

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NALOX-1 PHARMACEUTICALS, LLC,
Petitioner,

v.

OPIANT PHARMACEUTICALS, INC.,
Patent Owner

Case No. IPR2019-000685
U.S. Patent No. 9,211,253

**PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,211,253
AS OBVIOUS OVER WYSE**

TABLE OF CONTENTS

I. INTRODUCTION.....	1
II. IPR REQUIREMENTS UNDER 37 C.F.R. § 42.104	2
A. Grounds for Standing Under 37 C.F.R. § 42.104(a)	2
B. Identification of Challenge Under 37 C.F.R. § 42.104(b)	2
1. Statutory Grounds of Challenge.....	3
2. Statement of Non-Redundancy	3
3. Relief Requested	4
C. Mandatory Notices Under 37 C.F.R. § 42.8	4
1. Real Party-in-Interest Pursuant to 37 C.F.R. § 42.8(b)(1).....	4
2. Related Matters Under 37 C.F.R. § 42.8(b)(2)	5
3. Identification of Lead and Back-Up Counsel Under 37 C.F.R. § 42.8(b)(3).....	6
4. Service Information Under 37 C.F.R. § 42.8(b)(4).....	6
III. LEVEL OF ORDINARY SKILL IN THE ART.....	7
IV. OVERVIEW OF THE '253 PATENT	9
A. Summary of the Specification	9
B. Summary of the Claims	10
C. Summary of Relevant Portions of the File History.....	10
D. The '253 Patent Lacks Priority to the Filing Date of the '379 Provisional.....	10
V. BACKGROUND AND OVERVIEW OF TECHNOLOGY.....	13
A. A POSA Would Have Been Motivated to Develop Improved Intranasal Naloxone Formulations to Combat the Opioid Epidemic.....	13
B. A POSA Would Have Had the Know-How to Readily Develop an Improved Intranasal Naloxone Formulation.	16
1. The volume of the nasal cavity naturally limits the volume of a naloxone nasal spray to about 100 µL per spray.	17
2. A POSA would have been motivated to use a 4-6 mg naloxone dose to achieve desirable naloxone exposure levels.	18

3.	A POSA would have had adequate know-how and ability to select commonplace excipients to make a stable, well-tolerated intranasal naloxone formulation.	19
4.	A POSA would have been motivated to load an intranasal naloxone formulation into an easy-to-use single-dose, pre-primed nasal sprayer.	21
VI.	CLAIM CONSTRUCTION UNDER 37 C.F.R. § 42.104(b)(3)	22
A.	“pre-primed”	22
B.	“patient”	23
C.	“delivery time”	23
D.	“90% confidence interval for dose delivered per actuation is \pm about 2.0%” and “95% confidence interval for dose delivered per actuation is \pm about 2.5%”	23
VII.	SUMMARY OF THE PRIOR ART	24
A.	Wyse (U.S. Patent No. 9,192,570)	24
B.	Additional References	25
C.	Public Accessibility of the April 12, 2012 FDA Materials	26
VIII.	THE CHALLENGED CLAIMS ARE UNPATENTABLE	27
A.	Ground 1: Claims 1–3, 16–24, and 28–29 are obvious over Wyse (Nalox1007) in view of HPE (Nalox1012)	28
1.	Claim 1	28
2.	Claim 2	34
3.	Claim 3	36
4.	Claim 16	39
5.	Claims 17 and 18	40
6.	Claim 19	41
7.	Claims 20–23	41
8.	Claim 24	43
9.	Claims 28 and 29	43
B.	Ground 2: Claims 4–7, 10–15, and 25–27 are obvious over Wyse (Nalox1007) in view of Djupesland (Nalox1010) and HPE (Nalox1012)	45
1.	Claim 4	45
2.	Claim 5	46

Petition for *Inter Partes* Review of U.S. Patent No. 9,211,253

3.	Claim 6	46
4.	Claim 7	47
5.	Claims 10 and 11	47
6.	Claims 12–14.....	48
7.	Claim 15	49
8.	Claims 25–27.....	50
C.	Ground 3: Claims 8–9 are obvious over Wyse (Nalox1007) in view of Djupesland (Nalox1010), HPE (Nalox1012), and the '291 patent (Nalox1015).....	52
IX.	SECONDARY CONSIDERATIONS	54
A.	No teaching away	54
B.	No commercial success	58
C.	No long-felt but unmet need or failure of others.....	59
D.	No unexpected superior results	60
X.	CONCLUSION	60

TABLE OF EXHIBITS

Exhibit Number	Description
Nalox1001	U.S. Patent No. 9,211,253 (the '253 patent)
Nalox1002	Expert Declaration of Maureen Donovan
Nalox1003	Expert Declaration of Günther Hochhaus
Nalox1004	Excerpt of File History of U.S. Patent No. 9,561,177, Aug. 22, 2016 Office Action, Non-Final Rejection (Aug. 22, 2016 Non-Final Rejection)
Nalox1005	Excerpt of File History of U.S. Patent No. 9,561,177, Oct. 21, 2016 Amendment and Response to Office Action (Oct. 21, 2016 Response to Office Action)
Nalox1006	Excerpt of File History of U.S. Patent No. 9,561,177, Dec. 21, 2016 Office Action, Notice of Allowance and Fees Due (Notice of Allowance)
Nalox1007	U.S. Patent No. 9,192,570 (Wyse)
Nalox1008	Chinese Patent No. 1,575,795 (Wang)
Nalox1009	PCT International App. Pub. No. WO00/62757 (Davies)
Nalox1010	Djupesland, P., <i>Nasal Drug Delivery Device: Characteristics and Performance in a Clinical Perspective - A Review</i> , 3 Drug Deliv. & Transl. Res. 42–62 (2013) (Djupesland)
Nalox1011	Grassin-Delyle, S. et al., <i>Intranasal Drug Delivery: An Efficient and Non-invasive Route for Systemic Administration, Focus on Opioids</i> , 134 Pharm. & Ther. 366–79 (2012) (Grassin-Delyle)
Nalox1012	Handbook of Pharmaceutical Excipients, 56–60, 64–66, 78–81, 220–22, 242–44, 270-72, 441–45, 517–22, 596–98 (Rowe, R. et al. eds., 6th ed. 2009) (HPE)

Exhibit Number	Description
Nalox1013	Kushwaha, S. et al., <i>Advances in Nasal Trans-Mucosal Drug Delivery</i> , (1)7 J. Applied Pharm. Sci. 21–28 (2011) (Kushwaha)
Nalox1014	U.S. Patent No. 5,866,154 (Bahal)
Nalox1015	U.S. Patent No. 8,198,291 (the '291 patent)
Nalox1016	Wermeling, D., <i>A Response to the Opioid Overdose Epidemic: Naloxone Nasal Spray</i> , 3 Drug Deliv. & Transl. Res. 63–74 (2013) (Wermeling 2013)
Nalox1017	Alabama Department of Public Health, <i>Alabama EMS Patient Care Protocols</i> (7th ed., Oct. 2013) (Alabama EMS Protocols)
Nalox1018	Aptar Pharma, Press Release, Aptar Pharma Provides Unit-Dose Nasal Spray Technology for Treatment of Opioid Overdose (Apr. 20, 2016) (Aptar Press Release)
Nalox1019	Ashton, H. et al., <i>Best Evidence Topic Report Intranasal Naloxone in Suspected Opioid Overdose</i> , 23(3) Emerg. Med. J. 221–23 (2006) (Ashton)
Nalox1020	Barton, E. et al., <i>Intranasal Administration of Naloxone by Paramedics</i> , 6 Prehosp. Em. Care 54–58 (Barton 2002)
Nalox1021	Barton, E. et al., <i>Efficacy of Intranasal Naloxone as a Needleless Alternative for Treatment of Opioid Overdose in the Prehospital Setting</i> , 29(3) J. Emerg. Med. 265–71 (2005) (Barton 2005)
Nalox1022	Bitter, C. et al., <i>Nasal Drug Delivery in Humans</i> , 40 Curr. Probl. Dermatol. 20–35 (2011) (Bitter)
Nalox1023	Boyer, E., <i>Management of Opioid Analgesic Overdose</i> , 367(2) N. Engl. J. Med. 146–55 (2012) (Boyer)
Nalox1024	CDC, NDA No. 21-450 Clinical Pharmacology & Biopharmaceutics Review (2002) (Zomig Review)

Exhibit Number	Description
Nalox1025	Excerpt of Commonwealth of Kentucky, <i>Kentucky Patient Care Protocols</i> (Mar. 13, 2015) (Kentucky Patient Care Protocols)
Nalox1026	Costantino, H. et al., <i>Intranasal Delivery: Physiochemical and Therapeutic Aspects</i> , 337 <i>Int'l. J. of Pharm.</i> 1–24 (2007) (Constantino)
Nalox1027	Dowling, J. et al., <i>Population Pharmacokinetics of Intravenous, Intramuscular, and Intranasal Naloxone in Human Volunteers</i> , 30(4) <i>Ther. Drug. Monit.</i> 490–96 (2008) (Dowling)
Nalox1028	FDA, Center for Drug Evaluation and Research, <i>Guidance for Industry, Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation</i> (2002) (2002 FDA Guidance)
Nalox1029	FDA, Center for Drug Evaluation and Research, <i>Guidance for Industry, Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action</i> (2003) (2003 FDA Guidance)
Nalox1030	Freise, K. et al., <i>Naloxone Reversal of an Overdose of a Novel, Long-Acting Transdermal Fentanyl Solution in Laboratory Beagles</i> , 35(2) <i>J. Vet. Pharmacol. Therap.</i> 45–51 (2012) (Freise)
Nalox1031	Glende, O., <i>Development of non-injectable naloxone for pre-hospital reversal of opioid overdose: A Norwegian project and a review of international status</i> (May 2016) (unpublished M.A. thesis, Norwegian University of Science and Technology) (on file with Norwegian University of Science and Technology) (Glende)
Nalox1032	Hertz, S., <i>Naloxone for Outpatient Use: Data Required to Support an NDA</i> , PowerPoint Presentation (Hertz Presentation)
Nalox1033	Intentionally left blank

Exhibit Number	Description
Nalox1034	Kelly, A-M. et al., <i>Randomised Trial of Intranasal Versus Intramuscular Naloxone in Prehospital Treatment for Suspected Opioid Overdose</i> , 182(1) <i>Med. J. Austrl.</i> 24–27 (2005) (Kelly)
Nalox1035	Kerr, D. et al., <i>Intranasal Naloxone for the Treatment of Suspected Heroin Overdose</i> , 103 <i>Addiction</i> 379–86 (2008) (Kerr 2008)
Nalox1036	Kerr, D. et al., <i>Randomized Controlled Trial Comparing the Effectiveness & Safety of Intranasal & Intramuscular Naloxone for the Treatment of Suspected Heroin Overdose</i> , 104 <i>Addiction</i> 2067–74 (2009) (Kerr 2009)
Nalox1037	Kleiman-Wexler, R. et al., <i>Pharmacokinetics of Naloxone-An Insight into the Locus of Effect on Stress-Ulceration</i> , 251(2) <i>J. Pharmacol. Exp. Ther.</i> 435–38 (1989) (Kleiman-Wexler)
Nalox1038	Marple, B. et al., <i>Safety Review of Benzalkonium Chloride Used as a Preservative in Intranasal Solutions: An Overview of Conflicting Data and Opinions</i> , 130 <i>Otolaryngol Head Neck Surg.</i> 131–41 (2004) (Marple)
Nalox1039	Merck Index, <i>Isotonic Solutions</i> , MISC-47–69 (Windholz, M. et al. eds., 10th ed. 1983) (Merck Index)
Nalox1040	Merlin, M. et al., <i>Intranasal Naloxone Delivery is an Alternative to Intravenous Naloxone for Opioid Overdoses</i> , 28 <i>Am. J. Emerg. Med.</i> 296–303 (2010) (Merlin)
Nalox1041	Middleton, L. et al., <i>The Pharmacodynamic & Pharmacokinetic Profile of Intranasal Crushed Buprenorphine & Buprenorphine/Naloxone Tablets in Opioid Abusers</i> , 106(8) <i>Addiction</i> 1460–73 (2011) (Middleton)

Exhibit Number	Description
Nalox1042	Monitto, C. et al., <i>The Optimal Dose of Prophylactic Intravenous Naloxone in Ameliorating Opioid-Induced Side Effects in Children Receiving Intravenous Patient-Controlled Analgesia Morphine for Moderate to Severe Pain: A Dose Finding Study</i> , 113(4) <i>Anesthesia & Analgesia</i> 834–42 (2011) (Monitto)
Nalox1043	<i>Pharmacodynamic Agents</i> , in Foye's Principles of Medicinal Chemistry, 670 (Lemke, T. et al. eds., 6th ed. 2008) (Lemke)
Nalox1044	Physicians' Desk Reference, <i>NARCAN [Naloxone Hydrochloride Injection, USP], IMITREX Nasal Spray [Sumatriptan]</i> , 1300–02, 1546–50 (57th ed., 2003) (PDR 2003)
Nalox1045	Physicians' Desk Reference, <i>ZOMIG Nasal Spray [Zolmitriptan]</i> , 768–78 (64th ed., 2010) (PDR 2010)
Nalox1046	Robertson, T. et al., <i>Intranasal Versus Intravenous Naloxone for Prehospital Narcotic Overdose</i> , Abstract, 12(5)(1) <i>Acad. Emerg. Med.</i> 166–67 (2005) (Robertson 2005)
Nalox1047	Robertson, T. et al., <i>Intranasal Naloxone is a Viable Alternative to Intravenous Naloxone for Prehospital Narcotic Overdose</i> , 13 <i>Prehosp. Emerg. Care</i> 512–15 (2009) (Robertson 2009)
Nalox1048	<i>Role of Naloxone in Opioid Overdose Fatality Prevention; Public Workshop; Request for Comments</i> , 76 <i>Fed. Reg.</i> 71,348 (Nov. 17, 2011) (Role of Naloxone Fed. Reg. Notice)
Nalox1049	<i>Role of Naloxone in Opioid Overdose Fatality Prevention</i> FDA Meeting Transcript (Apr. 12, 2012) (2012 FDA Meeting)
Nalox1050	Rosanske, T., <i>Morphine</i> , in <i>Chemical Stability of Pharmaceuticals: A Handbook for Pharmacists</i> , 604–11 (Connors, K. et al. eds., 2d ed. 1986) (Rosanske)
Nalox1051	Sabzghabae, A. et al., <i>Naloxone Therapy in Opioid Overdose Patients: Intranasal or Intravenous? A Randomized Clinical Trial</i> , 10(2) <i>Arch. Med. Sci.</i> 309–14 (2014) (Sabzghabae)

Exhibit Number	Description
Nalox1052	Intentionally left blank
Nalox1053	Trows, S. et al., <i>Analytical Challenges and Regulatory Requirements for Nasal Drug Products in Europe and the U.S.</i> , 6 Pharm. 195–219 (2014) (Trows)
Nalox1054	United States Pharmacopeia and National Formulary (USP 36-NF 31) Vol 1., 54–55, 930–33 (2013) (USP)
Nalox1055	U.S. Patent Appl. No. 61/918,802 (the '802 Appl.)
Nalox1056	U.S. Patent No. 5,307,953 ('953 patent)
Nalox1057	U.S. Patent No. 5,813,570 ('570 patent)
Nalox1058	U.S. Provisional Patent Appl. No. 61/953,379 (the '379 provisional)
Nalox1059	Wermeling, D., <i>Opioid Harm Reduction Strategies: Focus on Expanded Access to Intranasal Naloxone</i> , 30(7) Pharmacotherapy 627–31 (2010) (Wermeling 2010)
Nalox1060	Loimer, N. et al, <i>Nasal Administration of Naloxone is as Effective as the Intravenous Route in Opiate Addicts</i> , 29(6) Int'l J. of Addictions 819–27 (1994) (Loimer)
Nalox1061	Doe-Simkins, M. et al., <i>Saved by the Nose: Bystander-Administered Intranasal Naloxone Hydrochloride for Opioid Overdose</i> , 99(5) Am. J. Pub. Health 788–91 (2009)
Nalox1062	McDermott, C. & Collins, N., <i>Prehospital Medication Administration: A Randomised Study Comparing Intranasal and Intravenous Routes</i> , Em. Med. Int'l. 1–5 (2012)
Nalox1063	Intentionally left blank
Nalox1064	Authenticating Affidavit of Christopher Butler (“Butler Affidavit”)
Nalox1065	Authenticating Affidavits of Rachel J. Watters

Exhibit Number	Description
Nalox1066	Authenticating Affidavit of Pamela Lipscomb

I. INTRODUCTION

Nalox-1 Pharmaceuticals, LLC (“Petitioner”) respectfully petitions for *inter partes* Review (“IPR”) of claims 1–29 (the “Challenged Claims”) of U.S. Patent No. 9,211,253 (“the ’253 patent”), purportedly owned by Opiant Pharmaceuticals, Inc. (“Patent Owner”). Nalox1001. For the reasons addressed below, the Challenged Claims should be found unpatentable and canceled.

The ’253 patent is listed in the FDA’s Approved Drug Products with Therapeutic Equivalence Evaluations (a.k.a. “The Orange Book”) as covering intranasal naloxone sold under the Narcan® name. Naloxone rapidly reverses opioid overdose – it is an opioid antagonist and acts to restore normal respiration to a person whose breathing is impaired from opioid overdose. Naloxone has been available since 1971 as an injection, and its intranasal administration has been known in the community since at least 1994 as a safe and effective opiate overdose treatment. Loimer (Nalox1060) at 819. Narcan® is currently the only FDA-approved single-use nasal spray indicated for the emergency treatment of known or suspected opioid overdose. Because of the Patent Owner’s listing of patents in The Orange Book, there are currently no generic versions of intranasal Narcan® on the market. Patent Owner’s disingenuous use and abuse of the patent system here is contrary to the Constitution’s requirement to “promote the progress of science and useful arts” by wrongfully monopolizing access to life-saving medicine until 2035, based on

generations-old science and the most obvious applications in this art.

The United States is in the throes of an opioid epidemic. According to the Centers for Disease Control and Prevention, on average, 130 Americans die each day from an opioid overdose, and in 2017, the number of overdose deaths involving opioids was six times higher than in 1999. There is a critical and urgent need in America for intranasal naloxone products intended for community use and which can be deployed in life-threatening circumstances – often by people who are not medically trained. America cannot afford to wait another day for affordable, safe, and effective intranasal naloxone. The '253 patent is a barrier wrongfully and shamefully preventing broader accessibility to this critically needed naloxone medication. Removal of the '253 patent (and its relatives) as a barrier will save American lives by facilitating rapid and expanded access to life-saving naloxone.

II. IPR REQUIREMENTS UNDER 37 C.F.R. § 42.104

A. Grounds for Standing Under 37 C.F.R. § 42.104(a)

Petitioner certifies that the '253 patent is available for IPR and that Petitioner is not barred or estopped from requesting an IPR challenging the claims on the grounds identified herein.

B. Identification of Challenge Under 37 C.F.R. § 42.104(b)

Petitioner requests that the Patent Trial and Appeal Board (“Board”) invalidate the challenged claims of the '253 patent for the reasons identified below.

1. Statutory Grounds of Challenge

Petitioner challenges claims 1–29 of the ’253 patent and requests that each claim be cancelled based on the following grounds, which are supported by the Declarations of Dr. Maureen Donovan (Nalox1002) and Dr. Günther Hochhaus (Nalox1003):

Ground	Claims	Basis	References
1	1–3, 16–24, 28–29	§103(a)	Wyse in view of HPE
2	4–7, 10–15, 25–27	§103(a)	Wyse in view of Djupesland and HPE
3	8–9	§103(a)	Wyse in view of Djupesland, HPE, and the ’291 patent

2. Statement of Non-Redundancy

This is Petitioner’s first challenge of the ’253 patent before the Board. Petitioner submits the grounds in this Petition are not redundant nor duplicative of the grounds previously presented to the Office in the ’253 patent. In particular, Wyse¹ was never fully and substantively considered during the prosecution of the ’253 patent. While cited, initialed in an Information Disclosure Statement (“IDS”), and listed on the face of the ’253 patent, Wyse was not relied on in making

¹ The published U.S. Application of Wyse, US 2015/0174061, was cited in an IDS during prosecution.

any substantive rejections in the '253 patent. In fact, the Office never rejected any claim during the prosecution of the '253 patent.

In situations where prior art, relied on in an IPR petition, was cited by Patent Owner in an IDS and nominally initialed by the Examiner, the Board has rejected Patent Owner's arguments in denying institution by declining to invoke 35 U.S.C. § 325(d). *See, e.g., Fox Factory, Inc., v. SRAM, LLC*, IPR2017-00472, Paper 10 at 8–9 (PTAB April 21, 2017); *Digital Check Corp. d/b/a ST Imaging v. e-Imagedata Corp.*, IPR2017-00178, Paper 6 at 12–13 (PTAB April 25, 2017); *Limelight Networks, Inc. v. Mass. Inst. of Tech.*, IPR2017-00249, Paper 9 at 7 (PTAB May 18, 2017); *Microsoft Corp. v. Parallel Networks Licensing, LLC*, IPR2015-00486, Paper 10 at 15 (PTAB July 15, 2015). Therefore, recognizing that the Board has discretion, Petitioner respectfully requests the Board not invoke 35 U.S.C. § 325(d), because Wyse was merely listed in an IDS and initialed by the Examiner, without substantive discussion of the references by the Examiner.

3. Relief Requested

Petitioner requests the Board cancel the Challenged Claims as being unpatentable under AIA 35 U.S.C. § 103(a).

C. Mandatory Notices Under 37 C.F.R. § 42.8

1. Real Party-in-Interest Pursuant to 37 C.F.R. § 42.8(b)(1)

Pursuant to 37 C.F.R. § 42.8(b)(1), Petitioner certifies that Nalox-1

Petition for *Inter Partes* Review of U.S. Patent No. 9,211,253

Pharmaceuticals, LLC, BCIM Partners III, LP, BCIM General Partner III, LP, Burford Capital Ireland DAC, BCIM PIII Holdings, LLC, Burford Capital Investment Management LLC, Burford Capital Holdings (UK) Limited, and Burford Capital Limited are the real parties in interest (collectively, “RPI”). Nalox-1 Pharmaceuticals, LLC, a Delaware limited liability company, is 100% owned by BCIM Partners III, LP, a Delaware limited partnership. BCIM General Partner III, LLC, a Delaware limited liability company, is the general partner of BCIM Partners III, LP, and Burford Capital Investment Management LLC is the investment manager to BCIM Partners III, LP. No other person has authority to direct or control (i) the timing of, filing of, content of, or any decisions or other activities relating to this Petition or (ii) any timing, future filings, content of, or any decisions or other activities relating to the future proceedings related to this Petition. All of the costs associated with this Petition are expected to be borne by Nalox-1 Pharmaceuticals, LLC, BCIM Partners III, LP, BCIM General Partner III, LP, Burford Capital Investment Management LLC and Burford Capital Holdings (UK) Limited.

2. Related Matters Under 37 C.F.R. § 42.8(b)(2)

Petitioner identifies the following judicial or administrative matters that would affect, or be affected by, a decision in this proceeding. Patent Owner has asserted the '253 patent in the following United States District Court civil actions: 2:18-cv-15287 (D.N.J.), 2:16-cv-07721 (D.N.J.) (consolidated). Petitioner is not a

Petition for *Inter Partes* Review of U.S. Patent No. 9,211,253

party to these actions. Petitioner is concurrently filing *inter partes* review petitions on related U.S. Patent Nos. 9,468,747; 9,561,177; 9,629,965; and 9,775,838, which are listed in The Orange Book as covering Narcan® nasal spray (naloxone).

3. Identification of Lead and Back-Up Counsel Under 37 C.F.R. § 42.8(b)(3)

Petitioner provides the following designation of counsel:

Lead Counsel	Back-Up Counsel
Dr. Yelee Y. Kim (Reg. No. 60,088) Telephone: 202.857.6147 Fax: 202.857.6395 Yelee.Kim@arentfox.com	Janine A. Carlan (Reg. No. 42,387) Telephone: 202.715.8506 Fax: 202.857.6395 Janine.Carlan@arentfox.com
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4. Service Information Under 37 C.F.R. § 42.8(b)(4)

Please address all correspondence to above-identified counsel at:

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 1717 K Street NW
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Petitioner consents to electronic service.

III. LEVEL OF ORDINARY SKILL IN THE ART

As it relates to the '253 patent, a person of ordinary skill in the art (“POSA”) would comprise a team of individuals having experience in drug development, and specifically the development of solution-based dosage forms such as intranasal dosage forms. Donovan (Nalox1002), ¶26; *see also* Hochhaus (Nalox1003), ¶22. This team would include at least one formulator with experience in preformulation testing for and selection of excipients for a solution-based dosage form (including intranasal dosage forms) to achieve a target pharmaceutical profile (hereafter “Formulator POSA”). Donovan (Nalox1002), ¶26. The Formulator POSA would likely have a Ph.D. in pharmacy, pharmaceuticals, pharmaceutical chemistry, or a similar field involving pharmaceutical formulations, and would have several years of experience in pharmaceutical formulation development, including development of solution-based dosage forms, including intranasal dosage forms. *Id.* Alternatively, such a Formulator POSA would have a Bachelor’s or Master’s degree in pharmacy, pharmaceutical chemistry, or a similar field involving pharmaceutical formulations, and would have many years of experience developing and testing pharmaceutical formulations. *Id.* The Formulator POSA would also have an understanding of the importance, use, and component elements of certain commercially-available

delivery systems for dosage forms, including inhalers, metered-dose nasal sprayers, and single-dose nasal sprayers, as well as the importance of the properties of the spray from such devices (including droplet size and spray plume geometry). *Id.*

The POSA team would also include drug development professionals with clinical, clinical pharmacology, and regulatory expertise relevant to the design and performance of a drug development strategy for solution-based dosage forms such as intranasal dosage forms, including testing and/or evaluating the fate of the drug in the body (i.e., pharmacokinetics, including the physiological and biopharmaceutical aspects of nasal drug absorption), testing and/or evaluating issues of safety and efficacy, and evaluating the regulatory requirements of a new dosage form. Hochhaus (Nalox1003), ¶22. Within the team, the clinical pharmacologist generally serves as a link between formulators and clinicians, and helps integrate formulation and clinical aspects of drug development. *Id.* Such a clinical pharmacologist would routinely collaborate with others, such as formulators and clinicians, to achieve a target pharmaceutical profile. *Id.*

A clinical pharmacologist member of the drug development team (hereinafter a “Pharmacologist POSA”) would have an advanced degree in pharmacy, clinical pharmacology, pharmaceuticals, or a similar field, and would have several years of experience in drug development, including the development of solution-based dosage forms, including nasal spray dosage forms. Hochhaus (Nalox1003), ¶23. The

person would also have an understanding of drug formulation/device combinations, including the selection of excipients and their relationship to drug exposure and clinical outcomes. *Id.*

IV. OVERVIEW OF THE '253 PATENT

The '253 patent, entitled “Nasal Drug Products and Methods of Their Use,” was filed March 16, 2015, and issued on December 15, 2015 from U.S. Application No. 14/659,472 (“the '472 Application”). The '253 patent claims priority to U.S. Provisional Application No. 61/953,379 filed on March 14, 2014.

A. Summary of the Specification

The '253 patent specification is generally directed towards naloxone drug products for nasal delivery. *Nalox1001* at 1:8–12. The '253 patent admits the maturity of naloxone (CAS Reg. No. 357-08-4), in use since at least the 1970s along with an array of published reports of naloxone’s safe and effective intranasal delivery as early as at least 1994. *Id.* at 2:44–47; 9:41–10:3. In particular, the '253 patent discloses “a single-use, pre-primed device adapted for nasal delivery of a pharmaceutical composition to a patient by one actuation of the device into the nostril of the patient.” *Id.* at 21:5–8. These compositions can be used in methods of treating opioid overdose or suspected opioid overdose, as well as symptoms such as respiratory depression resulting from opioid overdose. *See id.* at 22:52–61.

B. Summary of the Claims

The '253 patent includes a single independent claim and twenty eight dependent claims that depend directly or indirectly thereto. The claims of the '253 patent (recited in full in Donovan (Nalox1002), ¶¶92–94 and Hochhaus (Nalox1003), ¶¶38–39) generally relate to drug products adapted for nasal delivery comprising a single-use, pre-primed device for delivering a pharmaceutical composition comprising naloxone hydrochloride or a hydrate thereof, along with certain inactive ingredients. Nalox1001 at 1:8–12; Hochhaus (Nalox1003), ¶6; *see also*, Donovan (Nalox1002), ¶6.

C. Summary of Relevant Portions of the File History

The '253 patent was filed on March 16, 2015 and designated as the '472 Application. After a response to a Restriction Requirement, the USPTO issued a first Notice of Allowance on October 9, 2015 without rejecting any claims, where original claims 1–24 and new claims 30–34 were allowed. Patent Owner submitted a Request for Continued Examination (“RCE”) on October 29, 2015, and amended original claim 1 to limit the amount of stabilizing agent to “about 0.2 mg” as well as claims 12 and 15 to change claim dependencies. The USPTO issued a second Notice of Allowance on November 9, 2015.

D. The '253 Patent Lacks Priority to the Filing Date of the '379 Provisional.

The '253 patent claims priority to U.S. Provisional Application No.

Petition for *Inter Partes* Review of U.S. Patent No. 9,211,253

61/953,379 (“the ’379 provisional”), filed March 14, 2014. Nalox1001, Cover. In order for any claim of the ’253 patent to have priority to this application, the ’379 provisional must provide adequate written description support under 35 U.S.C. § 112 for that claim. *See* 35 U.S.C. § 119(e)(1). To adequately support the claims, the ’379 provisional must set forth the subject matter of the claims “in sufficient detail that one skilled in the art can clearly conclude that the inventor invented the claimed invention as of the filing date sought.” *Anascape, Ltd. v. Nintendo of America Inc.*, 601 F.3d 1333, 1335 (Fed. Cir. 2010). The ’379 provisional fails to support the ’253 patent claims, and thus the earliest date to which the ’253 patent can claim priority is March 16, 2015. Donovan (Nalox1002), ¶¶95–100.

The ’379 provisional fails to provide support for claim 1, from which all other claims depend. That claim recites delivery of a spray that contains the following ingredients in the following amounts:

between about 0.2 mg and about 1.2 mg of an isotonicity agent;

between about 0.005 mg and about 0.015 mg of a preservative;

about 0.2 mg of a stabilizing agent;

an amount of an acid sufficient to achieve a pH of² 3.5-5.5.

² The patent recites “a pH *or* 3.5-5.5.” (emphasis added). Petitioner believes this is a typographical error and reads the claim as reciting “a pH of 3.5-5.5.”

Nalox1001, claim 1. The '379 provisional does not disclose these limitations implicitly or explicitly. Donovan (Nalox1002), ¶98. Rather, the '379 provisional only provides general disclosure regarding the composition of the naloxone hydrochloride nasal spray, without reciting specific combinations of excipients or disclosing the quantities or concentrations in which those excipients are to be included. *See, e.g.*, '379 provisional (Nalox1058), [083]–[088]; *see also* Donovan (Nalox1002), ¶98.

Because the '379 provisional does not describe these limitations that the applicants considered their “invention,” the claims of the '253 patent cannot claim priority to it. “Entitlement to a filing date extends only to subject matter that is disclosed; not to that which is obvious.” *Research Corp. Techs. v. Microsoft Corp.*, 627 F.3d 859, 870 (Fed. Cir. 2010). Because the '379 provisional fails to provide any description from which a POSA could conclude that the applicants had possession of the claimed subject matter at the time of filing of the '379 provisional, a POSA would conclude that no claim of the '253 patent can claim priority to the filing date of the '379 provisional. Donovan (Nalox1002), ¶99. Thus, the priority date of the '253 patent is no earlier than March 16, 2015, which is the filing date of the application from which the '253 patent issued. Donovan (Nalox1002), ¶100.

V. BACKGROUND AND OVERVIEW OF TECHNOLOGY

A. A POSA Would Have Been Motivated to Develop Improved Intranasal Naloxone Formulations to Combat the Opioid Epidemic.

Opioid overdose remains a major medical problem in the United States. In 2008, “poisonings” surpassed motor vehicle accidents as the leading cause of injury deaths in the United States, 90% of which are caused by drugs. Wermeling 2013 (Nalox1016) at 63. Of these 36,500 poisoning deaths, approximately half involved opioids. *Id.* The Center for Disease Control has referred to prescription drug overdose deaths as having reached epidemic proportions in the United States. *Id.*

Naloxone is an opioid receptor antagonist that acts as an antidote for opioid overdose. Naloxone has been available as an injectable formulation for decades, and is administered to adults with known or suspected narcotic overdoses at doses of 0.4 to 2 mg. PDR (2003) (Nalox1044) at 1300; Donovan (Nalox1002), ¶43; Hochhaus (Nalox1003), ¶43. First approved by the U.S. Food and Drug Administration (FDA) in 1971, Narcan® (naloxone hydrochloride injection) is indicated for the “complete or partial reversal of opioid depression, including respiratory depression” and “diagnosis of suspected or known acute opioid overdosage.” PDR (2003) (Nalox1044) at 1300. However, injecting Narcan® carries some risk of needlestick injury to healthcare professionals, which can transmit blood-borne viruses, such as HIV and hepatitis C. Donovan (Nalox1002), ¶44; Hochhaus (Nalox1003), ¶44.

Moreover, frequent opioid users have vein damage, making it difficult for healthcare providers to access veins, delaying naloxone administration. *Id.* Furthermore, administering drugs with needles intravenously requires expertise largely lacking in the general population. *Id.*

To address these issues, several emergency medical systems (EMS) in the U.S. began administering injectable naloxone as a nasal spray. Donovan (Nalox1002), ¶45; Hochhaus (Nalox1003), ¶45. *See also* Loimer (Nalox1060) at 819, Doe-Simkins (Nalox1061) at 788, Ashton (Nalox1019) at 221. Some of these systems administered naloxone intranasally via syringes fitted with a spray device called the Mucosal Atomizer Device (“MAD”).



Figure 1. The Mucosal Atomizer Device (MAD[®]) attached to a syringe showing the spray pattern of medication.

Barton 2005 (Nalox1021) at 266–67; *see also*, Barton 2002 (Nalox1020) at 55; Robertson 2009 (Nalox1047) at 513; McDermott (Nalox1062) at 2; Hochhaus (Nalox1003), ¶45. By 2010, several U.S. EMS programs made intranasal (“IN”) administration of 2 mg naloxone in 2 mL of aqueous solution (2 mg/mL), the standard of care for patients with suspected narcotic overdose. Robertson 2009 (Nalox1047) at 513; Wermeling 2010 (Nalox1059) at 628; Hochhaus (Nalox1003), ¶46; *see also* Donovan (Nalox1002), ¶45.

Despite intranasal administration’s advantages, using the injectable solution as an intranasal spray had a plainly conspicuous problem: the formulation was

insufficiently concentrated to deliver an effective dose in a small enough volume to be retained in the nostrils. Donovan (Nalox1002), ¶46; Hochhaus (Nalox1003), ¶47. Accordingly, the prior art readily suggested that “[a]n improvement would be to design a ready-to-use product specifically optimized, concentrated, and formulated for nasal delivery” (Wermeling 2013 (Nalox1016) at 64) and that there remained a need for “[f]ormulations having a concentration suited for delivery to and absorption by the naris (i.e. nostril or nasal passage). . . .” Wyse (Nalox1007) at 3:8–10; *see also* Hochhaus (Nalox1003), ¶49.

Ample motivation thus existed for a POSA to design and develop an improved intranasal formulation of naloxone that could be placed in a nasal delivery device. Donovan (Nalox1002), ¶46; Hochhaus (Nalox1003), ¶49.

B. A POSA Would Have Had the Know-How to Readily Develop an Improved Intranasal Naloxone Formulation.

When designing the improved formulation, a POSA would have been motivated to a) increase the concentration of naloxone, such that the naloxone dose could be delivered in 100 µL of solution; b) increase the dose of naloxone to achieve exposure levels equivalent to a 2 mg naloxone injection; and c) select inactive ingredients, or excipients, to maintain the physical, chemical, and microbiological stability of naloxone. In addition, a POSA would have been motivated to load this formulation into an appropriate single-use nasal sprayer capable of consistently

delivering the naloxone nasal spray. *See* Donovan (Nalox1002), ¶46 and Hochhaus (Nalox1003), ¶54.

1. The volume of the nasal cavity naturally limits the volume of a naloxone nasal spray to about 100 µL per spray.

A POSA would have known the nasal cavity can only retain a limited volume (up to 100 µL per spray), while the delivery of larger volumes will result in runoff and reduce the systemic availability (i.e., the bioavailability) of the drug. *See, e.g.,* Bitter (Nalox1022) at 27–28; Wermeling 2013 (Nalox1016) at 65; Donovan (Nalox1002), ¶53; Hochhaus (Nalox1003), ¶57. As noted above, dilute naloxone solutions had this exact problem. *See* Hochhaus (Nalox1003), ¶58; *see also* Middleton (Nalox1041) at 8; Sabzghabae (Nalox1051) at 311. One study found that a 2 mg/5 mL naloxone solution had a naloxone bioavailability of about 4% (as compared to IV) due to subjects swallowing the naloxone solution. *See* Dowling (Nalox1027) at 493; Hochhaus (Nalox1003), ¶59; *see also* Donovan (Nalox1002), ¶53. Others found that more concentrated naloxone nasal sprays had bioavailability of about 40%. *See* Hochhaus (Nalox1003), ¶59; *see also* Donovan (Nalox1002), ¶53; Wyse (Nalox1007), Table 4. A POSA would have been motivated to further concentrate the naloxone spray into a single 100 µL spray to increase retention in the nasal cavity and thus naloxone bioavailability. *See* Hochhaus (Nalox1003), ¶59; Donovan (Nalox1002), ¶53.

2. A POSA would have been motivated to use a 4-6 mg naloxone dose to achieve desirable naloxone exposure levels.

A POSA also would have been motivated to deliver a naloxone dose of about 4-6 mg with such a nasal spray. By 2012, the FDA had provided a streamlined regulatory pathway to obtain marketing approval for intranasal naloxone formulations, which required an intranasal naloxone formulation to meet or exceed the exposure levels of an approved dose of the injection (i.e., 0.4 to 2 mg). 2012 FDA Meeting (Nalox1049) at 166, 169–70, 172; Hertz Presentation (Nalox1032) at 8, 14–15; Hochhaus (Nalox1003), ¶61. As rapid onset to restore the patient’s breathing was the goal of naloxone administration, and given the known lack of adverse effects even at very high doses, a Pharmacologist POSA would have chosen to err on the side of providing an intranasal naloxone formulation with exposure levels comparable to the largest of the FDA-recommended doses of injectable naloxone—i.e., 2 mg. Hochhaus (Nalox1003), ¶61.

As noted above, prior art concentrated intranasal naloxone formulations had bioavailability of about 40% as compared to injectable naloxone. *See* Hochhaus (Nalox1003), ¶59; *see also* Donovan (Nalox1002), ¶53; Wyse (Nalox1007), Table 4. Based on simple math, a POSA thus would have reasonably expected a 4-6 mg naloxone dose in a concentrated intranasal naloxone formulation to achieve

comparable exposure to the 2 mg dose of injectable naloxone. Donovan (Nalox1002), ¶56.

3. A POSA would have had adequate know-how and ability to select commonplace excipients to make a stable, well-tolerated intranasal naloxone formulation.

A Formulator POSA also would have been motivated to choose ingredients to render the formulation chemically and microbiologically stable. Ideally, nearly all of the naloxone active ingredient would remain present after storage; the solution would have resisted any changes in color or formation of particulate matter; and the solution would have been free of microbial growth or ingress. Donovan (Nalox1002), ¶50.

A Formulator POSA would have been concerned about naloxone degradation. Naloxone, like morphine, has a phenolic moiety, which would potentially render it susceptible to oxidative degradation in solution. *See* Donovan (Nalox1002), ¶49. A Formulator POSA would have been able to minimize such degradation by, *inter alia*, adjusting the pH of the solution below 5 to retard oxidation and adding disodium edetate, as the prior art disclosed that both strategies prevent naloxone oxidation. *See, e.g.*, Wyse (Nalox1007) at 25:8–40, 27:35–40; Bahal (Nalox1014) at 5:60–64; Donovan (Nalox1002), ¶51.

Microbiological stability would have been another goal. Donovan (Nalox1002), ¶52. Several prior art naloxone nasal sprays include antimicrobial

agents to help render them microbiologically stable. *See, e.g.*, Wyse (Nalox1007) at 7:21–28, Table 1; Davies (Nalox1009) at 3:27–4:2; Wang (Nalox1008) at 8:13–14; Donovan (Nalox1002), ¶52. A Formulator POSA would have been motivated to select benzalkonium chloride (“BAC”) as a preservative due to its broad antimicrobial activity. *See* Donovan (Nalox1002), ¶¶63–66. BAC is in the FDA’s inactive ingredients database for nasal preparations (HPE (Nalox1012) at 57), has been utilized in intranasal naloxone solutions (Wang (Nalox1008) at 6, claim 3; Davies (Nalox1009) at 3:27–4:2); and when incorporated into intranasal products is “safe and well tolerated for both short- and long-term use.” Marple (Nalox1038) at 140. It is also more effective against some of the bacteria or molds used in FDA-mandated antimicrobial effectiveness testing than other antimicrobial agents. *See* Donovan (Nalox1002), ¶¶63–66.

Based on the prior art, a Formulator POSA would have been motivated to include the following familiar ingredients in an intranasal naloxone formulation:

- sufficient hydrochloric acid to lower solution pH to about 4.5, in order to stabilize naloxone to oxidation while minimizing irritation (*see, e.g.*, Wyse (Nalox1007) at 8:1–4; Wang (Nalox1008) at 8:30–41; Donovan (Nalox1002), ¶59)
- disodium edetate to stabilize naloxone to oxidation and to promote naloxone absorption; (*see, e.g.*, Kushwaha (Nalox1013) at 25; Bahal

Petition for *Inter Partes* Review of U.S. Patent No. 9,211,253

(Nalox1014) at 2:44–50; Wyse (Nalox1007) at 7:17–20; Donovan (Nalox1002), ¶¶ 60–61; Hochhaus (Nalox1003), ¶72); and

- BAC as an antimicrobial preservative. (*see, e.g.*, Davies (Nalox1009) at 3:27–4:2; Hochhaus (Nalox1003), ¶73; Donovan (Nalox1002), ¶¶ 63–66).

Further, a Formulator POSA would have included sufficient sodium chloride to render the solution isotonic to slightly hypertonic. *See, e.g.*, Wyse (Nalox1007) at 7:64–66; Wang (Nalox1008) at 6, claim 2; Davies (Nalox1009) at 2:23–26; Donovan (Nalox1002), ¶58; Hochhaus (Nalox1003), ¶70.

4. A POSA would have been motivated to load an intranasal naloxone formulation into an easy-to-use single-dose, pre-primed nasal sprayer.

Finally, a POSA would have loaded this formulation into a single-use, pre-primed device for nasal administration. For naloxone, a Formulator POSA would have chosen such a nasal sprayer, as such a device requires no priming—which minimizes drug loss and makes the device immediately ready-to-use when needed—which is useful for drugs administered sporadically. Donovan (Nalox1002), ¶¶79–81; *see also* ‘953 patent (Nalox1056) at 1:6-20; ‘570 patent (Nalox1057) at 1:10-46. One such device (which is recommended for use with the naloxone nasal sprays of Wyse) is the Aptar device. Wyse (Nalox1007) at 10:53–58; *see also* Djupesland (Nalox1010) at 48–49. Such a device also would have been desirable, because such

single-use nasal sprayers were known to consistently deliver the same volume of spray. *See* '291 patent (Nalox1015) at 9:15–19; Donovan (Nalox1002), ¶90.

VI. CLAIM CONSTRUCTION UNDER 37 C.F.R. § 42.104(B)(3)

The Board recently finalized a rule revising the claim construction standard to coincide with the standard applied in federal courts in construing patent claims. 83 Fed. Reg. 197 (October 11, 2018). Claim terms in an IPR are now given “the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention.” *Philips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (*en banc*). Accordingly, for purposes of this proceeding only, the terms in the Challenged Claims, unless stated otherwise, should be given their ordinary and customary meaning as understood by a POSA at the time of the alleged invention and need not be further construed for this Petition.

A. “pre-primed”

The claims require a “pre-primed” device. The '253 patent defines the term “pre-primed” as “a device, such as a nasal spray which is capable of delivering a pharmaceutical composition to a patient in need thereof with the first actuation of the spray pump, i.e., without the need to prime the pump prior to dosing, such as by actuating the pump one or more times until a spray appears.” Nalox1001 at 11:60–65. A POSA would thus interpret the term “pre-primed” as defined in the specification of the '253 patent. *See* Donovan (Nalox1002), ¶106.

B. “patient”

The claims require the device to deliver a pharmaceutical composition to “a patient.” The ’253 patent defines the term “patient” as “any subject (preferably human) afflicted with a condition likely to benefit from a treatment with a therapeutically effective amount of an opioid antagonist.” Nalox1001 at 11:49–52. A Pharmacologist POSA would interpret the term “patient” to mean that the claims’ recitation of a “patient” covers a single subject. Hochhaus (Nalox1003), ¶78.

C. “delivery time”

Dependent claims 10 and 11 require the delivery of pharmaceutical composition to correspond to a claimed “delivery time.” The ’253 patent defines the term “delivery time” as “the amount of time that elapses between a determination made by a healthcare professional, or an untrained individual that an individual is in need of nasal delivery of an opioid antagonist and completion of the delivery.” Nalox1001 at 8:52–56. For the purposes of this petition, a POSA would interpret the term “delivery time” as defined in the specification of the ’253 patent. Donovan (Nalox1002), ¶107.

D. “90% confidence interval for dose delivered per actuation is \pm about 2.0%” and “95% confidence interval for dose delivered per actuation is \pm about 2.5%”

Dependent claims 8 and 9 require delivering the naloxone hydrochloride dihydrate pharmaceutical composition from a device wherein the “90% confidence

Petition for *Inter Partes* Review of U.S. Patent No. 9,211,253

interval for dose delivered per actuation is \pm about 2.0%” and “95% confidence interval for dose delivered per actuation is \pm about 2.5%,” respectively. Neither the specification nor the file history of the ’253 patent provide an explicit definition of these terms; however, the specification provides a definition for the term “confidence interval” as “*a range* of values which will include the true average value of a parameter of a specified percentage of the time.” Nalox1001 at 8:47–49 (emphasis added). Applying this definition, a POSA would interpret these terms as ranges—i.e., covering devices that had a either a 90% or 95% confidence interval for dose delivered per actuation within the claimed range, rather than exactly at the recited number, as greater consistency between dose delivered per actuation is desirable. Donovan (Nalox1002), ¶108.

VII. SUMMARY OF THE PRIOR ART**A. Wyse (U.S. Patent No. 9,192,570)**

Wyse (Nalox1007) was filed on December 19, 2014, and issued on November 24, 2015, does not share any named inventors with the ’253 patent, and was at no time assigned to any current or prior assignee of the ’253 patent, making it prior art under 35 U.S.C. § 102(a)(2).³ Wyse is directed to intranasal naloxone compositions and use thereof to treat opioid overdose. Wyse (Nalox1007) at 9:17–21. The

³ Because the earliest application to which the ’253 patent can claim priority was filed after March 16, 2013, the AIA prior art provisions apply.

intranasal naloxone compositions comprise about 5-50 mg/mL naloxone (*id.* at 6:50–61) and various excipients including isotonicity agents, preservatives, stabilizers and pH adjusters (*see, e.g., id.* at Table 1), and may be delivered in a volume of about 100 μ L per spray via a single-use device (*id.* at 10:53–56).

B. Additional References

HPE (Nalox1012) comprises excerpted monographs from the Handbook of Pharmaceutical Excipients, 6th Ed., which was published in 2009, making it prior art under 35 U.S.C. § 102(a)(1).

Djupesland (Nalox1010) is a journal article that was published online on October 18, 2012, making it prior art under 35 U.S.C. § 102(a)(1).

Bahal (Nalox1014) is a U.S. Patent that issued on February 2, 1999, making it prior art under 35 U.S.C. § 102(a)(1).

Kushwaha (Nalox1013) is a journal article that was published in 2011, making it prior art under 35 U.S.C. § 102(a)(1).

Wermeling 2013 (Nalox1016) is a journal article that was published in 2013, making it prior art under 35 U.S.C. § 102(a)(1).

The '291 patent (Nalox1015) issued on June 12, 2012, making it prior art under 35 U.S.C. § 102(a)(1).

In addition, each of the references relied upon and cited in section VIII were published prior to the March 16, 2015 priority date, including the April 12, 2012

FDA Materials (which include the Hertz presentation (Nalox1032) and the Meeting Transcript (Nalox1049)).

C. Public Accessibility of the April 12, 2012 FDA Materials

The April 12, 2012 FDA Materials, which have been relied upon as background materials regarding intranasal naloxone by both Dr. Hochhaus and Dr. Donovan, were publicly accessible before the March 16, 2015 priority date of the '253 patent. A reference is considered publicly accessible if it was disseminated or otherwise made available to the extent that interested persons ordinarily skilled in the subject matter, exercising reasonable diligence, could locate it. *See Jazz Pharms., Inc. v. Amneal Pharms., LLC*, 895 F.3d 1347, 1355 (Fed. Cir. 2018).

The April 12, 2012 FDA Materials were both disseminated and made available to the interested public. Notice of this April 12, 2012 meeting was published and disseminated in the Federal Register on November 17, 2011. Nalox1048. That notice specifically said that “future research needs related to making naloxone more widely available” would be addressed, including “the development of novel formulations.” *Id.* The notice further stated that materials and a transcript from the workshop would be made available on an FDA website, for which the URL was provided. *See id.* These materials were, indeed, locatable at this website no later than November of 2014, prior to the earliest effective filing date of the '253 patent, as evinced by their inclusion in the Internet Archive. *See Butler*

Declaration (Nalox1064). As such, these materials were disseminated to the interested public.

In addition, the materials were made available to the interested public. A Pharmacologist POSA would have readily known to go to these websites, including the FDA website, to seek information on regulatory issues that might be involved in the development of novel formulations of drugs. Hochhaus (Nalox1003), ¶¶79–82. Furthermore, a Pharmacologist POSA would have known to look in the Federal Register and on FDA’s website for meeting notices such as this, as FDA routinely publishes notices and guidance documents regarding standards for drug development that are used and observed by Pharmacologist POSAs in developing new drug products. *Id.* In particular, a Pharmacologist POSA interested in developing new formulations of naloxone would have been keenly interested in these materials, as they set forth a regulatory pathway for approval for such a product. *Id.* As these materials were available before March 16, 2015—the priority date of the ’253 patent—they are prior art under 35 U.S.C. § 102(a)(1).

VIII. THE CHALLENGED CLAIMS ARE UNPATENTABLE

Pursuant to 37 C.F.R. § 42.104(b)(4)-(5), the grounds for invalidity are set forth below.

A. Ground 1: Claims 1–3, 16–24, and 28–29 are obvious over Wyse (Nalox1007) in view of HPE (Nalox1012)

Claim 1 is the sole independent claim, and claims 2–3, 16–24, and 28–29 are dependent claims depending directly or indirectly on claim 1.

1. Claim 1

- a. “A single-use, pre-primed device adapted for nasal delivery of a pharmaceutical composition to a patient by one actuation of said device into one nostril of said patient, having a single reservoir comprising”*

The preamble of claim 1 recites “[a] single-use, pre-primed device adapted for nasal delivery of a pharmaceutical composition to a patient by one actuation of said device into one nostril of said patient, having a single reservoir.” Nalox1001, claim 1. Wyse discloses “in one aspect, the Aptar/Pfeiffer Unitdose delivery device may be used to deliver the disclosed compositions. In one aspect, the nasal spray device delivers a volume of about 100 μ L per spray. This delivery system is used in other approved nasal spray drug products....” Nalox1007 at 10:53–58. A Formulator POSA would have understood that this Aptar device is a common device specially adapted for nasal delivery of a pharmaceutical composition to a patient. Donovan (Nalox1002), ¶116. Wyse further discloses that “[t]he disclosed nasal spray device...may have one or more features selected from being single-use, needle-free, ready-to-use, disposable, and combinations thereof,” (Nalox1007 at 10:29–33), and suggests that the Aptar device is a prime example of such a device containing those

features. *Id.* at 10:45–48. A device that is both single-use and ready-to-use indicates that it is pre-primed, as other nasal spray devices require priming prior to use in order to deliver the correct dosage amounts. Donovan (Nalox1002), ¶117. This is also consistent with the definition of “pre-primed” in the ’253 patent. *Id.*, ¶106.

The fact that it is “single-use” as disclosed in Wyse further indicates that it is both pre-primed and that it only provides one spray into one nostril, as there are bi-dose devices that are also pre-primed. *Id.*, ¶118. Moreover, a Formulator POSA would have understood the Aptar device to be a single-use, pre-primed device adapted for the nasal delivery of a pharmaceutical composition to a patient by one actuation of the device in one nostril of the patient. Donovan (Nalox1002), ¶119; *see also* Patent Owner’s admission of prior art in ’253 patent, Nalox1001 at 15:42–16:48. Finally, the Aptar device “may comprise a container (glass vial),” which would constitute a single reservoir. Wyse (Nalox1007) at 10:58–59; *see also id.* at 10:35–37.

b. “a pharmaceutical composition which is an aqueous solution of about 100 μ L comprising:”

Claim 1 recites “a pharmaceutical composition which is an aqueous solution of about 100 μ L.” Nalox1001, claim 1. Wyse discloses solutions containing naloxone hydrochloride and naloxone hydrochloride dihydrate for intranasal administration. *See* Nalox1007 at 6:50–65 and 9:17–21. Wyse discloses that the

Aptar delivery device delivers the appropriate 100 μ L volume of the intranasal solution per actuation to a patient's nostril. *See id.* at 10:53–56. Wyse further discloses that “the compositions are formulated with a suitable carrier to form a pharmaceutically acceptable nasal spray. In one aspect, the carrier may comprise water, saline, dextrose, or other suitable aqueous... carriers suitable for application to the nasal mucosa.” *Id.* at 8:25–30.

c. “about 4 mg naloxone hydrochloride or a hydrate thereof;”

Claim 1 recites that the pharmaceutical composition comprises “about 4 mg naloxone hydrochloride or a hydrate thereof.” Nalox1001, claim 1. Wyse discloses this amount. In an IPR, a presumption of obviousness arises “when the ranges of a claimed composition overlap the ranges disclosed in the prior art,” *E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018). Here, the claimed amount falls squarely within the range disclosed in Wyse. Wyse discloses desirable solutions for intranasal administration containing between 5 mg/mL and 50 mg/mL of an opioid antagonist, which may be naloxone hydrochloride or naloxone hydrochloride dihydrate. *See* Nalox1007 at 6:50–65, 9:17–21. As addressed above, this composition may be placed in a common Aptar delivery device to deliver 100 μ L of this intranasal solution per actuation to a patient's nostril. *See id.* at 10:53–56. Given that volume, Wyse discloses an amount of about 0.5 mg to 5

mg naloxone hydrochloride or naloxone hydrochloride dihydrate in 100 μ L of solution. Donovan (Nalox1002), ¶126. This encompasses the claimed quantity of “about 4 mg naloxone hydrochloride or a hydrate thereof,” and thus this element is disclosed.

d. “between about 0.2 mg and about 1.2 mg of an isotonicity agent;”

Claim 1 further recites that the pharmaceutical composition includes “between about 0.2 mg and about 1.2 mg of an isotonicity agent.” Nalox1001, claim 1. Wyse discloses this conventional element. Wyse discloses adjusting the tonicity of the solution to between 300 and 500 mOsm/kg using sodium chloride. Nalox1007 at 7:64–67. A Formulator POSA would have understood sodium chloride (NaCl) is an isotonicity agent. *See* Nalox1001, claim 2; *see also* Donovan (Nalox1002), ¶130. Example 5 of Wyse also discloses a naloxone formulation containing 6.4 mg/mL of sodium chloride, which is approximately 0.64 mg in a 100 μ L solution. *See* Nalox1001, Table 13; *see also* Donovan (Nalox1002), ¶130.

e. “between about 0.005 mg and about 0.015 mg of a preservative;”

Claim 1 further recites that the pharmaceutical composition includes “between about 0.005 mg and about 0.015 mg of a preservative.” Nalox1001, claim 1. It would have been obvious to a Formulator POSA to include between about 0.005 to 0.015 mg of a conventional preservative in such a formulation from the disclosure of Wyse,

in view of HPE. Wyse discloses using a preservative (an antimicrobial agent) in an amount of 0.1% to 2% by weight of the formulation. Nalox1007 at 7:20–28; Donovan (Nalox1002), ¶134. While Wyse generally discloses that the formulation may include an “antimicrobial agent,” Wyse does not specifically identify in this passage the types of antimicrobial agents that may be used, which would have motivated a Formulator POSA to consult compendiums of pharmaceutical excipients, such as HPE, to determine what antimicrobial agents he or she should consider in developing a nasal formulation of naloxone. Donovan (Nalox1002), ¶134.

A Formulator POSA, in reviewing HPE, also would have known that antimicrobial agents have differing potencies, and thus may be included in aqueous compositions in different concentrations. Donovan (Nalox1002), ¶135. A Formulator POSA would have been particularly motivated to use benzalkonium chloride (“BAC”) as a preservative in such a nasal spray, as it is a commonly used antimicrobial preservative in FDA-approved nasal formulations that has a broad range of antimicrobial activities at low concentrations, such as 0.002-0.02 % w/v, HPE (Nalox1012) at 56; Donovan (Nalox1002), ¶64, ¶137.⁴ On the other hand,

⁴ Although Patent Owner asserted in a related application that Wyse would have taught away from use of BAC in a naloxone nasal spray, a Formulator POSA would not properly have regarded the disclosure of Wyse as teaching away from use of BAC. *See* section IX below.

benzyl alcohol—the preservative exemplified in Wyse—is usually used at concentrations such as 5 mg/mL (0.5 % w/v) because it is only moderately active against Gram-positive organisms and less active against Gram-negative bacteria such as *Pseudomonas aeruginosa* and *E. coli* species, (HPE (Nalox1012) at 64), which generally are included in an antimicrobial challenge tests for parenteral drug products. Donovan (Nalox1002), ¶136. Thus, while Wyse discloses using quantities of preservative between 0.1% w/v and 2% w/v, a Formulator POSA would have recognized from the disclosure of HPE that this was based on the specific choice of preservative—i.e, benzyl alcohol—and that different preservatives commonly used in nasal sprays—particularly BAC—will function at lower concentrations of between 0.002% w/v and 0.02% w/v (i.e., 0.002 mg/100 µL to 0.02 mg/100 µL) in nasal sprays. HPE (Nalox1012) at 56; Donovan (Nalox1002), ¶138.

f. “about 0.2 mg of a stabilizing agent;”

Claim 1 recites that the pharmaceutical composition comprises “about 0.2 mg of a stabilizing agent.” Nalox1001, claim 1. As addressed above, in an IPR, a presumption of obviousness arises when the ranges of a claimed composition overlap the ranges disclosed in the prior art. *E.I. DuPont de Nemours & Co.*, 904 F.3d at 1006. The prior art does so here: specifically, Wyse discloses including in the pharmaceutical composition “from about 2 mM to about 20 mM...disodium ethylene diamine tetraacetic acid (EDTA).” Nalox1007 at 7:17–20. Disodium

ethylene diamine tetraacetic acid is familiar and common disodium edetate, which is plainly defined as a stabilizing agent in the '253 patent. *See, e.g.*, Nalox1001 at 21:30. For a 100 μ L spray volume as disclosed by Wyse, the broadest range would equate to between about 0.07 mg to 0.67 mg of anhydrous disodium edetate. Donovan (Nalox1002), ¶141. “About 0.2 mg” of disodium edetate would thus fall well within the disclosed range of from about 2 mM to about 20 mM. *See id.*

g. “an amount of an acid sufficient to achieve a pH of 3.5-5.5.”

Claim 1 recites that the pharmaceutical composition includes “an amount of an acid sufficient to achieve a pH of 3.5-5.5.” Nalox1001, claim 1. Wyse discloses that “the compositions may further comprise...hydrochloric acid in an amount sufficient to adjust the pH to from about 3 to about 5.5, or from about 3.5 to about 5, or about 4 ± 0.5 .” Nalox1007 at 8:1–4. Wyse further discloses compositions in which the pH is adjusted to the desirable value of about 4.25 using hydrochloric acid, and within the common range of acidic pH nasal administration. *See id.* at 14:51–52.

2. Claim 2

Claim 2 depends from claim 1 and recites the limitations that “the isotonicity agent is NaCl; the preservative is benzalkonium chloride; the stabilizing agent is disodium edetate; and the acid is hydrochloric acid.” Nalox1001, claim 2. The disclosures of the prior art with regard to claim 1 are addressed above.

a. “the isotonicity agent is NaCl;”

Wyse discloses adding unremarkably common sodium chloride (i.e., NaCl) to adjust tonicity in an amount within the claimed range. Wyse thus discloses this element. Nalox1007 at 7:64–67 and Table 13; *see also* Donovan (Nalox1002), ¶150.

b. “the preservative is benzalkonium chloride;”

A Formulator POSA would have been particularly motivated to use conventional BAC as a preservative in a naloxone nasal spray, as it is a commonly used antimicrobial preservative in FDA-approved nasal formulations that has a broad range of antimicrobial activities at low concentrations. Donovan (Nalox1002), ¶64.

A Formulator POSA would have recognized that different preservatives are used at different concentrations. In particular, HPE discloses that BAC is usually used in nasal sprays at a concentration of 0.002–0.02% w/v. Nalox1012 at 56; Donovan (Nalox1002), ¶152. The claimed weight range of 0.005 mg to 0.015 mg in 100 µL of solution falls squarely within this range. Donovan (Nalox1002), ¶152. Moreover, a Formulator POSA would have been able to immediately envision using a concentration of 0.01% w/v (i.e., 0.01 mg per 100 µL of solution) of BAC from the disclosure of HPE, as HPE discloses that such concentrations are frequently used in small-volume parenteral products. Nalox1012 at 56; *see also* Donovan (Nalox1002), ¶152. It would have been obvious to incorporate BAC into a nasal

spray naloxone formulation in an amount of 0.005 mg to about 0.15 mg in a 100 μ L solution—particularly an amount of 0.01 mg—from the disclosure of Wyse in combination with HPE. Donovan (Nalox1002), ¶152.

c. “the stabilizing agent is disodium edetate;”

Wyse discloses the use of standard disodium edetate within ranges overlapping the claimed amount of 0.2 mg per 100 μ L. *See* Nalox1007 at 7:17–20, Donovan (Nalox1002), ¶155.

d. “and the acid is hydrochloric acid.”

Wyse discloses using common hydrochloric acid to adjust the pH of the solution to within the claimed range of 3.5 to 5.5. *See* Nalox1007 at 8:1–4 and 14:51–52, Donovan (Nalox1002), ¶156.

3. Claim 3

Claim 3 depends from claim 2 and recites the limitations that “the aqueous solution comprises: about 4.4 mg naloxone hydrochloride dihydrate; about 0.74 mg NaCl; about 0.01 mg benzalkonium chloride; about 0.2 mg disodium edetate; and an amount of hydrochloric acid sufficient to achieve a pH of 3.5-5.5.” Nalox1001, claim 3. The disclosures of the prior art with regard to claim 2 are addressed above.

a. “about 4.4 mg naloxone hydrochloride dihydrate;”

Wyse discloses an appropriate amount of about 0.5 mg to 5 mg naloxone hydrochloride or naloxone hydrochloride dihydrate in 100 μ L of solution (or, 5

mg/mL to 50 mg/mL). Nalox1007 at 6:50–65, 9:18–21. Further, a Formulator POSA would have recognized that one would have to modify the dose of naloxone hydrochloride (anhydrous) on a weight basis to account for the presence of the two water molecules associated with the crystalline solid.⁵ Donovan (Nalox1002), ¶159. Moreover, a Formulator POSA would have expected the anhydrous and dihydrate forms of naloxone hydrochloride, once dissolved in aqueous medium, to behave identically. *Id.*

b. “about 0.74 mg NaCl;”

Wyse suggests this element. Donovan (Nalox1002), ¶¶160–66. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *See E.I. DuPont de Nemours & Co.*, 904 F.3d at 1006. Here, Wyse discloses adjusting the tonicity of the solution to between 300 and 500 mOsm/kg using standard sodium chloride. Nalox1007 at 7:64–67. As Wyse discloses adjusting the tonicity of the solution to between 300 and 500 mOsm/kg, or more particularly to “within 365–425 mOsm,” (*id.* at 14:55–56), it would have been obvious to arrive at the quantity of sodium chloride through routine optimization of a result-effective variable. A Formulator POSA would have known that the function of adding sodium chloride to

⁵ A Formulator POSA would need to include about 1.1 times as much of the dihydrate as the anhydrous naloxone hydrochloride to achieve an identical quantity of naloxone. *See* Donovan (Nalox1002), ¶160, n. 13.

the solution was to adjust the tonicity, which would take into account the total quantity of solute particles in the solution (including from other ingredients). Donovan (Nalox1002), ¶160. A Formulator POSA would have optimized within this range by measuring the tonicity of the naloxone hydrochloride/disodium edetate/BAC solution and determining the appropriate amount of sodium chloride to add from that measurement in order to achieve the desired tonicity. *Id.*, ¶165.

Alternately, a Formulator POSA would have been able to predict approximately how much sodium chloride was needed, knowing the other components of the pharmaceutical solution and their concentrations. In this case, a Formulator POSA would have been able to determine the approximate amount of sodium chloride needed to adjust the tonicity of the solution to between 300 and 500 mOsm/kg. *See* Donovan (Nalox1002), ¶¶161–64. A Formulator POSA would have calculated a 4 mg/100 µL naloxone hydrochloride solution including 0.2 mg/100 µL disodium edetate and 0.01 mg/100µL BAC adjusted to a pH of between 3.5 and 5.5 using hydrochloric acid to be approximately osmotically equivalent to a 0.57/100µL NaCl solution; to adjust the tonicity of the solution to between 300 and 500 mOsm/kg would thus require between approximately 300 and 900 µg (0.3 to 0.9 mg) of NaCl per 100 µL of water, which range encompasses “about 0.74 mg” as claimed. *See id.*, ¶¶162–63. The narrower ranges disclosed in Wyse (i.e., between 365 mOsm/kg and 425 mOsm/kg) would have required adding about 500 to about 700

µg of NaCl per 100 µL of aqueous solution to adjust the tonicity between these targets. *See* Donovan (Nalox1002), ¶164. As such, the claimed quantity of 0.74 mg NaCl would have been obvious to a Formulator POSA. *Id.*, ¶168.

c. “about 0.01 mg benzalkonium chloride;”

A Formulator POSA would have been particularly motivated to use conventional BAC in an amount of 0.1% (w/v) (0.01 mg per 100 µL of solution) as a preservative in a naloxone nasal spray. *See also* Donovan (Nalox1002), ¶169.

d. “about 0.2 mg disodium edetate;”

Wyse discloses the use of common disodium edetate within ranges overlapping the claimed amount of 0.2 mg per 100 µL. *See* Nalox1007 at 7:17–20, Donovan (Nalox1002), ¶170.

e. “and an amount of hydrochloric acid sufficient to achieve a pH of⁶ 3.5-5.5.”

Wyse discloses using hydrochloric acid to adjust the pH of the solution to within the common and desirable claimed range of 3.5 to 5.5. *See* Nalox1007 at 8:1–4 and 14:51–52. Donovan (Nalox1002), ¶171.

4. Claim 16

Claim 16 depends from claim 1 and recites the limitation that “wherein said patient is an opioid overdose patient or a suspected opioid overdose patient.”

⁶ *See supra* n.2

Nalox1001, claim 16. The disclosures of the prior art with regard to claim 1 are addressed above.

Wyse discloses “methods of treating a known or suspected opioid overdose in a subject in need thereof, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject.” Nalox1007 at 9:17–21.

As intranasal naloxone had been widely and routinely used to safely and effectively treat opioid overdose (*see* Donovan (Nalox1002), ¶45 and Hochhaus (Nalox1003), ¶¶45–46), a Formulator POSA thus would have been motivated to use the modified formulation of claim 1 in the methods disclosed in Wyse with a reasonable expectation of success. *See* Donovan (Nalox1002), ¶¶172–76.

5. Claims 17 and 18

Claim 17 depends from claim 16 and recites the limitation that “the patient exhibits one or more symptoms” chosen from a *Markush* group including the symptom of “respiratory depression.” *See* Nalox1001, claim 17. Claim 18 depends from claim 17 and recites that “the patient exhibits respiratory depression.” *Id.*, claim 18. The disclosures of the prior art with regard to claim 16 are addressed above.

Wyse discloses methods of treating a known or suspected opioid overdose, which may be manifested by respiratory depression, with intranasal naloxone. *See* Nalox1007 at 9:33–35, 10:1–3; Donovan (Nalox1002), ¶¶177–85.

6. Claim 19

Claim 19 depends from claim 18 and recites the limitation that “said respiratory depression is caused by the illicit use of opioids, or by an accidental misuse of opioids during medical opioid therapy.” Nalox1001, claim 19. The disclosures of the prior art with regard to claim 18 are addressed above.

Wyse discloses that, “of the 36,500 drug poisoning deaths in 2008, 14,800 involved prescription opioid analgesics. Approximately 3,000 deaths also involved heroin overdose.” Nalox1007 at 1:41–44. A Formulator POSA would have known that intranasal naloxone administration could readily reverse the effects of opioid overdose resulting from both abuse of prescription opioid analgesics and heroin, as well as the accidental misuse of prescription opioid analgesics. *See* Donovan (Nalox1002), ¶188.

7. Claims 20–23

Claim 20 depends from claim 19 and recites the limitation that “said patient is free from respiratory depression for at least about 1 hour following treatment comprising essentially of delivery of said therapeutically effective amount of said opioid antagonist.” Nalox1001, claim 20. Claims 21, 22, and 23, which depend from claim 20, 21, and 22, respectively, recite similar limitations where the patient is free from respiratory depression for at least about 2, about 4, and about 6 hours,

respectively. *Id.*, claims 21–23. The disclosures of the prior art with regard to claim 19 are addressed above.

Wyse discloses “methods of treating a known or suspected opioid overdose in a subject in need thereof, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject.” Nalox1007 at 9:17–21. Wyse further discloses that “the phrase ‘treating an opioid overdose’ includes ‘reversing the effects of an opioid overdose.’” *Id.* at 9:35–37. Reversal of an opioid overdose would plainly include ensuring that the patient was free of respiratory depression for an indefinite period after the opioid overdose—that is, administration of naloxone would reverse the effects of the overdose such that they do not recur and the patient resumes normal breathing activity. Donovan (Nalox1002), ¶194.

Wyse further discloses a method for reversing the effects of opioid overdose by administering 200 µL of a 10 mg/mL naloxone solution divided into two half-doses (i.e., two 100 µL doses of 1 mg each, for a total dose of 2 mg), where each half-dose is administered intranasally. Nalox1007 at 10:13–24.

A Formulator POSA would have had a reasonable expectation of success that such intranasal administration of naloxone would reverse opioid overdose. Donovan (Nalox1002), ¶196. For example, Wermeling 2013 indicates that only 15–20% of cases require a repeat dose of naloxone, which indicates that approximately 80–85%

of opioid overdose patients have respiratory depression reversed indefinitely without a second dose of naloxone. *See* Nalox1016 at 71; *see also* Donovan (Nalox1002), ¶196.

8. Claim 24

Claim 24 depends from claim 16 and recites the limitation that “said patient is in a lying, supine, or recovery position.” Nalox1001, claim 24. The disclosures of the prior art with regard to claim 16 are addressed above.

Wyse further discloses a kit comprising a naloxone nasal spray composition with instructions to place “the individual on their back” prior to treatment. Nalox1007 at 12:12–17. Placing the individual on their back would plainly put the individual in a lying position. Donovan (Nalox1002), ¶201.

9. Claims 28 and 29

Claims 28 and 29 depend from claim 3 and recite said single actuation yields a plasma concentration of “ ≥ 0.2 ng/ml within 2.5 minutes in said patient,” and “ ≥ 1 ng/mL within 5 minutes in said patient,” respectively. Nalox1001, claims 28 and 29.

Wyse discloses pK data for administering 2 x 1 mg naloxone in 100 μ L of solution (2 mg/200 μ L). *See* Nalox1007 at 15:36–38 (“Treatment D”). Table 9 discloses the following maximum naloxone concentration values:

Table 9 disclosure	Equivalence in minutes
0.265 ng/mL after 0.03 hours	2 min
2.19 ng/mL after 0.08 hours	5 min
3.28 ng/mL after 0.17 hours	10 min

Nalox1007 at 19.

This indicates that at least one subject achieved that naloxone plasma concentration at that time point, which thus meets the claim limitation based on the definition of “patient” as presently construed. Hochhaus (Nalox1003), ¶¶78, 104, 111. A Pharmacologist POSA would have been intensely motivated to design an intranasal solution of naloxone that contained a higher dose of naloxone in a more concentrated solution (such as 4 mg/100 µL), with a reasonable expectation of success. *Id.*, ¶¶60–66. A Pharmacologist POSA would have expected that administering a higher dose of naloxone in a more concentrated solution would result in higher plasma levels in 2 minutes (*id.*, ¶104) and 5 minutes (*id.*, ¶111) as compared to those seen with the Wyse composition. *Id.*, ¶¶59, 104, 111. It thus would have been obvious to achieve a plasma concentration of naloxone of: ≥ 0.2 ng/mL within 2.5 minutes for claim 28 (*id.*, ¶104), ≥ 1 ng/mL within 5 minutes for claim 29 (*id.*, ¶111) to aid the subject in breathing normally again as quickly as possible. A Pharmacologist POSA would not have expected any differences in excipients (or amounts of excipients) between the compositions disclosed in Wyse

and the compositions of the claims (i.e., those suggested by Wyse and HPE) to be material to a determination of obviousness. *See* Hochhaus (Nalox1003), ¶¶104, 111. Accordingly, a Pharmacologist POSA would have found claim 28 (*id.*, ¶¶99–105) and claim 29 (*id.*, ¶¶106–12) obvious.

B. Ground 2: Claims 4–7, 10–15, and 25–27 are obvious over Wyse (Nalox1007) in view of Djupesland (Nalox1010) and HPE (Nalox1012).

Claims 4–7, 10–15, and 25–27 are dependent claims that depend directly or indirectly on independent claim 1. A detailed description of Wyse and HPE is provided above.

1. Claim 4

Claim 4 depends from claim 2 and recites the limitation that “said device is actuatable with one hand.” Nalox1001, claim 4. The disclosures of prior art with respect to claim 2 are addressed above.

While Wyse does not explicitly disclose that the Aptar delivery device is actuatable with one hand, Djupesland does. Donovan (Nalox1002), ¶209. Djupesland specifically states that “[t]he single- and duo-dose devices mentioned above...are held between the second and the third fingers with the thumb on the actuator.” *See* Nalox1010 at 49. This plainly reports such devices are actuated with one hand. *See* Donovan (Nalox1002), ¶209. A Formulator POSA would have been motivated to combine these teachings because both Wyse and Djupesland refer to

the same single-use nasal spray device, and Djupesland provides further direction and details on how to use the commercial Aptar device. *See* Donovan (Nalox1002), ¶209.

2. Claim 5

Claim 5 depends from claim 4 and recites the limitation that “the volume of said reservoir is not more than about 140 μL .” Nalox1001, claim 5. The disclosures of the prior art with regard to claim 4 are provided in the prior section.

Djupesland discloses that a volume of 125 μL is filled into Aptar/Pfeiffer single-dose devices to deliver a 100 μL spray volume. Nalox1010 at 49. Djupesland further discloses that single-use nasal spray devices, including the Aptar device, include a single reservoir. *See id.* A Formulator POSA would have recognized from the combined disclosures of Wyse and Djupesland that the volume of the reservoir could be as little as 125 μL to accommodate the necessary overflow to deliver a 100 μL volume of spray. Donovan (Nalox1002), ¶216. Thus, a Formulator POSA would have recognized that the volume of the reservoir could be as small as 125 μL . *Id.*

3. Claim 6

Claim 6 depends from claim 5 and recites the limitation that “wherein about 100 μL of said aqueous solution in said reservoir is delivered to said patient in one actuation.” Nalox1001, claim 6. The disclosures of the prior art with regard to claim 5 are addressed above.

Wyse discloses that “the nasal spray device delivers a volume of about 100 μ L per spray.” Nalox1007 at 10:53–58. Because the device described by Wyse is both “single use” and “delivers a volume of about 100 μ L per spray,” a Formulator POSA would have understood that Wyse plainly discloses this element and claim 6 would have been obvious. Donovan (Nalox1002), ¶¶219–21.

4. Claim 7

Claim 7 depends from claim 6 and recites the limitation that “the pharmaceutical composition which is an aqueous solution comprises about 4.4 mg naloxone hydrochloride dihydrate.” Nalox1001, claim 7. The disclosures of the prior art with regard to claim 6 are addressed above.

It would have been obvious to include about 4.4 mg naloxone hydrochloride dihydrate in the composition from the disclosure of Wyse. *See also* Donovan (Nalox1002), ¶¶222–24.

5. Claims 10 and 11

Claims 10 and 11 depend from claim 7 and recite the limitation that “the delivery time is less than about” 25 seconds and 20 seconds, respectively. Nalox1001, claims 10 and 11. The disclosures of prior art with regard to claim 7 are addressed above. The construction for “delivery time” is addressed above in section VI.C.

Wyse discloses that “there is a need for integrating compositions, methods,

and devices that can allow for an effective reversal of opioid overdose, but which eliminates or minimizes the use of needles.” Nalox1007 at 2:67–3:3. Further, Wyse discloses that there is a need for “effective formulations and methods of providing such compositions to an individual...for reversing opioid overdose, that can be *quickly* and *easily* used[.]” *Id.* at 3:3–6 (emphasis added). Wyse further discloses that the devices used for administering the compositions are “ready-to-use” and can be “assembled in the Unitdose delivery devices and packaged in 4” by 4” foil pouches, one device/pouch, heat-sealed and labeled as appropriate.” *Id.* at 10:31–33, 11:4–6. Each of these disclosures would lead a Formulator POSA to understand that Wyse was distinctly seeking to minimize the delivery time of naloxone to a patient to a matter of mere seconds by putting it in a ready-to-use nasal spray, which comports with the most fundamental goal of the treatment: when a patient is not breathing due to an opioid overdose, every second counts in getting the patient the naloxone antidote and breathing again. Donovan (Nalox1002), ¶228.

6. Claims 12–14

Claim 12 depends from claim 7 and recites the limitation that “wherein upon nasal delivery of said pharmaceutical composition to said patient, less than about 20% of said pharmaceutical composition leaves the nasal cavity via drainage into the nasopharynx or externally.” Nalox1001, claim 12. Claim 13 depends from claim 12 and recites that less than about 10% leaves the nasal cavity, and claim 14 depends

from claim 13 and recites that less than about 5% leaves the nasal cavity. *Id.*, claims 13 and 14. The disclosures of the prior art with regard to claim 7 are addressed above.

Wyse specifically discloses using the Aptar delivery device to deliver the disclosed compositions in a volume of about 100 μL per spray; this device is configured to deliver a single spray per naris. *See* Nalox1007 at 10:53–56. The 100 μL volume of liquid spray will not drip out or drain when placed on the surface of the nasal cavity. Donovan (Nalox1002), ¶234. Several references show that this volume is small enough to be retained in the nasal cavity: for instance, Wermeling 2013 discloses that “[t]he nasal cavity can retain 100–150 μL without causing immediate runoff out the front of the nose or down the nasopharynx.” Wermeling 2013 (Nalox1016) at 65; *see also* Donovan (Nalox1002), ¶234. Accordingly, a Formulator POSA would have found these limitations to be obvious over Wyse’s disclosure of administering a single 100 μL spray to a naris of a patient. Donovan (Nalox1002), ¶¶231–36.

7. Claim 15

Claim 15 depends from claim 7 and recites the limitation that “the plasma concentration versus time curve of said naloxone hydrochloride in said patient has a T_{max} of between about 20 and about 30 minutes.” The disclosures of the prior art with regard to claim 7 are addressed above.

Wyse further discloses that the administration of an intranasal naloxone

composition “results in a T_{\max} in a subject from about 0.1 hours to about 0.5 hours....” Nalox1007 at 9:43–44. This equates to a range of about 6 minutes to about 30 minutes, which overlaps with the claimed range. Hochhaus (Nalox1003), ¶89. A Pharmacologist POSA would have unequivocal motivation to design an intranasal solution of naloxone that achieved an early T_{\max} to cause normal breathing in an overdose victim as quickly as possible, and would have had a reasonable expectation of success based on the prior art. *See* Wyse (Nalox1007) at 16, Table 1; Middleton (Nalox1041) at 22; Hochhaus (Nalox1003), ¶67.

It thus would have been obvious to achieve the claimed T_{\max} in a patient being administered intranasal naloxone, to aid the subject in breathing normally again as quickly as possible. Hochhaus (Nalox1003), ¶89. Further, a Pharmacologist POSA would not have expected any differences in excipients (or amounts of excipients) between the compositions disclosed in Wyse and the compositions of the claims (i.e., those suggested by Wyse and HPE) to materially affect the T_{\max} . *Id.* Accordingly, claim 15 would have been obvious to a Pharmacologist POSA. *Id.*, ¶¶87–90.

8. Claims 25–27

Claims 25–27 each depend directly from claim 7 and recite said single actuation yields a plasma concentration of “ ≥ 0.2 ng/ml within 2.5 minutes in said patient,” “ ≥ 1 ng/mL within 5 minutes in said patient,” and “ ≥ 3 ng/mL within 10 minutes in said patient,” respectively. Nalox1001, claims 25–27. The disclosures of

prior art with regard to claim 7 are addressed above.

Wyse discloses pK data for administering 2 x 1 mg naloxone in 100 μ L of solution (2 mg/200 μ L). *See* Nalox1007 at 15:36–38 (“Treatment D”). Table 9 discloses the following maximum naloxone concentration values:

Table 9 disclosure	Equivalence in minutes
0.265 ng/mL after 0.03 hours	2 min
2.19 ng/mL after 0.08 hours	5 min
3.28 ng/mL after 0.17 hours	10 min

This indicates that at least one subject achieved that naloxone plasma concentration at that time point, which thus meets the claim limitation based on the definition of “patient” as presently construed. Hochhaus (Nalox1003), ¶¶78, 104, 118. A Pharmacologist POSA would have been intensely motivated to design an intranasal solution of naloxone that contained a higher dose of naloxone in a more concentrated solution (such as 4 mg/100 μ L), with a reasonable expectation of success. *Id.*, ¶59. A Pharmacologist POSA would have expected that administering a higher dose of naloxone in a more concentrated solution would result in higher plasma levels in 2 minutes (*id.*, ¶104), 5 minutes (*id.*, ¶111), and 10 minutes (*id.*, ¶118) than those seen with the Wyse composition. *Id.*, ¶¶59, 104, 111, 118. It thus would have been obvious to achieve a plasma concentration of naloxone of: ≥ 0.2 ng/mL within 2.5 minutes for claim 25 (*id.*, ¶104), ≥ 1 ng/mL within 5 minutes for claim 26 (*id.*, ¶111), and ≥ 3 ng/mL within 10 minutes for claim 27 (*id.*, ¶118) to aid

the subject in breathing normally again as quickly as possible. A Pharmacologist POSA would not have expected any differences in excipients (or amounts of excipients) between the compositions disclosed in Wyse and the compositions of the claims (i.e., those suggested by Wyse and HPE) to be material to a determination of obviousness. *See* Hochhaus (Nalox1003), ¶¶104, 111, 118. Accordingly, a Pharmacologist POSA would have found claim 25 (*id.*, ¶¶99–105), claim 26 (*id.*, ¶¶106–12), and claim 27 (*id.*, ¶¶113–19) obvious.

C. Ground 3: Claims 8–9 are obvious over Wyse (Nalox1007) in view of Djupesland (Nalox1010), HPE (Nalox1012), and the '291 patent (Nalox1015).

Claims 8 and 9 depend directly on claim 7. The disclosures of prior art with regard to claim 7 are addressed above. Claim 8 recites the limitation that “the 90% confidence interval for dose delivered per actuation is \pm about 2%.” Nalox1001, claim 8. Claim 9 recites the limitation that “the 95% confidence interval for dose delivered per actuation is \pm about 2.5%.” *Id.*, claim 9.

A Formulator POSA would have further combined the disclosure of the '291 patent with the disclosure of Wyse to arrive at the claimed device and formulation with a reasonable expectation of success. Donovan (Nalox1002), ¶242. While Wyse does not explicitly disclose the 90% or 95% confidence intervals of the dose delivered per actuation from the device disclosed, a Formulator POSA readily could have determined this for similar, if not identical, devices. *See id.* (Nalox1002), ¶243.

Further, a Formulator POSA would have been motivated to do so, as the uniformity of the delivered dose from one device to another is a key consideration in developing intranasal formulations. *See id.*, ¶87.

The '291 patent discloses a study in which it was found that the Pfeiffer Unitdose Second Generation Spray Device—a single-use, pre-primed device like the Aptar device disclosed in Wyse—has a 95% CI for the dose delivered over two sprays of about $\pm 1.5\%$ and a 90% CI for dose delivered over the two sprays of about $\pm 0.9\%$. *See* Nalox1015 at 8:2–4, 8:30–9:19; *see also* Donovan (Nalox1002), ¶¶243–45. This indicates that, for the Pfeiffer Unitdose Spray device in combination with the formulation disclosed in the '291 patent, the 90% confidence interval for dose delivered is within \pm about 2%, and that the 95% confidence interval for dose delivered is within \pm about 2.5%. Donovan (Nalox1002), ¶¶243–45.

A Formulator POSA would have been rigorously motivated to achieve similar results through selection of an appropriate delivery device that reproducibly and consistently delivered the same dose upon each actuation, and the '291 patent evidences that such devices were available to a Formulator POSA prior to March 16, 2015. Donovan (Nalox1002), ¶245; *see also id.*, ¶¶88–89.

A Formulator POSA also would reasonably have expected the device to behave similarly when used in combination with other formulations (including those suggested and taught by Wyse), as the reliability and repeatability of dose delivery

is a function of the device and the reproducibility of loading into the device. Donovan (Nalox1002), ¶246. The '291 patent specifically discloses that one advantage of the Pfeiffer devices is that “they have the capability of consistently delivering the pharmaceutical composition.” See Nalox1015 at 6:51–56; see also Donovan (Nalox1002), ¶246. Accordingly, claims 8 and 9 would have been obvious to a Formulator POSA. Donovan (Nalox1002), ¶¶237–48.

IX. SECONDARY CONSIDERATIONS

During the prosecution of related U.S. Patent No. 9,561,177 (“the '177 patent”), which the Petitioner is concurrently petitioning for IPR, patent applicants raised several secondary considerations of non-obviousness. None of these show that the claims of the '253 patent are not obvious.

A. No teaching away

The Applicants for the related '177 patent asserted that Wyse, as a whole, taught away from the claimed invention of the '177 patent. First, Applicants argued that Wyse taught away from using BAC in the formulation. Second, Applicants argued the prior art taught away from using a concentration of 4% (w/v) naloxone hydrochloride and doses of naloxone hydrochloride as high as 4 mg. Contrary to Applicants' assertion, Petitioner contends that the prior art does not teach away for the following reasons.

A POSA specifically would not have properly concluded that Wyse taught

away from using BAC with naloxone. Although Wyse discloses, in example 5, that “the use of benzalkonium chloride...resulted in an additional degradant in formulations 7, 9, 14, and 14A” (Wyse (Nalox1007) at 27:30–34) and that “benzalkonium chloride was not [acceptable], due to increased observed degradation,” (*id.* at 27:41–44), a POSA would not have granted such statements much merit for three reasons: (a) given that Wyse performed degradation testing on multiple different formulations combining multiple different excipients, it cannot be conclusively determined that any individual excipient was responsible for any instability issues in the disclosed formulation (Donovan (Nalox1002), ¶¶72–74); (b) none of the testing in Wyse indicated that the formulations with BAC specifically resulted in additional naloxone degradation, rather than degradation of another component (*id.*, ¶74); and (c) Wyse itself discloses a formulation—Formulation 12—that includes BAC but was not disclosed to result in additional degradants. *Id.*, ¶¶75–78. In total, the evidence does not show that BAC is *incompatible* with naloxone, and thus does not teach away from its inclusion in a naloxone formulation.

In addition, others reading the disclosure of Wyse have concluded that it does not teach away from using BAC. Though not prior art, a Norwegian graduate thesis published in 2016 contemporaneously reviewed the WIPO publication equivalent of Wyse, noting that the disclosure should not be understood to disparage the use of BAC, as the criticism of its use may be incorrectly based. (“Although the AntiOp

patent describes better observed degradation properties for a formulation lacking commonly used excipients in intranasal formulations...these excipients should not be depreciated based on this patent solely. Excipients such as the benzalkonium chloride (preservative) and glycerine (preservative, co-solvent and viscosity enhancer) may have been identified as unsuitable on wrong basis.”) Glende (Nalox1031) at 76. This is consistent with how other POSAs would read Wyse. Donovan (Nalox1002), ¶73. Thus, a POSA would not have concluded that Wyse taught away from using BAC. Donovan (Nalox1002), ¶¶63–78.

Second, a POSA would not consider the prior art as a whole taught away from using a 4 mg dose of naloxone hydrochloride or a hydrate thereof. During the prosecution of the '177 patent, Applicants argued the prior art taught away from using a 4 mg dose of naloxone, stating:

The highest intranasal dose reported in Wyse is 2 mg.... Indeed, the art as a whole taught away from an about 4 mg naloxone. Before the demonstrated success of Applicant's product showed otherwise, it was widely believed that a 4 mg initial dose could trigger precipitous withdrawal symptoms.

Oct. 21, 2016 Response to Office Action (Nalox1005) at 12. In support of this proposition, Applicants relied on an article from MedPage Today. A POSA would disagree that the prior art taught away from this dose. Donovan (Nalox1002), ¶546–49.

Wyse itself disclosed using 4 mg doses. Wyse, in fact, exemplified administering a 4 mg dose (2 mg intranasally, followed by another 2 mg intranasally in five minutes). *See* Nalox1007 at 23:40–55. Wyse disclosed such a dose as increasing exposure and mirroring “clinical practice,” indicating that such a dose would be reasonable in at least some patients. *Id.* at 24:1–6; *see also* Donovan (Nalox1002), ¶546. A POSA would thus not have been deterred from administration of a 4 mg dose of naloxone, as it was not expected that administering such a dose would result in precipitous withdrawal symptoms in all patients. Donovan (Nalox1002), ¶547. Moreover, the Examiner also explicitly noted that Wyse taught higher doses, as in the Reasons for Allowance, the Examiner specifically maintained that the “concentration range disclosed 5–50 mg/mL is considered to read on the instantly claimed amount,” i.e., a 4 mg dose. *See* Notice of Allowance (Nalox1006) at 7–8.

Further, a POSA, after reviewing the MedPage Today article, would not consider this article to teach away from the use of 4 mg naloxone. Hochhaus (Nalox1003), ¶123. Naloxone has a broad therapeutic window, with rarely reported serious adverse events, and the prior art discloses that repeated doses of naloxone may be administered, up to 10 mg. *Id.* A POSA would not have been dissuaded from utilizing a 4 mg initial dose of intranasal solution of naloxone because, as addressed above, such a dose would have been reasonably expected to achieve comparable

exposure to the 2 mg dose of injectable naloxone, a dose recommended at that time as a suitable initial starting dose in opioid overdose patients. *Id.* A POSA, therefore, would disagree that the prior art taught away from using a 4 mg naloxone dose. *Id.*, ¶¶122–23.

B. No commercial success

The '253 patent is listed in The Orange Book for Narcan® nasal spray. Patent Owner cannot show that Narcan® is commercially successful due to the features of the '253 patent. In particular, “if the feature that creates the commercial success was known in the prior art, the success is not pertinent.” *SightSound Techs., LLC v. Apple Inc.*, 809 F.3d 1307, 1319 (Fed. Cir. 2015) (citation omitted).

Insufficient evidence exists to demonstrate commercial success. Donovan (Nalox1002), ¶552. Prior intranasal naloxone formulations were known and used in the United States before Narcan® was marketed. *See* section V.A. Moreover, a POSA would have been motivated to develop more-concentrated formulations to address problems with the prior art formulations. *See* section V.B. The formulations claimed in the '253 patent are so similar to those disclosed in Wyse and the other cited references that it is difficult to see how any differences between the devices claimed in the '253 patent and the devices disclosed in those references contribute to Narcan®'s sales. *See* Donovan (Nalox1002), ¶551. Accordingly, a POSA would

conclude that there is little evidence of commercial success. Donovan (Nalox1002), ¶¶550–52.

C. No long-felt but unmet need or failure of others

There is no showing of long-felt or unresolved need. There is simply no evidence to suggest that the claimed formulation was outside of the skill of a POSA. *See* Donovan (Nalox1002), ¶¶554–55. The prior art clearly indicates that other intranasal formulations of naloxone were prepared and developed and also considered using naloxone doses higher than 1 mg or 2 mg intranasally. Donovan (Nalox1002), ¶554.

Any need for an FDA-approved formulation that provided equal or improved action compared to the approved injectable products was not “long-felt.” *See* Donovan (Nalox1002), ¶555. The FDA announced its requirements for a naloxone nasal spray in April of 2012, (*see* Hertz Presentation (Nalox1032) and 2012 FDA Meeting (Nalox1049)), and Wyse claims a priority date of December of 2013, including six months of stability data, indicating that a formulation had been selected by no later than June of 2013. *See* ’802 Appl. (Nalox1055) at [00145]. Likewise, the ’253 patent claims priority to an application filed in March of 2014, with 12 months of stability data. *See* ’379 provisional (Nalox1058) at 41. These timelines indicate the claimed subject matter was arrived at with little more than the

application of ordinary skill. Donovan (Nalox1002), ¶555. Likewise, there is little showing of failure of others, for essentially the same reasons. *Id.*, ¶556.

D. No unexpected superior results

The claimed invention fails to show unexpectedly superior results. A POSA would have found the pharmacokinetic results claimed in the '253 patent, and therefore the pharmacological effects, to be entirely expected. Hochhaus (Nalox1003), ¶125. Furthermore a POSA would not find any unexpected pharmacokinetic benefit or result that can be tied to any particular excipient contained in the intranasal formulation recited in the claims of the '253 patent. *Id.* Furthermore, the '253 patent specification and file histories do not disclose any other unexpected results from the claimed formulation or device.

X. CONCLUSION

As demonstrated above, a reasonable likelihood exists that the Challenged Claims are unpatentable. Accordingly, Petitioner respectfully requests that the *inter partes* review of the Challenged Claims of the '253 patent be granted and all claims be cancelled as invalid.

Petition for *Inter Partes* Review of U.S. Patent No. 9,211,253

Date: February 19, 2019

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), I hereby certify that this Petition complies with the type-volume limitation of 37 C.F.R. § 42.24(a)(1)(i) because it contains 12,627 words as determined by the Microsoft® Office Word word-processing system used to prepare the brief, excluding the parts of the Petition exempted by 37 C.F.R. § 42.24(a)(1).

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(b), the undersigned certifies that on this 19th day of February 2019, a complete and entire copy of this Petition for *Inter Partes* Review and Exhibits was provided via Federal Express to the Patent Owner by serving the correspondence address of record for the '253 patent and Patent Owner's litigation counsel:

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