while intravenous administration is the standard method of administering naloxone, it poses significant difficulties in the community setting where naloxone is likely to be administered by individuals lacking medical training. (Smyth Tr. 398:23–399:23, ECF No. 292; TX-3109.01.) Davies teaches that intranasal naloxone "can be given quickly and effectively without the need for the first-aider to find a blood vessel and give an intravenous injection." (Smyth Tr. 400:4–14; TX-3109.08.)

Davies describes the optimal device for administering intranasal naloxone to be "[a] spray applicator." (Smyth Tr. 399:11–15, 400:4–401:5; Illum Tr. 702:22–703:8, ECF No. 293; TX-3109.01.) He states that "suitable spray applicators are preferably single-trip devices."

(Smyth Tr. 400:4–401:5; TX-3109.04.) The device described in Davies is actuatable with a single hand. (*Id.* 411:10–18; TX-3109.07.) It delivers a volume of liquid between 20 and 100 microliters. (*Id.* 401:6–16; TX-3109.04–.05.) Adapt argues that the device in Davies is different from the Aptar UnitDose device in notable ways and, accordingly, a POSA would not read Davies and be motivated to select the Aptar device. (*See* ECF No. 287 ¶¶ 174–75.) Specifically, the device in Davies lacked a canula and failed to provide information relating to reservoir volume and the accuracy of the spray. (*Id.*) The Court finds these arguments unconvincing and finds Dr. Smyth's testimony on this subject persuasive. Dr. Smyth testified that because the Aptar UnitDose device was readily available on the market, a POSA would have been motivated to use it rather than attempt to modify the device in Davies. (Smyth Tr. 414:1–12.) A confidence interval of plus or minus 2.5% per actuation, which is found in the Patents-in-Suit, is "an inherent feature of the Aptar UnitDose device." (*Id.* 390:10–393:19.) The structural features of the Aptar UnitDose, including a reservoir, piston, and swirl chamber, are features of the device discussed by Davies.

As to the dose of naloxone, Davies describes a range of 0.2mg to 5.0mg as being appropriate. (*Id.* 402:9–12; Illum Tr. 705:9–13; TX-3109.05.) The Patents-in-Suit note that this range is disclosed by Davies. (*See* TX-0002.10; TX-0004.10.) The range of doses disclosed by Davies, combined with the volume disclosed by Davies, would result in a concentrated dose of naloxone. (Smyth II Tr. 1253:1–1254:6, ECF No. 295.)

As to a tonicity agent, the Kerr Formulation used sodium chloride. (Smyth Tr. 415.13–23; TX-3098.01.) Both Davies and Kerr discuss a sodium chloride concentration between 0.2 to 1.2mg per 100 microliters of solution. (Smyth Tr. 415:13–23.) The Court finds that a POSA could arrive at the range claimed in the Patents-in-Suit through routine optimization and experimentation. (*Id.* 415:24–416:11.)

Bahal preferred formulations that included sodium chloride as a tonicity agent and hydrochloric acid to adjust the pH of the solution. (*Id.*) Kerr also used hydrochloric acid. (*Id.*) The Court finds that a POSA could arrive at the range claimed in the Patents-in-Suit through routine optimization and experimentation.

The Kerr Formulation used BZK. (*Id*. 416:12–25.) Davies also states that formulation should have a slightly acidic pH and uses BZK as a preservative in one of his formulations. (*Id.* 402:20–403:7; TX-3109.05–.06.) The Court finds that a POSA could arrive at the range claimed in the Patents-in-Suit through routine optimization and experimentation.

Bahal stated that the "addition of a chelating agent, such as [EDTA], to the commercial formulation prevents naloxone degradation, even in the presence of oxygen and after autoclaving." (Smyth Tr. 407:20–408:1; TX-3009.10.) Bahal preferred a range of 0.0001% to 1.0%. (Smyth Tr. 408:2–4; TX-3009.10.)

In light of the prior art, Court finds, by clear and convincing evidence, that a POSA would have been motivated to combine Davies, Kerr 2009 / Kerr Formulation and Bahal and would have had a reasonable expectation of success in arriving at an improved intranasal naloxone product. (Smyth Tr. 408:11–24.)

3. The Prior Art as a Whole Does Not Teach Away from Using BZK as a Preservative in Intranasal Naloxone Formulations

Adapt argues the prior art, particularly Wyse, taught away from using BZK as a preservative in intranasal naloxone formulations and, therefore, a POSA would have not have been motivated to select it for their formulation. For the reasons discussed in detail below, the Court finds this argument unconvincing. Rather, the Court finds that, taken as a whole, the prior art did not teach away from using BZK and indeed BZK was commonly used in nasal formulations.

As discussed above, BZK is perhaps the most commonly used as a preservative in nasal formulations and has been used in over 200 intranasal products. (Smyth II Tr. 1281:16–24, ECF No. 295; Smyth Tr. 427:23–429:1, ECF No. 292; Illum Tr. 777:5–8, ECF No. 293.) Djupesland stated that more recent human studies found that BZK is safe and well-tolerated for chronic use. (Smyth Tr. 427:23–429:1; TX-3007.05.)[49] Naloxone is a medication that is dosed sporadically, leading a POSA to conclude that its safety profile would improve with such a use. (*Id.*) The Handbook of Pharmaceutical Excipients states that BZK concentrations between 0.002% and 0.02% are commonly used in intranasal formulations. (Smyth Tr. 430:7–24.) The Handbook also mentions that BZK is often used in conjunction with EDTA. (*Id*. 430:25–431:20; *see also* TX-3102.04.)

BZK frequently appears in the prior art as a stabilizing agent in intranasal naloxone formulations. Davies discusses a formulation using BZK and did not express any concerns about that formulation's stability. (Smyth Tr. 427:7–8; Illum Tr. 700:18–20; *see* TX-3109.)[50] The Kerr Formulation used a 0.01% concentration of BZK. (Smyth Tr. 427:9–17; Illum Tr. 613:23–614:9; *see* TX-3098.01.)[51] Dr. Kerr purchased 200 doses of her formulation for use in her 18-month study and ultimately used 80 doses, each of which was effective at reversing opioid overdose. (Smyth II Tr. 1282:18–1284:11; TX-3098.) The Court agrees with Dr. Smyth that a POSA would

[49] TX-3007 is described as, "Per Gisle Djupesland, 'Nasal drug delivery devices: Characteristics and performance in a clinical perspective – a review.'" (*See* ECF No. 338.) It was offered and admitted into evidence on August 27, 2019. (*Id.*)

[50] TX-3109 is international patent application no. WO 2000/062757. (*See* ECF No. 338.) It was offered and admitted on August 27, 2019. (*Id.*)

[51] TX-3098 is a facsimile from R. Kimpton to D. Kerr relating to naloxone intranasal trial. (*See* ECF No. 338.) It was offered and admitted into evidence on August 27, 2019. (*Id.*)

have inferred that the formulation was stable for that 18-month period. (*See id.*) Dr. Illum agreed that the Kerr Formulation would have been stable for at least one month. (Illum Tr. 805:2–9.)

Dr. Wyse filed his patent application on December 19, 2014, but it was not published and publicly available until June 25, 2015. (*See* TX-0048.01.)[52] Wyse conducted a preliminary screening study on nineteen different naloxone formulations, combined with various excipients. (Smyth Tr. 423:3–15.) A screening study is "a study conducted early on in your formulation development to identify potential formulations that could be used, [and] ingredients that could be used in your formulation." (*Id.*) The study also included the statement that "formulations were at pH of 5.0[] to accelerate degradation." (*See* TX-0048.22.) Because Wyse's study was a preliminary one, a POSA would understand that it was not a "rigorous or controlled study." (Smyth Tr. 424:16–20.) Wyse also did not test his formulations that contained BZK to determine the cause of the degradation. (*Id.* 424:21–425:6, 426:22–25.) Wyse's formulations that showed degradation when BZK was used as a preservative showed similar degradation when benzyl alcohol was used as a preservative instead. (Illum Tr. 796:22–798:17; *see* TX-0048.22–.24.)

The concentration of BZK used by Wyse was also significantly higher than the amount used in every other FDA-approved intranasal product. (Smyth Tr. 423:1–7; Illum Tr. 802:1–16.) Wyse used a formulation containing a 0.125% concentration of BZK, which is 8.5 times higher than the concentration used in the Patents-in-Suit. (Smyth Tr. 422:20–24; Illum Tr. 801:23–25, 803:5–16.) A POSA would have understood from Wyse that high concentrations of BZK can cause naloxone to degrade but would not have been dissuaded from using BZK in naloxone formulations in a lower dose. (Smyth Tr. 426:13–19.)

[52] TX-0048 is the Wyse reference; U.S. Patent No. 9,192,570. (*See* ECF No. 338.) It was offered on August 26, 2019 and admitted into evidence on August 27, 2019. (*Id.*)

Subsequent studies also cast doubt on the viability of Wyse's preliminary conclusions. Indeed, Wyse stated that BZK causes instability in a naloxone formulation, however Wyse did not conduct any additional rigorous testing of this result. (Smyth II Tr. 1278:16–1279:11; Illum Tr. 801:4–21; *see* TX-0048.23.) Wyse also came to the preliminary conclusion that methyl paraben was an "acceptable" preservative to use with naloxone formulations. (Smyth Tr. 425:7–12; TX-0048.23.) "However later studies indicated that common preservative[] methyl paraben . . . [was] found to relatively negatively impact the formulation." (*See* TX-0048.23; Smyth Tr. 425:10–426:9; Illum Tr. 801:8–21.)

Given that Wyse conducted no further studies relating to his BZK conclusion, the Court accords his findings lesser weight than the other prior art in this case. Additionally, Dr. Illum admitted there was no prior art before Wyse that taught away from the use of BZK due to stability issues with naloxone. (Illum Tr. 786:16–22; 788:12–24.) The Court, accordingly finds, by clear and convincing evidence, that the prior art as a whole did not teach away from using BZK with naloxone.

K. Plaintiffs Fail to Show Any Secondary Considerations of Nonobviousness to Support Patentability Sufficient to Overcome Teva's Prima Facie Showing of Obviousness

In light of the testimony given at trial and the exhibits entered into evidence, for the reasons set forth below, the Court finds that Adapt has failed to show any secondary considerations of nonobviousness sufficient to overcome Teva's prima facie case.

1. Unexpected Results

Adapt rests much of its argument regarding unexpected results by comparing the Patents-in-Suit to the formulation in Wyse. (*See* ECF No. 287 ¶¶ 224–242.) Dr. Illum testified that Wyse is the closest prior art to the Patents-in-Suit and that the claimed invention is unexpectedly

stable relative to the Wyse formulations. (Illum Tr. 668:6–22; 773:14–774:13, ECF No. 293.) Adapt asserts that the bioavailability of the claimed invention is significantly greater than that of the Wyse formulation, and contends a POSA would have found that unexpected. (Illum Tr. 764:24–765:2; *see also* ECF No. 287 ¶ 232.) The Court finds these arguments unconvincing.

First, the AntiOp formulation, which was based on the Wyse patent, contained "citric acid, [EDTA], benzyl alcohol, sodium chloride, purified water, and either hydrochloric acid or sodium hydroxide." (Smyth II Tr. 1269:3–16, ECF No. 295.) By contrast, the Patents-in-Suit contain EDTA, BZK, sodium chloride, and hydrochloric acid. (*Id.* 1269:17–22.) Dr. Smyth testified that a POSA would expect the use of BZK, instead of citric acid and benzyl alcohol, would affect the bioavailability of the formulation. (*Id.* 1269:24–1270:11.) This is because BZK is a permeation enhancer, which is a pharmaceutical excipient "that is utilized to cause a drug to permeate more readily across a membrane, like the nasal mucosa." (*Id.* 1270:16–19.) The Patents-in-Suit identify BZK as a permeation enhancer in their formulations. (*Id.* 1271:1–1272:3.) Dr. Smyth testified he has over twenty years of experience working with permeation enhancers and that prior to March 2015, it was "well-known" that BZK was used a permeation enhancer. (*Id.* 1270:16–25, 1271:25–1272:3.) The Court agrees with Dr. Smyth and finds that a POSA would expect that changing the excipients used in a formulation would affect its bioavailability. Increased bioavailability relative to the Wyse formulation, therefore, is not an unexpected result.

Adapt also argues that the C_{max} values of the Patents-in-Suit are significantly higher than that of the Wyse formulations and that a POSA would have found that unexpected. (ECF No. 287 ¶¶ 234–35; Illum Tr. 766:9–767:14.) On cross examination, however, Dr. Illum admitted she was not aware of any study that had shown a higher C_{max} value correlated with greater therapeutic

effect. (Illum Tr. 814:21–815:14.) The Court, therefore, does not find this to be evidence of an unexpected result.

Adapt contends that the increased half-life of the Patents-in-Suit, relative to the Wyse formulation, would have been unexpected to a POSA. (ECF No. 287 ¶¶ 236–37; Illum Tr. 768:18–769:17.) Dr. Smyth testified that the half-life reported in both the Patents-in-Suit and in Wyse was "variable" and that "the range of half-life that Wyse discloses overlaps the range that is disclosed in the [Patents-in-Suit.]" (Smyth II Tr. 1275:3–19.) He stated that a POSA, therefore, would not have found the difference in half-life to be significant. Dr. Smyth also noted a POSA would understand that differences in patient populations and how the formulations were administered would also account for that variability. (*Id.* 1275:3–1276:22.) Dr. Smyth noted, for example, that "Wyse had his subjects upright, standing" when administering naloxone "whereas in the [Patents-in-Suit], the subjects [that] were lying down for an hour." (*Id.*) This difference could affect how the medication was absorbed and, accordingly, its pharmacokinetic properties. (*Id.*) The Court, therefore, does not find this to be evidence of an unexpected result.

Finally, Adapt argues that the Patents-in-Suit were unexpectedly stable because Wyse taught away from using BZK due to its propensity to degrade naloxone. The Court finds this argument unconvincing. As discussed in section II.J.3, *supra*, Wyse used significantly more BZK than the claimed invention does. The Court incorporates its analysis from that section and reiterates its conclusion that the prior art did not teach away from using BZK with naloxone. The Court, therefore, does not find stability to be evidence of an unexpected result.

In light of the testimony given at trial and the exhibits entered into evidence, the Court does not find that there was evidence of unexpected results.

2. Commercial Success

The Court finds that Narcan's commercial success is attributable to the features already known in the prior art, Adapt's marketing strategies and tactics, and Narcan's strategic pricing, rather than the alleged novel features of the Patents-in-Suit.

The market for Narcan can be divided into two segments: the traditional retail market and the public-interest market. (Karas Tr. 927:8–22, 931:11–24, ECF No. 290.) Adapt argues that Narcan's commercial success is evidenced by its market performance relative to its competitors, including overall sales and number of units sold. (ECF No. 287 ¶¶ 281–82; Vigil Tr. 1540:1–1541:2, 1554:8–1556:22, ECF No. 298.) Dr. Vigil pointed to Emergent's acquisition of Adapt in October 2018, for $735 million as further evidence of its success because Narcan is Adapt's only marketed product. (Vigil Tr. 1591:2–11.) Adapt contends that there was substantial commercial incentive to develop the claimed invention before the priority date and, as evidence, points to the fact that Adapt, Indivior, Amphastar, Insys, Teva, and Actavis were actively developing needle-free naloxone products. (ECF No. 287 ¶ 287; Vigil Tr. 1590:17–1592:25; Hofmann Tr. 1687:9–1688:10, 1689:19–1690:10, ECF No. 298.) Limor Zahavi also testified that Teva estimated there was a $100 million market for intranasal naloxone. (Zahavi Tr. 83:1–84:4, ECF No. 296.)

However, Lightlake's own statements to the FDA prior to the pre-IND meeting render this conclusion tenuous. Indeed, the package Lightlake submitted to the FDA stated "[t]here is little if any commercial incentive for developing a new nasal naloxone drug product" and that "because of its widespread use, it most likely is not patentable because its use for opioid overdose is 'obvious.'" (Crystal Tr. 301:3–17, 302:14–20, ECF No. 292; Hofmann Tr. 1650:2–24; *see* TX-3079.14.) Lightlake also stated:

> [T]here is no conventional market for the product and thus classical market research does not apply. There is no conventional public consumer, there is no government purchaser (i.e., such as stockpiling for biodefense drugs), competing forms of the product already exist on the market (i.e., pharmacy compounded overdose rescue kits using generic components), and the pressure of cost is extreme.

(TX-3079.14.) "[T]he commercial viability as defined by conventional market research is dismal." (*Id.*)

Dr. Smyth testified that there was no nexus or causal relationship between the claimed invention and the alleged commercial success of Narcan. (Smyth II Tr. 1242:1–9.) Dr. Majumdar admitted on cross examination that when he conducted his nexus analysis, he did not consider what features of Narcan already appeared in the prior art. (Majumdar Tr. 1041:15–19, ECF No. 291.) Dr. Vigil, who was offered by Adapt and accepted by the Court as an expert in the economics of the pharmaceutical industry, identified efficacy, ease-of-use, the needle-free design, and stability as the features responsible for Narcan's marketplace success. (Vigil Tr. 1531:25–1532:6, 1579:22–1580:3.) As to efficacy, Dr. Majumdar admitted that it is not a claimed feature of the Patents-in-Suit. (Majumdar Tr. 1042:18–1045:24.) As disclosed in the prior art, Narcan is not unique in its ability to treat opioid overdose as naloxone has been approved since 1971. (Smyth II Tr. 1246:25–1247:10.) Dr. Smyth also opined that there was no evidence that Narcan is more efficacious than other intranasal naloxone formulations found in the prior art. (*Id.* 1247:3–10.) Dr. Majumdar similarly admitted that the phrases "ease-of-use" and "needle-free" do not appear in the asserted claims. (Majumdar Tr. 1038:21–1040:1–3.) The Court finds that these features are attributable to the Aptar UnitDose device and not the Patents-in-Suit. (*See* Smyth II Tr. 1242:22–1244:7; Hofmann Tr. 1622:25–1625:21.)

The Court finds that Narcan's commercial success is also attributable to Adapt's marketing efforts. In the retail segment, Adapt utilizes several marketing campaigns to promote the use of Narcan, including marketing directly to physicians and distributing nonpersonal direct mail, e-mail, print, and online advertising. (Hofmann Tr. 1627:9–1629:4; Karas Tr. 929:5–13, 970:5–25; Vigil Tr. 1567:16–1570:16.) Adapt also actively promotes Narcan in the public interest market segment. Mr. Karas offered testimony on Adapt's efforts to encourage the enactment of co-prescription legislation, wherein doctors who prescribe opioids would be required by law to also consider prescribing a naloxone product. (Karas Tr. 919:1–21.) Mr. Karas admitted there had been an increase in Narcan's sales following co-prescription legislation. (*Id.* 973:3–6.) Michael Potestio, Adapt's Vice President of Field Operations, also testified that his team would meet with states and their grant writers to educate them on Narcan and provide assistance with obtaining federal HHS or SAMHSA grants to expand access to Narcan. (Potestio Tr. 510:24–511:25, ECF No. 292.)

The Court also finds that Adapt's strategic pricing efforts played a substantial role in Narcan's success. (Hofmann Tr. 1642:4–1643:7.) By keeping Narcan's WAC price low, Adapt was able to secure priority formulary placement. (*Id.*) Mr. Hofmann similarly disagreed Dr. Vigil's conclusion that Evzio is cheaper than Narcan. (*Id.* 1643:8–1645:6.) Mr. Hofmann noted that Dr. Vigil failed to address the cost of the medication paid by the insurer, instead focusing solely on the out-of-pocket costs paid by the consumer. (*Id.*) Dr. Vigil's analysis ignored the "behind-the-scenes payments" made by insurers, Medicare, and Medicaid, and, therefore, "[didn't] tell the whole story in terms of how pharmaceutical products are reimbursed and who is paying the cost." (*Id.*)

In light of the testimony given at trial and the exhibits entered into evidence, the Court finds that Narcan's commercial success is attributable to the features already known in the prior art, Adapt's marketing strategies and tactics, and Narcan's strategic pricing, rather than the alleged novel features of the Patents-in-Suit.

3. Third-Party Praise

Adapt contends that Narcan has been widely praised by industry experts, medical personnel, and opioid patients. (Karas Tr. 964:7–967:7, ECF No. 290; Vigil Tr. 1583:9–1585:24, ECF No. 298.) Mr. Karas testified that the company often receives feedback from the various stakeholders, praising Narcan's efficacy, safety, ease-of-use, lack of required assembly, and needle-free route of administration. (Karas Tr. 964:18–965:15.) Dr. Smyth did not dispute that Narcan has been extensively praised. (Smyth II Tr. 1314:1–10, ECF No. 295.)

Teva argues that the praise Narcan has received is related to features already known in the prior art, rather than the claimed invention. Dr. Smyth testified that the individuals praising Narcan have generally been "representatives of police departments or public health representatives" rather than individuals possessing the qualities of a POSA. (*Id.* 1248:18–25.) Mr. Hofmann testified that the alleged praise was directed towards features that "[were] known in the prior art" and noted that praise relating to lack of assembly, needle-free administration, and ease-of-use were solely attributable to the Aptar UnitDose device rather than the claimed invention. (Hofmann Tr. 1655:23–1656:22, ECF No. 298.) Dr. Smyth testified that the praised 4mg concentrated dose is not compelling because the prior art—including Davies, Strang, and Wyse—disclosed a range of safe and effective doses of naloxone from 0.5mg to as high as 20mg. (Smyth II Tr. 1252:13–1255:24.)

The Court agrees with Dr. Smyth's assessment. In light of the testimony given at trial and the exhibits entered into evidence, the Court finds that Adapt failed to present compelling evidence or testimony of third-party praise relating to unique features of the claim invention that were not present in the prior art.

4. Failure of Others to Arrive at the Claimed Invention or Receive FDA Approval

Adapt argues that the asserted claims of the Patents-in-Suit are not obvious because no other company arrived at the claimed invention or received FDA-approval for their intranasal naloxone product. (ECF No. 287 ¶ 243.) As to Teva, Adapt contends that Teva only arrived at the 4mg dose after it saw the Patents-in-Suit. (*Id.* ¶ 244.) Other companies, including AntiOp/Indivior and Amphastar also did not arrive at the claimed invention. (*Id.* ¶ 245–48; Illum Tr. 734:8–742:7, ECF No. 293.) These companies also submitted their formulations for FDA approval but were rejected. (*Id.*) Mundipharma never sought FDA approval for their formulation. (*Id.*) The Court does not find these arguments persuasive.

First, Dr. Illum admitted on cross examination that her opinion relating to the failure of others was focused on the failure of other products to receive FDA approval. (Illum Tr. 811:17–23.) Dr. Smyth testified, however, that FDA approval "[was] not part of the claims" and that there are "examples of safe and effective community use intranasal naloxone that has not received FDA approval." (Smyth II Tr. 1257:14–24, ECF No. 295.) The MAD Kit, for example, is not an FDA-approved product for intranasal naloxone, but it is widely used in community settings to treat opioid overdoses. (*Id.* 1257:25–1258:7.) Dr. Smyth also noted that the Evzio product is FDA-approved and is "effective at reversing opioid overdose," has been approved for community use, and does not have an exposed needle. (*Id.* 1260:1–18.) The AntiOp product is also approved in other countries and Dr. Smyth testified that a POSA "would anticipate it would

be at least as effective as the MAD [Kit] naloxone." (*Id.* 1265:8–18.) In light of the testimony given at trial and the exhibits entered into evidence the Court finds that Adapt's proffered evidence regarding the alleged failures of others is not a significant indicia of nonobviousness.

5. Long-Felt but Unmet Need

Dr. Williams testified there was a long-felt but unmet need for an easy-to-use, needle-free naloxone product, particularly for use by lay people in the community. (Williams Tr. 1388:14–20, ECF No. 294.) Dr. Williams identified several deficiencies with existing naloxone products which he argued were proof of an unmet need. As to the MAD Kit, Dr. Williams testified that the kit itself is difficult to carry around, it requires assembly prior to use, and there are risks of breaking it. (*Id.* 1388:21–1389:1.) He also stated that while the MAD Kit was effective in the "EMS environment," he personally had not seen many patients who had been administered naloxone via a MAD Kit from someone in the lay community. (*Id.* 1389:2–7.) As to the Evzio device, although it does not have an exposed needle, it administers a dose of medication through a retractable needle. (*Id.* 1389:12–1390:21.) Dr. Williams noted that many individuals are scared of needles and that lay people may be hesitant to use a product that involves a needle for fear of sticking themselves. (*Id.*) On cross examination, Dr. Merlin admitted that Narcan had been given a "fast track" designation from the FDA. (Merlin II Tr. 1467:6–1468:24, ECF No. 294.) The FDA webpage describing the "fast track" process defined it as "a process designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need. The purpose is to get important new drugs to the patient earlier." (*Id.*) Dr. Smyth also acknowledged that the MAD Kit, while effective, had certain drawbacks including the need for assembly and that it delivered too much liquid to the nose. (Smyth Tr. 329:22–330:6, ECF No. 292.) Adapt also points to a statement by the inventor of the MAD Kit, Tim Wolfe, who noted that "it seems pretty

apparent to me that [Narcan] is probably a better method for delivery of nasal naloxone." (Merlin II Tr. 1480:21–1481:2; *see also* TX-1229.)[53]

Teva argues there was no long-felt unmet need for an efficacious naloxone product because such products have been effective prior to the introduction of Narcan. Dr. Illum testified that the MAD Kit was successful at reducing opioid overdose. (Illum Tr. 641:18–23, ECF No. 293.) Prior to March 2015, both the MAD Kit and the Evzio auto-injector were available for community use. (Merlin II Tr. 1448:9–12.) Dr. Merlin testified that he had personally trained individuals to use the MAD Kit for "at least two decades." (*Id.* 1449:3–20.) He stated it was "very easy" for a layperson to learn how to use the device and that the training generally only took ten minutes. (*Id.*) Given his experience, the Court found Dr. Merlin's testimony on this subject to be credible. Dr. Merlin's own work also indicated that laypersons could be trained to effectively treat opioid overdoses with intramuscular naloxone. (*See* TX-1261.03.)[54] The Walley 2013 reference also indicated that MAD Kits were easy to use. Dr. Walley conducted "a community project [that involved] giving the MAD dose device kits to the community." (Illum Tr. 635:11–18, ECF No. 293.) The findings appeared in a peer-reviewed article that was published in the *British Medical Journal*. (Merlin II Tr. 1451:1–1452:22, ECF No. 294.) Opioid users, family members, and social service agency members participated in the study. (*Id.* 1451:14–18.) The training provided in Walley 2013 ranged from ten minutes to one hour. (*Id.* 1451:19–23.) Dr. Walley concluded that bystanders were able to administer naloxone with a MAD Kit without much difficulty. (*Id.* 1452:7–17.)

[53] TX-1229 is described as "intranasal.net, Intranasal Naloxone Overview." (*See* ECF No. 338.) It was offered and admitted into evidence on September 6, 2019. (*Id.*)

[54] TX-1261 is described as "Merlin 2015, Assessment of the safety and ease of use of the naloxone auto-injector for the reversal of opioid overdose." (*See* ECF No. 338.) It was offered and admitted into evidence on September 6, 2019.

Dr. Williams admitted that despite Narcan's approval, ambulances in Rhode Island still carry the MAD Kit as an option to administer naloxone. (Williams Tr., 1395:6–22.) While Narcan may be an improvement over the MAD Kit, in light of the testimony given at trial and the exhibits entered into evidence, the Court finds that Narcan did not fill a significant long-felt but unmet need.

6. Evidence of Copying

Adapt argues that, after the Patents-in-Suit were published, Teva changed the dose in its formulation, Mundipharma changed its formulation and copied the dose of the claimed invention, and Evzio increased the dose of its intramuscular product to 2mg. (Illum Tr. 744:14–747:22, ECF No. 293.)

Dr. Smyth testified that, in his opinion, neither Mundipharma nor Evzio copied the Patents-in-Suit. (Smyth II Tr. 1284:15–1285:25, ECF No. 292.) Dr. Illum admitted that Mundipharma's formulation does not contain BZK or EDTA. (Illum Tr. 741:11–744:2.) Additionally, Evzio is an intramuscular product and not an intranasal product and does not use the same formulation as the Patents-in-Suit. (Smyth II Tr. 1286:4–14.) The Court, therefore, is ultimately skeptical that there is significant evidence of copying since the publication of the Patents-in-Suit.

7. Skepticism

The Court finds that there was not substantial skepticism from POSAs regarding a 4mg dose of intranasal naloxone.

Dr. Williams testified that prior to the claimed invention, he was skeptical of a 4mg intranasal dose, and in particular was concerned that there would be increased incidence of withdrawal symptoms. (Williams Tr. 1385:13–1386:3, ECF No. 294.) Eric Karas testified that Emergent submitted an application for a 2mg dose, even after the 4mg dose was approved, because

"there was feedback from various stakeholders in the advocacy space that the 4[mg] dose might have been too high and [could] potentially cause[] severe opioid withdrawal." (Karas Tr. 925:7–12, ECF No. 290.) Dr. Illum admitted, however, that the Patents-in-Suit did not solve the problem of the potential for a patient to suffer from acute withdrawal when receiving higher doses of naloxone. (Illum Tr. 855:11–21, ECF No. 293.) Dr. Williams also testified that he does not recommend the use of Narcan within his EMS system because of the 4mg dose, has never used in on an actual patient, and admitted that ambulances in Rhode Island still "carry a variety of ways of delivering naloxone, including the MAD Kit." (*Id.* 1395:6–22, 1428:21–25.)

The Court finds that these concerns are not sufficiently substantial to constitute objective indicia of nonobviousness. As discussed above, a dose of naloxone greater than 2mg was repeatedly disclosed in the prior art. Indeed, Strang discussed an intranasal dose of naloxone of 4mg. (Smyth Tr. 367:10–368:4, 368:24–371:22, 393:20–394:20, ECF No 292.) Strang also references various ranges for the preferred dose of naloxone, with 0.5mg to 20mg being the broadest suggested range. (Id. 368:24–369:10; TX-0054.06.) Strang also conducted pharmacokinetic studies wherein he administered intranasal naloxone to patients. (*Id.* 369:20–370:17.) Strang administered intranasal doses of 8 and 16 milligrams using 400 microliters of solution. (*Id.*)

During Lightlake's pre-IND meeting with the FDA, Lightlake discussed their plans to compare a 2mg dose of intranasal naloxone with the FDA-approved 2mg intramuscular dose. (TX-3088.10.) The FDA recommended that Lightlake consider a higher dose of naloxone for their proposed intranasal product. (Smyth Tr. 355:9–25; TX-3088.04.) The FDA further stated "[i]t would be acceptable if a more concentrated naloxone product, or a higher dose of naloxone was needed to achieve the targeted [pharmacokinetic] characteristics by the intranasal route."

(Smyth Tr. 356:22–357:9; TX-3088.04.) The KLJ E-Mail, although specifically highlighted by Adapt at trial, is also not evidence of skepticism. Kathryn Jones is not a formulator and is not a physician and, accordingly, is not a POSA. Any skepticism she expressed, therefore, is irrelevant.

In light of the testimony given at trial and the exhibits entered into evidence, the Court finds that there was not substantial skepticism concerning the Patents-in-Suit or the 4mg dose of naloxone.

III. CONCLUSIONS OF LAW

Issued patents are presumed valid. 35 U.S.C. § 282(a). To rebut this presumption, Defendants bear the burden of proving invalidity by clear and convincing evidence. *Titan Tire Corp. v. Case New Holland, Inc.*, 566 F.3d 1372, 1376 (Fed. Cir. 2009) ("Because of this presumption, an alleged infringer who raises invalidity as an affirmative defense has the ultimate burden of persuasion to prove invalidity by clear and convincing evidence, as well as the initial burden of going forward with evidence to support its invalidity allegation."). "Although not susceptible to precise definition, 'clear and convincing' evidence has been described as evidence which produces in the mind of the trier of fact 'an abiding conviction that the truth of [the] factual contentions are 'highly probable.'" *Buildex Inc. v. Kason Indus., Inc.*, 849 F.2d 1461, 1463 (Fed. Cir. 1988) (quoting *Colorado v. New Mexico*, 467 U.S. 310, 316 (1984)).

A. The General Law of Obviousness

To prove that an asserted claim of a patent is invalid as obvious under 35 U.S.C. § 103, a patent challenger bears the burden of establishing by clear and convincing evidence that the "differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains."

35 U.S.C. § 103; *see also Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1360–61 (Fed. Cir. 2007). Obviousness is a question of law that is predicated on several factual inquiries. *See Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17 (1966). Specifically, there are four basic factual inquiries which concern: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) objective indicia (secondary considerations) of nonobviousness, including unexpected results, success and praise in the industry, long-felt but unsolved need, failure of others, and other indicia. *See id.*; *see also KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 425–26 (2007).

The Federal Circuit has held that:

> Obviousness requires more than a mere showing that the prior art includes separate references covering each separate limitation in a claim under examination. Rather, obviousness requires the additional showing that a [POSA] at the time of the invention would have selected and combined those prior art elements in the normal course of research and development to yield the claimed invention.

Unigene Labs., Inc. v. Apotex, Inc., 655 F.3d 1352, 1360 (Fed. Cir. 2011) (citing *KSR Int'l Co*., 550 U.S. at 418). Moreover, the party challenging validity must show that a POSA "would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and . . . would have had a reasonable expectation of success in doing so." *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (quotation and citations omitted).

Courts "evaluate obviousness on a claim-by-claim basis." *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1303 (Fed. Cir. 2007). "Each claim of a patent (whether in independent, dependent, or multiple dependent form) shall be presumed valid independently of the validity of other claims; [and] dependent or multiple dependent claims shall be presumed valid

even though dependent upon an invalid claim." *Dayco Prod., Inc. v. Total Containment, Inc.*, 329 F.3d 1358, 1370–71 (Fed. Cir. 2003) (quoting 35 U.S.C. § 282).

B. The Level of Ordinary Skill in the Art

"A [POSA] is [] presumed to be one who thinks along the line of conventional wisdom in the art and is not one who undertakes to innovate, whether by patient, and often expensive, systematic research or by extraordinary insights." *Standard Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985). A POSA is "guided only by the prior art references and the then-accepted wisdom in the field." *In re Kotzab*, 217 F.3d 1365, 1369 (Fed. Cir. 2000). However, "[a POSA] is also a person of ordinary creativity, not an automaton." *KSR Int'l Co.*, 550 U.S. at 421. Indeed, "[a POSA] at the time of the invention interprets the prior art using common sense and appropriate perspective." *Unigene*, 655 F.3d at 1361. "The legal construct also presumes that all prior art references in the field of the invention are available to this hypothetical [POSA]." *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998) (citing *In re Carlson*, 983 F.2d 1032, 1038 (Fed. Cir. 1993)).

As discussed in section II.D. *supra*, the Court finds that, here, a POSA is an individual that would have had a bachelor's of science in the pharmaceutical sciences or related disciplines, including chemistry, and would have four to five years of experience developing intranasal drug products. Such a POSA might also possess a higher level of formal education but fewer years of practical experience. They would work with a team and rely in part on the knowledge of their skilled team members. A POSA would be supported by a team member with a medical degree with

several years of clinical experience treating opioid overdose patients in both the hospital and community settings.[55]

C. The Scope and Content of the Prior Art

Prior art consists of existing patents, printed publications, or something "in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention." 35 U.S.C. § 102(a)(1). "The use of patents as [prior art] is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain." *In re Heck*, 699 F.2d 1331, 1333 (Fed. Cir. 1983). "[I]n a [§] 103 inquiry, the fact that a specific [embodiment] is taught to be preferred is not controlling, since all disclosures of the prior art, including unpreferred embodiments, must be considered." *Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) (internal quotation omitted). Under this framework, the Court concludes that Strang, Kulkarni, Djupesland, Kerr 2009, Davies, Bahal, and Wyse all qualify as prior art.

The Court now considers whether the Kerr Formulation qualifies as prior art. A public use is "any use of [the claimed] invention by a person other than the inventor who is under no limitation, restriction or obligation of secrecy to the inventor." *Netscape Commc'ns Corp. v. Konrad*, 295 F.3d 1315, 1320 (Fed. Cir. 2002) (quoting *Petrolite Corp. v. Baker Hughes Inc.*, 96 F.3d 1423, 1425 (Fed. Cir. 1996)). "For prior art to anticipate because it has been 'used,' the use must be accessible to the public." *UCB, Inc. v. Watson Labs. Inc.*, 927 F.3d 1272, 1289 (Fed. Cir. 2019) (quoting *Minnesota Mining & Mfg. Co. v. Chemque, Inc.*, 303 F.3d 1294, 1301

[55] Dr. Smyth and Dr. Illum noted that they had both reviewed the parties' POSA definitions and that their opinions regarding obviousness would not be affected if one party's definition was applied by the Court over the other's. (Smyth Tr. 322:1–14, ECF No. 292, Illum Tr. 576:1–12, ECF No. 293.)

(Fed. Cir. 2002)). "[P]rior knowledge and use by a single person is sufficient." *Id.* (citing *Coffin v. Ogden*, 85 U.S. 120, 124 (1873)). A patient's use of a pharmaceutical product that contained an aspect of the claimed invention, before the priority date, qualifies as a prior use. *See UCB, Inc.*, 927 F.3d at 1291 ("[T]here is evidence that patient actually used the patches with Form II rotigotine crystals in it. The patient's use of the patches fairly counts as public use under § 102(a)."). When an individual fails to "make any discernible effort to maintain the [invention] as confidential," it qualifies as a public use. *See Baxter Int'l, Inc. v. COBE Labs., Inc.*, 88 F.3d 1054, 1058 (Fed. Cir. 1996). The Federal Circuit has repeatedly held that "the public use bar applies to obvious variants of the demonstrated public use." *Clock Spring, L.P. v. Wrapmaster, Inc.*, 560 F.3d 1317, 1326 (Fed. Cir. 2009) (citing *Konrad*, 295 F.3d at 1321).

Here, the Court finds that the Kerr Formulation qualifies as prior art under the public use test. The Kerr Formulation included naloxone hydrochloride 0.2%, sodium chloride, BZK 0.01%, purified water, and hydrochloric acid to adjust the pH of the solution. Dr. Kerr had no formal relationship with Lightlake and was under no limitation, restriction or obligation of secrecy to them. For the reasons discussed herein and in more detail in the Court's Findings of Fact, the Court concludes that the Kerr Formulation is prior art.

D. The Asserted Claims of the Patents-in-Suit are Obvious

A patent challenger must establish by clear and convincing evidence that the "differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103. A patent challenger must also show "by clear and convincing evidence 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." *Pfizer*, 480 F.3d at 1361 (citing *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1360 (Fed. Cir. 2006)).

1. The Asserted Claims Appear in the Prior Art

A claimed invention may be obvious even when the prior art does not teach each claim limitation, so long as the record contains some reason that would cause a POSA to modify the prior art to obtain the claimed invention. *Beckson Marine, Inc. v. NFM, Inc.*, 292 F.3d 718, 728 (Fed. Cir. 2002). A finding of obviousness cannot, however, be based on "the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention." *Crown Operations Int'l, Ltd. v. Solutia, Inc.*, 289 F.3d 1367, 1376 (Fed. Cir. 2002) (quoting *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534, 546 (Fed. Cir. 1998)). Instead "there must be a teaching or suggestion within the prior art, within the nature of the problem to be solved, or within the general knowledge of a [POSA] in the field of the invention, to look to particular sources, to select particular elements, and to combine them as combined by the inventor." *Id.* (citations omitted). "While an analysis of any teaching, suggestion, or motivation to combine elements from different prior art references is useful in an obviousness analysis, the overall inquiry must be expansive and flexible." *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1360 (Fed. Cir. 2012).

The Supreme Court has held that, for patents that claim a combination of known elements, "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co.*, 550 U.S. at 416. "A court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions." *Id.*

> Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue.

Id. at 418. "The conjunction or concert of known elements must contribute something; only when the whole in some way exceeds the sum of its parts is the accumulation of old devices patentable." *Great Atl. & Pac. Tea Co. v. Supermarket Equip. Corp.*, 340 U.S. 147, 152 (1950).

As discussed in detail in section II.J., *supra*, the Court finds that there is clear and convincing evidence the asserted claims of the Patents-in-Suit are obvious in light of the prior art. All asserted claims of the Patents-in-Suit appear in both the Strang / Kulkarni / Djupesland and Davies / Kerr 2009, Kerr Formulation / Bahal combinations. Looking at the interrelated teachings of the various prior art references, the Court finds there was a reason to combine the known elements. The Court also found that the Patents-in-Suit did not produce unexpected results.

2. A POSA Would Have Been Motivated to Combine Strang / Kulkarni / Djupesland and Davies / Kerr 2009, Kerr Formulation / Bahal and Would Have Had a Reasonable Expectation of Success

The Supreme Court has held that the obviousness inquiry requires "an expansive and flexible approach." *KSR Int'l Co.*, 550 U.S. at 415. "Under the correct analysis, any need or problem known in the field and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 402. "[T]he [obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a [POSA] would employ." *Id.* at 418. "Common sense teaches, however, that familiar items may have obvious uses beyond their primary

purposes, and in many cases a [POSA] will be able to fit the teachings of multiple patents together like pieces of a puzzle." *Id.* at 420.

"There is flexibility in our obviousness jurisprudence because a motivation may be found *implicitly* in the prior art. We do not have a rigid test that requires an actual teaching to combine before concluding that one of ordinary skill in the art would know to combine references." *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1291 (Fed. Cir. 2006).

> [The Federal Circuit] has repeatedly held that an implicit motivation to combine exists not only when a suggestion may be gleaned from the prior art as a whole, but when the 'improvement' is technology-independent and the combination of references results in a product or process that is more desirable, for example because it is stronger, cheaper, cleaner, faster, lighter, smaller, more durable, or more efficient.

DyStar, 464 F.3d at 1368.

> Because the desire to enhance commercial opportunities by improving a product or process is universal—and even common-sensical—[the Federal Circuit has] held that there exists in these situations a motivation to combine prior art references even absent any hint of suggestion in the references themselves. In such situations, the proper question is whether the ordinary artisan possesses knowledge and skills rendering him *capable* of combining the prior art references.

Id.

Here, as discussed in more detail in the Court's Findings of Fact, the Court concludes that there is clear and convincing evidence a POSA would have been able and motivated to combine the prior art references. Indeed, a POSA would have had the implicit motivation to improve on the MAD Kit because its shortcomings were well-known. Given the prior art references, a POSA would also have had a reasonable expectation of success. As to the 4mg dose, it was known in the prior art that the bioavailability of naloxone was lower when administered intranasally. A POSA,

therefore, would have recognized the need to increase the intranasal dose in order to match the bioavailability of the FDA-approved intramuscular dose.

3. The Prior Art Does Not Teach Away from a Higher Dose of Naloxone or Using BZK With Naloxone

"[A] patentee may rebut the presumption of obviousness by showing that the prior art taught away from the claimed range." *E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018) (citing *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311 (Fed. Cir. 2006)). "However, obviousness must be determined in light of all the facts, and there is no rule that a single reference that teaches away will mandate a finding of nonobviousness." *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006). "Rather, the prior art must be considered *as a whole* for what it teaches." *Id.* at 1166. "Where the prior art contains 'apparently conflicting' teachings (i.e., where some references teach the combination and others teach away from it) each reference must be considered 'for its power to suggest solutions to an artisan of ordinary skill. . . . consider[ing] the degree to which one reference might accurately discredit another.' *Id.* at 1165 (quoting *In re Young*, 927 F.2d 588, 591 (Fed. Cir. 1991)). "Evidence concerning whether the prior art teaches away from a given invention must relate to and be commensurate in scope with the ultimate claims at issue." *Idemitsu Kosan Co. v. SFC Co.*, 870 F.3d 1376, 1381 (Fed. Cir. 2017).

The Court finds that the prior art does not teach away from using a higher dose of naloxone, nor, when taken as a whole, does it teach away from using BZK as a preservative in naloxone formulations. As discussed in detail in section II.H., *supra*, a POSA would have thought a 4mg dose of intranasal naloxone was safe and would have preferred a higher starting dose in the community setting. Strang disclosed that naloxone could be administered safely in doses ranging from 0.5mg to 20mg and also recommended a starting dose of 4mg. The prior art also indicated

that patients who received intranasal naloxone in doses of 0.4mg to 2mg more often required redosing compared to patients who received an intramuscular dose. Prior to March 2015, a POSA would have known that a layperson using a MAD Kit to administer a 2mg dose of intranasal naloxone had to re-dose nearly half of the time. The time delay inherent in redosing poses significant health risks to a patient, including brain damage and death. A higher dose of naloxone is required to reverse an opioid overdose on a patient who had used more potent synthetic opioids like fentanyl. The prior art, therefore, did not teach away from a higher dose of naloxone.

As to the use of BZK with naloxone, the Court found the Wyse reference unpersuasive because the concentration of BZK used was 8.5 times greater than that in the Patents-in-Suit. Additionally, Wyse only conducted a preliminary screening studying relating to BZK. Wyse similarly conducted a preliminary screening study relating to the efficacy of methyl paraben as a preservative. However, when Wyse conducted subsequent rigorous studies relating to methyl paraben, the conclusions he reached as a result of his preliminary study were invalidated. Indeed, BZK is perhaps the most commonly used preservative in nasal formulations and has been used in over 200 intranasal products. The Davies reference and the Kerr Formulation also disclosed intranasal naloxone formulations that used BZK as a preservative. The prior art, therefore, did not teach away from using BZK with naloxone.

E. Plaintiffs Fail to Show Any Secondary Considerations of Nonobviousness to Support Patentability Sufficient to Overcome Teva's Prima Facie Showing of Obviousness

When conducting an obviousness analysis, a Court must also consider secondary considerations of nonobviousness, including commercial success, long-felt but unmet need, the failure of others, third-party praise, and more. *See KSR Int'l Co.*, 550 U.S. at 407 (citing *Graham*, 383 U.S. at 17–18). "*Graham* set forth a broad inquiry and invited courts, where

appropriate, to look at any secondary considerations that would prove instructive." *Id.* at 415. A Court's evaluation of objective indicia of nonobviousness "is not just a cumulative or confirmatory part of the obviousness calculus but [rather] constitutes independent evidence of nonobviousness." *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008). "These objective criteria help inoculate the obviousness analysis against hindsight." *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1378 (Fed. Cir. 2012). However, "[a]lthough secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion. *Pfizer*, 480 F.3d at 1372 (citing *Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988)). Indeed, the Federal Circuit has "often held [that] evidence of secondary considerations does not always overcome a strong prima facie showing of obviousness." *Asyst Techs., Inc. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008); *Sandt Tech., Ltd. v. Resco Metal & Plastics Corp.*, 264 F.3d 1344, 1355 (Fed. Cir. 2001) ("We see no error in the district court's conclusion in this case that the secondary considerations cannot overcome the strong evidence of obviousness presented.") As discussed in detail below, the Court concludes that Adapt's proffered indicia of nonobviousness are insufficient to overcome Teva's strong demonstration of obviousness.

1. No Nexus Exists Between the Secondary Considerations and the Asserted Claims

"Evidence of commercial success, or other secondary considerations, is only significant if there is a nexus between the claimed invention and the commercial success." *Ormco Corp.*, 463 F.3d at 1311–12. "Where the offered secondary consideration actually results from something other than what is both claimed and novel in the claim, there is no nexus to the merits of the claimed invention." *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (citing *Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1369 (Fed. Cir. 2011)). "For objective evidence [of

secondary indicia] to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the claimed invention." *In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995).

For the reasons discussed in the Court's Findings of Fact, the Court finds that Adapt has failed to establish a nexus between the asserted claims and the proffered secondary considerations of nonobviousness.

2. Unexpected Results

"When unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *Abbott Labs. v. Andrx Pharm., Inc.*, 452 F.3d 1331, 1345 (Fed. Cir. 2006) (citing *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991).) "One way for a patent applicant to rebut a prima facie case of obviousness is to make a showing of 'unexpected results,' *i.e.*, to show that the claimed invention exhibits some superior property or advantage that a [POSA] in the relevant art would have found surprising or unexpected." *In re Geisler*, 116 F.3d 1465, 1469 (Fed. Cir. 1997) (quoting *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995).

> Even though [a] modification results in great improvement and utility over the prior art, it may still not be patentable if the modification was within the capabilities of one skilled in the art, unless the claimed ranges produce a new and unexpected result which is different in kind and not merely in degree from the results of the prior art.

Iron Grip Barbell Co. v. USA Sports, Inc., 392 F.3d 1317, 1322 (Fed. Cir. 2004) (internal quotation omitted).

As discussed in the Court's Findings of Fact, the Court does not find the bioavailability, stability, or C_{max} of the Patents-in-Suit to be an unexpected result. The increased bioavailability of Narcan relative to the Wyse reference was attributable to Adapt's use of BZK rather than citric

acid as a permeation enhancer. BZK is a well-known permeation enhancer, and a POSA would not have been surprised by this result. The Court found that the higher C_{max} value of the Patents-in-Suit were not evidence of an unexpected result, because there was no evidence that a greater C_{max} value had a correlation to a greater clinical effect. Finally, the stability of the Patents-in-Suit fell within a range that was disclosed in the prior art and therefore not unexpected. Additionally, differences in methodology between the Wyse reference and the Patents-in-Suit could account for the range of half-lives that were observed. The Court, therefore, does not find that Adapt has presented significant evidence of unexpected results.

3. Commercial Success

"The patentee must establish a nexus between the evidence of commercial success and the patented invention." *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010) (citing *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996) (holding that the proponent must offer proof "that the sales were a direct result of the unique characteristics of the claimed invention"). "Commercial success due only to superior business acumen, or effective advertising, is of no relevance to a determination of whether the invention would have been obvious under 35 U.S.C. § 103." *Solder Removal Co. v. U.S. Int'l Trade Comm'n*, 582 F.2d 628, 637 (C.C.P.A. 1978); *see also Application of Thompson*, 545 F.2d 1290, 1295 (C.C.P.A. 1976) ("Although commercial success is averred, there is no evidence showing that such success was attributable to the merits of appellants' invention rather than to other factors such as advertising.") "If commercial success is due to an element in the prior art, no nexus exists." *Tokai Corp.*, 632 F.3d at 1369. Absent evidence that the "driving force behind the product sales was a direct result of the unique characteristics of the claimed inventions," no nexus exists. *WesternGeco LLC v. ION Geophysical Corp.*, 889 F.3d 1308, 1331 (Fed. Cir. 2018), *cert. denied*, 139 S. Ct. 1216 (2019) (citing *In re DBC*, 545 F.3d

1373, 1384 (Fed. Cir. 2008) (finding no nexus absent evidence that "the driving force behind [the allegedly successful product's sales] was the [claimed invention]")).

The Court finds that Narcan's commercial success is attributable to the features already known in the prior art, Adapt's marketing strategies and tactics, and Narcan's strategic pricing, rather than the alleged novel features of the Patents-in-Suit. Adapt's expert on the economics of the pharmaceutical industry, Dr. Vigil, identified efficacy, ease-of-use, the needle-free design, and stability as the features responsible for Narcan's marketplace success. However, as the Court discussed in its Findings of Fact, efficacy is not a claimed feature of the Patents-in-Suit, and the ease-of-use is attributable to the Aptar UnitDose device rather than the novel features of the Patents-in-Suit. The Court also found Adapt's marketing strategy, strategic pricing, and advocacy for co-prescription legislation also contributed significantly to Narcan's success. The Court concludes, therefore, that Adapt has failed to present significant evidence to overcome Teva's demonstration of obviousness.

4. Third-Party Praise

"[I]if there is evidence of industry praise in the record, it weighs in favor of the nonobviousness of the claimed invention." *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1334 (Fed. Cir. 2016); *see, e.g., Institut Pasteur & Universite Pierre Et Marie Curie v. Focarino*, 738 F.3d 1337, 1347 (Fed. Cir. 2013) ("[I]ndustry praise . . . provides probative and cogent evidence that one of ordinary skill in the art would not have reasonably expected [the claimed invention]."). "[I]ndustry praise of what was clearly rendered obvious by [the prior art] is not a persuasive secondary consideration." *Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013); *see, e.g., ClassCo, Inc. v. Apple, Inc.*, 838 F.3d 1214, 1220 (Fed. Cir. 2016) ("As the Board correctly explained, much of ClassCo's evidence of praise focused on conventional

features in the prior art. . . . The Board properly discounted this and other evidence relating to features that were in the prior art."). Praise from those who are not POSAs is not a useful indicator of obviousness. *Vulcan Eng'g Co. v. Fata Aluminium, Inc.*, 278 F.3d 1366, 1373 (Fed. Cir. 2002) ("Appreciation by contemporaries skilled in the field of the invention is a useful indicator of whether the invention would have been obvious to such persons at the time it was made.").

Here the Court finds that the third-party praise Narcan received was largely due to features already known in the prior art and often came from individuals who were not POSAs. Indeed, Dr. Smyth testified that the individuals praising Narcan have generally been "representatives of police departments or public health representatives" rather than individuals possessing the qualities of a POSA. Additionally, the praise related to Narcan's lack of an assembly requirement, needle-free administration, and ease-of-use, which were attributable to the Aptar UnitDose device rather than the Patents-in-Suit. The Court, therefore, finds that the proffered evidence of third-party praise does not rebut Teva's demonstration of obviousness.

5. Failure of Others

"[E]vidence of failed attempts by others could be determinative on the issue of obviousness." *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1285 (Fed. Cir. 2000). "Evidence that others tried but failed to develop a claimed invention may carry significant weight in an obviousness inquiry." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1081 (Fed. Cir. 2012). "[T]here can be little better evidence negating an expectation of success than actual reports of failure." *Id.* (citing *Boehringer Ingelheim Vetmedica, Inc. v. Schering–Plough Corp.*, 320 F.3d 1339, 1354 (Fed. Cir. 2003)). The Federal Circuit has "implicit[ly] accept[ed that evidence] of failure [of others] to obtain FDA

approval [i]s an appropriate benchmark in evaluating failure of others." *Pfizer Inc. v. Teva Pharm. USA, Inc.*, 460 F. Supp. 2d 659, 662 (D.N.J. 2006).

As discussed in the Court's Findings of Fact, Adapt's arguments regarding the failure of others were not convincing. This is particularly true in the case of intranasal naloxone. The MAD Kit, which uses intranasal naloxone to treat opioid overdoses, has repeatedly been found to be safe and efficacious, despite not being FDA-approved for such treatment. Dr. Williams testified that despite Narcan's approval, he does not recommend the use of Narcan within his EMS system because of the 4mg dose, has never used it on an actual patient, and admitted that ambulances in Rhode Island still "carry a variety of ways of delivering naloxone, including the MAD Kit." Dr. Illum also acknowledged that FDA approval is not an element of the Patents-in-Suit. The Court, therefore, finds that there is no significant evidence of the failure of others to arrive at the claimed invention.

6. Unmet Need

"Evidence of a long felt but unresolved need tends to show nonobviousness because it is reasonable to infer that the need would have not persisted had the solution been obvious." *WBIP, LLC*, 829 F.3d at 1332; *see, e.g., Iron Grip Barbell Co.*, 392 F.3d at 1325 ("Absent a showing of long-felt need or the failure of others, the mere passage of time without the claimed invention is not evidence of nonobviousness."). If the prior art discloses the solution, there is no long-felt unmet need. *In re Copaxone Consol. Cases*, No. 14-1171, 2017 WL 401943, at *23 (D. Del. Jan. 30, 2017), *aff'd sub nom. In Re: Copaxone Consol. Cases*, 906 F.3d 1013 (Fed. Cir. 2018) ("The court does not find that there was a long-felt, but unresolved need, probative of nonobviousness. Instead, the court finds that the prior art disclosed solutions to the long-felt need, and Teva simply won the race to the patent office."). To establish a long-felt unmet need, a party

must "explain how long this need was felt, or when the problem first arose" and demonstrate how the need was "alleviated by the patent." *Perfect Web Techs., Inc. v. InfoUSA, Inc.*, 587 F.3d 1324, 1332 (Fed. Cir. 2009)

Here, the prior art repeatedly discussed intranasal naloxone as a viable means of treating opioid overdose. While the MAD Kit had certain drawbacks, it was known to be safe and effective and had been used in the community setting. Narcan's ease of use features are not attributable to the claimed invention but rather the Aptar device. The Court finds, therefore, that Adapt failed to present sufficient evidence of a long-felt unmet need.

7. Evidence of Copying

To demonstrate secondary indicia of copying, a party must show:

> [E]vidence of efforts to replicate a specific product, which may be demonstrated through internal company documents, direct evidence such as disassembling a patented prototype, photographing its features, and using the photograph as a blueprint to build a replica, or access to the patented product combined with substantial similarity to the patented product.

Wyers, 616 F.3d at 1246 (citation omitted). "Copying may indeed be another form of flattering praise for inventive features, and thus evidence of copying tends to show nonobviousness." *WBIP, LLC*, 829 F.3d at 1336; *see also Windsurfing Int'l, Inc. v. AMF, Inc.*, 782 F.2d 995, 1000 (Fed. Cir. 1986) ("[C]opying the claimed invention, rather than one within the public domain, is indicative of nonobviousness."). "Copying by the accused infringer, however, has limited probative value in the absence of evidence of failed development efforts by the infringer[.]" *Friskit, Inc. v. Real Networks, Inc.*, 306 F. App'x 610, 617 (Fed. Cir. 2009).

"[E]vidence of copying in the ANDA [and generic drug] context is not probative of nonobviousness because a showing of bioequivalence is required for FDA approval." *Bayer Healthcare Pharm., Inc.*, 713 F.3d at 1377; *see also Purdue Pharma Prod. L.P. v. Par Pharm.,*

Inc., 377 F. App'x 978, 983 (Fed. Cir. 2010) ("[W]e do not find compelling Purdue's evidence of copying in the ANDA context where a showing of bioequivalency is required for FDA approval.").

As discussed in the Court's Findings of Fact, the Court finds Adapt's assertion that Mundipharma and Evzio subsequently copied the Patents-in-Suit to be unconvincing. Notably, Mundipharma's product does not contain BZK or EDTA, and Evzio is an intramuscular injectable product. In light of the relevant case law, the Court also finds that Teva adjusting the dose of their intranasal product after the publication of the Patents-in-Suit to be nonprobative.

8. Skepticism

"Evidence of industry skepticism weighs in favor of nonobviousness. If industry participants or [POSAs] are skeptical about whether or how a problem could be solved or the workability of the claimed solution, it favors nonobviousness." *WBIP, LLC*, 829 F.3d at 1335; *AstraZeneca LP v. Breath Ltd.*, 88 F. Supp. 3d 326, 382–83 (D.N.J.), *aff'd*, 603 F. App'x 999 (Fed. Cir. 2015) ("[S]kepticism of [POSAs] before the invention can demonstrate nonobviousness") (internal quotation omitted).

As discussed in the Court's Findings of Fact, the Court found there was not substantial skepticism of a 4mg intranasal naloxone product. Indeed, Naloxone was known to be a very safe medication and has been administered intranasally via the MAD Kit for many preceding the priority date of the Patents-in-Suit. During Lightlake's pre-IND meeting with the FDA, the FDA even recommended that Lightlake consider a higher dose of naloxone and suggested that a more concentrated dose might be required for an intranasal formulation. The Court also expressed skepticism regarding some of the testimony offered by Dr. Williams, noting that he had never used Narcan's 4mg spray on an actual patient and does not recommend the use of 4mg of intranasal naloxone even today.

IV. CONCLUSION

For the reasons set forth above, the Court finds: (1) Claims 7 and 9 of the '747 Patent are invalid; (2) Claim 4 of the '177 Patent is invalid; (3) Claims 21, 24, and 25 of the '965 Patent are invalid; and (4) Claims 2, 24, 33, and 38 of the '838 Patent are invalid. An accompanying Order will follow.

Date: June 5, 2020

s/ Brian R. Martinotti
HON. BRIAN R. MARTINOTTI
UNITED STATES DISTRICT JUDGE