UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE DEPOMED PATENT LITIGATION	Civil Action No.: 13-4507 (CCC-MF) **OPINION**

CECCHI, District Judge.

I. INTRODUCTION

This is a consolidated[1] Hatch-Waxman patent infringement action brought by Plaintiffs Depomed, Inc. ("Depomed") and Grünenthal GmbH ("Grünenthal") (collectively, "Plaintiffs"). The Defendants in the consolidated action are Actavis Elizabeth LLC, Actavis UT, Actavis LLC, Actavis, Inc. (collectively, "Actavis"), Roxane Laboratories, Inc. ("Roxane"), and Alkem Laboratories Ltd. ("Alkem").

Plaintiffs have asserted three patents against Defendants: U.S. Patent No. RE39,593 (the "'593 patent"), U.S. Patent No. 7,994,364 (the "'364 patent"), and U.S. Patent No. 8,536,130 (the "'130 patent") (collectively, the "patents-in-suit"), which are directed to compositions and methods relating to Plaintiffs' NUCYNTA® tapentadol hydrochloride products, including NUCYNTA® IR, NUCYNTA® ER, and NUCYNTA® Oral Solution.[2] Defendants have sought approval from the United States Food and Drug Administration ("FDA") to market generic

[1] This case, docket number 13-4507, is the lead case in the consolidated action. The member cases are 13-7803, 13-6929, 14-3941, 14-4617, and 15-6797.

[2] Plaintiffs have also asserted U.S. Patent No. 8,309,060 against Actavis. All proceedings relating to that patent have been stayed by Order entered on November 19, 2015 [ECF No. 287].

versions of tapentadol hydrochloride. Plaintiffs allege that Defendants will infringe the patents-in-suit by marketing their generic products.

The Court conducted a bench trial in this matter beginning March 9, 2016 through March 23, 2016. The parties submitted post-trial briefing and proposed findings of fact and conclusions of law on April 18, 2016. Closing arguments were held on April 27, 2016.[3]

This Opinion constitutes the Court's findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52(a). The findings of fact are based on the Court's observations and credibility determinations of the witnesses who testified and a thorough review of all the evidence admitted at trial. For the reasons stated herein, the Court finds as follows:

As to the '593 patent, Defendants have not met their burden of proving by clear and convincing evidence that the '593 patent is invalid. As Defendants stipulated to infringement of the '593 patent, judgment of infringement will be entered in favor of Plaintiffs on the '593 patent.

As to the '364 patent, Defendants have not met their burden of proving by clear and convincing evidence that the '364 patent is invalid. As Defendants stipulated to infringement of the '364 patent, judgment of infringement will be entered in favor of Plaintiffs on the '364 patent.

As to the '130 patent, Plaintiffs have met their burden of proving induced infringement of the '130 patent by a preponderance of the evidence as to Alkem. Plaintiffs have not met their burden of proving induced infringement of the '130 patent by a preponderance of the evidence as

[3] The parties stipulated to bifurcation of Actavis's third counterclaim to correct or delete the FDA use code for the '130 patent. [*See* ECF No. 407.] On May 9, 2016, this Court entered a Consent Order, adjourning that bifurcated hearing without date. [ECF No. 465.] On May 10, 2016, Plaintiffs filed a renewed motion to dismiss this counterclaim on the basis of mootness in light of actions taken by the FDA. [*See* ECF No. 466.] The parties have represented to the Court that they have requested clarification from the FDA on the current status of the use code. At this point, the Court will sever Actavis's counterclaim from the instant action and return it to its original docket, Case No. 15-6797.

to Actavis or Roxane. Plaintiffs have not met their burden of proving contributory infringement by a preponderance of the evidence against any of the Defendants. Defendants have not met their burden of proving by clear and convincing evidence that the '130 patent is invalid. Accordingly, judgment of infringement will be entered in favor of Plaintiffs against Alkem on the '130 patent. Judgment of noninfringement will be entered in favor of Actavis and Roxane on the '130 patent.

II. BACKGROUND

A. THE PARTIES

i. Plaintiff Grünenthal

Plaintiff Grünenthal is a corporation organized and existing under the laws of Germany. [Plaintiffs' Proposed Findings of Fact ("PFOF") ¶ 1; Pre-Trial Order ("PTO") ¶ 17.] Grünenthal owns all right, title, and interest in the patents-in-suit. [PFOF ¶ 2; PTO ¶¶ 18.]

ii. Plaintiff Depomed

Plaintiff Depomed is a California corporation. [PFOF ¶ 4; PTO ¶ 10.] Depomed is an exclusive licensee of the patents-in-suit, which it acquired from former plaintiff Janssen Pharmaceuticals, Inc. ("Janssen"). [PFOF ¶ 5; PTX-1563 at DM_0000020.] Depomed holds FDA-approved New Drug Applications ("NDA") for three formulations of NUCYNTA®—an immediate release formulation, an extended release formulation, and an oral solution—and it manufactures and markets NUCYNTA® branded products in the United States. [PFOF ¶ 8; PTO ¶¶ 11-16.]

iii. Defendant Actavis

Defendant Actavis submitted Abbreviated New Drug Application ("ANDA") Nos. 204791, 204972, and 206657 to the FDA, seeking approval to engage in the commercial manufacture, use, importation, offer for sale, and sale of generic tapentadol hydrochloride immediate release tablets, tapentadol hydrochloride extended release tablets, and 20 mg/mL

tapentadol hydrochloride oral solution, respectively. [PFOF ¶ 10; PTO ¶¶ 55, 60.] All three of Actavis's ANDAs have received tentative approval from the FDA, subject to this Court's resolution of the patent issues related to the patents-in-suit. [*See* PFOF ¶¶ 13-14.]

iv. Defendant Roxane

Defendant Roxane submitted ANDA Nos. 205057 and 206418 to the FDA, seeking approval to engage in the commercial manufacture, use, importation, offer for sale, and sale of generic tapentadol hydrochloride immediate release tablets and tapentadol hydrochloride extended release tablets, respectively. [PFOF ¶ 20; PTO ¶¶ 91, 96.] Roxane's ANDA No. 205057 for the immediate release formulation of tapentadol hydrochloride has received tentative approval from the FDA, subject to this Court's resolution of the patent issues related to the patents-in-suit. [PFOF ¶ 22.]

v. Defendant Alkem

Defendant Alkem submitted ANDA Nos. 205015 and 205016 to the FDA, seeking approval to engage in the commercial manufacture, use, importation, offer for sale, and sale of generic tapentadol hydrochloride immediate release tablets and tapentadol hydrochloride extended release tablets, respectively. [PFOF ¶ 16; PTO ¶¶ 75, 80, 81.] Alkem's ANDA No. 205015 has received tentative approval from the FDA, subject to this Court's resolution of the patent issues related to the patents-in-suit. [PFOF ¶ 18.]

B. THE PATENTS-IN-SUIT

i. The '593 patent

The '593 patent, entitled "1-PHENYL-3-DIMETHYLAMINOPROPANE COMPOUNDS WITH A PHARMACOLOGICAL EFFECTS", was issued by the United States Patent and Trademark Office ("USPTO") on April 24, 2007. [PFOF ¶ 25; PTO ¶ 23.] The '593 patent relates generally to a class of compounds and methods of using those compounds. [PTX-312.]

The '593 patent is a reissue of U.S. Patent No. 6,248,737 (the "'737 patent"), which was filed on June 6, 1995 and issued on June 19, 2001. [PFOF ¶ 28; PTO ¶ 26.] The '737 patent claims priority to German Patent Application No. 44 26 245.0, which was filed on July 23, 1994. [PFOF ¶ 29; PTO ¶ 27.]

The inventors listed on the '593 patent are Helmut Buschmann, Wolfgang Strassburger, and Elmar Friedrichs. [PTX-312.] The '593 patent was assigned to Grünenthal on July 17, 1995 and the assignment was recorded with the USPTO on August 1, 1995. [PFOF ¶ 27; PTO ¶ 25.]

ii. The '364 patent

The '364 patent, entitled "CRYSTALLINE FORMS OF (-)-(1R,2R)-3-(3-DIMETHYLAMINO-1-ETHYL-2-METHYLPROPYL)-PHENOL HCL," was issued by the USPTO on August 9, 2011. [PFOF ¶ 31; PTO ¶ 34.] The '364 patent relates generally to a crystalline form of tapentadol hydrochloride. [PTX-1458.]

The '364 patent issued from U.S. Patent App. No. 12/634,777, which was filed on December 10, 2009. [PFOF ¶ 33; PTO ¶ 37.] The '364 patent claims priority to European App. No. 04015091, which was filed on June 28, 2004. [PFOF ¶ 34; PTO ¶ 38.]

The inventors listed on the '364 patent are Andreas Fischer, Helmut Buschmann, Michael Gruss, and Dagmar Lischke. [PTX-1458.] The '364 patent was assigned to Grünenthal by the various inventors on April 13, 16, and 26, 2007 and the assignment was recorded with the USPTO on May 23, 2007. [PFOF ¶ 32; PTO ¶ 36.]

iii. The '130 patent

The '130 patent, entitled "USE OF 1 PHENYL-3-DIMETHYLAMINO-PROPANE COMPOUNDS FOR TREATING NEUROPATHIC PAIN," was issued by the USPTO on September 17, 2013. [PFOF ¶ 36; PTO ¶ 44.] The '130 patent relates generally to methods of using tapentadol hydrochloride to treat polyneuropathic pain. [PTX-485.]

The '130 patent issued from U.S. Patent App. No. 12/850,208, which was filed on August 4, 2010. [PFOF ¶ 38 PTO ¶ 47.] The '130 patent claims priority to German Patent App. No. 10 2007 012 165.4, which was filed on March 12, 2007. [PFOF ¶ 39; PTO ¶ 48.]

The inventors listed on the '130 patent are Thomas Christoph, Elmar Friedrichs, Babette-Yvonne Koegel, and Murielle Meen. [PTX-485.] The '130 patent was assigned to Grünenthal by the various inventors on September 16, 19, and 27, 2009 and the assignment was recorded with the USPTO on October 1, 2009. [PFOF ¶ 37; PTO ¶ 46.]

C. ISSUES TO BE DECIDED

Plaintiffs have asserted the following claims against Defendants:

'593 patent: Claims 8, 61, 117, and 147 [PFOF ¶ 30]

'364 patent: Claims 1, 2, 3, and 25 [PFOF ¶ 35]

'130 patent: Claims 1 and 2 (against all Defendants)

Claims 3 and 6 (against Alkem only) [PFOF ¶ 40]

Defendants have stipulated to infringement of the '593 and '364 patents. [ECF No. 400.] Defendants contend that the '593 patent is invalid, that the '364 patent is invalid and unenforceable, and that the '130 patent is not infringed and invalid.

The following issues must be decided by the Court.

i. <u>'593 Patent – Invalidity</u>

1. <u>Obviousness:</u> Defendants allege the asserted claims of the '593 patent would have been obvious to a Person of Ordinary Skill in the Art ("POSA") under 35 U.S.C. § 103.

2. <u>Utility:</u> Defendants allege that the asserted claims of the '593 patent lack utility under 35 U.S.C. § 101.

3. <u>Written Description:</u> Defendants allege that asserted claims 61, 117, and 147 of the '593 patent do not meet the written description requirement of 35 U.S.C. § 112.

4. Original Patent: Defendants allege that asserted claims 61, 117, and 147 of the '593 patent do not satisfy the original patent rule of 35 U.S.C. § 251.

5. Enablement: Defendants allege that asserted claim 8 of the '593 patent does not meet the enablement requirement of 35 U.S.C. § 112.

ii. '364 Patent – Invalidity

1. Inherent Anticipation: Defendants allege that the asserted claims of the '364 patent are inherently anticipated under 35 U.S.C. § 102.

2. Obviousness: Defendants allege that the asserted claims of the '364 patent would have been obvious to a POSA under 35 U.S.C. § 103.

3. Utility: Defendants allege that the asserted claims of the '364 patent lack utility under 35 U.S.C. § 101.

iii. '364 Patent – Unenforceability

1. Unclean Hands: Defendants allege that the '364 patent is unenforceable because the patentee acted with unclean hands during prosecution of the patent before the USPTO.

iv. '130 Patent – Infringement

1. Induced Infringement: Plaintiffs allege that Defendants will induce infringement of the asserted claims of the '130 patent under 35 U.S.C. § 271(b).

2. Contributory Infringement: Plaintiffs allege that Defendants will contribute to infringement of the asserted claims of the '130 patent under 35 U.S.C. § 271(c).

v. '130 Patent – Invalidity

1. Anticipation: Defendants allege that the asserted claims of the '130 patent are invalid as anticipated under 35 U.S.C. § 102.

2. Obviousness-type Double Patenting: Defendants allege that the asserted claims of the '130 patent are invalid under the doctrine of obviousness-type double patenting.

D. TRIAL WITNESSES

The following witnesses appeared and provided live testimony during the bench trial.

i. Plaintiffs' Fact Witnesses

1. Jack Anders

The Court heard testimony from Mr. Jack Anders, who is the Vice President of finance at Depomed. [3/9 Tr. (Anders) at 180.] Mr. Anders provided background testimony about Depomed as a company. He also testified about Depomed's purchase of the NUCYNTA® drug franchise from former Plaintiff Janssen Pharmaceuticals. Mr. Anders' testimony is relevant to the issue of irreparable harm.

2. Helmut Buschmann

The Court heard testimony from Helmut Buschmann, Ph.D. Dr. Buschmann is an inventor of the '593 patent and the '364 patent. [PTO at 293.] He is a former employee of Grünenthal, where he worked from 1992 through 2002. [3/10 Tr. (Buschmann) at 8:4-5.] While at Grünenthal, he ran a laboratory in the Synthetic Chemistry department and was later promoted to head of the department. [3/10 Tr. (Buschmann) at 8:6-9:8.] Dr. Buschmann's testimony is relevant to the issues of the validity of the '593 patent and the '364 patent.

3. Michael Gruss

The Court heard testimony from Michael Gruss, Ph.D. Dr. Gruss is an inventor of the '364 patent. [PTO at 293.] He is a former employee of Grünenthal, where he worked from 2000 through 2015. [3/10/2015 Tr. (Gruss) at 227:9-15.] While at Grünenthal, he was the head of a laboratory in the Process Development department. [3/10/2015 Tr. (Gruss) at 227:21-22.] Dr. Gruss's testimony is relevant to the issue of the validity of the '364 patent.

4. Thomas Christoph

The Court heard testimony from Thomas Christoph, Ph.D. Dr. Christoph is an inventor of the '130 patent. [PTO at 293.] He is an employee of Grünenthal, where has worked since 1996.

[3/14 a.m.[4] Tr. (Christoph) at 11:10-15.] Dr. Christoph began as the head of a laboratory in the Department of Pharmacology at Grünenthal, and was later promoted to head of the department. [3/14 a.m. Tr. (Christoph) at 11:10-20.] Dr. Christoph's testimony is relevant to the issue of the validity of the '130 patent.

5. Juergen Haeussler

The Court heard testimony from Juergen Haeussler, Ph.D. Dr. Haeussler is a scientist at Janssen. [PTO at 293.] Dr. Haeussler provided testimony regarding the FDA approval process for the NUCYNTA® products. His testimony is relevant mostly on the issue of induced and contributory infringement of the '130 patent.

ii. Plaintiffs' Expert Witnesses

1. William Roush

The Court heard expert testimony from William Roush, Ph.D. Dr. Roush's testimony is relevant to the issues of the validity and enforceability of the patents-in-suit.

2. Michael Ossipov

The Court heard expert testimony from Michael Ossipov, Ph.D. Dr. Ossipov's testimony is relevant to the issues of the validity of the '593 patent and the '130 patent.

3. Joel Bernstein

The Court heard expert testimony from Joel Bernstein, Ph.D. Dr. Bernstein's testimony is relevant to the issues of the validity and enforceability of the '364 patent.

4. Michelle Brown

The Court heard expert testimony from Michelle Brown, M.D. Dr. Brown's testimony is relevant to the issues of the infringement and validity of the '130 patent.

[4] "a.m." refers to the transcript from the morning session.

iii. Defendants' Expert Witnesses

1. Stephen Martin

The Court heard expert testimony from Stephen Martin, Ph.D. Dr. Martin's testimony is relevant to the issue of the invalidity of the '593 patent, specifically obviousness.

2. Christian Wolf

The Court heard expert testimony from Christian Wolf, Ph.D. Dr. Wolf's testimony is relevant to the issue of the invalidity of the '593 patent, specifically enablement and written description.

3. Jeffry Mogil

The Court heard expert testimony from Jeffry Mogil, Ph.D. Dr. Mogil's testimony is relevant to the issue of the invalidity of the '593 patent, specifically utility and enablement.

4. Jonathan W. Steed

The Court heard expert testimony from Jonathan W. Steed, Ph.D. Dr. Steed's testimony is relevant to the issue of the invalidity of the '364 patent, specifically inherent anticipation and obviousness.

5. Adam J. Matzger

The Court heard expert testimony from Adam J. Matzger, Ph.D. Dr. Matzger's testimony is relevant to the issue of the invalidity and unenforceability of the '364 patent, specifically utility and unclean hands.

6. Asokumar Buvanendran

The Court heard expert testimony from Asokumar Buvanendran, M.D. Dr. Buvanendran's testimony is relevant to the issues of noninfringement and invalidity of the '130 patent.

7. Michael Weinberger

The Court heard expert testimony from Michael Weinberger, M.D. Dr. Weinberger's testimony is relevant to the issues of noninfringement and invalidity of the '130 patent.

E. SCIENTIFIC PRINCIPLES

The three patents at issue involve principles of organic chemistry (specifically, stereochemistry), crystal forms of compounds (*i.e.*, polymorphism), and the treatment of different categories of pain. The following is an introduction to some of the scientific principles at issue in this litigation.

i. Stereochemistry

Stereochemistry is the branch of chemistry concerned with the three-dimensional arrangement of compounds and the effect it has on chemical reactions. "Molecules that have the same chemical substituents, but different spatial arrangements, are referred to as stereoisomers." *Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1372 (Fed. Cir. 2006). Importantly, stereoisomers of a drug substance can have different biological effects. [*See* Claim Construction Opinion, ECF No. 332 at 3.]

Stereoisomers may have different physical properties, such as solubility, melting point, chromatographic mobility, and rotation of plain polarized light. [*Id.*] By convention, stereoisomers that rotate polarized light to the right are referred to as (+) or "d"; stereoisomers that rotate polarized light to the left are referred to as (–) or "l." *Sanofi-Synthelabo*, 470 F.3d at 1372 & n.1.; *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 348 F. Supp. 2d 713, 720-21 (N.D. W. Va. 2004);

There are two types of stereoisomers: (1) enantiomers and (2) diastereomers. "Enantiomers are a pair of stereoisomers that are non-superimposable mirror images of each other . . . ." *Pfizer, Inc. v. Ranbaxy Labs. Ltd.*, 457 F.3d 1284, 1286 (Fed. Cir. 2006). This characteristic is "often

likened to the relative structures of a person's right and left hands." *Ortho-McNeil*, 348 F. Supp. 2d at 720. A molecule may have a maximum of one enantiomer—there is only one other molecule that can be its mirror image. Enantiomers have the same melting points as each other and they rotate plain polarized light in equal but opposite directions.

"Diastereomers," in contrast, are stereoisomers that are not mirror images of each other. [*See* Claim Construction Opinion, ECF No. 332 at 3.] Diastereomers have different physical properties such as solubility, melting point temperature, chromatographic mobility, etc. [*See id.*]

The number of diastereomers (and, by extension, the number of stereoisomers) that a molecule has is determined by the number of chiral centers in the molecule. A chiral center is a carbon atom that is bonded to four different substituent groups.

As part of stereochemistry nomenclature conventions, chemists use "R" and "S" as descriptors to convey information about the spatial arrangement of the compound. [DFOF ¶ 562; 3/17 Tr. (Wolf) at 138:8-139:17.] *See Ortho-McNeil*, 348 F. Supp. 2d at 720-21 ("Chemists also distinguish between enantiomers by designating an enantiomer as either 'R' or 'S' based upon the arrangement of certain atoms at the enantiomer's 'chiral center.' Where one enantiomer is an 'R,' the other will be an 'S.'").

ii. <u>Polymorphs</u>

Polymorphism is the ability of a chemical compound to crystallize in more than one crystal structure. [PFOF ¶ 142; 3/10 Tr. (Gruss) at 228:12-14.] Polymorphism occurs when there is more than one way of packing the molecules of a particular compound in a three-dimensional space. [PFOF ¶ 142; 3/15 Tr. (Steed) at 188:18-189:6.] Each crystal structure of a compound is referred to as a "polymorph."

A study of the polymorphs of a compound is referred to as a "polymorph investigation" or a "polymorph screen." A polymorph investigation involves applying various parameters to the

crystallization of a compound (*e.g.*, temperature ranges, solvents) in order to understand and characterize the solid state landscape of the compound under investigation. [PFOF ¶ 143; 3/10 Tr. (Gruss) at 228:15-21; 3/21 Tr. (Bernstein) at 214:11-215:13.] A polymorph investigation may involve the analytical techniques of X-ray Powder Diffraction ("XRPD"), X-ray Single Crystal Diffraction, Differential Scanning Calorimetry ("DSC"), thermogravimetric analysis ("TGA"), variable temperature XRPD, stage microscopy, and spectroscopic methods. [PFOF ¶ 144; 3/10 Tr. (Gruss) at 228:22-229:6; 3/15 Tr. (Steed) at 189:7-18.] While there are many techniques that may be used as part of a polymorph investigation, XRPD is considered the "gold standard" to identify the crystal form of a particular sample. [PFOF ¶ 147; 3/10 Tr. (Gruss) at 229:7-20.]

XRPD is a technique used to obtain an identification of the crystal structure of a given compound by measuring the diffraction of X-rays applied to that sample. [PFOF ¶ 145; 3/10 Tr. (Gruss) at 229:7-12; 3/21 Tr. (Bernstein) at 223:6-15.] The output from the XRPD technique is known as a "diffraction pattern." [PFOF ¶¶ 145-146; 3/10 Tr. (Gruss) at 229:7-12; 3/21 Tr. (Bernstein) at 223:6-15; 3/15 Tr. (Steed) at 190:4-11.] A diffraction pattern is characteristic of the particular crystal packing arrangement of a solid. [PFOF ¶ 146; 3/15 Tr. (Steed) at 190:4-11.] Each crystal structure (*i.e.*, each polymorph of a particular compound) has its own unique diffraction pattern. [PFOF ¶ 146; 3/15 Tr. (Steed) at 190:4-11.]

DSC is a technique in which heat is applied to a sample and a reference, and the difference in the amount of heat the samples take up is measured. [PFOF ¶ 149; 3/10 Tr. (Gruss) at 230:7-12, 241:2-17; 3/15 Tr. (Steed) at 189:14-18.] This technique can be used to detect solid phase transitions, such as melting or the transition from one polymorphic form to another. [PFOF ¶ 149; 3/10 Tr. (Gruss) at 230:7-12, 241:2-17; 3/15 Tr. (Steed) at 189:14-18.]

iii. Pain

1. Definition of "pain" and categories of pain

The word "pain" refers to a symptom, rather than an actual cause of symptoms. [PFOF ¶ 77; DTX-1667_0001; 3/14 p.m. Tr. (Brown) at 38:10-12.] The word "pain" can be defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." [PFOF ¶ 77; DTX-1667_0001; DTX-2012_0006; 3/14 p.m. Tr. (Brown) at 38:5-15.]

Pain can be characterized in a number of different ways. One way to characterize pain is by the length of time the pain lasts. "Acute pain" is pain that generally lasts between approximately three to six months, and is expected to self-limit, meaning that it will heal over time. [PFOF ¶ 78; 3/14 p.m. Tr. (Brown) at 40:1-3.] "Chronic pain" is pain that generally lasts longer than six months, and is not expected to heal. [PFOF ¶ 79; 3/14 p.m. Tr. (Brown) at 40:4-7.]

Another way to characterize pain is by the intensity of the pain. Pain can be measured in terms of grades such as mild, moderate, or severe. [PFOF ¶ 80; 3/14 p.m. Tr. (Brown) at 41:15-18.] Severe pain is the most intense type of pain. [PFOF ¶ 80; 3/14 p.m. Tr. (Brown) at 41:15-18.]

A third way to characterize pain is by the type of tissue damage causing the pain. For purposes of this litigation, the crucial distinction is between "nociceptive pain" and "neuropathic pain."

Nociceptive pain is pain that arises from actual or threatened damage to non-nerve tissue and is due to the activation of nociceptors from, for instance, a noxious stimulus. [PFOF ¶ 81; DTX-1667_0005; 3/11 Tr. (Weinberger) at 167:9-168:16; 3/14 p.m. Tr. (Brown) at 38:23-39:1.] Nociceptive pain is due to excessive stimulation of nociceptors localized in the skin, viscera, and other organs. [DTX-2012_0006.] Patients typically describe nociceptive pain as a throbbing or

aching pain. [PFOF ¶ 82; 3/14 p.m. Tr. (Brown) at 39:1-3.] Some examples of nociceptive pain include hitting a thumb with a hammer, a broken bone, or incisions made during surgery. [PFOF ¶ 82; 3/14 p.m. Tr. (Brown) at 39:1-3; 3/11 Tr. (Weinberger) at 168:6-16; 3/21 Tr. (Buvanendran) at 35:4-9.] Nociceptive pain can be either acute or chronic [PFOF ¶ 83; 3/14 p.m. Tr. (Brown) at 40:15-17] and it can be severe [PFOF ¶ 84; 3/14 p.m. Tr. (Brown) at 41:19-21].

Neuropathic pain is pain that is caused by a lesion or disease of the somatosensory nervous system, and therefore involves actual nerve tissue damage. [PFOF ¶ 85; DTX-1667_0004; 3/11 Tr. (Weinberger) at 168:17-21; 3/14 p.m. Tr. (Brown) at 39:6-9.] This is in contrast to nociceptive pain, which occurs with a normally functioning somatosensory nervous system. [DTX-1667_0005.] Neuropathic pain occurs due to a dysfunction of a nerve or group of nerves. [DTX-2012_0006.] Neuropathic pain is separate and distinct from nociceptive pain and patients describe the two differently. [PFOF ¶ 86; 3/14 p.m. Tr. (Brown) at 39:9-10; 3/11 Tr. (Weinberger) at 169:2-8.] Patients generally describe neuropathic pain as a burning, electrical, shocking, or pins and needles sensation. [PFOF ¶ 87; 3/14 p.m. Tr. (Brown) at 39:10-12; 3/11 Tr. (Weinberger) at 166:19-24.] Neuropathic pain can be severe. [PFOF ¶ 91; 3/14 p.m. Tr. (Brown) at 41:19-23; 3/21 Tr. (Buvanendran) at 41:9-11; 3/11 Tr. (Weinberger) at 186:21-23, 226:23-25.] Neuropathic pain can be, and often is, chronic because nerves and nerve tissue that are damaged do not regenerate readily. [PFOF ¶ 90; 3/14 p.m. Tr. (Brown) at 40:18-41:13; 3/21 Tr. (Buvanendran) at 41:9-11; 3/11 Tr. (Weinberger) at 226:23-227:8.] Because of this, neuropathic pain is more difficult to treat and harder to control than nociceptive pain. [PFOF ¶ 90; 3/14 p.m. Tr. (Brown) at 41:9-13.]

Within the category of neuropathic pain, mononeuropathic pain is pain that involves damage to a single nerve. [PFOF ¶ 89; 3/21 Tr. (Buvanendran) at 34:2-5.] Polyneuropathic pain is pain that involves multiple nerves. [PFOF ¶ 88 3/21 Tr. (Buvanendran) at 34:6-7.]

2. Treatment of Pain

The term "analgesia" refers to "absence of pain in response to stimulation which would normally be painful." [DTX-1667_0002.] In some contexts, the term "analgesia" has been used interchangeably with the term "antinociception" to refer to "a reduction in 'spontaneous' pain, or the pain elicited by a noxious stimulus." [DTX-2012_0006; 3/14 p.m. Tr. (Christoph) at 21:20-22:11.]

When dealing with pain, there are receptors in the body that are involved in signaling pain from the site of injury to the brain. [3/22 a.m. Tr. (Roush) at 77:13-16.] The human body has native ligands that interact with these receptors to ameliorate pain. [3/22 a.m. Tr. (Roush) at 77:18-21.]

There are many different compounds known to exhibit analgesic activity. These compounds can be categorized into classes by referring to their mechanism of analgesic action. One broad characterization is the distinction between agonists and antagonists. An agonist is a molecule that out-competes the native ligand by binding more tightly to the receptor. [3/22 a.m. Tr. (Roush) at 77:22-24.] An agonist drug "kicks the receptor into high gear, turns it on, and you get a much amplified effect, much amplified signal." [3/22 a.m. Tr. (Roush) at 77:24-78:1.] An antagonist drug, on the other hand is "the light switch to shut it off. So, an antagonist can bind, usually at the same site that it binds differently such that it shuts the whole thing off. It prevents, the antagonist prevents both the agonist and/or the native ligand from binding." [3/22 a.m. Tr. (Roush) at 78:2-7.]

One well-known group of agonists is known as the opioid agonists, which exhibit a mechanism of action generally referred to as "opioid activity" by binding to the body's opioid receptors. [*See* 3/22 a.m. Tr. (Roush) at 76:16-18.] Within the broad class of opioid agonists, there are three types—*mu*-opioid agonists, *kappa*-opioid agonists, and *delta*-opioid agonists. [3/22 a.m. Tr. (Roush) at 76:18-23, 81:3-6, 84:2-5.]

It is well-known that the opioid receptors are not the only biological target for achieving analgesia. [3/22 a.m. Tr. (Roush) at 84:12-14.] Other drugs achieve analgesia by way of reuptake antagonism. [*See* 3/22 a.m. Tr. (Roush) at 86:13-16.] One example is norepinephrine reuptake inhibitors, which antagonize norepinephrine receptors. [*See* 3/22 a.m. Tr. (Roush) at 86:13-22.] Another example is serotonin reuptake inhibitors, which antagonize serotonin receptors. [*See* 3/22 a.m. Tr. (Roush) at 97:7-10].

There are analgesics that interact with multiple receptors in the body. [*See* 3/22 a.m. Tr. (Roush) at 87:16-88:2.] These analgesic drugs are generally said to exhibit "polypharmacology." The "notion of polypharmacology really reflects the fact that we have a drug that's hitting at least two different targets that both, if you will, independently or cooperatively contribute to the analgesic property that arises from use of those compounds." [3/22 a.m. Tr. (Roush) at 87:23-88:2.] One example of a drug that exhibits polypharmacology is tramadol, which was known to possess both opioid activity (specifically, *mu*-opioid agonism) and non-opioid activity (specifically, norepinephrine reuptake inhibition and serotonin reuptake inhibition). [PFOF ¶ 93; DFOF ¶¶ 11, 15-20; DTX-866; DTX-1027; 3/16 Tr. (Martin) at 190:23-192:19, 194:25-195:13; 3/10 Tr. (Buschmann) at 89:14-18; 3/22 a.m. Tr. (Roush) 93:8-94:23, 99:2-101:11; PTX-57.]

F. BACKGROUND OF THE INVENTIONS

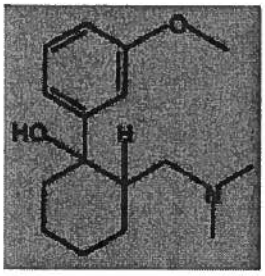
i. Invention of Tapentadol Hydrochloride

Dr. Helmut Buschmann first synthesized tapentadol hydrochloride in his lab at Grünenthal on January 26, 1994. [PFOF ¶ 118; 3/10 Tr. (Buschmann) at 26:11-27:2; PTX-345 at GRT-NUC00018944.] Dr. Buschmann's synthesis of tapentadol hydrochloride was done in the context of his work on a project at Grünenthal called the "Tramadol Successor" project. [PFOF ¶ 118; *See* 3/10 Tr. (Buschmann) at 10:7-12:7, 21:13-27:2; DTX-1027.] Therefore, the story of the invention of tapentadol hydrochloride begins with tramadol.

1. Tramadol

Grünenthal discovered tramadol in the early 1960s. [PFOF ¶ 92; 3/10 Tr. (Buschmann) at 10:4-6.] Tramadol was the first compound that Grünenthal developed successfully to market. [PFOF ¶ 92; Kogel Depo. at 111:20-22.]

As initially synthesized, tramadol was a mixture of the four possible stereoisomers resulting from variation of the two chiral centers in the following molecule:



The four stereoisomers consist of the two *threo* (or *trans*) enantiomers and the two *erythro* (or *cis*) enantiomers. [PFOF ¶ 92; DTX-2052_0002.] The *threo* enantiomers are the (*R*,*R*) and (*S*,*S*) stereoisomers and the *erythro* enantiomers are the (*R*,*S*) and (*S*,*R*) stereoisomers. [PFOF ¶ 92; DTX-2052_0002.]

As a marketed drug, tramadol is administered as a racemic mixture comprised of the two *threo* enantiomers: the (+) or (*R*,*R*) enantiomer and the (–) or (*S*,*S*) enantiomer. [PFOF ¶ 93; PTX-57 at ACT-TAP0016893.] The metabolite of each of these enantiomers, referred to as *O*-desmethyltramadol[5] ("ODMT"), also shows activity *in vitro*. [PFOF ¶ 93; DTX-691_0002.] Thus, the activity of tramadol in the body, can be viewed as the result of a mixture of four compounds—the two tramadol enantiomers and the two ODMT metabolites.

Tramadol is a complex drug that possesses both opioid and non-opioid mechanisms of action. [PFOF ¶ 92; DFOF ¶¶ 11, 15-20; DTX-866; DTX-1027.] Tramadol has three biological targets that contribute to its analgesic activity: (1) *mu*-opioid activity; (2) serotonin reuptake inhibition activity; and (3) norepinephrine reuptake inhibition activity. [PFOF ¶ 93; 3/22 a.m. Tr. (Roush) at 93:8-94:23, 99:2-101:11; 3/17 Tr. (Martin) at 65:9-24, 3/10 Tr. (Buschmann) at 9:18-10:6; PTX-57; DTX-1027.] Each of the four compounds in the tramadol mixture affects these biological targets to different degrees. [PFOF ¶ 93; DFOF ¶¶ 11, 15-20; DTX-866; DTX-1027; 3/22 a.m. Tr. (Roush) 93:8-94:23, 99:2-101:11; PTX-57.] Moreover, the enantiomers of tramadol are known to exhibit a synergistic effect *in vivo* on the patient, and both enantiomers are required for tramadol to provide its desired analgesic effect. [PFOF ¶ 93; DFOF ¶¶ 11, 15-20; DTX-866; DTX-1027; 3/22 a.m. Tr. (Roush) 93:8-94:23, 99:2-101:11; PTX-57.]

Tramadol is a relatively weak opioid, as it exhibits two to five time less potency than strong opioids. [PFOF ¶ 94; PTX-630 at GRT-NUC00183866; 3/23 Tr. (Brown at 20:19-21:2.] Tramadol also produces side effects that limit its use. [PFOF ¶ 94; DTX-1027_0006.]

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[5] The term "desmethyl" refers to a compound that has "lost the methyl group." Tramadol is a compound that has a methoxy group (also referred to as an "O-CH_3" or "O-methyl" group) on its aromatic ring. When tramadol is administered to a human, it gets metabolized by enzymes in the liver to ODMT by the removal of the methyl group from the aromatic oxygen. [*See* 3/16 Tr. (Martin) at 199:11-200:6.]

2. Tramadol Successor project at Grünenthal

Beginning in 1988, Grünenthal began focusing on discovering an analgesic by modifying the structure common to the enantiomers of tramadol. [PFOF ¶ 95; DTX-1027; 3/10 Tr. (Buschmann) at 10:7-27:2; DTX-1144_T.] In 1991, Grünenthal created a development memorandum for the "Tramadol Successor" project (the "Tramadol Successor Memorandum") that summarized the project's starting point, objectives, scientific rationale, methods, and strategies. [PFOF ¶ 96; DTX-1027.] The Tramadol Successor Memorandum contained a list of desirable characteristics for a successor drug, including: (1) being a single molecule (*i.e.*, unlike tramadol, which is a mixture of stereoisomers); (2) having good oral bioavailability; and (3) having no active metabolites (*i.e.*, unlike tramadol). [PFOF ¶ 97; DTX-1027_0008; 3/10 Tr. (Buschmann) at 12:8-13.] This list of desirable characteristics did not provide information about what the structural components of the molecule should be. [PFOF ¶ 97; 3/10 Tr. (Buschmann) at 12:8-13; 18:24-19:3.]

The Tramadol Successor Memorandum summarized the features that Grünenthal viewed as vital in a successor compound:

As shown in Fig. 3 using the example of the Tramadol molecule, opioid analgesics are characterized by 3 structural elements:

a) - an aromatic ring

b) - a tertiary nitrogen atom

c) -a partial structure holding the two first two components together in the correct configuration and at the correct distance.

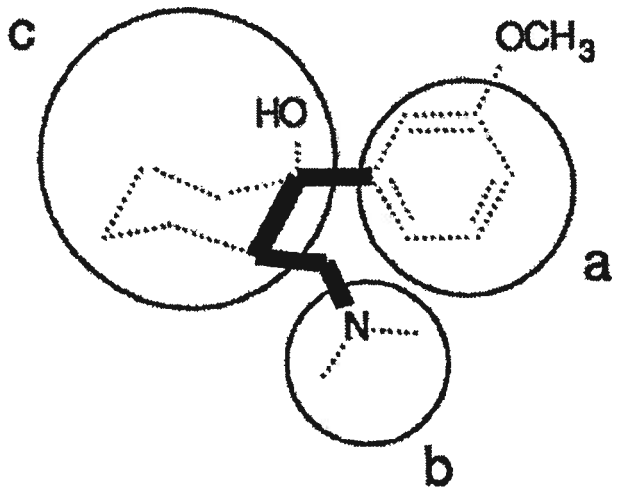


Figure 3: The basic elements for an effect on the opioid receptor on the example of the Tramadol molecule

[PFOF ¶ 99; DTX-1027_0013; 3/10 Tr. (Buschmann) at 14:21-15:4.] Grünenthal's strategy, as summarized in the Tramadol Successor Memorandum, was to "systematically vary the control structure of Tramadol," which involved many potential sources of variation, including those noted in circles a, b, and c in the figure shown above. [PFOF ¶ 100; DTX-1027_0013.]

By October 1991, Grünenthal had synthesized and tested approximately 550 new compounds as part of its Tramadol Successor project. [PFOF ¶ 101; 3/10 Tr. (Buschmann) at 11:22-12:1; DTX-1027_0013.] The following is a summary of Grünenthal's understanding of the components of tramadol:

a) With respect to circle "a" in the figure, Grünenthal viewed the aromatic ring system as important, but it contemplated that the ring system could have different substituents or could include more than one ring. [PFOF ¶ 102; DTX-1027_0013; 3/10 Tr. (Buschmann) at 15:5-18.]

b) With respect to circle "b" in the figure, Grünenthal viewed the tertiary nitrogen atom (*i.e.*, nitrogen atom fully substituted with three substituents) as important, but contemplated different substituents than those found in tramadol. [PFOF ¶ 103; DTX-1027_0013; 3/10 Tr. (Buschmann) at 15:19-16:8.]

c) With respect to circle "c" in the figure, Grünenthal considered it important to have a structure holding the first two components (the aromatic ring and the nitrogen) "together in the correct configuration and at the correct distance." [DTX-1027_0013.] It was known that a ring system restricts the conformation of the molecule to achieve this objective and allow the molecule to have optimal interaction with the targeted receptors. [PFOF ¶ 104; DTX-1027_0013; 3/10 Tr. (Buschmann) at 16:9-17:20.] Thus, the existence of a ring structure was considered important, although different size rings and substituted rings were contemplated. [PFOF ¶ 104; DTX-1027_0013; 3/10 Tr. (Buschmann) at 16:9-17:20.] Also with respect to circle "c," Grünenthal considered the hydroxyl (OH) group to be a crucial element for receptor interaction. [PFOF ¶ 105; 3/10 Tr. (Buschmann) at 17:21-18:1; DTX-1027_0013.]

Grünenthal segmented the active substances that had been synthesized as part of the Tramadol Successor project into four categories: (1) substances without opioid component; (2) substances with non-opioid effect, in addition to a weak opioid effect; (3) substances with a

balanced ratio of opioid and non-opioid component; and (4) substances with a predominant to exclusive opioid effect. [PFOF ¶ 106; 3/10 Tr. (Buschmann) at 18:2-19:3; DTX-1027_0016, DTX-1027_0028.] Grünenthal believed that "in order to minimize the opioid side effects, attention should be paid to a balanced ratio of opioid to non-opioid active components." [PFOF ¶ 106; DTX-1027_0007.] But Grünenthal scientists were unable to predict what pharmacological activity the test compounds would have (and therefore to which classification each would belong) based on the structure of the synthesized substances. [PFOF ¶ 108; 3/10 Tr. (Buschmann) at 18:2-19:3.]

As of the October 1991 Tramadol Successor Memorandum, scientists at Grünenthal did not know if it would be possible to create a new analgesic with the desired opioid and non-opioid activity, and they were pessimistic about the chances of achieving the desired characteristics in a single molecule. [PFOF ¶ 109; 3/10 Tr. (Buschmann) at 13:13-16, 19:16-22; DTX-1027_0009.] The Tramadol Successor Memorandum stated:

> The work carried out so far indicates, however, that not all the desired properties can be combined in one molecule. The search for the ideal substance must be continued, with the realistically very low prospect of success.

[DTX-1027_0031.]

3. Dr. Buschmann's work

In May 1992, Grünenthal hired Dr. Buschmann to run one of its laboratories. [PFOF ¶ 111; 3/10 Tr. (Buschmann) at 8:4-9:8.] Dr. Buschmann was provided a copy of the Tramadol Successor Memorandum and was assigned to synthesize compounds with potential analgesic activity as part of the project. [PFOF ¶ 112; 3/10 Tr. (Buschmann) at 10:7-11:5.] Dr. Buschmann's work consisted of the iterative process of synthesizing compounds, testing synthesized compounds for pharmacological activity, and using the test results to inform decisions about varying the structure

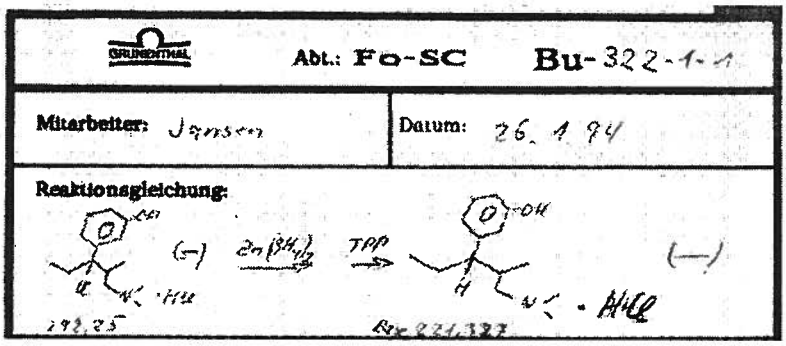
of subsequent synthesized compounds. [PFOF ¶ 113; 3/10 Tr. (Buschmann) at 23:19-24:20, 28:20-29:5.]

Consistent with the Tramadol Successor Memorandum's guidance, many of the compounds that Dr. Buschmann synthesized retained a cyclic structure. [PFOF ¶ 114; 3/10 Tr. (Buschmann) 21:13-15.] However, Dr. Buschmann also received permission to experiment with compounds that had a linear carbon chain structure. [PFOF ¶ 115; 3/10 Tr. (Buschmann) at 21:8-22:11.] Despite his receiving permission to synthesize linear compounds, many of Dr. Buschmann's colleagues, including his superiors, viewed his decision with disfavor, believing that the linear compounds would not be viable candidates for an analgesic drug because of their flexibility. [PFOF ¶ 115; 3/10 Tr. (Buschmann) at 22:1-7.] Consistent with the concerns about linear compounds, the first linear compound that Dr. Buschmann synthesized had low activity in a screening assay. [PFOF ¶ 116; 3/10 Tr. (Buschmann) at 22:17-23:18, 24:24-26:3; PTX-330 at GRT-NUC00014312.] Thus, to appease his superiors, Dr. Buschmann continued to synthesize cyclic compounds as well. [PFOF ¶ 115; 3/10 Tr. (Buschmann) at 22:8-16.]

By 1994, Grünenthal had begun to doubt whether any possible candidates for development of an analgesic drug would emerge from the Tramadol Successor project and considered stopping the project entirely. [PFOF ¶ 117; 3/10 Tr. (Buschmann) at 19:23-20:15.] At that time, Dr. Wolfgang Strassburger, the head of computational and chemical modeling at Grünenthal and an inventor on the '593 patent, opined in an internal memorandum dated January 19, 1994 that there was "no real prospect of success" for developing a tramadol successor with the desired profile. [PFOF ¶ 117; PTX-534_T; 3/10 Tr. (Buschmann) at 20:16-21:5, 80:11-24.] One week later, on January 26, 1994, Dr. Buschmann synthesized tapentadol hydrochloride. [PFOF ¶ 118; PTX-345 at GRT-NUC00018944; 3/10 Tr. (Buschmann) at 27:1-2.]

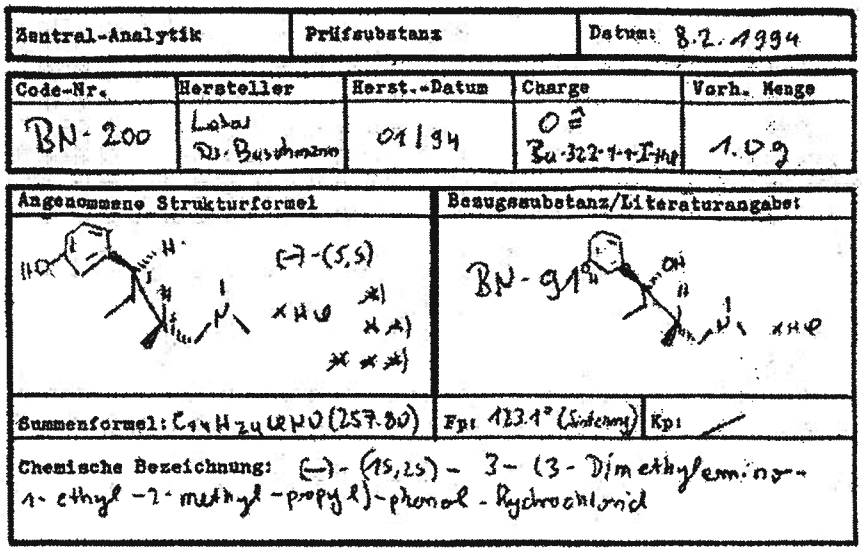
4. Dr. Buschmann's syntheses of tapentadol hydrochloride

Tapentadol hydrochloride was identified by Grünenthal as "Bu-322" because it was the 322nd compound synthesized in Dr. Buschmann's lab. [PFOF ¶ 118; 3/10 Tr. (Buschmann) at 27:6-12; PTX-345 at GRT-NUC00018944.] The first batch synthesized by Dr. Buschmann, which has been referred to as "Batch #0," was termed "Bu-322-1-1." [PFOF ¶ 118; 3/10 Tr. (Buschmann) at 27:13-19.] Dr. Buschmann's laboratory notebook from January 26, 1994 contains a description of the final step of the synthesis of Batch #0, which includes the two-dimensional structural formula (*i.e.*, without stereochemistry representations) for tapentadol hydrochloride:



[PTX-345 at GRT-NUC00018944.]

Tapentadol hydrochloride was also identified by Grünenthal as "BN-200" because it was the 200th compound sent from Dr. Buschmann's lab for pharmacological testing. [PFOF ¶ 118 3/10 Tr. (Buschmann) at 28:2-8; PTX-326 at GRT-NUC00013281.] Dr. Buschmann's laboratory notebook from February 8, 1994 depicts the three-dimensional structural formula for tapentadol hydrochloride:



Zentral-Analytik	Prüfsubstanz	Datum: 8.2.1994

Code-Nr.	Hersteller	Herst.-Datum	Charge	Vorh. Menge
BN-200	Labor Dr. Buschmann	01/94	02 Bu-322-1-1-I-HP	1.0 g

Angenommene Strukturformel	Bezugssubstanz/Literaturangabe:
(-)-(5,5)	BN-91

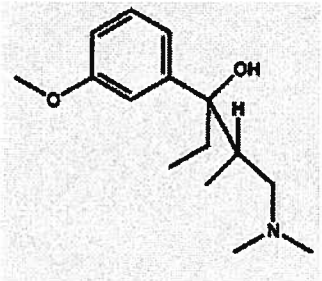
Summenformel: $C_{14}H_{24}ClNO$ (257.80)	Fp: 123.1° (Siebert)	Kp:

Chemische Bezeichnung: (-)-(1S,2S)-3-(3-Dimethylamino-1-ethyl-2-methyl-propyl)-phenol-Hydrochlorid

[PTX-326 at GRT-NUC00013281.]

Dr. Buschmann's first synthesis of tapentadol hydrochloride followed a synthetic methodology using a starting material that was generated by treating a ketone with an aromatic Grignard reagent to generate a mixture of stereoisomers of a compound called Bu-41.[6] Dr. Buschmann testified that there were four steps involved in the synthesis of Batch #0:

[6] Based on the testimony regarding the naming conventions employed by Grünenthal, the Court understands that Bu-41 was the 41st compound that had been synthesized in Dr. Buschmann's laboratory. Dr. Buschmann testified that Bu-41 has the following chemical structure:



[*See* 3/10 Tr. (Buschmann) at 29:6-30:2; Buschmann Demonstrative at 3; *see also* 3/10 Tr. (Buschmann) at 27:9-16.]

1. The first step of the Batch #0 synthesis involved separating the stereoisomers of Bu-41 into (+) Bu-41 and (–) Bu-41. [PFOF ¶ 121; 3/10 Tr. (Buschmann) at 30:2-3; 3/22 p.m. Tr. (Roush) at 10:12-24.]
2. The second step of the Batch #0 synthesis involved using the (–) Bu-41 stereoisomer and cleaving the phenolic methyl ether to yield the free phenol. [PFOF ¶ 121; 3/10 Tr. (Buschmann) at 30:3-5; 3/22 p.m. Tr. (Roush) at 11:8-12, 24:10-19.]
3. The third step of the Batch #0 synthesis involved replacing the aliphatic hydroxyl (OH) group with chlorine. [PFOF ¶ 121; 3/10 Tr. (Buschmann) at 30:6-7; 3/22 p.m. Tr. (Roush) at 10:25-11:4, 24:10-19.]
4. The fourth step of the Batch #0 synthesis involved replacing the chlorine atom with a hydrogen atom. [PFOF ¶ 121; 3/10 Tr. (Buschmann) at 30:7-9; 3/22 p.m. Tr. (Roush) at 11:5-7, 24:10-19.]

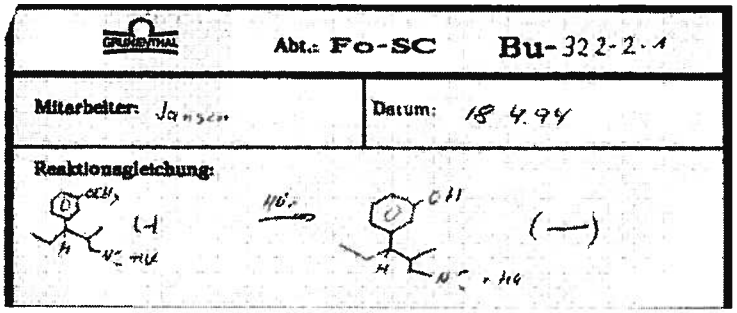
Dr. Buschmann's Batch #0 synthesis was specifically designed to retain the stereochemistry of his starting compound, (–) Bu-41 through the final product—*i.e.*, the functional groups attached to the two chiral carbons in the molecule stayed in the same relative positions from (–) Bu-41, through each intermediate step, to Bu-322. [PFOF ¶ 122; 3/10 Tr. (Buschmann) at 30:10-31:8; Buschmann Demonstrative[7] at Pages 5-7; 3/22 p.m. Tr. (Roush) at 14:8-16:10; Roush Demonstrative at Pages 46-48, 50.]

[7] Some of the citations in this Opinion include the demonstratives presented by the witnesses at trial. The demonstratives do not constitute evidence. Any demonstrative included in the citations is for convenience and informational purposes only and is to be understood in the context of the testimony given in conjunction with the demonstrative.

Dr. Buschmann sent samples of Batch #0 to Grünenthal's analytic department, which performed an independent analysis of the compound's purity, structure, and stability through a number of tests. [PFOF ¶ 123; 3/10 Tr. (Buschmann) at 31:9-37:10, 42:4-15; PTX-326 at GRT-NUC00013281-94.] After characterization, the samples were transferred to Grünenthal's pharmacological department, where they were tested *in vivo* through the mouse writhing test under the supervision of Dr. Elmar Friedrichs, who is one of the inventors of the '593 patent. [PFOF ¶ 124; 3/10 Tr. (Buschmann) at 43:3-49:11; PTX-1602 at GRT-NUC00008123-8135.]

After the initial testing of tapentadol hydrochloride showed that it had promising characteristics and it was recommended for further pharmacological testing, Dr. Buschmann resynthesized the compound in April 1994 in order to make larger amounts for additional testing.[8] [PFOF ¶ 125; 3/10 Tr. (Buschmann) at 37:11-22.] This resynthesis of the compound yielded a batch of tapentadol hydrochloride termed "Bu-322-2-1," and is commonly referred to as "Batch #1." [PFOF ¶ 125; 3/10 Tr. (Buschmann) at 37:23-38:25; PTX-345 at GRT-NUC00018952-53.] Dr. Buschmann's laboratory notebook from April 18, 1994 contains a description of the final step of the synthesis of Batch #1, which includes the two-dimensional structural formula (*i.e.*, without stereochemistry representations) for tapentadol hydrochloride:

[8] The original search for drug compounds at Grünenthal begins (as did Dr. Buschmann's original synthesis of tapentadol hydrochloride) in the Medicinal/Synthetic Chemistry department, which generally involves small amounts of material (up to around 1 gram). [PFOF ¶ 162; 3/10 Tr. (Gruss) at 255:11-20; 3/10 Tr. (Buschmann) at 76:7-77:2.] Later, scale up to amounts from 10 grams to kilograms occurs in the Chemical Development and Process Development departments. [*Id.*] When a process for producing a compound is scaled up, the original synthetic route from the Synthetic Chemistry department is often changed in order to increase chemical yields and achieve the correct quantity of material. [PFOF ¶ 163; 3/10 Tr. (Buschmann) at 77:3-13.] This was the case for tapentadol. [PFOF ¶ 163; 3/10 Tr. (Buschmann) at 77:14-16.]



[PTX-345 at GRT-NUC00018952.]

Dr. Buschmann testified that there were four steps involved in the synthesis of Batch #1:

1. The first step of the Batch #1 synthesis was identical to the first step of the Batch #0 synthesis and involved separating the stereoisomers of Bu-41 into (+) Bu-41 and (–) Bu-41. [PFOF ¶ 126; 3/10 Tr. (Buschmann) at 39:2-11, 30:2-3; 3/22 p.m. Tr. (Roush) at 10:12-24, 26:12-18.]
2. The second step of the Batch #1 synthesis involved using the (–) Bu-41 stereoisomer and replacing the aliphatic hydroxyl (OH) group with chlorine. [PFOF ¶ 126; 3/10 Tr. (Buschmann) at 39:2-11, 30:6-7; 3/22 p.m. Tr. (Roush) at 10:25-11:4, 26:12-18.]
3. The third step of the Batch #1 synthesis involved replacing the chlorine atom with a hydrogen atom. [PFOF ¶ 126; 3/10 Tr. (Buschmann) at 39:2-11, 30:7-9; 3/22 p.m. Tr. (Roush) at 11:5-7, 26:12-18.]
4. The fourth step of the Batch #1 synthesis involved cleaving the phenolic methyl ether to yield the free phenol. [PFOF ¶ 126; 3/10 Tr. (Buschmann) at 39:2-11, 30:3-5; 3/22 p.m. Tr. (Roush) at 11:8-12, 26:12-18.]

The Batch #1 synthesis contains the same steps as the Batch #0 synthesis but the order of transformations was changed. [PFOF ¶ 127; 3/10 Tr. (Buschmann) at 39:2-11; 3/22 p.m. Tr. (Roush) at 24:10-19.] The chemistries (including the retention of stereochemistry) were identical.

[PFOF ¶ 127; 3/10 Tr. (Buschmann) at 39:2-11; 3/22 p.m. Tr. (Roush) at 24:10-19.] Dr. Buschmann testified that reason for changing the order of steps was to make it easier to synthesize multigram quantities of the final product. [PFOF ¶ 127; 3/10 Tr. (Buschmann) at 39:5-41:3.]

After Dr. Buschmann synthesized Batch #1, he sent a sample to the analytical department for analysis of its purity to ensure that it would be appropriate to use it in further experiments in animals. [PFOF ¶ 129; 3/10 Tr. (Buschmann) at 41:19-43:2; DTX-1183.] Samples of Batch #1 were subsequently used for further pharmacological testing. [PFOF ¶ 129; 3/10 Tr. (Buschmann) at 43:3-45:2.]

ii. Prosecution of the '593 Patent

Beginning in late February 1994 and continuing up to and after the July 23, 1994 filing date of the original German patent application that led to the '593 patent, Grünenthal obtained isolated animal test data from the mouse writhing test[9] for tapentadol hydrochloride as well as other compounds falling within the claims of the '593 patent. [PFOF ¶ 131; 3/10 Tr. (Buschmann) at 45:8-49:11; PTX-1602 at GRT-NUC0008123-35.] Dr. Buschmann's synthesis of linear 1-phenyl-3-dimethylaminopropane compounds, as well as the work of Dr. Wolfgang Strassburger and Dr. Elmar Friedrichs to analyze and test the compounds, led to the filing of German Patent Application 44 26 245.0 and issuance of the '737 patent, which was later reissued as the '593 patent. [PFOF ¶ 132; 3/10 Tr. (Buschmann) at 62:21-63:9; Friedrichs Depo. at 131:17-20; PTX-668, PTX-303, PTX-306, PTX-312.]

[9] In the mouse writhing test, mice are injected with pheylquinone, causing them to experience nociceptive pain and writhe in an easily observable and stereotypic manner. [PFOF ¶ 338; 3/23 Tr. (Ossipov) at 118:24-121:4.] The analogous condition in humans is peritonitis, which is very painful. [PFOF ¶ 338; 3/23 Tr. (Ossipov) at 199:6-22.]

The synthesis of tapentadol hydrochloride is disclosed in Example 25 of the '593 patent. [PFOF ¶ 133; 3/22 p.m. Tr. (Roush) at 8:17-22, 10:7-11:12.] The synthesis in Example 25 (which incorporates the synthesis steps disclosed in Example 2 and Example 24) contains the same steps as Dr. Buschmann's Batch #1 synthesis. [PFOF ¶ 133; 3/22 p.m. Tr. (Roush) at 10:7-11:12, 26:12-18 3/10 Tr. (Buschmann) at 56:15-25, PTX-345 at GRT-NUC00018953; PTX-312 at 19:12-30.] The chemical structure disclosed in Example 25 of the original German application, the U.S. application, the '737 patent, and the '593 patent is the same structure drawn in Dr. Buschmann's laboratory notebook for tapentadol hydrochloride. [PFOF ¶ 134; 3/10 Tr. (Buschmann) at 57:9-12, 63:10-22, 67:2-7; 3/22 p.m. Tr. (Roush) at 9:2-10:6; PTX-303 at GRT-NUC00008515, PTX-306 at GRT-NUC00009333, PTX-345 at GRT-NUC00018953, PTX-668 at JN_NUCYNTA_0058138, PTX-312 at GRT-NUC00009605.] While Example 25 states that tapentadol hydrochloride "crystallised out" at the end of the synthesis ['593 patent at 19:19:9], the patent does not discuss the solid state crystal form of tapentadol hydrochloride.

The specifications of the German application, the '737 patent, and the '593 patent discuss mouse writhing test pharmacological investigations that Grünenthal undertook with respect to 1-phenyl-3-dimethylaminopropane compounds disclosed and claimed by the '593 patent. [PFOF ¶ 135; 3/22 p.m. Tr. (Roush) at 23:9-18; 3/23 Tr. (Ossipov) at 115:19-25; PTX-303; PTX-306; PTX-312; PTX-668.] A table is provided in the specification recording data resulting from these tests. The numerical ED_{50} values[10] or % inhibition values for certain compositions were recorded in the table. [PFOF ¶ 135; 3/22 p.m. Tr. (Roush) at 23:9-18; 3/23 Tr. (Ossipov) at 115:19-25.]

[10] An ED_{50} value refers to the effective dose at which the number of mouse writhes is inhibited by 50%. This value is derived from a statistical analysis of the dose-response curve, and at least three dosing levels are required to generate an ED_{50} value. [PFOF ¶¶ 345-346; '593 patent at 22:3-40; 3/23 Tr. (Ossipov) at 125:11-18, 128:14-17; Friedrichs Depo. at 207:1-10.]

iii. Further Development of Tapentadol Hydrochloride

After filing a patent application, Grünenthal continued to test tapentadol hydrochloride and other candidates developed through the Tramadol Successor project. [PFOF ¶ 137.] In February 1995, tapentadol hydrochloride was one of eight compounds (including both linear and cyclic compounds) that Grünenthal accepted for further development and Phase I clinical testing in humans. [PFOF ¶ 137; 3/10 Tr. (Buschmann) at 73:19-74:16; PTX-537_T at GRT-NUC00067193_T-94_T.] In March 1995, tapentadol hydrochloride was one of four (of the eight) compounds that Grünenthal selected for further development. [PFOF ¶ 138; Friedrichs Depo at 114:10-115:7, 116:9-18.] In August 1997, Grünenthal reported positive clinical results for tapentadol hydrochloride, which led to its selection as a candidate for the large-scale clinical trials that ultimately supported the marketing approval for tapentadol hydrochloride. [PFOF ¶¶ 139-140; 3/10 Tr. (Buschmann) at 74:17-76:6, 79:11-24; PTX-597_T at GRT-NUC00150198_T.]

Among other areas of development, two areas in which Grünenthal focused were (1) investigation of the crystalline forms of tapentadol hydrochloride (*i.e.*, the work that led to the '364 patent) and (2) investigation of tapentadol hydrochloride's ability to treat neuropathic pain (*i.e.*, the work that led to the '130 patent).

1. Crystalline forms of tapentadol hydrochloride

a. Establishment of solid state facilities at Grünenthal

Up until the late 1990's, Grünenthal had focused its work entirely on the synthesis of organic compounds and had hired only organic chemists to work on synthesizing organic compounds. [PFOF ¶¶ 150, 153; 3/10 Tr. (Gruss) at 230:13-231:6, 236:14-22; 3/10 Tr. (Buschmann) at 78:14-79:10.] The work leading to the '593 patent had not included any investigation of solid state crystalline forms of the compounds. [*Id.*] In the late 1990's, Dr. Buschmann began discussions with Grünenthal management about solid state and crystalline

polymorph investigations, which had never been done at Grünenthal. [PFOF ¶¶ 150-151; 3/10 Tr. (Buschmann) at 78:5-79:10; 3/10 Tr. (Gruss) at 230:13-231:6, 236:14-22, 266:11-19.]

At that time, Dr. Buschmann requested that a technician in the Analytical Chemistry department named Dagmar Lischke (an inventor of the '364 patent), perform some preliminary studies of the crystal structure of several compounds, including tapentadol hydrochloride. [PFOF ¶ 154; 3/10 Tr. (Gruss) at 231:7-15, 233:4-8.] Also at that time, Dr. Andreas Fischer (an inventor of the '364 patent) performed XRPD and single crystal diffraction analyses on a sample of tapentadol hydrochloride for Grünenthal.[11] [PFOF ¶ 156; Fischer Depo. at 63:10-12; 3/10 Tr. (Gruss) at 266:20-24.]

In May 2000, Dr. Buschmann hired Dr. Michael Gruss, the first inorganic chemist ever employed at Grünenthal, to establish solid state facilities at Grünenthal. [PFOF ¶¶ 152, 153; 3/10 Tr. (Buschmann) at 78:14-79:10; 3/10 Tr. (Gruss) at 227:11-228:10, 266:11-19.] Dr. Gruss was the first person to perform systematic solid state investigations at Grünenthal (unlike Ms. Lischke's work, which had been individual tests done by request). [PFOF ¶ 157; 3/10 Tr. (Gruss) at 230:22-231:21.] Dr. Gruss began his work at Grünenthal by investigating a handful, but not all, of the compounds under development. [PFOF ¶¶ 157-158; 3/10 Tr. (Gruss) at 231:19-232:1.] Shortly after joining Grünenthal, Dr. Gruss became involved with solid state investigations of tapentadol hydrochloride. [PFOF ¶ 159; 3/10 Tr. (Gruss) at 232:2-10.]

b. Solid state investigation of tapentadol hydrochloride

The core group of people that worked on the solid state investigation of tapentadol hydrochloride were Dr. Gruss, Dr. Buschmann, Dr. Fischer, and Ms. Lischke (the four inventors

[11] Dr. Fischer was at the time working at an external research organization called F & E Analytics, but he later joined Grünenthal in 2001. [PFOF ¶ 156; Fischer Depo. at 63:6-7; 3/10 Tr. (Gruss) at 232:17-25.]

of the '364 patent). [PFOF ¶ 160; 3/10 Tr. (Gruss) at 232:11-16.] Prior to Dr. Gruss's arrival at Grünenthal, Ms. Lischke had performed DSC and TGA studies on tapentadol hydrochloride and she suspected that five or six crystal forms of tapentadol hydrochloride existed. [PFOF ¶¶ 154-155; 3/10 Tr. (Gruss) at 231:7-15, 233:4-8, 233:24-234:3; 239:21-24.] As discussed above, before this time (*e.g.*, during the work that lead to the '593 patent) Grünenthal did not have knowledge of the crystalline polymorphic forms of tapentadol hydrochloride. [*See* PFOF ¶¶ 150, 153; 3/10 Tr. (Gruss) at 230:13-231:6, 236:14-22; 3/10 Tr. (Buschmann) at 78:14-79:10.]

After Dr. Gruss joined Grünenthal, he and Ms. Lischke collected samples of tapentadol hydrochloride from various departments at Grünenthal (which had samples produced by different synthetic methods) to study further. [PFOF ¶ 161; 3/10 Tr. (Gruss) at 234:9-12, 254:18-256:15.] Dr. Gruss and Ms. Lischke also collected new samples of tapentadol hydrochloride and obtained new solid state analytical data on the samples. [PFOF ¶ 164; 3/10 Tr. (Gruss) at 234:4-8.] In 2001, Dr. Gruss reviewed the XRPD and DSC data on the tapentadol hydrochloride samples and discovered that there were two crystal forms of tapentadol hydrochloride, Form A and Form B. [PFOF ¶¶ 165, 168; 3/10 Tr. (Gruss) at 234:13-18.]

Among the samples Dr. Gruss analyzed in 2001 was Dr. Buschmann's Batch #0, which had been synthesized in 1994. [PFOF ¶ 175; 3/10 Tr. (Gruss) at 244:9-10.] Dr. Gruss testified that the diffraction pattern for Batch #0 showed only Form B. [PFOF ¶ 175; 3/10 Tr. (Gruss) at 244:11-20.]

Grünenthal subsequently commissioned one of its employees, a technician named Marita Müeller, to attempt to resynthesize tapentadol hydrochloride following the method of Example 25 of the '737 patent. [PFOF ¶ 175; 3/10 Tr. (Gruss) at 257:10-24.] Ms. Müeller successfully synthesized tapentadol hydrochloride twice. [PFOF ¶ 394; 3/16 Tr. (Steed) at 44:19-22; 3/16 Tr.

(Matzger) at 112:11-14; 3/22 p.m. Tr. (Roush) at 29:7-23.] The diffraction patterns for both compounds produced by Ms. Müeller's syntheses showed only Form B. [PFOF ¶ 175; 3/10 Tr. (Gruss) at 259:16-260:3, 261:11-19; PTX-491.] Thus, Grünenthal concluded that the synthesis of Example 25 produces Form B of tapentadol hydrochloride. [*See id.*]

Of the other samples that Dr. Gruss had collected from different departments at Grünenthal, some of the patterns did not appear at first to match the pattern for Form A or the pattern for Form B, and Dr. Gruss considered whether there might be additional polymorphic forms. [PFOF ¶ 167; 3/10 Tr. (Gruss) at 246:3-247:5.] However, after analyzing the patterns, he determined that every sample was either Form A, Form B, or a mixture of the two forms, thus confirming that Grünenthal had only discovered the existence of two polymorphic forms. [PFOF ¶ 167; 3/10 Tr. (Gruss) at 246:3-247:5.]

From its internal investigations, Grünenthal was aware of the existence of Form A of tapentadol hydrochloride, which it concluded was the newly discovered form that had not been produced by the method of Example 25. [PFOF ¶ 173; 3/10 Tr. (Gruss) at 237:23-238:3; Fischer Depo. at 63:10-12; PTX-511_T.] Grünenthal had done some additional work investigating the forms, including determining the lattice parameters of Form B and performing single crystal structure analysis on Form A. [PFOF ¶ 173; 3/10 Tr. (Gruss) at 237:23-238:3; Fischer Depo. at 63:10-12; PTX-511_T.]

In addition to the internal solid state investigations, Dr. Gruss and Dr. Buschmann also hired an external company called SSCI to conduct systematic polymorphism investigations on tapentadol hydrochloride. [PFOF ¶ 171; 3/10 Tr. (Gruss) at 236:14-237:22.] In 2003, Grünenthal hired another external company called Crystallics to conduct further investigations on the crystallization of tapentadol hydrochloride. [PFOF ¶ 174; 3/10 Tr. (Gruss) at 238:4-14.] There

was continuous work on the investigation of the crystal forms of tapentadol hydrochloride at least until Dr. Gruss left the company in 2010. [PFOF ¶ 174; 3/10 Tr. (Gruss) at 234:4-8, 235:13-23.]

2. Treatment of neuropathic pain with tapentadol

In 1996, Grünenthal hired Dr. Thomas Christoph (an inventor of the '130 patent) to start a neuropathic pain department and perform neuropathic pain studies on tapentadol hydrochloride. [PFOF ¶ 176; 3/14 a.m. Tr. (Christoph) at 11:10-12:5.] Prior to hiring Dr. Christoph, Grünenthal lacked the capabilities to perform *in vivo* neuropathic pain modeling. [PFOF ¶ 176; 3/14 a.m. Tr. (Christoph) at 12:10-15.] Neuropathic pain studies generally involve damaging a nerve to induce hypersensitivity. [PFOF ¶ 176; 3/14 a.m. Tr. (Christoph) at 16:17-17:3.] At the time, there were a number of models available for studying neuropathic pain.

a. Mononeuropathic pain studies

Beginning in 1998, Dr. Christoph first studied tapentadol hydrochloride using the Bennett model and the Chung model, both of which are mononeuropathic pain models. [PFOF ¶¶ 177-178; 3/14 a.m. Tr. (Christoph) at 17:4-23:24; PTX-452; PTX-453.] The results of each study showed that tapentadol hydrochloride demonstrated a dose-dependent inhibition of mononeuropathic pain. [PFOF ¶¶ 177-178; 3/14 a.m. Tr. (Christoph) at 20:15-18, 23:1-10; PTX-452 at GRT-NUC44427; PTX-453 at GRT-NUC44513.]

In 2000, Dr. Christoph supervised tolerance and cross tolerance tests on tapentadol hydrochloride using the Bennett model to investigate the extent to which subjects become resistant to tapentadol hydrochloride when it is used continuously to treat mononeuropathic pain. [PFOF ¶ 179; 3/14 a.m. Tr. (Christoph) at 23:25-24:5; PTX-477).] These tests indicated that tapentadol hydrochloride inhibits neuropathic pain through a mechanism of action in addition to opiate receptor antagonism. [PFOF ¶ 179; PTX-477 at GRT-NUC00054638; 3/14 a.m. Tr. (Christoph) at 23:18-29:9.] Later experiments demonstrated that tapentadol hydrochloride possessed both a

mu-opioid and a noradrenergic (*i.e.*, norepinephrine reuptake inhibition) mechanism of action. [PFOF ¶ 180; PTX-737 at JN_NUCYNTA_0321242; 3/14 a.m. Tr. (Christoph) at 55:9-56:7.] Dr. Christoph also demonstrated that tapentadol hydrochloride lacks a serotonergic (*i.e.*, serotonin reuptake inhibition) mechanism of action. [PFOF ¶ 180; PTX-744 at JN_NUCYNTA_715982 ("Thus, the current study demonstrates contribution of μ-opioidergic and noradrenergic but not serotonergic activity of [tapentadol hydrochloride] in the spinal nerve ligation model of neuropathic pain."); 3/14 a.m. Tr. (Christoph) at 57:13-16.]

b. Polyneuropathic pain studies

After conducting mononeuropathic studies, Dr. Christoph wanted to perform polyneuropathic pain trials but his laboratory at Grünenthal lacked the capabilities. [PFOF ¶ 181; 3/14 a.m. Tr. (Christoph) at 29:20-22.] Grünenthal hired Dr. Murielle Meen (an inventor of the '130 patent) to assist Dr. Christoph in developing and implementing polyneuropathic pain models. [PFOF ¶ 181; 3/14 a.m. Tr. (Christoph) at 29:23-30:4.]

The first polyneuropathic pain model used in Dr. Christoph's lab was the streptozotocin ("STZ") model. [PFOF ¶ 182; 3/14 a.m. Tr. (Christoph) at 29:13-19; PTX-454.] Streptozotocin induces diabetes in rats, leading to diabetic polyneuropathic pain. [PFOF ¶ 182; 3/14 a.m. Tr. (Christoph) at 29:13-19, 30:15-31:25.] The evidence from the STZ experiments demonstrated that tapentadol hydrochloride was effective in treating polyneuropathic pain. [PFOF ¶ 183; 3/14 a.m. Tr. (Christoph) at 32:21-33:14; PTX-454 at GRT-NUC44807.] Because pain wiring in rats is similar to that of humans, based on the *in vivo* evidence from the STZ model in rats, Dr. Christoph expected that tapentadol hydrochloride would be effective for treating polyneuropathic pain in humans. [PFOF ¶ 184; PTX-454 at GRT-NUC00044810; 3/14 a.m. Tr. (Christoph) at 33:15-34:4, 17:9-23.] Subsequent to the STZ model, Dr. Christoph obtained additional evidence supporting

the ability of tapentadol hydrochloride to treat polyneuropathic pain by using the vincristine model. [PFOF ¶ 185; PTX-455 at GRT-NUC44840; 3/14 a.m. Tr. (Christoph) at 34:8-35:1, 35:18-24.]

G. THE PRODUCTS AT ISSUE

i. Plaintiffs' NUCYNTA® products

1. NUCYNTA® IR

On January 22, 2008, Janssen submitted NDA No. 22304 to the FDA for approval of NUCYNTA® IR (50, 75, 100 mg) immediate release tablets. [PFOF ¶ 41; PTX-829 at JN_NUCYNTA_1634456.] At the time, Janssen also submitted a clinical overview to health authorities, including the FDA, in support of its efforts to gain approval for NUCYNTA® IR. [PFOF ¶ 42; PTX-1555; 3/11 Tr. (Haeussler) at 109:14-110:2.] Janssen's submission demonstrated the efficacy of tapentadol hydrochloride through pain studies of bunionectomies and end-stage degenerative joint disease. [PFOF ¶ 43; PTX-1555 at JN_NUCYNTA_0319295-97.] Preclinical and clinical testing demonstrated that tapentadol hydrochloride, due to its dual mechanisms of action, provided the benefit of delivering pain relief similar to opioids but with an improved tolerability profile and reduced side effects. [PFOF ¶ 44; 3/11 Tr. (Haeussler) at 110:3-113:5; PTX-1555 at JN_NUCYNTA_0319284-85.] On November 20, 2008, the FDA approved NDA No. 22304 for NUCYNTA® IR (50, 75, 100 mg). [PFOF ¶ 45; PTX-829 at JN_NUCYNTA_1634456.] NUCYNTA® IR is indicated for "the management of moderate to severe acute pain in adults." [PFOF ¶ 47; PTX-829 at JN_NUCYNTA_1634456.]

2. NUCYNTA® Oral Solution

On December 15, 2011, Janssen submitted NDA No. 203794 to the FDA for approval of NUCYNTA® oral solution (20 mg/mL). [PFOF ¶ 48; PTX-829 at JN_NUCYNTA_1634456.] On October 15, 2012, the FDA approved NDA No. 203794. [PFOF ¶ 49; PTX-829 at JN_NUCYNTA_1634456.] The NUCYNTA® oral solution (20 mg/mL) is indicated for "the

management of moderate to severe acute pain in adults." [PFOF ¶ 50; PTX-829 at JN_NUCYNTA_1634456.]

3. NUCYNTA® ER

a. Original NUCYNTA® ER label with one indication

On November 30, 2009, Janssen submitted NDA No. 200533 to the FDA for approval of NUCYNTA® ER (50, 100, 150, 200, 250 mg) extended release tablets. [PFOF ¶ 51; PTX-829 at JN_NUCYNTA_1634457.] At the time, Janssen also submitted a clinical overview to health authorities, including the FDA, in support of its efforts to gain approval for NUCYNTA® ER. [PFOF ¶ 52; PTX-1551; 3/11 Tr. (Haeussler) at 113:6-22.]

Prior to submitting its NDA for NUCYNTA® ER, Janssen met with the FDA to discuss the specific data requirements that the FDA would need to make a decision on approval. [PFOF ¶ 53; 3/11 Tr. (Haeussler) at 113:23-114:9.] Dr. Haeussler testified that Janssen expressed interest at that time in obtaining approval for two indications—one indication for the management of chronic moderate to severe pain ("Indication 1") and a second indication for diabetic peripheral neuropathic pain ("Indication 2"). [PFOF ¶ 53; 3/11 Tr. (Haeussler) at 114:10-15.] The FDA explained that, in order for Janssen to obtain approval for Indication 1, Janssen would need to provide evidence of two positive, clinically relevant studies of different pain conditions. [PFOF ¶ 54; 3/11 Tr. (Haeussler) at 116:12-117:19.] The FDA stated that one of the two studies could be a study on pain associated with diabetic peripheral neuropathy ("DPN"). [PFOF ¶ 54; 3/11 Tr. (Haeussler) at 116:22-117:1.]

Janssen then inquired what the FDA would require in order to approve Indication 2. [3/11 Tr. (Haeussler) at 117:2-7.] The FDA responded "that like for any specific indication, they required replicative evidence which means that two positive studies are required in the same condition specifically to get that specific indication label." [3/11 Tr. (Haeussler) at 117:2-7.]

Janssen's November 2009 submission to FDA sought approval for only Indication 1 (*i.e.*, treatment of moderate to severe chronic pain). [*See* PTX-829 at JN_NUCYNTA_1634457.] Janssen supported its claims of efficacy for Indication 1 with studies of three pain conditions—(1) chronic lower back pain ("CLBP"), (2) chronic painful osteoarthritis ("OA"), and (3) DPN.[12] [PFOF ¶ 55; 3/11 Tr. (Haeussler) at 117:8-19; PTX-1551 at JN_NUCYNTA_0074680.] Dr. Haeussler testified that Janssen selected these three chronic pain conditions based on FDA guidance and because they are three of the most common chronic pain conditions that present with pain severe enough to warrant opioid therapy. [PFOF ¶ 56; DFOF ¶ 2536; 3/11 Tr. (Haeussler) at 118:14-24; PTX-1551 at JN_NUCYNTA_0074683.]

On August 25, 2011, the FDA approved NDA No. 200533 for NUCYNTA® ER (50, 100, 150, 200, 250 mg). [PFOF ¶ 60; PTX-829 at JN_NUCYNTA_1634457.] From this FDA approval, Janssen obtained permission to market its NUCYNTA® ER product for Indication 1. [PFOF ¶ 61; PTX-1499 at JN_NUCYNTA_0273432.] Specifically, the approved label stated:

> NUCYNTA® ER is an opioid analgesic indicated for the management of moderate to severe chronic pain in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

[DFOF ¶ 2514; PTX-1499 at JN_NUCYNTA_0273432.]

In approving the label, the FDA found only the CLBP and DPN studies (but not the OA study) to be positive and sufficient for inclusion in the NUCYNTA® ER label. [PFOF ¶¶ 61-62; PTX-1499 at JN_NUCYNTA_0273457-59; 3/11 Tr. (Haeussler) at 121:17-122:16.] Accordingly, the label contained summaries of these two clinical studies demonstrating the efficacy of

[12] The DPN study in Janssen's submission to show the efficacy of NUCYNTA® ER for Indication 1 was identified as PAI-3015/KF36. [PFOF ¶ 59; 3/11 Tr. (Hauessler) at 118:25-119:25; PTX-727; PTX-1551 at JN_NUCYNTA_0074680.]

NUCYNTA® ER for the treatment of moderate to severe chronic pain. [DFOF ¶ 2515; PTX-1499 at JN_NUCYNTA_0273457-59.]

b. Current NUCYNTA® ER label with two indications

On October 28, 2011, Janssen submitted a supplemental NDA to the FDA seeking approval of an additional indication for NUCYNTA® ER. [PFOF ¶ 65; PTX-829 at JN_NUCYNTA_1634457.] Specifically, Janssen sought approval of Indication 2 for the treatment of neuropathic pain associated with DPN. [PFOF ¶ 65; PTX-829 at JN_NUCYNTA_1634457.] To obtain approval for Indication 2, Janssen successfully conducted a second DPN study[13] that was virtually the same as the first DPN study Janssen had submitted in support of Indication 1. [PFOF ¶ 67; 3/11 Tr. (Haeussler) at 127:24-128:18.] On August 28, 2012, the FDA approved Janssen's supplemental NDA, giving Janssen permission to market NUCYNTA® ER for Indication 2. [PFOF ¶ 68; PTX-829 at JN_NUCYNTA_1634457.] Specifically, the new approved label stated:

> NUCYNTA® ER is an opioid agonist indicated for the management of:
>
> - moderate to severe chronic pain in adults
> - neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults
>
> when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

[13] This second DPN study was identified as PAI-3027/KF56. [PTX-732.]

[PFOF ¶ 69; PTX-695; 3/11 Tr. (Haeussler) at 128:19-129:17.] The new approved label identified and described the CLBP and DPN studies from the original label as well as the second DPN study.[14] [PFOF ¶ 70; PTX-695 at JN_NUCYNTA_0064256-58.]

The wording of the two indications was later updated in 2014 as part of the FDA's efforts to harmonize opioid-related labels. [PFOF ¶ 71 3/11 Tr. (Haeussler) at 129:18-130:1.] Accordingly, the current approved label for NUCYNTA® ER states:

> NUCYNTA® ER is an opioid agonist indicated for the management of:
>
> - pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
>
> - neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

[PFOF ¶ 75; PTX-1383; PTX-829 at JN_NUCYNTA_1634457.]

ii. Defendants' tapentadol hydrochloride products

1. Actavis

a. Actavis's tapentadol hydrochloride immediate release tablets

Actavis submitted ANDA No. 204971 to the FDA under Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)), seeking FDA approval to engage in the commercial manufacture, use, importation, offer for sale, and sale of generic 50 mg, 75 mg and 100 mg tapentadol hydrochloride tablets. [PTO ¶ 55.] ANDA No. 204971 contains certifications pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV),[15] alleging that the claims of the '593 and '364

[14] In the label, the two DPN studies were referred to as "DPN-1" and "DPN-2." [PTX-695 at JN_NUCYNTA_0064257-58.]

[15] This certification is referred to as a "Paragraph IV certification."

patents are "invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, importation, offer for sale, or sale" of the proposed drug products that are the subject of Actavis' ANDA" No. 204971. [PTO ¶ 56.] On or about August 1, 2013, Janssen and Grünenthal received a letter dated July 30, 2013 constituting the notice of ANDA No. 204971, including the Paragraph IV certification(s), required by 21 U.S.C. § 355(j)(2)(B)(i)-(ii). [PTO ¶ 57.] Actavis was aware of the '593 and '364 patents at the time it submitted ANDA No. 204971 to the FDA. [PTO ¶ 58.] On August 14, 2013, under the provisions of the Hatch-Waxman Act, Janssen and Grünenthal timely amended their Complaint for infringement of the '593 and '364 patents to include ANDA No. 204971. [*See* Case No. 13-4507, ECF No. 12.]

Actavis's proposed generic NUCYNTA® IR product that is the subject of ANDA No. 204971 contains tapentadol hydrochloride. [PTO ¶ 103.] That product contains crystalline Form A of tapentadol hydrochloride. [PTO ¶ 104.]

b. Actavis's tapentadol hydrochloride oral solution

Watson Laboratories ("Watson") submitted ANDA No. 206657 to the FDA under Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)), seeking FDA approval to engage in the commercial manufacture, use, importation, offer for sale, and sale of a generic tapentadol oral solution of 20 mg/mL. [PTO ¶ 69.] On March 9, 2015, Watson notified the Court that Watson had changed its name to Actavis Laboratories UT, Inc. [PTO ¶ 70; Case No. 2:14-cv-04617-CCC-MF, ECF No. 64.] Actavis's ANDA No. 206657 contains a Paragraph IV certification alleging that the '593 and '364 patents "are invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, importation, offer for sale or sale of the" ANDA No. 206657 Product. [PTO ¶ 71.] From on or about June 12, 2014 to on or about June 24, Janssen and Grünenthal received letters constituting notice of ANDA No. 206657, including the Paragraph IV certification, required by 21 U.S.C. § 355(j)(2)(B)(i)-(ii). [PTO ¶ 72.] Actavis was aware of

the '593 and '364 patents when ANDA 206657 was submitted to the FDA. [PTO ¶ 73.] Under the provisions of the Hatch-Waxman Act, Janssen and Grünenthal timely commenced litigation against Watson, now Actavis UT, on July 23, 2014. [PTO ¶ 74; Case No. 14-4617, ECF No. 1.]

The proposed generic NUCYNTA® oral solution product that is the subject of ANDA No. 206657 contains tapentadol hydrochloride. [PTO ¶ 105.] Actavis uses and has used crystalline Form A of tapentadol hydrochloride to manufacture its proposed generic NUCYNTA® oral solution product that is the subject of ANDA No. 206657. [PTO ¶ 106.]

c. Actavis's tapentadol hydrochloride extended release tablets

Actavis submitted ANDA No. 204972 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)), seeking FDA approval to engage in the commercial manufacture, use, importation, offer for sale, and sale of generic 50 mg, 100 mg, 150 mg, 200 mg and 250 mg tapentadol hydrochloride extended release tablets. [PTO ¶ 60.] Actavis's ANDA No. 204972 contains Paragraph IV certifications alleging that the '593 and '364 patents are "invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, importation, offer for sale, or sale of the proposed drug products that are the subject of Actavis' ANDA" No. 204972. [PTO ¶ 61.] On or about June 13, 2013, Janssen and Grünenthal received a letter dated June 12, 2013 constituting the notice of ANDA No. 204972, including the Paragraph IV certifications to the '593 and '364 patents, required by 21 U.S.C. § 355(j)(2)(B)(i)-(ii). [PTO ¶ 62.] Actavis was aware of the '593 and '364 patents at the time it submitted ANDA No. 204972 to the FDA. [PTO ¶ 63.] Under the provisions of the Hatch-Waxman Act, Janssen and Grünenthal timely commenced litigation against Actavis on July 25, 2013. [PTO ¶ 64; Case No. 13-4507, ECF No. 1.]

Actavis has been aware of the existence of the '130 patent since at least September 17, 2013. [PTO ¶ 63.] Actavis's ANDA No. 204972 does not contain a Paragraph IV

certification as to the '130 patent. [PTO ¶ 64.] Rather, it contains a statement pursuant to 21 U.S.C. § 355(j)(2)(A)(viii)[16] stating that "its proposed labelling for Tapentadol Extended-Release Tablets, 50 mg, 100 mg, 150 mg, 200 mg and 250 mg does not contain any indications covered by" the '130 patent. [PTO ¶ 64.] Actavis filed the Section viii statement on or about March 15, 2015. [PTO ¶ 65.] Actavis's Section viii statement and proposed label submitted therewith, "carved out" Indication 2 from its proposed ANDA No. 204972 products. [PTO ¶ 66.] Indication 1 remains in Actavis's proposed label for its proposed ANDA No. 204972 products. [PTO ¶ 66.] Depomed and Grünenthal commenced litigation against Actavis concerning the '130 patent on September 11, 2015. [PTO ¶ 67; Case No. 15-6797, ECF No. 1.] Although Actavis moved to dismiss the Complaint, the Court allowed Plaintiffs' claim for declaratory judgment of induced infringement and contributory infringement to proceed to trial. [Case No. 15-6797, ECF No. 55.]

Actavis's proposed generic NUCYNTA® ER product that is the subject of ANDA No. 204972 contains tapentadol hydrochloride. [PTO ¶ 103.] That product contains crystalline Form A of tapentadol hydrochloride. [PTO ¶ 104.]

Actavis's proposed label has only one indication. The label states:

> Tapendadol extended-release is an opioid agonist indicated for the management of:
>
> - Pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

[DFOF ¶ 2558; DTX-1653_0124; 3/11 Tr. (Weinberger) at 183:11-16.] In addition to carving out Indication 2 from its proposed label, Actavis has carved out all other references to neuropathic

[16] This statement is referred to as a "Section viii statement."

pain or neuropathy that are contained in the NUCYNTA® ER label. [DFOF ¶ 2559; DTX-1653.] Thus, Actavis's proposed label does not contain the words "neuropathic pain," "neuropathy," "polyneuropathic pain," or "polyneuropathy." [DFOF ¶ 2560; 3/11 Tr. (Weinberger) at 186:4-14; 3/14 p.m. Tr. (Brown) at 112:12-21.] Actavis's proposed label does not contain information about either the DPN-1 or the DPN-2 clinical trials. [DFOF ¶ 2561; DTX-1653.] The only clinical trial summary in Actavis's proposed label is that of the CLBP study. [*Id.*]

2. Roxane

a. Roxane's tapentadol hydrochloride immediate release tablets

Roxane submitted ANDA No. 205057 to the FDA under Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)), seeking FDA approval to engage in the commercial manufacture, use, importation, offer for sale, and sale of generic 50 mg, 75 mg, and 100 mg tapentadol hydrochloride tablets. [PTO ¶ 91.] Roxane's ANDA No. 205057 contains a Paragraph IV certification alleging that the '593 and '364 patents are "invalid, not infringed, and/or unenforceable." [PTO ¶ 92.] From on or about October 8, 2013 to on or about October 21, 2013, Janssen and Grünenthal each received a letter dated October 3, 2013 constituting notice of ANDA No. 205057, including the Paragraph IV certification, required by 21 U.S.C. § 355(j)(2)(B)(i)-(ii). [PTO ¶ 93.] Roxane was aware of the '593 and '364 patents at the time it submitted ANDA No. 205057 to the FDA. [PTO ¶ 94.] Under the provisions of the Hatch-Waxman Act, Janssen and Grünenthal timely commenced litigation against Roxane on November 14, 2013. [PTO ¶ 91; Case No. 13-6929, ECF No. 1.]

Roxane's proposed generic NUCYNTA® IR product that is the subject of ANDA No. 205057 contains tapentadol hydrochloride. [PTO ¶ 107.] That product contains crystalline Form A of tapentadol hydrochloride. [PTO ¶ 108.]

b. Roxane's tapentadol hydrochloride extended release tablets

Roxane submitted ANDA No. 206418 to the FDA under Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)), seeking FDA approval to engage in the commercial manufacture, use, importation, offer for sale, and sale of generic 50 mg, 100 mg, 150 mg, 200 mg, and 250 mg tapentadol hydrochloride extended release tablets. [PTO ¶ 96.] Roxane's ANDA No. 206418 contained a Paragraph IV certification alleging that the '593, '364, and '130 patents "are invalid, are not infringed, and/or are unenforceable." [PTO ¶ 97.] From on or about May 9, 2014 to on or about May 14, 2014, Janssen and Grünenthal each received a letter dated May 8, 2014 constituting notice of ANDA No. 206418, including the Paragraph IV certification, required by 21 U.S.C. § 355(j)(2)(B)(i)-(ii). [PTO ¶ 98.] Roxane was aware of the '593, '364, and '130 patents at the time it submitted ANDA No. 206418 to the FDA. [PTO ¶ 99.] Under the provisions of the Hatch-Waxman Act, Janssen and Grünenthal timely commenced litigation against Roxane on June 19, 2014 [PTO ¶ 100; Case No. 14-3941, ECF No. 1.]

Roxane's proposed generic NUCYNTA® ER product that is the subject of ANDA No. 206418 contains tapentadol hydrochloride. [PTO ¶ 107.] That product contains crystalline Form A of tapentadol hydrochloride. [PTO ¶ 108.]

Roxane's original proposed label for its ANDA product included the same two indications for which NUCYNTA® ER is currently approved, although with the outdated wording prior to the FDA regulations harmonizing opioid labels. [DFOF ¶ 2548; 3/21 Tr. (Buvanendran) at 37:25-38:8.] As filed, Roxane's proposed label stated:

> Tapentadol Extended-Release Tablets are an opioid agonist indicated for the management of:
>
> - moderate to severe chronic pain in adults
> - neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults

> when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

[DFOF ¶ 2547; DTX-1589.]

On April 17, 2015, Roxane amended its ANDA No. 206418 by converting its Paragraph IV certification as to the '130 patent into a Section viii statement, stating that "the labeling for the drug product for which [Roxane] is seeking approval does not include the indication that is covered by" the '130 patent. [PTO ¶ 101; DFOF ¶¶ 2549-2551; PTX-922.] Roxane's Section viii statement, and proposed label submitted therewith, "carved out" Indication 2 as well as all other references to neuropathic pain from its proposed label. [PTO ¶ 102; DFOF ¶ 2549; DTX-2020; DTX-1566; DTX-1568.] Indication 1 remains in Roxane's proposed label. [PTO ¶ 102; DFOF ¶ 2550; DTX-1566.]

Roxane's proposed label does not contain information about either the DPN-1 or the DPN-2 clinical trials. [DFOF ¶ 2553; DTX-1566.] The only clinical trial summary in Roxane's proposed label is that of the CLBP study. [*Id.*] Furthermore, Roxane's proposed label does not contain the words "neuropathic pain" or "neuropathy," other than the following language:

> *Information describing the use of Tapentadol Extended Release Tablets in patients with Neuropathic Pain Associated with Diabetic Peripheral Neuropathy is approved for Janssen Pharmaceuticals, Inc. However, due to Janssen Pharmaceuticals, Inc.'s marketing exclusivity rights, this drug is not labeled with that information.*

[DFOF ¶¶ 2552, 2554; DTX-1566.]

3. Alkem

a. Alkem's tapentadol hydrochloride immediate release tablets

Alkem submitted ANDA No. 205015 to the FDA under Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)), seeking FDA approval to engage in the commercial manufacture, use, importation, offer for sale, and sale of generic 50 mg, 75 mg and 100 mg

tapentadol hydrochloride tablets. [PTO ¶ 75.] ANDA No. 205015 contains Paragraph IV certification(s) alleging that the claims of the '593 and '364 patents are "invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, or sale of the drug product described by Alkem's ANDA" No. 205015. [PTO ¶ 76.] On or about June 20, 2013, Janssen and Grünenthal received a letter dated June 19, 2013 constituting the notice of ANDA No. 205015, including the Paragraph IV certification(s), required by 21 U.S.C. § 355(j)(2)(B)(i)-(ii). [PTO ¶ 77.] Alkem was aware of the '593 and '364 patents at the time it submitted ANDA No. 205015 to the FDA. [PTO ¶ 78.] Under the provisions of the Hatch-Waxman Act, Janssen and Grünenthal timely commenced litigation against Alkem on July 25, 2013. [PTO ¶ 79; ECF No. 1.]

Alkem's proposed generic NUCYNTA® IR product that is the subject of ANDA No. 205015 contains tapentadol hydrochloride. [PTO ¶ 109.] That product contains crystalline Form A of tapentadol hydrochloride. [PTO ¶ 110.]

b. Alkem's tapentadol hydrochloride extended release tablets

Alkem submitted ANDA No. 205016 to the FDA under Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)), seeking FDA approval to engage in the commercial manufacture, use, importation, offer for sale, or sale of at least generic 100 mg, 200 mg and 250 mg tapentadol hydrochloride extended release tablets. [PTO ¶ 80.] Alkem's ANDA No. 205016 was amended to further seek FDA approval to engage in the commercial manufacture, use, importation, offer for sale, or sale of generic 50 mg and 150 mg tapentadol hydrochloride extended release tablets. [PTO ¶ 81.] ANDA No. 205016 contains Paragraph IV certification(s) that the patents-in-suit are "invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, or sale of the drug product described by Alkem's ANDA" No. 205016. [PTO ¶ 82.] On or about July 1, 2013, Janssen and Grünenthal received a letter dated June 28, 2013 constituting the notice of ANDA No. 205016, including the Paragraph IV certifications to the '593

and '364 patents, required by 21 U.S.C. § 355(j)(2)(B)(i)-(ii). [PTO ¶ 83.] Under the provisions of the Hatch-Waxman Act, Janssen and Grünenthal timely commenced litigation against Alkem on the '593 and '364 patents on July 25, 2013. [PTO ¶ 84; Case No. 13-4507, ECF No. 1.] On or about November 14, 2013, Janssen and Grünenthal received a letter dated November 13, 2013 constituting the notice of Alkem's amendment of ANDA No. 205016, including the Paragraph IV certification to the '130 patent, required by 21 U.S.C. § 355(j)(2)(B)(i)-(ii). [PTO ¶ 85.] Under the provisions of the Hatch-Waxman Act, Janssen and Grünenthal timely commenced litigation against Alkem on the '130 patent on December 23, 2013. [PTO ¶ 86; Case No. 13-7803, ECF No. 1.] On or about July 8, 2014 and July 9, 2014 Janssen and Grünenthal each received a letter dated July 7, 2014, constituting the notice of Alkem's amendment of ANDA No. 205016, including the Paragraph IV certifications, required by 21 U.S.C. § 355(j)(2)(B)(i)-(ii). [PTO ¶ 87.] Under the provisions of the Hatch-Waxman Act, Janssen and Grünenthal timely amended their complaints against Alkem on August 20, 2014. [PTO ¶¶ 88-89; Case No. 13-7803, ECF No. 57; Case No. 13-4507, ECF No. 146.] Alkem was aware of the '593 and '364 patents at the time it submitted ANDA No. 205016 to the FDA. Alkem was aware of the '130 patent at the time it submitted its amendment to ANDA No. 205016 identified in its November 13, 2013 notice letter to the FDA. [PTO ¶ 90.]

Alkem's proposed generic NUCYNTA® ER product that is the subject of ANDA No. 205016 contains tapentadol hydrochloride. [PTO ¶ 109.] That product contains crystalline Form A of tapentadol hydrochloride. [PTO ¶ 110.] Alkem's proposed label for its ANDA product contains the same two indications as NUCYNTA® ER:

> Tapentadol extended release tablets are opioid agonist indicated for the management of:

- pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

- neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

[PTX-225.] Alkem's label also contains information about the same clinical studies as the NUCYNTA® ER label. [*Id.*]

III. LEGAL STANDARDS

A. INFRINGEMENT

Under the Patent Act:

> [W]hoever without authority makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent therefor, infringes the patent.

35 U.S.C. § 271(a). The statute also prohibits a person from indirectly infringing a patent. *See* 35 U.S.C. § 271(b)-(c). The two types of indirect infringement are induced infringement, *see* 35 U.S.C. § 271(b), and contributory infringement, *see* 35 U.S.C. § 271(c). "The patentee bears the burden of proving infringement by a preponderance of the evidence." *SRI Int'l v. Matsushita Elec. Corp.*, 775 F.2d 1107, 1123 (Fed. Cir. 1985)

i. Induced Infringement

Under 35 U.S.C. § 271(b), "[w]hoever actively induces infringement of a patent shall be liable as an infringer." A threshold question in the inducement analysis is whether there is evidence of direct infringement by another. *Limelight Networks, Inc. v. Akamai Techs., Inc.*, 134 S. Ct. 2111, 2117 (2014) ("[W]here there has been no direct infringement, there can be no inducement of infringement under § 271(b)."); *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1056 (Fed. Cir. 2010). Once it is determined that there is evidence of direct infringement by

another, the Court must determine whether the defendant has the requisite specific intent to encourage that direct infringement. *AstraZeneca*, 633 F.3d at 1056.

To establish induced infringement, a patent holder must demonstrate that the infringer "'knowingly induced infringement and possessed specific intent to encourage another's [direct] infringement.'" *Id.* (quoting *DSU Med. Corp. v. JMS Co.*, 471 F.3d 1293, 1306 (Fed. Cir. 2006)). The Federal Circuit has stated that circumstantial evidence can be sufficient to support a finding of specific intent. *Id.* at 1060.

In 2015, the Federal Circuit provided the following summary of the law of inducement:

> Infringement only exists where there is evidence that goes beyond a product's characteristics or the knowledge that it may be put to infringing uses. Inducement can be found where there is [e]vidence of active steps taken to encourage direct infringement, which can in turn be found in advertising an infringing use or instructing how to engage in an infringing use. But such instructions need to evidence intent to *encourage* infringement. The question is not just whether instructions describ[e] the infringing mode, but whether the instructions teach an infringing use of the device *such that* we are willing to infer from those instructions an affirmative intent to infringe the patent. Merely describ[ing] an infringing mode is not the same as recommend[ing], encourag[ing], or promot[ing] an infringing use, or suggesting that an infringing use should be performed.

Takeda Pharm. U.S.A., Inc. v. West-Ward Pharm. Corp., 785 F.3d 625, 630-31 (Fed. Cir. 2015) (citations, footnote, and internal quotation marks omitted). The *Takeda* court went on to discuss the applicability of these principles "in the Hatch-Waxman context where, as here, it is alleged that the drug label induces infringement by physicians." *Id.* at 631. The *Takeda* court stated:

> The label must encourage, recommend, or promote infringement. The mere existence of direct infringement by physicians, while necessary to find liability for induced infringement, is not sufficient for inducement. As we stated in [a prior case] in the ANDA context, it is well-established that mere knowledge of possible infringement by others does not amount to inducement; specific intent and action to induce must be proven.

Id. (internal citations and quotation marks omitted).

ii. Contributory Infringement

Under 35 U.S.C. § 271(c),

> Whoever offers to sell or sells within the United States or imports into the United States a component of a patented machine, manufacture, combination or composition, or a material or apparatus for use in practicing a patented process, constituting a material part of the invention, knowing the same to be especially made or especially adapted for use in an infringement of such patent, and not a staple article or commodity of commerce suitable for substantial noninfringing use, shall be liable as a contributory infringer.

Contributory infringement is found where: (1) there is direct infringement; (2) the accused infringer had knowledge of the patent at issue; (3) the product has no substantial non-infringing uses; and (4) the product is a material part of the invention. *Fujitsu Ltd. v. Netyear Inc.*, 620 F.3d 1321, 1326 (Fed. Cir. 2010).

Once a patentee has made out a *prima facie* showing that a product is not "suitable for substantial non-infringing use," the burden then shifts to the accused infringer to demonstrate otherwise. *Golden Blount, Inc. v. Robert H. Peterson Co.*, 438 F.3d 1354, 1363 (Fed. Cir. 2006). A non-infringing use is "substantial" if it is "not unusual, far-fetched, illusory, impractical, occasional, aberrant, or experimental." *Vita-Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317, 1327 (Fed. Cir. 2009). The inquiry is "essentially a quantitative one"—"substantial non-infringing use can be shown when 'a significant number of [uses] would be non-infringing.'" *Pickholtz v. Rainbow Techs., Inc.*, 260 F. Supp. 2d 980, 989 (N.D. Cal. 2003) (quoting *Sony Corp. of Am. V. Universal Studios*, 464 US 417, 443 (1984)).

B. INVALIDITY

Issued patents are presumed valid. *See* 35 U.S.C. § 282. To rebut this presumption, Defendants bear the burden of proving invalidity by clear and convincing evidence. *Titan Tire*

Corp. v. Case New Holland, Inc., 566 F.3d 1372, 1376 (Fed. Cir. 2009) ("Because of this presumption, an alleged infringer who raises invalidity as an affirmative defense has the ultimate burden of persuasion to prove invalidity by clear and convincing evidence, as well as the initial burden of going forward with evidence to support its invalidity allegation.").

i. **Utility – 35 U.S.C. § 101**

The utility requirement is established in 35 U.S.C. § 101 ("Whoever invents or discovers any new and *useful* process, machine, manufacture, or composition of matter . . . ." (emphasis added)). A "patent may not be granted to an invention unless substantial or practical utility for the invention has been discovered and disclosed." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1563 (Fed. Cir. 1996). It is the claims that "define the invention to be tested for utility." *Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 956 (Fed. Cir. 1983).

"The threshold of utility is not high: An invention is 'useful' under section 101 if it is capable of providing some identifiable benefit." *Juicy Whip, Inc. v. Orange Bang, Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). An application need only "show that an invention is useful" and "disclose a use which is not so vague as to be meaningless." *In re Fisher*, 421 F.3d 1365, 1371 (Fed. Cir. 2005). To lack utility, "the claimed device must be totally incapable of achieving a useful result." *Juicy Whip*, 185 F.3d at 1366 (internal citation omitted).

With respect to pharmaceutical patents, the Federal Circuit "has long held that practical utility may be shown by adequate evidence of any pharmacological activity." *Fujikawa*, 93 F.3d at 1564. The Federal Circuit further noted:

> It may be difficult to predict, however, whether a novel compound will exhibit pharmacological activity, even when the behavior of analogous compounds is known to those skilled in the art. Consequently, testing is often required to establish practical utility. But the test results need not absolutely prove that the compound is pharmacologically active. All that is required is that the tests be *reasonably* indicative of the desired pharmacological response. In

> other words, there must be a sufficient correlation between the tests and an asserted pharmacological activity so as to convince those skilled in the art, to a reasonable probability, that the novel compound will exhibit the asserted pharmacological behavior.

Id. (internal quotations and citations omitted).

ii. Anticipation – 35 U.S.C. § 102

1. Anticipation

A reference is anticipatory under 35 U.S.C. § 102(b) if "the prior art reference . . . disclose[s] each and every feature of the claimed invention, either explicitly or inherently." *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1375 (Fed. Cir. 2006) (citation omitted). Whether a prior art reference anticipates a patent claim is a question of fact and must be proven by clear and convincing evidence. *See Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000).

2. Inherent Anticipation

Under 35 U.S.C. § 102, "a [claim] limitation or the entire invention is inherent and in the public domain if it is the 'natural result flowing from' the explicit disclosure of the prior art." *Schering Corp. v. Geneva Pharm., Inc.*, 339 F.3d 1373, 1379 (Fed. Cir. 2003) (quoting *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 970 (Fed. Cir. 2001)). "[A]nticipation by inherent disclosure is appropriate only when the reference discloses prior art that must *necessarily* include the unstated limitation . . . ." *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002). "Inherency, however, *may* not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Cont'l Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991) (internal quotation marks and citations omitted). To prove inherent anticipation, a party must show that, though a feature of the invention is not explicitly disclosed in the prior art, it "necessarily and inevitably" flows from

practice of the prior art. *See Schering Corp.*, 339 F.3d at 1379. "Inherent anticipation requires that the missing descriptive material is 'necessarily present,' not merely probably or possibly present, in the prior art." *Trintec Indus., Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1295 (Fed. Cir. 2002). Therefore, if the teachings of the prior art can be practiced in a way that yields a product lacking the allegedly inherent property, the prior art in question does not inherently anticipate. *See Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047-48 (Fed. Cir. 1995) (finding no inherent anticipation where testing evidence demonstrated that the prior art example could yield crystals of either the claimed polymorph or a different polymorph).

iii. Obviousness – 35 U.S.C. § 103

To prove that an asserted claim of a patent is invalid as obvious under 35 U.S.C. § 103, Defendants bear the burden of establishing by clear and convincing evidence that the "differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious to a person having ordinary skill in the art." 35 U.S.C. § 103(a). Obviousness is a question of law that is predicated on several factual inquiries. *See Richardson-Vicks v. Upjohn Co.*, 122 F.3d 1476, 1479 (Fed. Cir. 1997). Specifically, there are four considerations: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) secondary considerations of non-obviousness, such as long-felt but unsolved need, failure of others, praise by others in the industry, and unexpected results. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

A party challenging the validity of a patent based on obviousness must demonstrate by clear and convincing evidence that the invention described in the patent would have been obvious to a POSA at the time the invention was made. In determining what would have been obvious to a POSA, the use of hindsight is not permitted. *See KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398,

421 (2007) (cautioning against "the distortion caused by hindsight bias" and "arguments reliant upon *ex post* reasoning"). In *KSR*, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *Id.* at 418-19.

"Obviousness does not require absolute predictability of success," but rather, requires "a reasonable expectation of success." *See Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (quoting *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988)). Obviousness "cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). While the Federal Circuit has noted that pharmaceuticals can be an "unpredictable art" to the extent that results may be unexpected, it also recognizes that evidence of a "finite number of identified, predictable solutions" or alternatives "might support an inference of obviousness." *See Eisai Co. Ltd. v. Dr. Reddy's Labs. Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008).

iv. <u>Enablement – 35 U.S.C. § 112</u>

A patent specification must contain a written description "of the manner and process of making and using [the invention], in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains . . . to make and use the same . . . ." 35 U.S.C. § 112. To be enabled, the specification must teach a POSA "how to make and use the full scope of the claimed invention without undue experimentation." *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1378 (Fed. Cir. 2009) (citation omitted). A patentee need not "include in the specification that which is already known and available to [a POSA]" and "not every last detail is to be described, else patent specifications would turn into production specifications, which they

were never intended to be." *Koito Mfg. Co. v. Turn-Key-Tech, LLC*, 381 F.3d 1142, 1156 (Fed. Cir. 2004) (citation omitted).

"Enablement is not precluded by the necessity for some experimentation such as routine screening." *In re Wands*, 858 F.2d 731, 736-37 (Fed. Cir. 1988). Furthermore, the test for undue experimentation "is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Id.* at 737 (citation omitted). The *Wands* factors that may be considered in determining whether a disclosure would require undue experimentation include: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. *Id.*

v. **Written Description – 35 U.S.C. § 112**

A patent's specification must "contain a written description of the invention." 35 U.S.C. § 112. The specification must "reasonably convey[] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharm. Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). The test for written description "requires an objective inquiry into the four corners of the specification from the perspective of a [POSA]." *Id.*

"[W]hether a patent complies with the written description requirement will necessarily vary depending on the context. Specifically, the level of detail required . . . varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology." *Id* (citation omitted). Regarding new compounds, an adequate written description "requires a precise definition, such as by structure, formula, chemical name, physical properties, or other properties . . ." *Id.* at 1350.

vi. Original Patent – 35 U.S.C. § 251

A patentee is precluded from obtaining a reissue patent to cover any invention other than "the invention disclosed in the original patent." 35 U.S.C. § 251. A reissue application must find support in the original patent's description such that the original description "clearly allow[s] persons of ordinary skill in the art to recognize that the inventor invented what is claimed." *Antares Pharma, Inc. v. Medac Pharma Inc.*, 771 F.3d 1354, 1362 (Fed. Cir. 2014) (citation omitted). The original patent rule requires that new claims must be to matter "explicitly disclosed and taught" rather than merely "suggested or indicated in the specification." *Id.* at 1361.

vii. Obviousness-Type Double Patenting

The judicially created doctrine of obviousness-type double patenting exists to prevent a patentee from securing a second patent on the same or obvious variation of an earlier-expiring patent claim, and thus improperly extending the right to exclude others from practicing the invention. *Abbvie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Trust*, 764 F.3d 1366, 1373-74 (Fed. Cir. 2014). Obviousness-type double patenting is analyzed by first construing the two claims and then determining whether the differences between the earlier and later claim render the later-expiring claim patentably distinct from the earlier-expiring claim. *Id.* at 1374. The question of whether the claims are patentably distinct is based on a POSA's understanding as of the filing date of the later-expiring claim. *Amgen Inc. v. Hoffman-LaRoche Ltd.*, 580 F.3d 1340, 1355 (Fed. Cir. 2009).

C. UNENFORCEABILITY

i. Unclean Hands

The doctrine of unclean hands is based on "the equitable maxim that 'he who comes into equity must come with clean hands.'" *Precision Instrument Mfg. Co. v. Auto. Maint. Mach. Co.*, 324 U.S. 806, 814 (1945). This doctrine operates to prevent litigants who have themselves

engaged in misconduct from prevailing on claims in equity. "As an equitable doctrine, application of unclean hands rests within the sound discretion of the trial court." *In re New Valley Corp.*, 181 F.3d 517, 525 (3d Cir. 1999); *see also Precision Instrument*, 324 U.S. at 815 ("This maxim necessarily gives wide range to the equity court's use of discretion in refusing to aid the unclean litigant. It is 'not bound by formula or restrained by any limitation that tends to trammel the free and just exercise of discretion.'" (quoting *Keystone Driller Co. v. Gen. Excavator Co.*, 290 U.S. 240, 245 (1933)).

Courts of equity "apply the maxim requiring clean hands only where some unconscionable act of one coming for relief has immediate and necessary relation to the equity that he seeks in respect of the matter in litigation." *See Keystone Driller*, 290 U.S. at 245. "Any willful act concerning the cause of action which rightfully can be said to transgress equitable standards of conduct is sufficient cause for the invocation of the maxim . . . ." *Precision Instrument*, 324 U.S. at 815.

In the patent context, the doctrine of unclean hands may render a patent unenforceable by a patentee who has engaged in misconduct in practicing before the United States Patent and Trademark Office ("USPTO"). *See generally Therasense, Inc. v. Becton, Dickinson & Co.*, 649 F.3d 1276, 1306-07 (Fed. Cir. 2011). In this context, an unclean hands defense must be evaluated with an eye toward the nature of patent prosecution, which is an ex parte non-adversarial proceeding in which the USPTO relies heavily on the applicant's duty to disclose information material to patentability. *See* 37 C.F.R. § 1.56 ("Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the [USPTO], which includes a duty to disclose to the [USPTO] all information known to that individual to be material to patentability . . . ."). The Supreme Court has noted:

> By reason of the nature of an application for patent, the relationship of attorneys to the [USPTO] requires the highest degree of candor and good faith. In its relation to applicants, the [USPTO] . . . must rely upon their integrity and deal with them in a spirit of trust and confidence.

Kingsland v. Dorsey, 338 U.S. 318, 319-20 (1949); *see also U.S. Indus. v. Norton Co.*, Case No. 80-359, 1980 U.S. Dist. LEXIS 16801, at *37-38 (N.D.N.Y Oct. 22, 1980) ("Given . . . the recognition that patent prosecutions are *ex parte*, non-adversarial proceedings, a relationship of trust exists between the applicant and the [USPTO]. The trust relationship is essential to a workable patent system because the [USPTO] is compelled to rely on the applicants for disclosure of many of the facts upon which its decisions are based. Consequently, the highest standards of honesty, good faith and candor by the applicants is required." (internal citations omitted)).

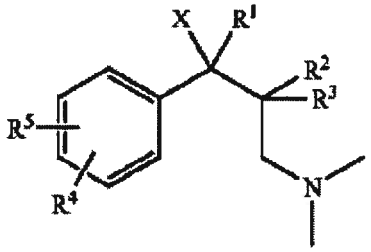
The doctrine of unclean hands generally requires a showing of intent. *See Therasense*, 649 F.3d at 1290. "Because direct evidence of deceptive intent is rare, a district court may infer intent from indirect and circumstantial evidence." *Id.*; *see also Bankers Trust Co. of W. N.Y. v. Crawford*, 781 F.2d 39, 44 (3d Cir. 1986) ("Bad faith may be established by circumstantial evidence and each case must depend on its peculiar facts."). "But deceptive intent must be 'the single most reasonable inference drawn from the evidence.'" *Ohio Willow Wood Co. v. Alps S., LLC*, 813 F.3d 1350, 1358 (Fed. Cir. 2016) (quoting *Therasense*).

IV. DISCUSSION

A. '593 PATENT – INVALIDITY

Plaintiffs have asserted claims 8, 61, 117, and 147 of the '593 patent. Defendants contend that each of these claims is invalid. As discussed above, to rebut the presumption that the '593 patent is valid, Defendants bear the burden of proving invalidity by clear and convincing evidence. *Titan Tire*, 566 F.3d at 1376.

Claim 8 is a method claim directed to "a method of treating a mammal suffering from pain" comprising administering a compound that is a member of a genus of 1-phenyl-3-dimethylaminopropane chemical compounds:

> **8.** A method of treating a mammal suffering from pain, said method comprising administering to said mammal an effective analgesic amount of a 1-phenyl-3-dimethyl-aminopropane compound corresponding to formula I
>
> I
>
> 
>
> wherein
>
> X represents OH, F, Cl, H or an $OCOR^6$ group in which R^6 is a C_{1-3}-alkyl group;
>
> R^1 is a C_{1-4}-alkyl group;
>
> R^2 represents H or a C_{1-4}-alkyl group and R^3 represents H or a straight chain C_{1-4}-alkyl group, or R^2 and R^3 together form a C_{4-7} cycloalkyl radical, and
>
> R^5 represents H, and R^4 represents meta-O—Z,
> where Z is H, C_{1-3}-alkyl, $PO(OC_{1-4}alkyl)_2$, $CO(OC_{1-5}$-alkyl), $CONH—C_6H_4—(C_{1-3}$-alkyl) or $CO—C_6H_4—R^7$, in which R^7 is ortho-$OCOC_{1-3}$-alkyl or meta- or para-$CH_2N(R^8)_2$, where R^8 is C_{1-4}-alkyl or 4-morpholino,
>
> or R^4 represents meta-S—C_{1-3}-alkyl, meta-Cl, meta-F, meta-$CR^9R^{10}R^{11}$, ortho-OH, ortho-O—C_{2-3}-alkyl, para-F or para-$CR^9R^{10}R^{11}$, where R^9, R^{10} and R^{11} independently represent H or F, or
>
> R^5 represents para-Cl, para-F, para-OH or para-O—C_{1-3}-alkyl, and R^4 represents meta-Cl, meta-F, meta-OH or meta-O—C_{1-3}-alkyl, or
>
> R^4 and R^5 together represent 3,4-OCH=CH— or 3,4-OCH=CHO—, or a salt thereof with a physiologically acceptable acid.

['593 patent at 24:64-25:34.] It is undisputed that tapentadol hydrochloride is one of the chemical compounds that is within the scope of the genus in claim 8. [*See* '593 patent at 19:12-22.] Specifically, tapentadol hydrochloride is a chemical compound of claim 8, wherein:

> X represents H (hydrogen);
> R^1 is a C_2 alkyl group (ethyl group);
> R^2 represents H (hydrogen);
> R^3 represents a C_1 alkyl group (methyl group);
> R^4 represents a meta-OH group (hydroxyl group);
> R^5 represents H (hydrogen); and
> the "salt thereof" is hydrochloride.

[*Compare* '593 patent at 25:1-34, *with* '593 patent at 19:12-22.]

Claim 61 is a species claim directed to the chemical compound tapentadol hydrochloride:

> ***61. (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride (−21).***

['593 patent at 32:19-20.]

Claim 117 is a dependent claim, depending from method claim 8, wherein the specific compound to be administered is tapentadol hydrochloride:

> ***117. A method according to claim 8, wherein the compound is (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride (−21).***

['593 patent at 38:8-10.]

Claim 147 is directed to a pharmaceutically acceptable salt of tapentadol:

> ***147. A pharmaceutically acceptable salt of (−)-(1R,2R)-3R-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol.***

['593 patent at 40:31-32.] The hydrochloride salt of tapentadol (*i.e.* tapentadol hydrochloride) is one such pharmaceutically acceptable salt.

i. '593 Patent Obviousness

Defendants contend that asserted claims 8, 61, 117, and 147 of the '593 patent are invalid for obviousness under 35 U.S.C. § 103. [PTO ¶¶ 1463, 989-1119.] Defendants bear the burden of proving by clear and convincing evidence that the invention described in the asserted claims of the '593 patent—tapentadol hydrochloride and its use to treat pain—would have been obvious to a POSA in 1994 at the time the invention was made. *See KSR*, 550 U.S. at 413.

Defendants' obviousness contentions are based on the "lead compound" analysis that the Federal Circuit has established for determining obviousness of chemical compounds. [PTO ¶¶ 991-1081; Defendants' Post-Trial Brief ("Defs. Br.") at 2.] On this issue, Defendants presented the expert testimony of Dr. Steven Martin, who opined that the prior art would have motivated a POSA to select tramadol as a lead compound and then modify it to arrive at the claimed invention, tapentadol hydrochloride. [*See generally* 3/16 Tr. (Martin) at 161:17-286:9; 3/17 Tr. (Martin) at 4:17-131:1.]

Plaintiffs contend that Defendants' obviousness analysis is improperly driven by hindsight. [PTO ¶¶ 367-517; Plaintiffs' Post-Trial Brief ("Pls. Br.") at 16.] On this issue, Plaintiffs presented the expert testimony of Dr. William Roush, who testified credibly that the prior art would not have motivated the selection of tramadol (either as a racemic mixture, its individual enantiomers, or its metabolites) as a lead compound. Dr. Roush further testified that, even had a POSA begun with tramadol as a lead compound, the prior art did not motivate the modifications necessary to arrive at tapentadol hydrochloride. [*See generally* 3/22 a.m. Tr. (Roush) at 49:18-136:5; 3/22 p.m. Tr. (Roush) at 4:3-161:20.]

1. The law of chemical obviousness

In describing its "lead compound" analysis, the Federal Circuit has stated:

> Proof of obviousness based on structural similarity requires clear and convincing evidence that a medicinal chemist of ordinary skill would have been motivated to select and then to modify a prior art compound (*e.g.*, a lead compound) to arrive at a claimed compound with a reasonable expectation of success that the new compound would have similar or improved properties compared with the old.

Daiichi Sankyo Co. v. Matrix Labs., Ltd., 619 F.3d 1346, 1352 (Fed. Cir. 2010) (citations omitted). Thus, the two step analysis requires a showing by clear and convincing evidence that (1) "a chemis [17] of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts," and (2) "the prior art would have supplied one of ordinary skill in the art with a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success." *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291-92 (Fed. Cir. 2012) (citations omitted).

2. Analysis of the chemical obviousness of tapentadol hydrochloride

For the reasons that follow, the Court finds that Defendants have not met their burden of proving either element of the lead compound analysis by clear and convincing evidence. First, Defendants have not clearly and convincingly shown that a POSA would have selected tramadol or its metabolites as lead compounds. Second, Defendants have not clearly and convincingly shown that the prior art motivates the modifications necessary to convert the lead compound (tramadol) to the claimed invention (tapentadol hydrochloride).

a. Selection of tramadol as a lead compound

The problem that the inventors addressed and solved by the inventions claimed in the '593 patent was the discovery of new analgesics. The patent's specification describes this

[17] The parties are in substantial agreement as to the definition of a POSA with respect to the '593 patent, which would include education and experience in organic chemistry, medicinal chemistry, and synthesizing organic compounds. [*See* PFOF ¶ 252; DFOF ¶ 7.]

purpose, noting that "the treatment of chronic and non-chronic pain conditions is of great importance in medicine." [PFOF ¶ 253; PTX-312 at 1:19-57.]

In developing a new analgesic, a POSA in 1994 would have been interested in optimizing analgesic potency of a drug in order to administer lower doses of the drug and thereby minimize side effects resulting from off-target properties. [PFOF ¶ 256; 3/22 a.m. Tr. (Roush) at 73:19-22, 75:16-25.] A POSA would have also been interested in reducing side effects, but would have recognized that no drug is completely safe, in part because no drug binds cleanly to only one biological target. [PFOF ¶ 257; 3/17 Tr. (Martin) at 85:1-25.] A POSA would have therefore recognized that, in choosing a starting point for developing a new analgesic, every potential drug would have had problems that a POSA would have sought to overcome through investigation of the structure-activity relationship ("SAR") of the drug. [PFOF ¶ 259; 3/22 a.m. Tr. (Roush) at 76:1-10.]

i. Selection of tramadol from among the large universe of potential starting points

In selecting a lead compound for further development of an improved analgesic, a POSA would become familiar with the universe of compounds that have analgesic activity. [DFOF ¶ 9; 3/16 Tr. (Martin) at 187:21-188:11.] A POSA would investigate the analgesic properties of those compounds, including the mechanisms of analgesic activity and the known side effects. [*Id.*]

A POSA in 1994 had a large universe of potential compounds from which to choose a starting point. The '593 patent lists a number of classes of compounds known to treat chronic and non-chronic pain conditions, including opioids and other compounds such as tramadol, as examples previously known in the art. [PFOF ¶ 253; PTX-312 at 1:19-57.] The prior art includes publications disclosing several classes of compounds of which a POSA would have known and from which a POSA could have chosen a lead compound for developing a new analgesic. [PFOF

¶ 254; 3/22 a.m. Tr. (Roush) at 68:13-69:11.] Each class of compounds can be defined in terms of its mechanisms of action or in terms of its biological targets for achieving analgesia. [PFOF ¶ 254; 3/22 a.m. Tr. (Roush) at 69:3-6.]

One class of compounds from which a POSA could have chosen a starting point for developing a new analgesic was morphine derivatives. [PFOF ¶ 255; 3/22 a.m. Tr. (Roush) at 71:17-72:11.] It was well known that morphine analogues could be developed into new analgesics. [PFOF ¶ 255; 3/22 a.m. Tr. (Roush) at 71:17-72:11; *see generally* PTX-188; PTX-1055).] In developing morphine analogues, medicinal chemists had tried to simplify the morphine core structure by removing functional groups from it. [PFOF ¶ 255; 3/22 a.m. Tr. (Roush) at 72:12-23; 3/16 Tr. (Martin) at 204:5-18, 262:22-25, 267:4-7.] Medicinal chemists had also tried to add complexity to the morphine core structure by adding functional groups to it. [PFOF ¶ 255; 3/22 a.m. Tr. (Roush) at 72:23-73:17; 3/17 Tr. (Martin) at 99:5-10.] Many analogues of morphine were known to be more potent than morphine. [PFOF ¶ 258; 3/22 a.m. Tr. (Roush) at 73:23-74:25; PTX-1055.] While morphine and its derivatives were known to have side effects, such side effects would not have dissuaded a POSA from choosing morphine or its derivatives as a starting point. [PFOF ¶ 259; 3/22 a.m. Tr. (Roush) at 75:8-25.]

Additional classes of compounds that a POSA would have been motivated to investigate when choosing a starting point for developing a new analgesic were opioid agonists, including *mu*-opioid agonists, *kappa*-opioid agonists, and *delta*-opioid agonists. [PFOF ¶¶ 260-65; 3/22 a.m. Tr. (Roush) at 76:15-84:9, DFOF ¶ 10; 3/16 Tr. (Martin) at 189:7-12; PTX-139; PTX-188; PTX-1055.] One prior art *mu*-opioid agonist (4-aryl-4-dimethylaminocyclohexane) was known to be 10,000 times more potent than morphine. [PFOF ¶ 262; 3/22 a.m. Tr. (Roush) at 78:11-79:3; PTX-1055 at 391.] *Kappa*-opioid and *delta*-opioid agonists were known to have advantages over

mu-opioid agonists, such as reduction or elimination of side effects including respiratory depression, cardiac toxicity, dependency, addiction, and constipation. [PFOF ¶¶ 263-64; 3/22 a.m. Tr. (Roush) at 81:7-83:22; PTX-188 at ALK_TAP_0000424; PTX-139 at ACT-TAP0186379.]

A POSA would also have been motivated to investigate additional classes of compounds, such as cannabinoids (which a POSA would have expected to have different activities and side effects from opioids) [PFOF ¶ 266; 3/22 a.m. Tr. (Roush) at 84:10-85:9], non-steroidal anti-inflammatory drugs ("NSAIDs"), specific COX-2 inhibitors [PFOF ¶ 267; 3/22 a.m. Tr. (Roush) at 85:10-86:9], α_2-adrenoceptor (*i.e.*, norepinephrine) reuptake antagonists, tricyclic antidepressants, and GABA receptor agonists [PFOF ¶ 268; 3/22 a.m. Tr. (Roush) at 86:10-87:12].

Finally, a POSA could have investigated the family of compounds known to exhibit polypharmacology. [PFOF ¶ 269; 3/22 a.m. Tr. (Roush) at 87:13-88:10.] These compounds exhibit multiple mechanisms of analgesic action by interacting with more than one analgesic receptor target, cooperatively contributing to the compounds' analgesic activity. [PFOF ¶ 269; 3/22 a.m. Tr. (Roush) at 87:13-88:10; *see also* PTX-139.] Of the class of compounds exhibiting pharmacology, compounds exhibiting both opioid and non-opioid activity, such as tramadol, are just one subset. [*See* PFOF ¶ 269; *Cf.* 3/22 p.m. Tr. (Roush) at 50:17-20.]

From this large number of potential starting compounds, Defendants focus their arguments on tramadol and its metabolites. [Defs. Br. at 3.] Tramadol is a compound known to exhibit polypharmacology. [PFOF ¶ 269; DFOF ¶ 11; 3/16 Tr. (Martin) at 190:23-192:19; 3/22 a.m. Tr. (Roush) at 93:22-94:3; 3/10 Tr. (Buschmann) at 89:14-90:3.] Specifically, tramadol is known to possess both opioid and non-opioid activities. [PFOF ¶ 269; DFOF ¶ 11; 3/16 Tr. (Martin) at 190:23-192:19; 3/22 a.m. Tr. (Roush) at 93:22-94:3; 3/10 Tr. (Buschmann) at 89:14-90:3. DTX-1027_0004; DTX-866.] As of 1994, tramadol was the only such compound that was known

to be safe and effective based on clinical trials in humans and approved for sale in Europe. [DFOF ¶ 12; 3/22 p.m. Tr. (Roush) at 66:5-71:15; DTX-2059; DTX-2060.] Defendants argue, based on the testimony of Dr. Martin, that because tramadol was "atypical" in its possession of both opioid and non-opioid activities, a POSA would have been motivated to investigate it as a lead compound. [Defs. Br. at 4; DFOF ¶ 20; 3/16 Tr. (Martin) at 190:23-192:23, 194:25-195:13; *see also* DFOF ¶¶ 9-43.]

Defendants' argument assumes that a POSA would have been specifically motivated to investigate compounds with polypharmacology and more specifically compounds possessing both opioid and non-opioid activities. [*See* 3/16 Tr. (Martin) at 223:5-6 ("I think initially our goal was to find something with the dual mode of action.").] Defendants' expert, however, did not provide a sufficient explanation for this assumption. Plaintiffs' expert, Dr. Roush, opined that Dr. Martin's focus on this opioid/non-opioid combination as the driving factor for lead compound selection was driven by hindsight—*i.e.*, he worked backwards from his knowledge that the patented invention, tapentadol hydrochloride, possesses both opioid and non-opioid activity. [3/22 a.m. Tr. (Roush) at 70:11-71:8; 92:15-93:5.] Further, Plaintiffs presented evidence that a POSA would have been dissuaded from starting with compounds exhibiting polypharmacology because the unpredictable effects of structural changes on a compound's biological function are often multiplied when multiple mechanisms of action are involved. [PFOF ¶ 270; 3/22 p.m. Tr. (Roush) at 158:21-159:14.]

The evidence showed it was publicly known that many pharmaceutical firms were actively seeking to develop new analgesics as of July 1994. [PFOF ¶ 287; 3/10 Tr. (Buschmann) at 52:24-54:25; 3/22 a.m. Tr. (Roush) at 89:2-90:9, 91:19-22; 3/22 p.m. Tr. (Roush) at 4:3-7:15; DTX-1144_0018-25.] At least 52 different analgesic drug development efforts were ongoing at

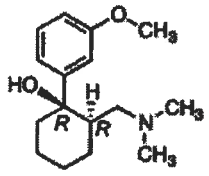
that time, with researchers investigating a variety of biological pathways. [*Id.*] Only Grünenthal began with tramadol as a starting point. [PFOF ¶ 288; 3/10 Tr. (Buschmann) at 52:24-54:25; 3/22 a.m. Tr. (Roush) at 91:19-22; 3/22 p.m. Tr. (Roush) at 6:22-7:6. In fact, Dr. Buschmann testified that Grünenthal's internal choice to pursue a compound with multiple mechanisms of action was regarded as risky because most pharmaceutical companies screen potential drug candidates to focus on the development of single-molecule drugs with activity optimized for a single target. [PFOF ¶ 107; 3/10 Tr. (Buschmann) at 13:17-14:20.]

In light of the evidence presented, Defendants have not proven by clear and convincing evidence that a POSA would have been motivated to select tramadol as a lead compound from among the vast number of potential starting points.

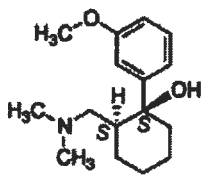
ii. Selection of (-)-ODMT from among the four compounds of tramadol and ODMT

As explained above, tramadol can be viewed as a mixture of four compounds—the two enantiomers of tramadol and the metabolite of each. [DFOF ¶ 21; 3/16 Tr. (Martin) at 197:8-200:6.] The tramadol mixture of enantiomers, the ODMT mixture of enantiomers, and each of the four individual compounds were studied in the prior art for their analgesic activity. [DFOF ¶ 22; 3/16 Tr. (Martin) at 200:12-24.] The following is a summary of the evidence Dr. Martin presented about the prior art teachings:

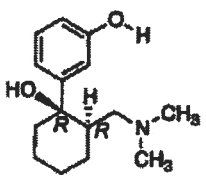
Date	Prior Art	Summary
1978	Flick	Racemic tramadol and O-desmethyltramadol
1978	Frankus	Tramadol, two enantiomers of tramadol, cis- form of tramadol
1988	Hennies	Racemic tramadol and O-desmethyltramadol
1992	Driessen I	Racemic tramadol, two enantiomers of tramadol, racemic O-desmethyltramadol
1993	Driessen II	Racemic tramadol, two enantiomers of tramadol, racemic O-desmethyltramadol
1992	Raffa I	Racemic tramadol
1993	Raffa II	Racemic tramadol, two enantiomers of tramadol
1993	Sevcik	Enantiomers of tramadol and O-desmethyltramadol



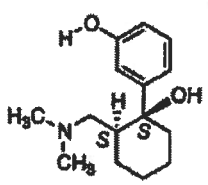
(+)-tramadol



(–)-tramadol



(+)-O-desmethyltramadol



(–)-O-desmethyltramadol

[*See* 3/16 Tr. (Martin) at 200:25-202:6; Martin Demonstrative at 17.] From the evidence presented, Defendants contend that a POSA would have determined that the (–) enantiomer of ODMT (also known as "S,S-ODMT") would be the most promising individual compound to select as a lead compound. [DFOF ¶ 39; 3/16 Tr. (Martin) at 222:22-224:2; Martin Demonstrative at 20.] Defendants' contention is based on Dr. Martin's analysis of the prior art teachings that S,S-ODMT had a dual mechanism of action, that no metabolism of S,S-ODMT is necessary because it already lacks the aryl methyl group, that it is more active than R,R-Tramadol, and that it has low serotonin activity. [*See* DFOF ¶¶ 22-39; 3/16 Tr. (Martin) at 200:25-222:21; Martin Demonstrative at 20; DTX-691; DTX-758; DTX-694; DTX-733; DTX-736.] Defendants assert that Dr. Martin's analysis was based exclusively on references which qualify as prior art to the '593 patent and he

did not use hindsight driven analysis in reaching his opinions. [DFOF ¶¶ 40-43; 3/16 Tr. (Martin) at 224:3-225:11.]

Plaintiffs presented evidence that a POSA would not have been motivated to separate the enantiomers of tramadol. [*See generally* PFOF ¶¶ 276-281; 3/22 a.m. Tr. (Roush) at 94:4-23.] Specifically, because it was known that the different enantiomers and metabolite enantiomers exhibited different mechanisms of action, it was necessary to administer both enantiomers of tramadol. [PFOF ¶¶ 276-77; 3/22 a.m. Tr. (Roush) at 94:4-23; Roush Demonstrative at 18; PTX-57; DTX-691; DTX-694; DTX-736; DTX-758; DTX-866.] In fact, the prior art taught that the antinociceptive action of tramadol resulted from a complimentary and synergistic interaction of the enantiomers and metabolites. [PFOF ¶¶ 277-78; 3/22 a.m. Tr. (Roush) at 94:19-23; PTX-57; 3/17 Tr. (Martin) at 65:9-66:17.] The evidence showed that prior to July 1994, all known clinical use of tramadol involved administration of both enantiomers, with no evidence of the individual enantiomers of tramadol ever being clinically administered separately. [PFOF ¶ 281; 3/17 Tr. (Martin) at 61:19-24.]

Plaintiffs also presented evidence that a POSA would not have had an expectation of successfully obtaining all three of tramadol's mechanisms of action by administering only one of the enantiomers or metabolites. [*See generally* PFOF ¶¶ 282-289; 3/22 a.m. Tr. (Roush) at 94:22-98:23; Roush Demonstrative at 18-19.] As explained above, tramadol exhibits three mechanisms of action—(1) *mu*-opioid activity, (2) norepinephrine reuptake inhibition, and (3) serotonin reuptake inhibition. [PFOF ¶¶ 92-93; 3/22 a.m. Tr. (Roush) at 93:8-94:23, 99:2-101:11; PTX-57; DTX-1027.] The tramadol enantiomers affect these three targets to different degrees. [PFOF ¶¶ 92-93; 3/22 a.m. Tr. (Roush) at 93:8-94:23, 99:2-101:11; PTX-57; DTX-1027.] Plaintiffs' expert opined that a POSA would not have been motivated to select one of the

enantiomers (or metabolites) and modify it so as to produce the results that could simply be achieved by administering the racemic mixture. [PFOF ¶¶ 282-283; 3/22 a.m. Tr. (Roush) at 94:22-96:20, 119:3-120:14.]

Ultimately, Plaintiffs' evidence demonstrated that the clinical profile of tramadol was known to result from the fortuitous interaction of the tramadol enantiomers on analgesia but not on side effects. [PFOF ¶ 280; 3/22 a.m. Tr. (Roush) at 100:13-21; 3/17 Tr. (Martin) at 67:25-68:11; PTX-57.] Defendants have not proven by clear and convincing evidence that a POSA investigating tramadol would have been motivated to specifically choose as a starting point the (-)-ODMT compound over the other three compounds in the tramadol mixture.

b. Modification of tramadol to achieve tapentadol

By 1978, the SAR of tramadol had been studied extensively, as documented in a paper by researchers named K. Flick, E. Frankus, and E. Friedrichs. [DFOF ¶¶ 44-46; DTX-715 (German); DTX-834 (English)[18]; 3/16 Tr. (Martin) at 227:25-230:3.] Defendants contend that, based on the findings of *Flick* and others about the SAR of tramadol, a POSA would have identified the "pharmacophore"—the structural components of tramadol that were essential for biological activity and therefore should not be altered. [DFOF ¶¶ 44-47; *Flick* at DTX-834_0012-15; 3/16 Tr. (Martin) at 229:25-230:3.]

Defendants' expert, Dr. Martin, opined that the prior art would have informed a POSA that the tramadol pharmacophore consists of three elements. [*See generally* DFOF ¶¶ 47-62; 3/16 Tr. (Martin) at 230:4-261:16].

1. Dr. Martin opined that the first element of the tramadol pharmacophore is the dimethylamino group, which was known to significantly interact with the opioid

[18] This Opinion will refer to DTX-834, which is the English version of the paper, as "*Flick*."

receptor. [*See* DFOF ¶¶ 48-50; 3/16 Tr. (Martin) at 230:4-240:8; *Flick* at Table 3, DTX-834_0012 ("The analgesic activity is associated with the dimethylamino group. The replacement of one or both methyl groups with hydrogen eliminates the activity. Substitution with higher alkyl groups or with substituents in which the nitrogen was integrated into a ring system also leads to loss of effect.").]

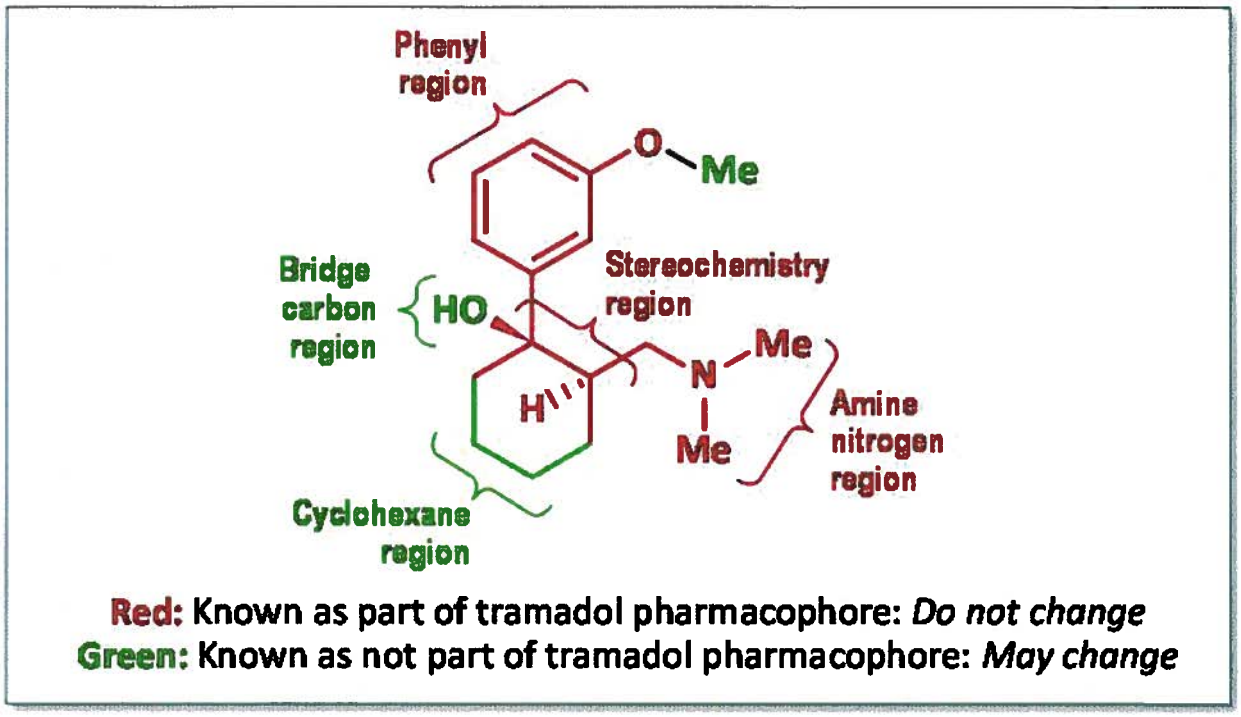
2. Dr. Martin opined that the second element of the pharmacophore is the aromatic oxygen substituent, which *Flick* teaches should either be meta-hydroxy or meta-methoxy. [*See* DFOF ¶¶ 51-54; 3/16 Tr. (Martin) at 247:2-252:13; *Flick* at Table 5.]
3. Dr. Martin opined that the third element of the tramadol pharmacophore is the relative stereochemistry. [*See* DFOF ¶¶ 57-59; 3/16 Tr. (Martin) at 254:13-258:3; DTX-717 (German); DTX-2052 (English).[19]]

After identifying the tramadol pharmacophore, Dr. Martin posited that a POSA would have been motivated to investigate changing the other elements of tramadol—*i.e.*, those elements that were not part of the pharmacophore.

1. One change Dr. Martin discussed was the substitution on the aromatic oxygen. [*See* DFOF ¶¶ 52-54; 3/16 Tr. (Martin) at 247:2-252:13, 261:3-5; *Flick* at Table 5.]
2. A second change Dr. Martin proposed investigating was the substitution on the bridge carbon. [*See* DFOF ¶¶ 55-56; 3/16 Tr. (Martin) at 241:16-245:10, 261:6-7; 262:9-263:17; *Flick* at Table 4.]
3. A third portion of the molecule Dr. Martin proposed changing was the cyclohexane region. [*See* DFOF ¶¶ 60-61; 3/16 Tr. (Martin) at 252:14-23, 261:8-11, 263:18-24; *Flick* at Table 4.]

[19] This Opinion will refer to DTX-2052, which is the English version of the paper, as "*Frankus*."

Based on his conclusions and proposed changes, Dr. Martin summarized his interpretation of the tramadol pharmacophore with the following depiction:



[*See* DFOF ¶ 62.]

Having identified the tramadol pharmacophore, Dr. Martin opined that the prior art would have motivated a POSA to make the following changes to the molecule [*see generally* DFOF ¶¶ 63-78; 3/16 Tr. (Martin) at 261:17-271:2]:

1. Dr. Martin opined that it was known that the meta-hydroxy group on the aromatic oxygen showed more analgesic activity than the meta-methoxy group. [*See* DFOF ¶¶ 51-54; 3/16 Tr. (Martin) at 247:2-252:13; *Flick* at Table 5, DTX-834_0012 ("The free m-hydroxyl group gives the best strengthening of action . . . .").]
2. Dr. Martin proposed replacing the bridge carbon hydroxyl with a hydrogen, which he opined was known to result in no significant loss of analgesic activity. [*See* DFOF ¶¶ 64-66; 3/16 Tr. (Martin) at 262:7-263:17; DTX-834_0012 ("The bridge

carbon in 1-position on the cyclohexane ring can have a hydroxyl group as the fourth substituent, and with only slight loss of activity, a halogen atom. A hydrogen radical also leads to only a slight loss of activity . . . .").] Dr. Martin suggested that the motivation to make this change would be to simplify the molecule. [3/16 Tr. (Martin) at 262:19-263:15.]

3. Finally, Dr. Martin proposed opening the cyclohexane ring. [*See* DFOF ¶¶ 67-78 3/16 Tr. (Martin) at 263:18-286:6; *Flick*; DTX-736 ("*Sevcik*"); DTX-739 ("*Spassov*").]

Plaintiffs presented evidence that a POSA would not have been motivated to make these modifications. The Court addresses Dr. Martin's proposed modifications and Plaintiff's evidence below.

i. Chemical modifications generally

Plaintiffs' expert testified that a conservative estimate of the modifications that a POSA could have made to tramadol presents almost half a million different possible compounds. [PFOF ¶ 292; 3/22 a.m. Tr. (Roush) at 102:8-103:17; 3/22 p.m. Tr. (Roush) at 82:4-83:18.] This estimate is only a small selection of the possible modifications that a POSA would have considered. [PFOF ¶ 292; 3/22 a.m. Tr. (Roush) at 102:8-103:17.] The prior art references that guided Dr. Martin investigated only about thirty individual compositions, which would not have illuminated to a POSA the biological effect that would arise from many other modifications. [PFOF ¶ 293; 3/10 Tr. (Buschmann) at 215:21-216:7; 3/22 a.m. Tr. (Roush) at 103:18-104:12, 105:8-14; 3/17 Tr. (Martin) at 108:3-14; *Flick.*] Plaintiffs presented evidence of other references that did investigate other such modifications that Dr. Martin does not appear to have considered. [PFOF ¶ 295; 3/22 a.m. Tr. (Roush) at 107:17-109:8; PTX-1055 at 396.] Lastly, Dr. Buschmann explained that the *Flick* reference, on which Dr. Martin relied, investigated mixtures of stereoisomers of the studied

compounds without separating the compounds based on their stereochemistry. [PFOF ¶ 294; *Flick*; 3/10 Tr. (Buschmann) at 217:4-218:8; 3/16 Tr. (Martin) at 233:4-13.]

ii. Aromatic Oxygen

Dr. Martin's proposed change regarding the substitution of the aromatic oxygen is encompassed within his analysis of the lead compound selection. [*See supra* Section IV.A.i.2.a.ii.] The Court concluded that it would not have been obvious to select S,S-ODMT from the mixture of tramadol and its metabolites. [*Id.*] Accordingly, the Court does not find it would have been obvious to reduce the methoxy group on the aromatic oxygen to a hydroxy group.

iii. The bridge carbon hydroxyl group

Dr. Martin testified that *Flick* demonstrated that removing the bridge carbon hydroxyl group resulted in no substantial loss of analgesic activity. [*See* DFOF ¶¶ 64-65; 3/16 Tr. (Martin) at 262:7-263:15; *Flick* at Table 4.] Defendants posited that a POSA would have been motivated to make this change to simplify the molecule, in keeping with the opioid tradition of simplifying analgesics based on morphine. [*See* DFOF ¶ 66; 3/16 Tr. (Martin) at 262:19-263:15.] Plaintiffs, however, presented evidence that researchers had made many changes to morphine, not limiting themselves to "simplifying" the molecule. [PFOF ¶ 255; 3/22 a.m. Tr. (Roush) at 72:23-73:17; 3/17 Tr. (Martin) at 99:5-10.] Furthermore, Dr. Roush testified that while the removal of the hydroxyl group impacted the analgesic activity slightly, it also made the molecule almost twice as toxic. [PFOF ¶¶ 325; 3/22 a.m. Tr. (Roush) at 130:9-133:2; *Flick* at Table 4.] Finally, Dr. Martin admitted that the bridge carbon hydroxyl group tends to stabilize a conformation resembling tramadol due to the hydrogen bond with the tertiary amine, so a POSA would likely have been motivated to retain that group rather than reducing it to hydrogen. [PFOF ¶ 326; 3/17 Tr. (Martin) at 104:3-105:2.] Thus Defendants have not proven by clear and convincing evidence that a POSA would have been motivated to remove the bridge carbon hydroxyl group.

iv. The cyclohexane ring

Regarding the cyclohexane ring, Dr. Martin opined that it would have been obvious to a POSA to undergo the following analysis based on the prior art:

(1) First, a POSA would have learned from *Flick* not to make the cyclohexane ring bigger or smaller. [*See* DFOF ¶ 68; 3/16 Tr. (Martin) at 261:10-11; *Flick* at Table 4.]

(2) Next, a POSA would have decided not to complicate the molecule by adding substituents to the cyclohexane ring. [*See* DFOF ¶ 69; 3/16 Tr. (Martin) at 266:18-267:10.]

(3) Therefore, a POSA would have instead been motivated to open the cyclohexane ring and prepare linear analogs of tramadol [*see* DFOF ¶ 70; 3/16 Tr. (Martin) at 267:11-269:15] by either cleaving one of the bonds in the ring ("scission") [*see* DFOF ¶ 71; 3/17 Tr. (Martin) at 18:13-22:21] or by removing one of the carbons in the ring ("excision") [*see* DFOF ¶ 71; 3/16 Tr. (Martin) at 270:24-271:2].

(4) Having decided to open the cyclohexane ring, a POSA would have avoided scission of a carbon-carbon bond in the cyclohexane ring because such an approach would not allow the methyl groups in the resulting open-chain molecule to occupy the same spatial positions. [*See* DFOF ¶¶ 72-73; 3/17 Tr. (Martin) at 20:7-22:21.]

(5) Thus, a POSA would have chosen excision as the method of opening the cyclohexane ring, and would have determined that excising one of two possible carbons in the cyclohexane ring would produce compounds that

would be likely to exhibit analgesic behavior. [*See* DFOF ¶¶ 74-77; 3/17 Tr. (Martin) at 23:1-24:19; DTX-739.]

(6) Finally, a POSA would have known, based on prior art references and Newman projections which carbon to excise. [*See* DFOF ¶¶ 76-78; 3/17 Tr. (Martin) at 23:1-24:19; *see also* 3/17 Tr. (Martin) at 7:8-14:5.]

In response to Dr. Martin's opinions regarding the cyclohexane ring, Dr. Roush testified for Plaintiffs that a POSA would not have opened the ring to make linear compounds in the first place. [*See generally* PFOF ¶¶ 300-309; 3/22 a.m. Tr. (Roush) at 79:7-24, 109:9-116:17.] Dr. Roush further testified that, even if a POSA were to open the ring, a POSA would not have been motivated to cleave a carbon-carbon bond in the ring (scission) or to remove a carbon (excision). [*See generally* PFOF ¶¶ 310-315; 3/22 a.m. Tr. (Roush) at 116:23-123:4.] Dr. Roush also testified that a POSA would not have found Dr. Martin's references to present a compelling motivation to modify tramadol. [*See generally* PFOF ¶¶ 316-24; 3/22 a.m. Tr. (Roush) at 123:5-133:21.]

First, it was known that the cyclohexane ring in tramadol restricts the conformational options that the molecule has, thereby improving its propensity to bind to receptors. [PFOF ¶¶ 301, 303-04; 3/22 a.m. Tr. (Roush) at 79:7-24, 109:25-111:20, 114:1-22; PTX-871 at JN_NUCYNTA_1656858 ("A central tenet in structure-based design is that the binding affinity of a ligand will be improved if its conformational motion can be restricted to that of the bound state."); PTX-1055 at 390-91 ("From a structural point of view, cyclohexane forms the common element of a variety of analgesics that are otherwise difficult to classify. The alicyclic ring system serves to restrict conformational options in all derivatives that contain it . . . ."); 3/17 Tr. (Martin) at 80:8-81:20.] Examples were known in the art of more flexible analogues of cyclic analgesics having poorer analgesic activity. [PFOF ¶¶ 307-08; 3/22 a.m. Tr. (Roush) at 115:1-116:17;

PTX-185.] In fact, of the molecules investigated in *Flick*—the paper which Defendants consider "[t]he most relevant prior art reference for the SAR of tramadol and related compounds" [*see* DFOF ¶ 45]—none were linear molecules. [PFOF ¶ 302; *Flick*; 3/10 Tr. (Buschmann) at 216:16-217:3, 3/17 Tr. (Martin) at 38:23-25, 108:15-18, 110:4-9.]

Second, Plaintiffs presented evidence of the numerous possibilities that existed (and lack of guidance from the prior art regarding those possibilities) had a POSA decided to open the cyclohexane ring. [PFOF ¶ 310; 3/22 a.m. Tr. (Roush) at 116:23-117:15.] A POSA would have had a choice of at least three bonds to cleave (five if not concerned with maintaining the stereochemistry). [PFOF ¶¶ 311-312; 3/22 a.m. Tr. (Roush) at 117:16-118:10; Roush Demonstrative at 29-34.] A POSA would have also had a choice of at least two carbons to excise. [PFOF ¶¶ 314-315; 3/22 a.m. Tr. (Roush) at 120:21-123:4.] And, once the ring was open, a POSA would have had a choice of substituting or removing carbons or other groups. [PFOF ¶ 313; 3/22 a.m. Tr. (Roush) at 117:3-119:2.]

Third, Plaintiffs presented evidence that the linear compounds tested by the *Spassov* and *Nazarov* references on which Dr. Martin relied would not have motivated a POSA to open the cyclohexane ring. The *Spassov* compounds were not tested for, or known to have, analgesic activity. [PFOF ¶ 316; 3/22 a.m. Tr. (Roush) at 123:5-124:17; PTX-61.] Regarding *Nazarov*, Plaintiffs presented evidence that the one compound shown to have biological activity possessed the bridge carbon hydroxyl group (which Dr. Martin proposed replacing), possessed a benzene ring lacking a hydroxyl substituent (unlike tramadol), was shown to have pharmacological properties distinct from analgesia, and involved a stereoselective synthesis that would have produced the wrong stereochemistry. [PFOF ¶¶ 317-321; 3/22 a.m. Tr. (Roush) at 124:18-130:8; PTX-54 at ACT-TAP0016872-73; 3/17 Tr. (Martin) at 31:10-36:7.] Plaintiffs also note that, while

the Nazarov paper was available to the authors of *Flick*, it did not motivate those researchers to investigate linear compounds. [PFOF ¶ 322; 3/17 Tr. (Martin) at 38:5-25.]

In light of the evidence set forth, Defendants have not proven clearly and convincingly that it would have been obvious to a POSA based on the prior art to make the modifications necessary to go from tramadol to tapentadol.

3. The '593 patent is not obvious

Having reviewed the evidence presented by the parties, the Court finds that Defendants' lead compound contentions derive from a knowledge of the claimed inventions and the starting point the inventors actually took rather than a view of the options available to a POSA in 1994. [Plaintiffs' Conclusions of Law ("PCOL") ¶¶ 630-631.] Defendants have failed to clearly and convincingly show that a POSA would have selected tramadol (or any of its individual enantiomers, *O*-desmethyl metabolites, or any combination thereof) as lead compounds for developing a new analgesic as of July 23, 1994. [PCOL ¶ 628.] Defendants have also failed to clearly and convincingly show that the prior art would have supplied one of ordinary skill in the art with a reason or motivation to modify tramadol to make tapentadol hydrochloride with a reasonable expectation of success. The Court, therefore, finds that Defendants have failed to meet their burden of proving by clear and convincing evidence that any of the asserted claims of the '593 patent are obvious under 35 U.S.C. § 103.

ii. '593 Patent Utility

Defendants have challenged the utility of the '593 patent. [PTO ¶¶ 1465, 1168-1181.] To prove that the '593 patent lacks utility, Defendants must demonstrate that the patent contains inadequate evidence of pharmacological activity. *See Fujikawa*, 93 F.3d at 1564. On this issue, Defendants presented the expert testimony of Dr. Christian Wolf and Dr. Jeffrey Mogil. Plaintiffs presented the expert testimony of Dr. Michael Ossipov.

Defendants' utility argument proceeds in two parts. First, Defendants contend that the '593 patent contains no testing to support the "desired pharmacological response." Second, Defendants contend that the testing that is contained within the '593 patent specification is insufficient to convince one of skill in the art to a reasonable probability that the compound of the asserted claims exhibits any pharmacological response. The Court addresses these arguments in turn.

1. The "desired pharmacological response"

Defendants contend that, as a matter of law, the '593 patent must contain "testing to support 'the underlying object of the present invention.'" [*See* Defs. Br. at 11.] Defendants suggest that the underlying object was "to 'provide substances with an analgesic effect, which are suitable for the treatment of severe pain without giving rise to the side effects which are typical of opioids.'" [*See* Defs. Br. at 11.] Defendants alternatively suggest that the underlying object was "a pronounced analgesic effect which is significantly enhanced compared with that of tramadol." [*See* DFOF ¶ 508.] Either way, Defendants contend that, because the '593 patent undisputedly does not contain side effect testing or comparative testing to tramadol, its utility has not been demonstrated. [DFOF ¶¶ 507, 508; 3/23 Tr. (Ossipov) at 169:11-172:8; 3/11 Tr. (Mogil) at 257:10-20, 266:14-19; 3/22 p.m. Tr. (Roush) at 107:7-22.]

Plaintiffs argue, however, that the utility stated in claim 8 is treatment of pain in mammals. [Pls. Br. at 27; *see* PFOF ¶ 359.] While Defendants rely on specification statements about the "object of the invention," the asserted claims do not make any reference to side effects or tramadol. [*See id.*; *see also* '593 patent at claims 8, 61, 117, and 147.] *Raytheon*, 724 F.2d at 956 (the claims "define the invention to be tested for utility"). The Court agrees with Plaintiffs that the utility of the asserted claims is analgesia. Accordingly, the lack of side effect testing or comparative testing to tramadol in the '593 patent does not lead to the conclusion that the patent lacks utility.

2. The testing in the patent

Defendants contend that, even acknowledging the utility of the asserted claims as analgesia, the testing in the specification of the patent is insufficient to establish analgesia. [*See* Defs. Br. at 11.] Plaintiffs presented evidence that the '593 patent discloses that the asserted claims have utility through its discussion of *in vivo* test data from the mouse writhing model. [PFOF ¶ 337; '593 patent at 21:53-22:40.] Defendants argue that the mouse writhing test, which is undisputedly the only test for analgesia disclosed in the patent, is not reasonably indicative of analgesia. [*See* DFOF ¶ 514-532; *see generally* 3/11 Tr. (Mogil) at 256:19-277:15.] Defendants also contend that, while the '593 patent contains mouse writhing test data for some of the compounds disclosed, it contains no data regarding the analgesic activity of the compound of Example 25 in the '593 patent, which is the compound claimed in asserted claims 61, 117, and 147. (Defs. Br. at 11; *see generally* DFOF ¶¶ 510, 512-513; *see generally* 3/11 Tr. (Mogil) at 262:10-264:15; 3/17 Tr. (Wolf) at 142:7-23.]

a. The reliability of the mouse writhing test, generally

Plaintiffs presented evidence that the mouse writhing test is a reliable, fundamental, and industry standard test for detecting compounds with antinociceptive analgesic activity. [PFOF ¶ 337; 3/23 Tr. (Ossipov) at 119:9-120:1; Friedichs Depo. at 166:13-16, 201:6-13.] Scientific publications recognize the mouse writhing test as a widely used, reliable animal model for identifying compounds with antinociceptive analgesic activity, and the model has been recognized as one of the three most reliable animal models for nociceptive pain. [PFOF ¶ 339; 3/23 Tr. (Ossipov) at 119:9-120:1; PTX-929; PTX-746; DTX-165; DTX-170.] Defendants' own expert, Dr. Mogil, agreed that the mouse writhing test was commonly used in 1994. [PFOF ¶ 340; 3/11 Tr. (Mogil) at 299:4-7.]

Dr. Mogil's testimony included extensive criticism of the mouse writhing test itself. One criticism was that the mouse writhing test could produce false positives due to non-responsiveness of some test subjects to the irritant. [*See* PFOF ¶ 360; 3/11 Tr. (Mogil) at 305:15-24.] A second criticism was the non-specificity of the mouse writhing test due to writhing inhibition caused by non-analgesics. [*See* PFOF ¶ 361; DFOF ¶¶ 521-524; 3/11 Tr. (Mogil) at 267:5-273:10; DTX-170 at Table 3; DTX-1576_0022; DTX-165_0003 ("Because of the lack of specificity, caution is required in interpreting the results, until other tests have been performed.").] A third criticism was the sensitivity of the test to analgesic manipulations, which renders the test susceptible to confounding factors such as stress-induced analgesia, whereby stress itself can reduce pain. [*See* PFOF ¶ 362; DFOF ¶¶ 525-526; 3/11 Tr. (Mogil) at 273:11-276:22; DTX-166_0009-10, DTX-1576_0013, DTX-177_0002.] A fourth criticism was the potential for confounding responses, such as motor impairment and sedation, which can inhibit writhing activity without producing analgesia. [*See* PFOF ¶ 364; DFOF ¶ 527; 3/11 Tr. (Mogil) at 276:23-277:15; DTX-1576_0020 ("[A] decrease in the number of writhes is not indicative of antinociception if it is accompanied by gross motoric disturbances such as muscle relaxation or paralysis.").] And a fifth criticism was the potential for difficulty in counting writhes. [*See* PFOF ¶ 365; *see also* 3/11 Tr. (Mogil) at 258:14-18; 3/23 Tr. (Ossipov) at 126:14-21.]

In response to Dr. Mogil's criticisms of the mouse writhing test, Plaintiffs demonstrated (on cross examination of Dr. Mogil and through the testimony of Dr. Ossipov) that these concerns would be alleviated by a competent technician. [PFOF ¶ 365; 3/23 Tr. (Ossipov) at 157:14-19.] Such a technician would be able to administer the test without inducing stress [PFOF ¶ 362; 3/23 Tr. (Ossipov) at 120:2-21, 151:24-154:9], would be able to apply consistent criteria to count the writhes of a mouse, and would have no difficulty identifying nonresponsiveness, non-specificity,

and motor impairment. [PFOF ¶¶ 360-365; 3/11 Tr. (Mogil) at 304:8-305:15; 3/23 Tr. (Ossipov) at 154:10-155:23.]

Dr. Mogil also criticized the '593 patent for relying solely on the mouse writhing test without providing evidence of additional testing to confirm the mouse writhing test conclusions, as Defendants contend would be standard practice in scientific publications. [*See* PFOF ¶ 366; DFOF ¶¶ 514-519; 3/11 Tr. (Mogil) at 254:3-259:12 269:18-270:22, DTX-1576_0011, 0022.] Defendants presented evidence of scientific literature stating that "no model is reliably predictive" and inferences should be made "only through the judicious use of complimentary models of nociception and assessments of motoric function." [DFOF ¶ 517; DTX-1576_0011, 0022).] Defendants also elicited testimony from the experts concerning the value of having multiple complimentary models of pain to test for analgesia. [DFOF ¶¶ 514, 516, 531; 3/11 Tr. (Mogil) at 254:3-259:12; 3/23 Tr. (Ossipov) at 181:20-196:2.] However, the law does not require that a patent's disclosure meet the same standard as a peer-reviewed journal publication. *See* 35 U.S.C. § 112. In any event, Plaintiffs provided evidence of scientific publications containing only mouse writhing test data. [PFOF ¶ 366; 3/23 Tr. (Ossipov) at 229:3-230:18, 150:24-151:9; PTX-746 at JN_NUCYNTA_0749749.] Furthermore, despite his criticism of the mouse writhing test on the stand, Dr. Mogil admitted that he has used the mouse writhing test and in his past writing he has called the writhing test "the only major nociceptive test largely developed, and still used, on mice." [PFOF 340; 3/11 Tr. (Mogil) at 309:25-310:3, 311:24-312:1; DTX-166_0018.]

b. The mouse writhing test, as applied to the '593 patent

The '593 patent explains that the "analgesic effectiveness of the compounds according to the invention" was investigated in the "phenylquinone-induced writhing test," and it provides information regarding that testing, including the number of mice that received each dose, the type of mice used, and the testing procedure. [PFOF ¶ 342; '593 patent at 21:55-67.] The patent

discloses data from the mouse writhing test for many of the compounds disclosed, including a summary table disclosing test results for 24 compounds. [FOF ¶ 343 '593 patent at 22:15-40.] The summary table reports ED_{50} values for 18 compounds within the claimed class of compounds. [PFOF ¶ 344; '593 patent at 22:3-40; 3/23 Tr. (Ossipov) at 128:14-17.] The remaining six entries in the summary table report the percent by which the number of writhes was reduced for mice given a 25 mg/kg dose of the test compound. [PFOF ¶ 349; '593 patent at 22:15-40.] A POSA in 1994 would have appreciated that the summary table of mouse writhing data in the '593 patent discloses test results for over 800 mice.[20] [PFOF ¶ 35; 3/23 Tr. (Ossipov) at 144:20-145:4.] The ED_{50} values in the table were calculated "with a 95% confidence level"[21] using software that performs regression analysis. [PFOF ¶ 347; '593 patent at 22:3-10; 3/23 Tr. (Ossipov) at 123:21-124:1.] A control group was used to generate the values in the table (*i.e.*, the values were generated "by comparison with mice tested in parallel to which only phenylquinone had been administered"). [PFOF ¶¶ 348-49; '593 patent at 22:3-40; 3/23 Tr. (Ossipov) at 123:10-20, 124:16-125:4).] A dose dependent response in the mouse writhing test is strong evidence of antinociception, and the ED_{50} values reported in the '593 patent provide this strong evidence. [PFOF ¶ 346; 3/23 Tr. (Ossipov) at 129:13-21.]

As stated in the '593 patent, "[a]ll of the compounds according to the invention which were investigated exhibited a pronounced analgesic effect." [PFOF ¶ 351; '593 patent at 22:11-13.] Plaintiffs' expert, Dr. Ossipov, testified that he is very confident that all the tested

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[20] The patent discloses that there were ten mice per dose. With a minimum of three dose groups, plus a control group, for each of the eighteen ED_{50} values (40 mice each), and a 25 mg/kg dosing level group, plus a control group, for each of the six tested for percent inhibition (20 mice each), the table represents a minimum of 840 mice. [PFOF ¶ 350; '593 patent at 21:60-61; 3/23 Tr. (Ossipov) at 123:3-9, 125:5-8.]

[21] A 95% confidence level indicates a 95% probability that a repeated experiment would contain an ED_{50} value between the confidence intervals. [PFOF ¶ 347; 3/23 Tr. (Ossipov) at 128:18-23.]

compounds investigated in the summary table demonstrated the inhibition of nociceptive pain. [PFOF ¶ 343; 3/23 Tr. (Ossipov) at 124:8-15.]

The compounds covered by the asserted claims of the '593 patent all have the same core chemical structure, the structure illustrated in claim 8. [PFOF ¶ 341; *see* '593 patent).] Defendants did not present evidence of a single compound without analgesic activity that has a structure that would be covered by any of the asserted claims. [*See* PFOF ¶ 358.] Accordingly, a POSA would have had a reasonable expectation that Example 25 (tapentadol hydrochloride) would have a dose-dependent antinociceptive effect due to its structural similarity to the family of compounds that demonstrated analgesic activity.[22] [PFOF ¶ 357; 3/23 Tr. (Ossipov) at 149:5-15; PCOL ¶¶ 609-610.] *See Glaxosmithkline LLC v. Baner Pharmacaps, Inc.*, No. 11-046, 2013 U.S. Dist. LEXIS 112440, at *78 (D. Del. Aug. 9, 2013) ("[A] specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented *must* be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter *unless* there is reason for one skilled in the art to question the objective truth of the statement of utility or its scope." (citation omitted)), *aff'd*, 744 F.3d 725 (Fed. Cir. 2014); Manual of Patent Examining Procedure § 2107.02(I) ("Where an applicant has established utility for a species that falls within an identified genus of compounds, and presents a generic claim covering the genus, as a general matter, that claim should be treated as being sufficient under 35 U.S.C. 101. Only where it can be established that other species clearly encompassed by the claim do not have utility should a

[22] The parties presented evidence concerning declarations submitted to the USPTO during prosecution of the '737 patent, containing at least some data obtained after the original filing date of the patent. [*See* PFOF ¶¶ 352-356; DFOF ¶¶ 533-543.] The parties dispute whether post-filing data may be used to establish utility and whether the patentees should be entitled to the 1994 priority date. [PCOL ¶ 611; DCOL ¶¶ 510-512]. Because the Court finds that the data presented in the '593 patent specification is sufficient to support the utility of the asserted claims, the Court makes no findings as to the admissibility of the prosecution declarations on the question of utility.

rejection be imposed on the generic claim."); *see also, e.g.*, *In re Brana*, 51 F.3d 1560, 1567 (Fed. Cir. 1995) ("[A]pplicants provided . . . test results showing that several compounds within the scope of the claims exhibited significant [pharmacological activity] . . . . Such evidence alone should have been sufficient to satisfy applicants' burden."); *In re Jolles*, 628 F.2d 1322, 1327 (C.C.P.A 1980) (finding that the Board of Patent Appeals and Interferences "erred . . . by failing to give sufficient weight to the similarity of the remaining claimed derivatives to the derivative [that had been tested] . . . .").

3. The asserted claims of the '593 patent do not lack utility

Based on the evidence presented, the Court finds that Defendants have not met their burden of clearly and convincingly proving that the asserted claims of the '593 patent lack utility under 35 U.S.C. § 101.

iii. '593 Patent Written Description and Original Patent

Defendants contend that asserted claims 61, 117, and 147 of the '593 patent lack written description under 35 U.S.C. § 112. [PTO ¶¶ 1464, 1155-62.] Defendants further contend that those same claims in the '593 patent do not meet the "original patent" requirement set forth in 35 U.S.C. § 251. [PTO ¶¶ 1163-1167.] To prove that the '593 patent lacks written description under 35 U.S.C. § 112, Defendants bear the burden of demonstrating by clear and convincing evidence that a POSA would not have understood from the disclosure within the patent specification that the inventor "had possession" of the tapentadol hydrochloride claimed in claims 61, 117, and 147. *See Ariad*, 598 F.3d at 1351. Similarly, to prove that the '593 patent fails to meet the "original patent" requirement of 35 U.S.C. § 256, Defendants must clearly and convincingly show that the tapentadol hydrochloride of reissued claims 61, 117, and 147 was not taught by the original patent's description. *See Antares*, 771 F.3d at 1361-62.

On this issue, Defendants presented the expert testimony of Dr. Christian Wolf, who opined that the '593 patent does not contain "structural data" that would allow a POSA to conclude that the inventors possessed the compound claimed in claims 61, 117, and 147. [*See generally* DFOF ¶¶ 552-558; *see also* Defs. Br. at 15; 3/17 Tr. (Wolf) at 149:22-150:16.] Dr. Wolf also opined on mistakes in the original and reissue patent specifications and the prosecution history. [*See generally* DFOF ¶¶ 558, 561-66; *see also* Defs. Br. at 15-16; 3/17 Tr. (Wolf) at 154:18-155:22; 156:25-160:18.] Based on these mistakes, Defendants' argue that from the alleged "numerous irreconcilable discrepancies about the identity of the compound of Example 25 in the specification . . . a POSA would conclude the inventors did not know what they possessed, let alone the ultimately claimed . . . species." [*See* Defs. Br. at 15.]

Plaintiffs contend that the subject matter of claims 61, 117, and 147 is adequately disclosed and that those claims satisfy the requirements of the original patent rule. On this issue, Plaintiffs presented the testimony of Dr. Roush, who opined on the chemical structure drawn in conjunction with Example 25 and the disclosure of the routine chemistry steps that a POSA could follow to synthesize the depicted molecule. [PFOF ¶ 385; 3/22 p.m. Tr. (Roush) at 8:8-9:1; *see also* PCOL ¶ 652; Pls. Br. at 32-33.] It is undisputed that the drawing in Example 25 is a correct depiction of the compound claimed in claims 61, 117, and 147, and that the drawing and the synthetic steps have not changed over the lifetime of the prosecution and reissue of the patent. [PCOL ¶ 653; 3/17 Tr. (Wolf) at 208:5-20; 3/10 Tr. (Buschmann) at 57:9-12, 63:15-22, 67:2-7.] Furthermore, Plaintiffs presented the testimony of Dr. Buschmann, an inventor of the '593 patent, who provided credible testimony to explain each of the alleged "discrepancies." [3/10 Tr. (Buschmann) at 57:22-61:6, 61:19-62:18, 63:23-67:1.]

1. Sufficiency of the disclosure

The structural formula depicted in conjunction with Example 25 and designated as "-21" is undisputedly tapentadol hydrochloride, the compound claimed in claims 61, 117, and 147. [PFOF ¶ 377; 3/16 Tr. (Steed) at 52:19-53:7; 3/17 Tr. (Wolf) at 155:23-156:2.] The structure includes three dimensional indicators indicating the molecule's stereochemistry. [PFOF ¶ 379; 3/22 p.m. Tr. (Roush) at 134:23-135:8.] Defendants' expert, Dr. Wolf, admitted that a structure can be sufficient to describe a molecule to a POSA without analytical structural data, assuming that a POSA could look into the specification and find evidence that the inventors did invent what they claimed they invented. [*See* PFOF ¶ 380; 3/17 Tr. (Wolf) at 178:10-18.] Plaintiffs' expert, Dr. Roush, discussed that evidence in the specification, testifying that a POSA would rely on the chemical structure drawn and also on the synthesis steps disclosed as part of the detailed reaction scheme. [PFOF ¶ 383; 3/22 p.m. Tr. (Roush) at 11:13-12:14.]

Dr. Wolf testified that a POSA could verify whether he or she had prepared the structure depicted in Example 25 using analytical techniques that were well known, such as Nuclear Magnetic Resonance ("NMR") and Infrared ("IR") spectroscopy. [PFOF ¶ 381; 3/17 Tr. (Wolf) at 185:5-186:3.] Defendants argue that such techniques should have been disclosed in the patent specification. [Defs. Br. at 15.] Although Dr. Wolf cited three references discussing the types of structural data that can be used to identify chemical compounds, none of those references purports to contain any statement about the law of written description as it pertains to patents in the chemical field. [PFOF ¶ 382; 3/17 Tr. (Wolf) at 186:16-18, 186:25-187:21.]

In light of the evidence presented, the Court finds that the combination of the depicted structure in Example 25 with the collection of synthetic steps consistent with that final structure was sufficient to indicate to a POSA that the patentees were in possession of the invention claimed in claims 61, 117, and 147.

2. Discrepancies in the disclosure

Defendants argue that, notwithstanding the structural drawing and the synthetic steps in Example 25, discrepancies in the disclosure of the '593 patent would indicate to a POSA that the inventors were not in possession of the tapentadol hydrochloride claimed in claims 61, 117 and 147. Specifically, Defendants presented evidence that the melting point and optical rotation data disclosed for the compound of Example 25 would indicate to a POSA that the steps of Example 25 do not result in tapentadol hydrochloride and do not result in a compound that is the enantiomer of Example 24 as the drawn structure of Example 25 indicates. [*See* DFOF ¶ 558; 3/17 Tr. (Wolf) at 149:22-150:16, 154:8-155:22.] Defendants also rely on mistakes made in the "R" and "S" stereochemistry descriptors, which were written as "(1S,2S)" in the original patent application, amended to "(1R,2S)" during prosecution leading to the issuance of the original '737 patent, and reissued as "(1R,2R)" in the '593 patent. [DFOF ¶¶ 561-566; 3/17 Tr. (Wolf) at 156:25-160:18; 3/10 Tr. (Buschmann) at 133:7-16, DTX-950_034.] These mistakes, Defendants argue, would prevent a POSA from concluding that the inventors were in possession of the claimed invention—tapentadol hydrochloride.

This Court construed the claim term "(–)-(1R,2R)-3-3(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride (–21)" to mean "the chemical compound (–)-(1R,2R)-3-3(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride depicted by the structural formula identified by the number (–21) in Example 25 of the RE593 patent." [ECF No. 332.] In doing so, the Court declined to adopt Defendants' proposed construction for the term, through which Defendants sought to incorporate limitations requiring a specific melting point and optical rotation. [PFOF ¶ 375; ECF No. 332.]

It is undisputed that the compounds depicted by the structural formulas drawn in Examples 24 and 25 are enantiomers. [PFOF ¶ 386; 3/17 Tr. (Wolf) at 192:25-193:1.] Dr.

Buschmann testified about the discrepancy between the melting points, stating that the patent drafter incorrectly transcribed the melting point from his laboratory notebook. [3/10 Tr. (Buschmann) at 61:11-18.] Dr. Roush testified that the optical rotation discrepancy between the compounds of Example 24 and 25 was likely within the range of measurement error, and was certainly not large enough to make a POSA question that they were enantiomers. [3/22 p.m. Tr. (Roush) at 17:12-19:14.] As for the "R" and "S" stereochemistry descriptors, Dr. Buschmann explained the reasonable mistake that resulted in the incorrect naming of the molecule in the original application and the issued '737 patent, a mistake that was ultimately corrected in the '593 patent. [3/10 Tr. (Buschmann) at 57:22-61:6, 61:23-62:18, 63:23-67:1.] In light of the evidence presented about the structural formula and the synthetic steps, the Court finds that the mistakes and/or discrepancies in the description of Example 25 would not cause a POSA to question that the inventors had in fact invented the molecule depicted by the drawn structure, which is undisputedly tapentadol hydrochloride claimed in claims 61, 117, and 147.

3. The asserted claims of the '593 patent satisfy the written description and original patent requirements

This Court finds that the disclosure of the synthetic steps and the structural formula of Example 25 in the original application is sufficient to meet the written description and original patent requirements. A POSA would understand that the inventors possessed the tapentadol hydrochloride depicted by the drawn molecule at the time the original application was filed. Therefore, Defendants have not met their burden of proving by clear and convincing evidence that the '593 patent lacks written description under 35 U.S.C. § 112 or fails to satisfy the original patent requirement under 35 U.S.C. § 251.

iv. '593 Patent Enablement

Defendants contend that asserted claim 8 is not enabled in accordance with the requirements of 35 U.S.C. § 112. [PTO ¶¶ 1192-1207.] To prove that claim 8 is not enabled, Defendants bear the burden of demonstrating by clear and convincing evidence that the disclosure of the '593 patent would not teach a POSA "how to make and use the full scope of the claimed invention without undue experimentation." *See Martek*, 579 F.3d at 1378. On this issue, Defendants presented the testimony of Dr. Wolf and Dr. Mogil. Plaintiffs argue that the full scope of claim 8 has been enabled by the specification. On this issue, Plaintiffs presented the testimony of Dr. Ossipov.

Claim 8 encompasses over 11 million compounds, which correspond to over 600 million salts. [DFOF ¶ 571; 3/17 Tr. (Wolf) at 164:13-165:10.] Defendants contend that the analgesic activity of new compounds must be determined empirically for each new compound. [*See* DFOF ¶ 576; 3/11 Tr. (Mogil) at 291:4-11; Friedrichs Depo. at 214:17-215:5; 3/23 Tr. (Ossipov) at 210:4-10.] Defendants therefore posit that in order to make and use the full scope of claim 8, a POSA would need to first synthesize, purify, and identify each of the compounds, and then perform appropriate animal model testing on a compound-by-compound basis to assess purported analgesic activity, a process which would require 10-12 days per compound. [*See* DFOF ¶ 572; 3/11 Tr. (Mogil) at 286:19-287:17; 3/17 Tr. (Wolf) at 163:21-169:7.] It is undisputed that, if such a process were required to enable the claim, that process would require years to perform and billions of mice. [DFOF ¶ 572; 3/11 Tr. (Mogil) at 287:8-17; 3/23 Tr. (Ossipov) at 158:16-22, 209:12-212:7.]

However, this Court is not persuaded that the enablement law requires the making and testing of every one of the 11 million species in genus claim 8. *See In re Bundy*, 642 F.2d 430, 434 (C.C.P.A. 1981) ("Requiring specific testing of the thousands of prostaglandin analogs encompassed by the present claim in order to satisfy the how-to-use requirement of § 112 would

delay disclosure and frustrate, rather than further, the interests of the public."); *In re Angstadt*, 537 F.2d 498, 502-03 (C.C.P.A. 1976) ("To require [disclosure of a test with every species covered by the claim] would apparently necessitate a patent application or applications with 'thousands' of examples or the disclosure of 'thousands' of catalysts along with information as to whether each exhibits catalytic behavior . . . ." (footnote omitted)). As a practical matter, it would be "absurd" to require the testing of every single compound in genus claim 8. [PFOF ¶ 369; 3/23 Tr. (Ossipov) at 158:16-159:5.] "Such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments [and] would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed." *Angstadt*, 537 F.2d at 502-03.

Rather, the law requires that a POSA be able to practice the full scope of the claims without undue experimentation. To meet that requirement, Plaintiffs presented evidence that a POSA would be able to make and test any compound encompassed by genus claim 8 as a matter of routine experimentation. [PFOF ¶¶ 372-73; 3/23 Tr. (Ossipov) at 159:6-14.] In fact, Defendants' experts admitted that the work required to test and synthesize each compound would be routine. [PFOF ¶ 373; 3/11 Tr. (Mogil) at 317:9-20.]

Plaintiffs also presented evidence that a representative number of the compounds encompassed within claim 8 were tested and all exhibited antinociceptive activity, and that a POSA would reasonably believe that other structurally similar compounds in the same family would have antinociceptive effects. [PFOF ¶ 369; 3/23 Tr. (Ossipov) at 149:7-15.] Defendants have not identified any compound within the class of compounds covered by claim 8 that lacks nociceptive activity. [*See* PFOF ¶ 371.] Nor have Defendants identified any compounds within genus claim 8

that would be difficult to make or test, considering the guidance provided by the patent. [*See* PFOF ¶¶ 372-73; 3/23 Tr. (Ossipov) at 159:6-14.]

In light of the evidence presented, Defendants have not met their burden of proving by clear and convincing evidence that claim 8 is not enabled.

B. '364 PATENT – INVALIDITY

Plaintiffs have asserted claims 1, 2, 3, and 25 of the '364 patent. Defendants contend that each of these claims is invalid.

Independent claim 1 and dependent claims 2 and 3 are each directed to a specific crystalline form of tapentadol hydrochloride, namely polymorph Form A. [*See* '364 patent at 18:66-67, 19:5-6, 19:11-12.] The claims are drafted such that the crystalline Form A is described in terms of its X-ray diffraction pattern:

> The invention claimed is:
>
> **1**. A crystalline Form A of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride exhibiting at least X-ray lines (2-theta values) in a powder diffraction pattern when measured using Cu K_α radiation at 15.1±0.2, 16.0±0.2, 18.9±0.2, 20.4±0.2, 22.5±0.2, 27.3±0.2, 29.3±0.2 and 30.4±0.2.
>
> **2**. The crystalline Form A of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride according to claim **1** exhibiting at least X-ray lines (2-theta values) in a powder diffraction when measured using Cu K_α radiation at 14.5±0.2, 18.2±0.2, 20.4±0.2, 21.7±0.2 and 25.5±0.2.
>
> **3**. The crystalline Form A of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride according to claim **1** exhibiting an X-ray pattern (2-theta values) in a powder diffraction when measured using Cu K_α radiation essentially the same as that provided in FIG. **1**.

['364 patent at 18:65-19:15.]

Claim 25 is directed to a pharmaceutical composition comprising crystalline Form A of tapentadol hydrochloride, described in terms of its X-ray diffraction pattern.

> **25.** A solid pharmaceutical composition comprising, as an active ingredient, a crystalline Form A of (–)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride exhibiting at least X-ray lines (2-theta values) in a powder diffraction pattern when measured using Cu K_α radiation at 15.1±0.2, 16.0±0.2, 18.9±0.2, 20.4±0.2, 22.5±0.2, 27.3±0.2, 29.3±0.2 and 30.4±0.2, and at least one suitable additive or auxiliary substance.

['364 patent at 20:56-63.]

i. Inherent Anticipation

Defendants contend that the asserted claims of the '364 patent are invalid under 35 U.S.C. § 102(b) as inherently anticipated by Example 25 of the '737 patent. [PTO ¶ 1469.] To prove that the '364 patent is inherently anticipated, Defendants bear the burden of proving by clear and convincing evidence that Example 25 "necessarily and inevitably" produces the claimed invention, Form A of tapentadol hydrochloride. *See Schering*, 339 F.3d at 1379.

Defendants argue that polymorphic Form A of tapentadol hydrochloride in the asserted claims, is inherently anticipated because "Example 25 of the '737 patent describes a procedure for making tapentadol hydrochloride crystals that inevitably results in at least some Form A." [Defs. Br. at 18.] On this issue, Defendants presented the testimony of Dr. Jonathan Steed and Dr. Adam Matzger. Plaintiffs respond that Defendants have not proven that the procedure set forth in Example 25 necessarily and inevitably results in Form A. On this issue, Plaintiffs presented the testimony of Dr. Joel Bernstein and Dr. William Roush.

It is undisputed that the '737 patent (including Example 25) does not explicitly mention polymorphs and it does not disclose the crystal form of any chemical compound, including tapentadol hydrochloride. Ultimately, the dispute on this issue is whether Defendants have met their burden of proving by clear and convincing evidence that the practice of the procedure set forth in Example 25 "necessarily and inevitably" results in the production of polymorphic Form A

of tapentadol hydrochloride. *See Schering*, 339 F.3d at 1379. For the reasons that follow, the Court finds that Defendants have failed to meet that heavy burden.

1. The procedure set forth in Example 25 of the '737 patent

While the invention claimed in the '364 patent is a specific polymorphic form—namely, Form A—of tapentadol hydrochloride, Example 25 of the '737 patent describes a procedure for synthesizing tapentadol hydrochloride without reference to the polymorphic form being synthesized. The Court begins by discussing that procedure, which contains three steps:[23]

(1) Step 1 involves a series of sub-step reactions in which compound (-1) is reacted under the specified conditions to synthesize compound (-22).[24] ['737 patent at 18:51-19:2.]

(2) Step 2 involves a series of sub-step reactions in which compound (-22) is reacted under the specified conditions to synthesize compound (-23).[25] ['737 patent at 19:18-47.]

[23] The '593 patent does not explicitly disclose the three steps of Example 25 but instead states that they are identical to the three steps of Example 24, with the only difference being the starting material. The starting material for Example 25 is compound (-1), chemically named (–)-(2S,3S)-1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol hydrochloride. Compound (-1) is the enantiomer of (+1), which is the starting material for Example 24. Accordingly, to convert the procedure of Example 24 to the procedure of Example 25, each "(+)" becomes a "(–)"and each "R" becomes an "S", and vice versa.

[24] The chemical name of compound (-22) is (–)-(2S,3S)-[3-Chloro-3-(3-methoxyphenyl)-2-methylpentyl]-dimethylamine hydrochloride.

[25] The chemical name of compound (-23) is (–)-(2S,3S)-[3-(3-methoxyphenyl)-2-methylpentyl]-dimethylamine hydrochloride.

(3) Step 3 involves a series of sub-step reactions in which compound (-23) is reacted under the specified conditions to synthesize compound (-21),[26] which is tapentadol hydrochloride. ['737 patent at 19:49-67.]

[*See* 3/15 Tr. (Steed) at 191:19-193:19; Steed Demonstrative 4.] The tapentadol hydrochloride product is not formed until the end of Step 3 of the three-step synthesis described in Example 25. [DFOF ¶ 1009; 3/15 Tr. (Steed) at 190:20-191:11, 193:11-19.]

In the first sub-step of Step 3, compound (-23) is dissolved in hydrobromic acid, at which point it is no longer a crystalline solid because it is in solution. [DFOF ¶ 109; '737 patent at 19:52-53; 3/10 Tr. (Buschmann) at 176:8-21.] Once the compound is in solution, the Step 3 sub-step reactions first result in the free base form of tapentadol (*i.e.*, tapentadol without the hydrochloride) in solution. [DFOF ¶ 1010; 3/15 Tr. (Steed) at 193:11-19.] The final sub-step reaction in Step 3 (addition of trimethylchlorosilane/water to the solution) is the point in the synthesis at which the tapentadol hydrochloride product crystallizes out of the solution. [DFOF ¶ 1010; 3/15 Tr. (Steed) at 191:4-11, 193:20-25; 3/21 Tr. (Bernstein) at 262:17-23.]

2. Evidence presented on inherent anticipation

On the issue of inherent anticipation, the parties presented evidence of samples of tapentadol hydrochloride that were purportedly synthesized in accordance with the procedure of Example 25. The Court addresses these samples as follows.

a. The University of Wisconsin

In support of their inherent anticipation contention, Defendants commissioned scientists at the University of Wisconsin to perform a synthesis that Defendants contend is consistent with the

[26] The chemical name of compound (-21) is (–)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride.

procedure of Example 25. The University of Wisconsin scientists' task was "to reproduce step three of Example 25." [PFOF ¶ 417; 3/16 Tr. (Steed) at 32:6-19, 33:16-20.] Dr. Steed testified as to the University of Wisconsin scientists' performance of each of the sub-step reactions in Step 3, which resulted in the crystallization of the white powder tapentadol hydrochloride product sample. [DFOF ¶¶ 1019-1022; DTX-298; 3/15 Tr. (Steed) at 206:22-213:10; Steed Demonstratives 6-7.] The XRPD analysis that was performed on the product sample shows that the University of Wisconsin scientists produced a mixture of Form A and Form B—*i.e.*, they produced some Form A tapentadol hydrochloride crystals and some Form B tapentadol hydrochloride crystals. [DFOF ¶ 1023; DTX-297; 3/15 Tr. (Steed) at 215:13-217:20; 3/22 a.m. Tr. (Bernstein) at 6:8-11.] This result, Defendants contend, is proof that performing the procedure of Example 25 produces Form A of tapentadol hydrochloride in anticipation of the '364 patent.

In challenging Defendants' inherent anticipation evidence, Plaintiffs contend that the University of Wisconsin scientists did not faithfully follow the procedure of Example 25 because they only performed Step 3 of the synthesis and did not start at the beginning with Step 1. [PFOF ¶ 416; 3/15 Tr. (Steed) at 195:18-196:3, 205:14-18.] Plaintiffs contend that, in general, a faithful reproduction requires going back to the beginning of the procedure and starting where the inventor started because each step in the procedure can affect the nature of the final product. [*See* PFOF ¶¶ 422-23; 3/21 Tr. (Bernstein) at 238:15-18, 238:22-239:5; 3/16 Tr. (Steed) at 28:11-16.] In this case, Plaintiffs' expert testified that a faithful reproduction would have required completing each of the steps in Example 25. [*See* PFOF ¶ 422; 3/22 p.m. Tr. (Roush) at 42:22-43:2.] As discussed below, Plaintiffs presented evidence of syntheses in which a Grünenthal technician performed all of the steps of Example 25. [*See infra.*] Because the University of Wisconsin's synthesis did not

begin at Step 1, Plaintiffs contend it was "a truncated 'reproduction' . . . unfaithful to Example 25" [*see* Pls. Br. at 36] and is, therefore, not proof of inherent anticipation.

Defendants responded to Plaintiffs' criticism of the University of Wisconsin sample by offering Dr. Steed's explanation of the reasoning behind Defendants' decision to only commission the performance of Step 3. Dr. Steed explained that Defendants commissioned only Step 3 (and not Steps 1 and 2) because the starting material for Step 3 is known and is immediately placed into solution at the beginning of Step 3, at which point the sample does not have a crystal structure. [*See* DFOF ¶¶ 1008-1009; '737 patent at 19:52-53; 3/15 Tr. (Steed) at 191:4-24, 193:11-19; 3/10 Tr. (Buschmann) at 176:8-21.] The remainder of Step 3 occurs in solution and the crystallized tapentadol hydrochloride does not form until the very last sub-step reaction of Step 3. [DFOF ¶ 1010; 3/15 Tr. (Steed) at 191:4-11, 193:20-25; 3/21 Tr. (Bernstein) at 262:17-23.] Accordingly, Defendants contend that Step 3 is "the only one that's relevant in terms of defining the polymorphic form and of course the conditions under which it occurs." [*See* DFOF ¶ 1010; 3/15 Tr. (Steed) at 194:8-10, 205:19-206:1.]

Ultimately, the parties have offered competing views as to whether the University of Wisconsin faithfully performed the procedure of Example 25. It is Defendants' burden to prove inherent anticipation by clear and convincing evidence. The record reflects only one synthesis by the University of Wisconsin scientists, which consisted of less than all of the steps enumerated in the patent and produced a mixture of Form A and Form B crystals. Plaintiffs contend that the University of Wisconsin testing is insufficient given its shortcomings, particularly in light of the remainder of the record.

b. Grünenthal technician Marita Müeller

In further opposition to Defendants' inherent anticipation position, Plaintiffs presented evidence of their own samples of tapentadol hydrochloride synthesized using what they contend

was the procedure of Example 25. Grünenthal technician Marita Müeller made four attempts (three in 2002 and one in 2009) to synthesize tapentadol hydrochloride in accordance with the procedure of Example 25. [PFOF ¶ 393; 3/10 Tr. (Gruss) at 257:17-24.] Ms. Müeller began at the beginning of Example 25 and performed each step of the synthesis. [PFOF ¶ 394; 3/22 a.m. Tr. (Roush) at 27:9-28:13.] It is undisputed that two of Ms. Müeller's syntheses (her first and third syntheses) produced tapentadol hydrochloride samples that contained only Form B. [PFOF ¶ 394; 3/16 Tr. (Steed) at 44:19-22; 3/16 Tr. (Matzger) at 112:11-14; 3/22 p.m. Tr. (Roush) at 29:7-23.] In 2002, and again at trial, Dr. Gruss reviewed the results of XRPD analysis from Ms. Müeller's tapentadol hydrochloride samples and concluded that both of Ms. Müeller's samples produced only Form B with no Form A. [PFOF ¶¶ 397-98; 3/10 Tr. (Gruss) at 259:21-260:3, 260:15-262:22; PTX-491_C.] The expert witnesses agreed with Dr. Gruss's conclusions. [PFOF ¶¶ 399-400, 401, 409; 3/21 Tr. (Bernstein) at 222:12-228:10; Bernstein Demonstrative at 13-17; DTX-491_C; 3/16 Tr. (Steed) at 7:17-8:18.] Thus, Plaintiffs contend, following the procedure of Example 25 can produce tapentadol hydrochloride that is only Form B.

Defendants, however, challenge Ms. Müeller's syntheses as unfaithful to Example 25. Defendants' expert, Dr. Steed, reviewed the records of Ms. Müeller's work and testified that, in his opinion, Ms. Müeller made mistakes in her synthetic process that rendered her syntheses unfaithful to Example 25. [DFOF ¶¶ 1045-46; 3/15 Tr. (Steed) at 218:11-219:9, 220:22-221:5.] Plaintiffs, responded by presenting evidence Dr. Steed's criticisms were inaccurate or irrelevant. [*See, e.g.,* PFOF ¶ 394; 3/22 p.m. Tr. (Roush) at 27:9-28:13.]

Specifically, Dr. Steed first identified problems with the amount and character of Ms. Müeller's starting material [3/15 Tr. (Steed) at 221:11-18; PTX-567_T at GRT-NUC00110768_T] but he later admitted that the experiment was appropriately scaled [PFOF ¶ 404; 3/16 Tr. (Steed)

at 42:2-5]. Second, Dr. Steed noted problems with the drying step which could result in bromide impurities [DFOF ¶ 1049; 3/15 Tr. (Steed) at 224:25-225:25] but Dr. Roush explained that the drying was sufficient and would not result in impurities [PFOF ¶ 406; 3/22 p.m. Tr. (Roush) at 32:22-33:11]. Third, Dr. Steed testified that Ms. Müeller failed to premix TMCS (trimethylchlorosilane) and water in the final crystallization step such that hydrochloric acid was not generated and impurities were introduced [DFOF ¶ 1050; 3/15 Tr. (Steed) at 226:1-25; PTX-567_T] but Dr. Roush testified that it would have been unsafe to premix the TMCS and water and that adding them separately would not change the reaction [PFOF ¶ 407; 3/22 p.m. Tr. (Roush) at 34:21-35:25]. Fourth, Dr. Steed noted that at the end of Ms. Müeller's synthesis, when crystals did not fall out of the solution spontaneously, she improvised by immersing the mixture in an ice bath to get a solid. [*See* DFOF ¶ 1051; 3/15 Tr. (Steed) at 227:1-14; Müeller Depo. at 63:14-24, 64:25-65:2, 65:5-11, 66:4-19.] But Dr. Roush testified that stirring in an ice bath is a standard laboratory procedure in order to obtain crystals. [PFOF ¶ 408; 3/22 p.m. Tr. (Roush) at 36:12-38:1.]

Defendants also presented the testimony of Drs. Steed and Matzger that the beige or yellow color of Ms. Müeller's tapentadol hydrochloride product samples was indicative of an impure product. [DFOF ¶¶ 1052-53, 1056; DTX-1202; DTX-1206; 3/10 Tr. (Buschmann) at 128:4-18; Müeller Depo. at 68:6-9, 78:1-5; PTX-567_T at GRT-NUC00110768_T; DTX-10003_0015; 3/16 Tr. (Matzger) at 99:7-14; 3/15 Tr. (Steed) at 227:15-19, 228:19-21.] However, Dr. Roush confirmed that color is not necessarily indicative of an impure product. [3/22 p.m. Tr. (Roush) at 29:24-30:21.] Furthermore, there is no color identified in Example 25. [PFOF ¶ 414; 3/16 Tr. (Matzger) at 131:24-132:1.]

Defendants do not dispute that Ms. Müeller's syntheses resulted in tapentadol hydrochloride or that it was Form B. [*See* 3/16 Tr. (Steed) at 7:17-8:22.] Defendants' criticisms of Ms. Müeller's work largely focused on impurities. [*See, e.g.*, 3/15 Tr. (Steed) at 218:11-219:9; 3/16 Tr. (Matzger) at 111:1-4, 18-21.] Defendants have posited the theory that the presence of impurities can cause a synthesis to result in Form B rather than Form A and, therefore, Ms. Müeller's work was not a faithful reproduction of Example 25 because it contained too many impurities. [*See, e.g.*, 3/15 Tr. (Steed) at 194:11-22; 3/21 Tr. (Bernstein) at 256:21-257:18; *see also* DFOF ¶¶ 1060-78; DTX-1158_0002-03; DTX-1242; 3/21 Tr. (Bernstein) at 268:3-6, 271:20-272:14, 274:14-19, 277:11-20; 3/10 Tr. (Buschmann) at 201:23-202:2; 3/15 Tr. (Steed) at 194:11-22; DTX-1242_0013; DTX-1075_0008; DTX-1279_0003-04; 3/16 Tr. (Matzger) at 84:25-85:22, 87:18-22, 88:7-21.] Defendants argue that when Example 25 is faithfully performed, the product will be largely free of impurities and Form A will result. [*Id.*]

However, Plaintiffs emphasize that Example 25 does not contain a purity limitation. [PFOF ¶ 414; 3/16 Tr. (Matzger) at 131:12-21.] Indeed, Defendants' experts admitted that a POSA performing Example 25 would expect to get some impurities because all chemical samples have impurities and they were unable to provide a "firm answer" on how much impurities would be too much to constitute a faithful reproduction of Example 25. [PFOF ¶¶ 412-13; 3/16 Tr. (Steed) at 21:14-25, 34:18-19, 3/16 Tr. (Matzger) at 114:22-24, 115:11-13, 116:14-24, 118:4-18.] Thus, Plaintiffs contend, Defendants' impurities theory is a red herring that does not impact whether or not the reproduction of Example 25 was faithful. [*See* Pls. Br. at 37.]

Similar to the University of Wisconsin sample discussed above, the parties have offered extensive competing evidence as to whether Ms. Müeller's syntheses were faithful reproductions of Example 25. Notwithstanding Defendants' challenges, Ms. Müeller's syntheses, during which

she performed all of the steps of Example 25 and produced Form B, weigh against a determination that Defendants have proven inherent anticipation by clear and convincing evidence.

c. '364 patent Example 2 starting material

There is one additional tapentadol hydrochloride sample on which Defendants rely to demonstrate inherent anticipation. That sample is the internal Grünenthal sample that was the starting material for '364 patent Example 2 ("Ex. 2 Starting Material"), which Defendants point to as a sample of Form A prepared according to Example 25. [DFOF ¶¶ 1024-28; DTX-144_0007-09; DTX-1001_0005, 13-14 (Tables 1-3); 3/11 Tr. (Gruss) at 56:11-14, 62:24-63:1; '364 patent at 5:39-41.] However, as discussed, the parties have differing views on what constitutes a faithful performance of Example 25. [*See supra*.] Given the dearth of evidence as to the execution of the process for preparing the Ex. 2 Starting Material, the Court does not find this sample to be sufficient evidence that performing Example 25 necessarily and inevitably produces Form A.

3. Defendants' evidence does not carry their burden on inherent anticipation

"[I]f the teaching of the prior art can be practiced in a way that yields a product lacking the allegedly inherent property, the prior art in question does not inherently anticipate." *Cephalon, Inc. v. Watson Labs., Inc.*, 939 F. Supp. 2d 456, 465 (D. Del. 2013). Thus it is insufficient for Defendants to demonstrate that performing Example 25 ***can*** produce Form A; rather, they must show by clear and convincing evidence that performing Example 25 ***necessarily and inevitably*** produces Form A—*i.e.*, that Example 25 cannot be performed without producing Form A. *See Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047-48 (Fed. Cir. 1995) (affirming the district court's finding of no inherent anticipation where testing evidence demonstrated that the prior art example "could yield crystals of either polymorph").

Defendants have posited that Example 25 produced Form A crystals on two occasions—the University Wisconsin's sample and the Ex. 2 Starting Material. Defendants have failed to put

forth sufficient evidence to meet their burden of showing that Example 25 necessarily and inevitably produces Form A crystals. In fact, the University of Wisconsin's synthesis generated a mixture of Form A crystals and Form B crystals, thus suggesting that the prior art example could yield crystals of either the claimed polymorph or a different polymorph. *See Cephalon*, 939 F. Supp. 2d at 465. Defendants have not clearly convinced this Court that Example 25 cannot be performed without producing Form A. Moreover, Ms. Müeller performed what Plaintiffs have argued was a faithful reproduction of Example 25 and got what Defendants admit was a sample of only Form B tapentadol hydrochloride. [*See supra.*]

Under the law, even if Defendants have shown that following the procedure of Example 25 ***can*** produce Form A tapentadol hydrochloride, that showing would be insufficient to meet their burden on inherent anticipation. *Cephalon*, 939 F. Supp. 2d at 465. The evidence presented at trial by both parties leaves this Court unconvinced that practicing the procedure of Example 25 will ***necessarily and inevitably*** result in Form A. *See Glaxo*, 52 F.3d at 1047-48; *Cephalon*, 939 F. Supp. 2d at 470 ("[T]he court concludes that the defendants have not met their burden of demonstrating that [the prior art example] necessarily and inevitably results in [the claimed polymorph form] and, therefore, have not proved invalidity by inherent anticipation."). Accordingly, the Court finds that the '364 patent is not inherently anticipated by Example 25 of the '737 patent.

ii. Obviousness

Defendants allege that the asserted claims of the '364 patent are invalid for obviousness under 35 U.S.C. § 103. [PTO ¶¶ 1470, 1246-62.] To prove that the '364 patent is obvious, Defendants bear the burden of proving by clear and convincing evidence that the invention of the '364 patent—polymorphic Form A of tapentadol hydrochloride—would have been obvious to a POSA in 2004 at the time of the invention. *See KSR*, 550 U.S. 398.

Defendants contend that Form A of tapentadol hydrochloride would have been obvious in view of the '737 patent in combination with common knowledge in the field about polymorph screening such as found in FDA Guidance [DTX-290] and a 1995 article about polymorph screening published by Dr. Stephen Byrn (the "Byrn article") [DTX-755]. On this issue, Defendants presented the testimony of Dr. Steed. Plaintiffs argue that the claims of the '364 patent were not obvious because polymorphism and the claimed Form A are fundamentally unpredictable. [PTO ¶¶ 697-716; Pls. Br. at 38.] On this issue, Plaintiffs presented the testimony of Dr. Joel Bernstein.

1. Obviousness analysis

As discussed above, the obviousness inquiry requires analysis of four factors: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) secondary considerations of non-obviousness. *See Graham*, 383 U.S. at 17-18.

a. The scope and content of the prior art

In analyzing the question of obviousness, the Court must first look at the scope and content of the prior art. *See Graham*, 383 U.S. at 17-18. In this case, the Court evaluates the disclosure of the '737 patent as well as the prior art knowledge about crystalline forms and polymorph screening.

i. The '737 patent

The '737 patent discloses many compounds, one of which is tapentadol hydrochloride. [PFOF ¶ 450; 3/21 Tr. (Bernstein) at 209:14-21; 3/22 a.m. Tr. (Bernstein) at 18:7-17.] The '737 patent states that tapentadol hydrochloride is made in crystalline form, but it does not discuss the crystal structure. [DFOF ¶ 1502; 3/15 Tr. (Steed) at 253:17-21; 3/21 Tr. (Bernstein) at 220:9-12.] The word "polymorph" does not appear in the '737 patent.

ii. Knowledge about crystal forms

The crystal form landscape for a particular compound can include polymorphs, solvates, hydrates, and polymorphs of solvates and hydrates. [PFOF ¶ 442; 3/21 Tr. (Bernstein) at 211:1-212:17.] Dr. Bernstein testified that about 30 to 35% of all compounds are polymorphic. [PFOF ¶ 446; 3/21 Tr. (Bernstein) at 202:23-203:1.] However, it is impossible to predict whether a compound will have multiple crystalline forms, how many it will have, and which forms it will have. [PFOF ¶¶ 443-47; 3/21 Tr. (Bernstein) at 197:6-14 ("[N]o crystal form is predictable."), 200:15-201:19 ("[T]here is no, no molecular feature which can be used as a predictor of polymorphism."), 204:19-205:25; PTX-681 at 241 ("[T]he state of our knowledge and understanding of the phenomenon of polymorphism is still such that we cannot predict with any degree of confidence if a compound will be polymorphic, prescribe how to make possible (unknown) polymorphs, or predict what their properties might be."); DTX-930_0022 ("Unlike salts, which for the most part can be prophetically claimed based on an understanding of the chemical structure of the compound and its ionization constants, the existence and identity of hydrates, solvates, co-crystals and polymorphs have defied prediction."); PTX-693 at JN_NUCYNTA_0064169 ("One of the continuing scandals in the physical sciences is that it remains in general impossible to predict the structure of even the simplest crystalline solids from a knowledge of their chemical composition.").]

iii. Polymorph screening

As early as 1987, the FDA had issued guidelines indicating that "[a]ppropriate analytical procedures should be used to determine whether (or not) polymorphism occurs." [DFOF ¶ 1503; DTX-290_0037; 3/15 Tr. (Steed) at 253:25-255:8.] Such appropriate measures include polymorph screening. [3/15 Tr. (Steed) at 253:21-24; *see also* DFOF ¶ 1504; DTX-755_0001 ("Interest in the subject of pharmaceutical solids stems in part from the [FDA]'s drug substance guideline that

states 'appropriate' analytical procedures should be used to detect polymorphic, hydrated or amorphous forms of the drug substance.").]

Dr. Steed testified that screening for polymorphs is a routine part of pharmaceutical companies' drug development. [3/15 Tr. (Steed) at 253:21-24.] Dr. Buschmann testified that, regardless of regulatory guidelines, it was important to know if tapentadol hydrochloride was polymorphic "not only [for] the regulatory bodies, it was important for any further developments that, to have knowledge of solid form characteristics." [DFOF ¶ 1506; 3/10 Tr. (Buschmann) at 162:16-163:4; *see also* 3/11 Tr. (Gruss) at 78:1-19.] Once tapentadol hydrochloride entered clinical development, Grünenthal considered it "important also to take consideration of the so-called solid phase of the compound intended for oral use," which included "investigat[ing] the hydrochloride salt if different polymorphs may exist." [DFOF ¶ 1503; 3/10 Tr. (Buschmann) at 77:17-78:4.] By 2000, Grünenthal generally understood that pharmaceutical companies "take consideration of polymorphism when they are developing pharmaceutical compounds." [DFOF ¶ 1510; 3/11 Tr. (Gruss) at 77:1-19.]

A POSA would have understood as of June 2004 how to conduct a polymorph screen and there were publications that provided guidance on how to do such a screen. [*See* DFOF ¶¶ 1514, 1520; 3/15 Tr. (Steed) at 255:9-14.] Dr. Gruss understood at that time that polymorph screening was a common technique that involved using different common solvents and temperatures to test for polymorphs. [DFOF ¶ 1515; 3/10 Tr. (Gruss) at 228:15-21 ("[P]olymorph investigation is to apply various parameters on the crystallization like temperature ranges, like various solvents to extend as broad as possible range of investigations in order to understand and characterize the compounds or the compound under consideration.").] Dr. Bernstein has written that "[c]rystallization from solution is one of the first laboratory skills that chemists acquire, and

applying variations to the conventional methods has been the traditional strategy in the search for polymorphs." [DFOF ¶ 1516; PTX-1037 at 3.] Dr. Bernstein has also written that "[o]ne traditional strategy for screening a compound for polymorphic behavior involves the trial of a variety of solvents and solvent mixtures." [DFOF ¶ 1519; PTX-1041 at 252.]

Defendants presented the Byrn article as evidence of the knowledge in the art about common solvents and techniques that should be used in polymorph screens. [DFOF ¶ 1520; DTX-755.] The Byrn article explains steps to detect polymorphism. [DFOF ¶ 1521; DTX-755.] The Byrn article states that "[t]he first step in the polymorphs decision tree is to crystallize the substance from a number of different solvents in order to attempt to answer the question: Are polymorphs possible?" [DFOF ¶ 1522; DTX-755_0002.] The Byrn article specifically lists certain solvents to use in the recrystallization experiments, including "water, methanol, ethanol, propanol, isopropanol, acetone, acetonitrile, ethyl acetate, hexane and mixtures if appropriate." [*Id.*] Figure 1 of the article is a "Flowchart/decision tree for polymorphs." [DFOF ¶ 1521; DTX-755_0002.] The first question in the decision tree is "Polymorphs Discovered?" [*Id.*] To answer this question, the paper states "Different Recrystallizing Solvents (different polarity) – vary temperature, concentration, agitation, pH." [*Id.*] Figure 1 also identifies techniques (including XRPD) that can be used to "Test for Polymorphs." [*Id.*]

b. The level of ordinary skill in the art

The parties have proposed substantially similar definitions of a POSA for the '364 patent. All parties agree that a POSA would be a chemist, chemical engineer, or someone in a similar field who has experience in development, preparation, and characterization of polymorphic forms of compounds. [*See* PFOF ¶ 390; 3/16 Tr. (Matzger) at 69:24-70:16.]

c. The differences between the claimed subject matter and the prior art

The claimed subject matter is a polymorph form of tapentadol hydrochloride, which is one of the many compounds disclosed in the '737 patent. There is nothing in particular in the '737 patent that would have motivated a POSA studying crystal structure to select tapentadol hydrochloride from amongst the many compounds disclosed in the '737 patent. [PFOF ¶ 451; 3/16 Tr. (Steed) at 50:5-10.]

Had a POSA chosen to study the crystal form of tapentadol hydrochloride (from amongst the compounds in '737 patent), its crystal structure could have taken many forms. Had a POSA specifically decided to screen for polymorphs of tapentadol hydrochloride, a POSA would not have been able to look at the structure of tapentadol hydrochloride and predict whether it is polymorphic. [PFOF ¶ 452; 3/10 Tr. (Gruss) at 267:13-21 ("Q. Could the polymorphism of Tapentadol have been predicted from the chemical structure? A. Not to my understanding it could have not been predicted at that point in time."); 3/21 Tr. (Bernstein) at 206:3-7; 3/16 Tr. (Steed) at 50:15-20.] If it had been known that tapentadol hydrochloride was polymorphic, a POSA could not have predicted how many crystal forms it would have. [PFOF ¶ 453; 3/21 Tr. (Bernstein) at 220:23-221:3; 3/16 Tr. (Steed) at 51:2-5.] Finally, if it had been known that tapentadol had two polymorph forms, a POSA could not have predicted the structure, properties, or relative stability of any of the forms. [PFOF ¶ 454; 3/21 Tr. (Bernstein) at 221:1-11; 3/16 Tr. (Steed) at 51:6-10.]

Defendants contend that it was straightforward for Grünenthal to ask SSCI (a company founded by the same Dr. Byrn who authored the Byrn article) to "produce as many new forms of [tapentadol hydrochloride] as possible." [DFOF ¶¶ 1523-1524; 3/22 a.m. Tr. (Bernstein) at 23:6-10; 3/11 Tr. (Gruss) at 19:8-15.] Defendants presented evidence suggesting that SSCI followed known procedures (including using eight of the nine solvents listed in the Byrn article and different cooling and evaporation conditions) to conduct the polymorph screen and arrive at

the conclusion that tapentadol hydrochloride had two polymorphic forms—Form A and Form B. [DFOF ¶¶ 1525-1526; DTX-755_0002; DTX-1087_0018-19; DTX-1001_0014-15; 3/22 a.m. Tr. (Bernstein) at 28:14-29:5; 3/15 Tr. (Steed) at 257:23-259:1.] Defendants argue that "a routine polymorph screen, like the one described in the Byrn article, would have revealed Form A of tapentadol hydrochloride" as one of the two polymorphs. [DFOF ¶ 1528; 3/15 Tr. (Steed) at 259:18-260:2.]

Plaintiffs, however, presented evidence that the Byrn article merely summarized the initial question as whether a compound was polymorphic or not, condensing the many variables listed in other prior art references into a few lines. [PFOF ¶ 461; DTX-930_0003; 3/22 a.m. Tr. (Bernstein) at 44:5-45:12; DTX-755.] Plaintiffs also presented evidence that, while "solution crystallization" is a known technique that may be used to explore the polymorph landscape, it is a technique that includes a large variety of conditions that could be appropriate for a particular polymorph screen, including solvent, temperature, stirring, cooling rate, seeding, and whether an anti-solvent is used. [PFOF ¶ 459; 3/21 Tr. (Bernstein) at 214:12-215:8.] The variability of these conditions produces a huge number of possible choices that must be made during the course of a polymorph screen. [PFOF ¶ 457; 3/21 Tr. (Bernstein) at 213:20-214:10.] Ultimately, there is no way to know how a screen will proceed before beginning to experiment and a POSA has no way of knowing whether more than one form will exist or what the physical properties of the forms are. [PFOF ¶ 464; 3/21 Tr. (Bernstein) at 218:20-24, 219:21-221:11.]

In sum, Plaintiffs demonstrated that, while each individual technique performed during a polymorph screen may be routine, polymorph screening consists of an unpredictable application of those routine techniques. [*See* PCOL ¶ 668.] Plaintiffs further showed that the results of the polymorph screen—*i.e.*, the determination of the structure and properties of the polymorph forms

of tapentadol hydrochloride—would have been impossible to predict. [PFOF ¶ 452; 3/10 Tr. (Gruss) at 267:13-21; *see also* PFOF ¶¶ 443-47; 3/21 Tr. (Bernstein) at 197:6-14, 200:15-201:19, 204:19-205:25; PTX-681 at 241; DTX-930_0022; PTX-693 at JN_NUCYNTA_0064169.] As "predictability is a touchstone of obviousness," *Depuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009), Defendants have failed to meet their burden of demonstrating that the specific polymorph Form A of tapentadol hydrochloride was obvious. *See Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1358 (Fed. Cir. 2008) ("To the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on . . . 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable.").

d. Secondary considerations of nonobviousness

Neither party focused on secondary considerations of nonobviousness for the '364 patent. Accordingly, this factor does not impact the analysis.

2. Obviousness in Polymorph Patent Cases

In making this obviousness challenge to the '364 patent, Defendants are the latest in a line of defendants who have argued that newly discovered polymorphs should not be patentable under the law of obviousness. *See, e.g.*, *Cephalon*, 939 F. Supp. 2d at 490; *Merck & Cie v. Watson Labs., Inc.*, 125 F. Supp. 3d 503 (D. Del. 2015), *rev'd on other grounds*, 822 F.3d 1347 (Fed. Cir. 2016); *Takeda Pharm. Co. v. Handa Pharm., LLC,* Case No. C-11-00840, 2013 U.S. Dist. LEXIS 187604, at *232-33 (N.D. Cal. Oct. 17, 2013). In each case the defendants contended that a POSA would have been motivated to discover the claimed polymorph, and in each case the court rejected this argument. *Id.* In *Cephalon*, the court specifically noted that "for a patent challenger to establish obviousness, it is insufficient to allege a general motivation to discover an undefined solution that could take many possible forms." 939 F. Supp. 2d at 500; *see also Innogenetics, N.V. v. Abbott*

Labs., 512 F.3d 1363, 1373-74 (Fed. Cir. 2008) ("[K]knowledge of a problem and motivation to solve it are entirely different from motivation to combine particular references to reach the particular claimed method."). In *Takeda*, the court stated that "here the invention involved the selection from a broad range of available but unpredictable techniques to try to create a previously non-existent crystalline compound whose structure could not be predicted." 2013 U.S. Dist. LEXIS 187604, at *233.

Defendants attempt to distinguish the present case by arguing that "[e]ach court that has declined to find polymorph screening renders polymorph patent claims invalid has lacked the benefit of the Byrn article, or any article that evidences how the patentee followed the specific and express teachings of the prior art . . . ." [*See* DCOL ¶ 1014.] However, the Byrn article was published in 1995, long before many of the cases discussed above. [*See* DTX-755.] Moreover, while it is undisputed in this case that methods for conducting polymorph screening were known in the art, the relevant question is whether such knowledge renders the patent obvious in what courts have described as the "decidedly unpredictable field" of polymorphism. *See Cephalon*, 939 F. Supp. 2d at 501-02.

Defendants attempt to discredit Dr. Bernstein's testimony by noting his opinion that "no polymorph patent can ever be obvious" "[b]ecause [polymorphism] is not predictable." [DFOF ¶ 1530; 3/22 a.m. Tr. (Bernstein) at 30:23-31:19.] While this Court does not speak on the hypothetical question of whether every polymorph patent is nonobvious, the Court notes that Defendants' argument appears to imply the opposite extreme—that every polymorph patent is obvious. This Court does not make such a finding, which would contravene the findings of other district courts and the Federal Circuit. Accordingly, the Court finds that the asserted claims of the '364 patent are not obvious.

iii. Utility

Defendants allege that the asserted claims of the '364 patent are invalid for failure to meet the utility requirement of 35 U.S.C. § 101. [PTO ¶¶ 1471, 1288-95.] To prove that the '364 patent lacks utility, Defendants bear the burden of clearly and convincingly demonstrating that the disclosure does not provide adequate evidence of the benefit of Form A of tapentadol hydrochloride. *See Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 F. App'x 917, 925 (Fed. Cir. 2011).

Specifically, Defendants contend that the statement of utility in the '364 patent is vague and insufficient. [*see* Defs. Br. at 31; DFOF ¶¶ 2001-2013.] Alternatively, Defendants argue that the '364 does not demonstrate the superior stability of Form A over Form B, which is the stated utility. [*See* Defs. Br. at 32-33; DFOF ¶¶ 2014-27.] On this issue, Defendants presented the testimony of Dr. Matzger. Plaintiffs respond that the '364 patent has clear utility under the relevant standard. On this issue, Plaintiffs presented the testimony of Dr. Bernstein.

To establish utility, an application need only "show that an invention is useful" and "disclose a use which is not so vague as to be meaningless." *Fisher*, 421 F.3d at 1371. The '364 patent discloses several uses for Form A, such as providing "new solid forms of [tapentadol hydrochloride] useful in the treatment or inhibition of pain." ['364 patent at 1:42-45.] The '364 patent explicitly references the '737 patent [*see* '364 patent at 1:46], which teaches that tapentadol hydrochloride is useful for treating pain. [*See supra* Section IV.A.ii.] In 2004, it was generally known in the art that tapentadol hydrochloride was useful as an analgesic. [PFOF ¶ 466; DTX-260_0072; 3/22 a.m. Tr. (Bernstein) at 20:12-21:7.] Furthermore, there is no dispute that Form A of tapentadol hydrochloride is useful as an analgesic. [PFOF ¶ 465; 3/16 Tr. (Matzger) at 121:15-17; 3/21 Tr. (Bernstein) at 195:23-196:3.]

In addition to being useful as an analgesic, the '364 patent states:

> Crystalline Form A according to the invention has the same pharmacological activity as Form B but is more stable under ambient conditions. It can be advantageously used as active ingredient in pharmaceutical compositions."

['364 patent at 4:13-17.] Defendants contend that this statement is ambiguous because the terms "stable" and "ambient conditions" are not defined in the patent. [*See* DFOF ¶¶ 2003, 2006-12.] However, the Court understands these terms the same way all of the witnesses appeared to understand the terms—that Form A is the form that tends to persist (and that Form B will tend to convert to Form A) at room temperature. [*See* 3/15 Tr. (Steed) at 234:3-6 ("Q. What evidence have you seen that form A is the stable form at room temperature and that form B converts to form A at that temperature? A. The evidence is abundant."); 3/16 Tr. (Matzger) at 107:6-11 ("Q. Now, Doctor, in your opinion, is Form A of tapentadol hydrochloride the more stable form? A. Yes, of pure tapentadol hydrochloride, I think there's little question that it's the more stable form. Q. And it's more stable at room temperature? A. Yes."); 3/21 Tr. (Bernstein) at 268:3-6 ("Q. And in terms of impurities, when we're looking at the forms B and A, you agree that in fact form A is the stable form at room temperature, correct? A. That's correct."); 3/10 Tr. (Gruss) at 226:14-18 ("It is crystalline form A, Tapentadol hydrochloride, which is thermodynamically[27] stable at room temperature and more stable than the other known form B. Q. More stable than form B. Is that what you are saying? A. Yes.").]

Defendants also contend that thermodynamic stability is not necessarily useful. [*See* Defs. Br. at 32; DFOF ¶ ¶¶ 2014-22.] Defendants support this argument with evidence suggesting that the less stable form of a compound could be more pharmaceutically desirable in some instances [*see* DFOF ¶¶ 2014-20] and they contend that there is nothing in the '364 patent to suggest that

[27] *See* Errata to Trial Transcripts, ECF No. 511-1 at 10.

the more stable form of tapentadol hydrochloride is the more useful form for pharmaceutical activity [*see* DFOF ¶¶ 2020-21]. Defendants' argument, however, appears to import a requirement into the patent statute that the claimed invention be "better" than the prior art—a requirement which the Federal Circuit has declined to find in the statute. *See Demaco Corp. v. F. Von Langsdorff Licensing, Ltd.*, 851 F.2d 1387, 1390 (Fed. Cir. 1988) ("The patent statute does not require that a patentable invention be superior to all prior devices."). Moreover, Dr. Matzger admitted that in order to establish utility, the '364 patent need not establish that Form A is superior to Form B. [PFOF ¶ 470; 3/16 Tr. (Matzger) at 121:11-14.]

Lastly, Defendants contend that, even if stability is the utility of the invention, the disclosure of the '364 patent does not contain sufficient data to support the statement that Form A is more stable. [*See* Defs. Br. at 33; DFOF ¶¶ 2023-26.] However, Example 16 of the '364 patent demonstrates that Form A converts to Form B between 40 and 50 degrees Celsius (which is above room temperature)—and thus Form A is more stable at room temperature. [PFOF ¶ 471; '364 patent at 18:53-57; 3/16 Tr. (Matzger) at 80:14-18, 122:17-25; 3/21 Tr. (Bernstein) at 196:4-197:1.] Dr. Steed agreed with this conclusion; he concluded from Example 16 that Form A and Form B are an "enantiotropic pair," with Form A being stable at room temperature and Form B being stable at higher temperatures. [PFOF ¶ 473; 3/15 Tr. (Steed) at 234:13-235:21.] Thus, Example 16 of the '364 patent provides the evidence to support the statement in the patent that Form A is more stable.

For the foregoing reasons, the Court finds that Defendants have not met their burden of proving by clear and convincing evidence that the asserted claims of the '364 patent lack utility.

C. '364 PATENT – UNENFORCEABILITY

i. Unclean Hands

Defendants contend that Plaintiffs should be barred from enforcing the '364 patent under the doctrine of unclean hands. [PTO ¶¶ 1468, 1263-1287.] On this issue, Defendants bear the burden of demonstrating clearly and convincingly that the patentees intentionally engaged in misconduct during prosecution of the patent that would render it inequitable for the patent to be enforced. *See Therasense*, 649 F.3d 1276.

Specifically, Defendants argue that Grünenthal's inequitable misconduct before the USPTO was the fundamental reason the patent was granted. [*See* Defs. Br. at 34.] The '364 patent represents that Grünenthal had "surprisingly found" "a new form (Form A) of [tapentadol] hydrochloride which is different from the form already known (Form B) obtained by the procedure described in example 25 of U.S. Patent No. 6,248,737 and U.S. Pat. No. 6,344,558 as well as EP 693 475 B1." [DFOF ¶ 2028; '364 patent at 1:58-63; *see also* DTX-87_0009 ("[T]he new crystalline form A is distinct from the hitherto known crystalline form disclosed in US patent nos. 6,248,737 and 6,344,558, referred to in the application as crystalline form B.").] In the "statement of reasons for allowance" of the '364 patent, the USPTO Examiner stated:

> The crystalline form recited in the instant claims and supported by the instant Figures and throughout the specification is novel and nonobvious over the closest prior art disclosed in United States Patent no. 6,248,737. In the instant case, Applicant's[*sic*] compared the form of the closest prior art with the new crystalline form. As claimed, the new crystalline form is novel and nonobvious over the prior art form in view of the evidence provided in the instant specification.

[DFOF ¶ 2029; DTX-1361_0006.] Defendants contend that Grünenthal withheld information and provided misleading information that calls into question the veracity of the statement in the patent

and the Examiner's conclusions. Plaintiffs respond that Grünenthal did not act with unclean hands in procuring the '364 patent. [PTO ¶¶ 721-756.]

1. Presence of Form A in Grünenthal samples

Defendants contend that Form A was present in samples of tapentadol hydrochloride prepared at Grünenthal and SSCI and that it was misleading for Grünenthal to withhold that information from the USPTO. [*See* Defs. Br. at 34-35; DFOF ¶ 2035; DTX-1060; DTX-1088; DTX-1087_0016; DTX-1075; DTX-1242_0013; 3/16 Tr. (Matzger) at 84:24-88:21; *see also* 3/16 Tr. (Matzger) at 140:4-141:7.] However, as questions of novelty and obviousness are dependent on public disclosures and uses, the presence of Form A in non-public internal samples would not have formed the basis for the Examiner to reject the claims of the '364 patent. *See* 35 U.S.C. § 102 ("A person shall be entitled to a patent unless—[]the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention . . . ."). The relevant patentability question regarding the '364 patent, as discussed extensively above, is whether Example 25 necessarily and inevitably produces Form A. [PCOL ¶ 694; PFOF ¶ 482; 3/16 Tr. (Matzger) at 155:12-16.] The Examiner noted that the patentee had distinguished Form A from the form in the prior art Example 25. [DFOF ¶ 2029; DTX-1361_0006.] Plaintiffs presented evidence demonstrating that Grünenthal believed that Example 25 produced Form B [*See supra* (Marita Müeller's syntheses)], which is consistent with what Grünenthal told the Examiner. Defendants have not presented evidence showing that during prosecution Grünenthal believed that Example 25 would produce Form A and intentionally withheld that information. [*See* PCOL ¶ 694.]

2. Figure 4 in the '364 patent

Defendants contend that Grünenthal misleadingly implied that the Form B XRPD pattern in the '364 patent was generated from a tapentadol hydrochloride sample synthesized using the

procedure of Example 25 of the '737 patent, when in fact it was not.[28] [*See* Defs. Br. at 34-35.] However, the patent states only that Figure 4 is the XRPD pattern for Form B [*see* DFOF ¶ 2032; '364 patent at Fig. 4 ("XRPD pattern of Form B")], which it undisputedly is. [*See* PFOF ¶ 486; 3/16 Tr. (Matzger) at 135:24-136:17.]

The '364 patent does not say that Figure 4 is the XRPD pattern for a sample produced by the procedure of Example 25 of the '737 patent, nor does the '364 patent say that Figure 4 is the XRPD pattern for a sample discussed in any of its specific examples. Defendants appear to contend that those statements are implied by the language of some of the examples in the patent that discuss Form B having been prepared according to Example 25 of the '737 patent. [*See, e.g.,* [DFOF ¶¶ 2030-31; '364 patent at 7:35-37, 8:1-17.] Defendants also appear to ask this Court to infer deceptive intent on the part of Grünenthal for making those implied statements. [*See* DFOF ¶ 2041.] On the evidence presented and under the relevant standard for showing unclean hands, the Court does not make such findings.

Moreover, the law is clear that to find unclean hands, "deceptive intent must be 'the single most reasonable inference drawn from the evidence.'" *Ohio Willow Wood*, 813 F.3d at 1358. Here, Dr. Fischer (an inventor of the '364 patent) testified that his choice of the representative Form B pattern to be included in the patent application was not based on deceptive intent but rather his judgment as to "which were the best ones [he] had at that point in time." [*See* PFOF ¶ 488; Fischer Depo. at 292:1-10; *see also* PFOF ¶ 487; 3/16 Tr. (Matzger) at 129:13-19 (conceding that

[28] It is undisputed that the XRPD pattern of Figure 4 was generated from a sample of tapentadol hydrochloride that was not prepared according to Example 25 of the '737 patent. [DFOF ¶ 2033; 3/16 Tr. (Matzger) at 89:19-90:6; DTX-146_0022-23 (Requests for Admission Nos. 21 and 22); DTX-39_0067 (Responses to 30(b)(6) topics).]

a POSA would choose a pattern with good signal to noise ratio).] Accordingly, the Court does not find that the source of Figure 4 forms a basis for unclean hands.

3. Example 2 in the '364 patent

Defendants contend that the '364 patent is misleading because its described methods for preparing samples "were never actually performed as written in the specification." [*See* DFOF ¶ 2037.] Defendants specifically point to Example 2 in the '364 patent, which begins with "tapentadol hydrochloride [] prepared according to example 25." [DFOF ¶ 2038; '364 patent at 5:39-41.]

Defendants appear to argue that, although the Ex. 2 Starting Material was demonstrated to be Form A [*see supra* ('364 patent inherent anticipation)], Example 2 misleadingly implies that it was Form B [*see* DFOF ¶¶ 2037-38]. However, Example 2 in the '364 patent states only that the starting material was tapentadol hydrochloride, not that it was Form B. [*See* '364 patent at 5:39-41.] Moreover, the first step of Example 2 was to dissolve the tapentadol hydrochloride in acetone, at which point the tapentadol hydrochloride in solution is no longer in crystalline form. [PFOF ¶ 491; '364 patent at 5:41-45; 3/16 Tr. (Matzger) at 139:22-25; 140:1-140:3; *see also*; 3/21 Tr. (Bernstein) at 293:10-24.] As there is no false or misleading statement in the patent, the Court does not find that Example 2 forms a basis for unclean hands.

4. Raman Spectroscopy

Defendants contend that, though several examples in the '364 patent conclude by saying that the form produced "was proven by . . . RAMAN microscopic analysis," that procedure was not actually done. [DFOF ¶ 2040; 3/16 Tr. (Matzger) at 137:10-138:14; 159:10-19.] Dr. Matzger distinguished between "RAMAN spectroscopy" (which was done) and "RAMAN microspectroscopy or microscopy" (which Dr. Matzger asserted was not done). [DFOF ¶ 2040; 3/16 Tr. (Matzger) at 159:8-19.]

For the following reasons, however, the Court does not find that the '364 patent's statement about "RAMAN microscopic analysis" provides a basis for a finding of unclean hands. Other than Dr. Matzger's unexplained testimony that there is a difference between "RAMAN spectroscopy" and "RAMAN microspectroscopy," there is no other evidence in the record discussing what the difference is. Furthermore, to the extent there is a difference between the two, the record contains insufficient evidence for the Court to conclude that Grünenthal made an intentional misrepresentation. Ultimately, the sparse record on this issue does not allow Defendants to meet their burden on the defense of unclean hands.

In light of the foregoing, the Court finds that Defendants have not met their burden of clearly and convincingly proving that the '364 patent is unenforceable due to unclean hands.

D. '130 PATENT – INFRINGEMENT

Plaintiffs have asserted claims 1 and 2 of the '130 patent against all Defendants. Plaintiffs have also asserted claims 3 and 6 of the '130 patent against Alkem only.

Independent claim 1 and dependent claim 2 of the '130 patent are directed to a method of treating polyneuropathic pain by administering tapentadol hydrochloride:

> **What is claimed is:**
>
> **1. A method of treating polyneuropathic pain in a subject suffering therefrom, said method comprising administering to said subject an effective polyneuropathic pain inhibiting amount of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol**
> **or a pharmaceutically acceptable salt thereof.**
>
> **2. A method according to claim 1, comprising administering a hydrochloride salt of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol.**

['130 patent at 18:65-19:15.]

Dependent claim 3 and independent claim 6 of the '130 patent are directed to a method of treating a specific type of polyneuropathic pain—namely diabetic polyneuropathy or diabetic polyneuropathic pain—by administering tapentadol hydrochloride.

> **3. A method according to claim 1, wherein said polyneuropathic pain is diabetic polyneuropathic pain.**
>
> **6. A method of treating diabetic polyneuropathy in a subject suffering therefrom, said method comprising administering to said subject a pharmacologically effective amount of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol or a pharmaceutically acceptable salt thereof.**

['130 patent at 18:10-11, 18:16-21.]

i. Induced Infringement under 35 U.S.C. § 271(b)

Plaintiffs allege that by selling their tapentadol hydrochloride extended release tablet products, Defendants will induce infringement of the '130 patent in violation of 35 U.S.C. § 271(b). To prove induced infringement of claims 1 and 2, Plaintiffs bear the burden of demonstrating by a preponderance of the evidence that Defendants possess specific intent to encourage others to administer tapentadol hydrochloride to treat polyneuropathic pain.[29] *See AstraZeneca*, 633 F.3d at 1056. [*See* '130 patent, claims 1 and 2.] Plaintiffs must prove that Defendants possess the specific intent to actively encourage physicians, pharmacists, or patients to infringe the patent—not merely evidence that Defendants will describe a way of infringing or permit infringement. *See Takeda*, 785 F.3d at 630-31; *AstraZeneca*, 633 F.3d at 1056; *see also Shire LLC v. Amneal Pharm., LLC*, No. 11-3781, 2014 U.S. Dist. LEXIS 85369, at *15-16 (D.N.J.

[29] Similarly, to prove induced infringement by Alkem of claims 3 and 6, Plaintiffs must demonstrate that Alkem specifically intends to encourage others to administer tapentadol hydrochloride to treat DPN. [*See* '130 patent, claims 3 and 6.]

June 23, 2014) (finding that a permitted use is not necessarily an encouraged use), *aff'd and reversed on other grounds*, 802 F.3d 1301 (Fed. Cir. 2015).

In determining whether Defendants possess the requisite specific intent, it is the actions of the Defendants—in this case, the instructions in the label itself—that must be evaluated. *See Takeda*, 785 F.3d at 634. Information outside the label (*e.g.*, a physician's knowledge) is not sufficient to meet the standard. *See id.* at 631 ("The label must encourage, recommend, or promote infringement."); *see also United Therapeutics Corp. v. Sandoz, Inc.*, No. 12-1617, 2014 U.S. Dist. LEXIS 121573, at *55 (D.N.J. Aug. 29, 2014) ("If some physicians nonetheless choose to prescribe [the defendant's product] for [the patented method] . . . , the Court finds that they will do so based on their own independent belief that [prescribing the defendant's product for the patented method] provides a benefit for their patients. [The defendant]'s label does not instruct them to do so. It is not enough that a user following the instructions may end up practicing the patented method." (internal quotation marks omitted)).

1. Actavis[30]

To prove that Actavis is liable for induced infringement, Plaintiffs must demonstrate that Actavis possesses specific intent to encourage the use of its tapentadol hydrochloride extended release product for the treatment of polyneuropathic pain. Plaintiffs' evidence of this specific intent must be directed to Actavis's actions—*i.e.*, the instructions Actavis has placed in the label of its product. *See Takeda*, 785 F.3d at 634.

[30] For convenience, this section of the Opinion is drafted with resepect to Defendant Actavis. The factual findings and legal conclusions in this section also apply to Defendant Roxane. The Court will address separately the additional information contained within Roxane's label. [*See infra.* Section IV.D.i.2.]

a. Actavis's label does not encourage treatment of polyneuropathic pain.

Actavis's proposed label carves out Indication 2 but Indication 1 remains in the label. [PTO ¶ 66.] The label states:

> Tapendadol extended-release is an opioid agonist indicated for the management of:
>
> - Pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

[DFOF ¶ 2558; DTX-1653_0124; 3/11 Tr. (Weinberger) at 183:11-16.] In addition to carving out Indication 2 from its proposed label, Actavis has carved out all other references to neuropathic pain or neuropathy that are contained in the NUCYNTA® ER label. [DFOF ¶ 2559; DTX-1653.] Thus, Actavis's proposed label does not contain the words "neuropathic pain," "neuropathy," "polyneuropathic pain," or "polyneuropathy." [DFOF ¶ 2560; 3/11 Tr. (Weinberger) at 186:4-14; 3/14 p.m. Tr. (Brown) at 112:12-21.] Actavis's proposed label does not contain information about DPN clinical trials. [DFOF ¶ 2561; DTX-1653.] The only clinical trial summary in Actavis's proposed label is the CLBP study. [*Id.*]

Plaintiffs contend that, despite Actavis having carved out Indication 2 (the DPN indication) and all references to neuropathic pain from its label, Actavis still specifically intends for its product to be used to treat polyneuropathic pain. As support for this contention, Plaintiffs note that polyneuropathic pain often manifests as severe chronic pain and that it is likely that some doctors, pharmacists, and patients will use Actavis's tapentadol hydrochloride extended release product to treat polyneuropathic pain. [PFOF ¶ 221; 3/14 p.m. Tr. (Brown) at 40:18-41:23; 3/21 Tr. (Buvanendran) at 41:9-11; 3/11 Tr. (Weinberger) at 186:21-23, 226:23-227:8.] Actavis responds that, under the law of inducement, its knowledge that some physicians, pharmacists, and patients may use its product in a manner that infringes the '130 patent is insufficient to meet the specific

intent requirement for induced infringement. [*See* Defs. Br. at 39; DFOF ¶¶ 2564-65, 2569; DCOL ¶¶ 2502-2507.] Actavis further contends that, to the contrary, its act of carving out Indication 2 and references to neuropathic pain is evidence of the opposite intent—*i.e.*, intent *not* to induce. [*See* DFOF ¶ 2563.] *See Otsuka Pharm. Co., LTD. v. Torrent Pharm. Ltd.*, 99 F. Supp. 3d 461, 485 (D.N.J. 2015) ("The fact that . . . [the d]efendants actively and voluntarily removed any reference to the allegedly infringing indication, in turn, belies any suggestion that these [d]efendants acted with the specific intention to encourage infringement. Indeed, this affirmative action would seem to negate any reasonable inference of an active intent to induce infringement.").

Plaintiffs cannot meet their burden on induced infringement merely by showing that Actavis knows its product will be used to treat polyneuropathic pain. "This would seem to too easily transform that which we have held is 'legally irrelevant'—mere knowledge of infringing uses—into induced infringement." *Takeda*, 785 F.3d at 632 (citation omitted). Accordingly, Plaintiffs assert two theories as to how Actavis's label evidences specific intent to encourage infringement. Plaintiffs' first theory is that, despite the carve-out of the DPN indication, Actavis still intends for its product to be used to treat DPN because DPN is encompassed by Indication 1. [*See* PFOF ¶¶ 226, 228.] Plaintiffs' second theory is that, even with the carve-out, the inclusion of CLBP in the label is evidence that Actavis intends for its product to be used to treat polyneuropathic pain. [PFOF ¶¶ 222-225.] To support these theories, Plaintiffs rely on the testimony of Dr. Michele Brown.[31] Actavis responds by relying on the testimony of Drs.

[31] Defendants elicited testimony from Dr. Brown on cross examination concerning her professional connections with Depomed and Janssen. [*See* DFOF ¶¶ 2570-2573.] Dr. Brown was formerly a member of Janssen's Speakers' Bureau, she is currently a member of Depomed's Speakers' Bureau, and she has testified as an expert for Depomed in other cases. [DFOF ¶¶ 2573; 3/15 Tr. (Brown) at 4:20-5:6, 14:1-25.] As part of her relationship with Depomed, one of her specific responsibilities has been to educate other practitioners about Depomed's NUCYNTA® products. [DFOF ¶ 2571; 3/15 Tr. (Brown) at 6:2-13:5.]

Weinberger and Buvanendran. For the following reasons, the Court does not find either of Plaintiffs' theories persuasive.

i. Actavis's label does not contain evidence that Actavis intends for its product to be used to treat DPN

Plaintiffs contend that, despite Actavis having carved out Indication 2 (the DPN indication) from its label, Actavis still intends for its product to be used in the treatment of DPN. However, Plaintiffs have not pointed to anything in Actavis's label that could be construed as evidence of intent for the product to treat DPN. Instead, as illustrated below, Plaintiffs' evidence on this point focuses on their own NUCYNTA® ER label rather than Actavis's label. *See Takeda*, 785 F.3d at 634 (noting that, for a finding of inducement, the label of the allegedly infringing product must encourage infringement). Indeed, Dr. Brown admitted that her opinions relied on her knowledge of the exact information that Actavis carved out (*i.e.*, the presence of the DPN indication and the summary of DPN studies in the NUCYNTA® ER label).[32] [DFOF ¶ 2575; 3/14 p.m. Tr. (Brown) at 79:8-11, 80:6-81:5, 104:25-106:2; 3/15 Tr. (Brown) at 39:22-41:22.]

For example, Plaintiffs assert (and heavily rely on the notion) that that treatment of DPN is an "on-label"[33] use of Actavis's product even though Actavis's product only contains

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[32] As previously noted, Defendants presented testimony of Dr. Brown's professional relationship with Depomed, particularly regarding the NUCYNTA® products. In addition to arguing that this relationship impeaches Dr. Brown's credibility, Defendants contend that, because she has intimate knowledge of and familiarity with NUCYNTA® and tapentadol hydrochloride, her opinions about Actavis's label are not reflective of how an ordinary physician would read the labels. [*See* DFOF ¶ 2574.] *See Acorda Therapeutics Inc. v. Apotex Inc.*, No. 07-4937, 2011 U.S. Dist. LEXIS 102875, at *54 (D.N.J. Sept. 6, 2011) ("[The doctor]'s analysis was not that of a[n] ordinary doctor, who [the plaintiff] alleges will directly infringe the claims. [The doctor] is a paid member of the [plaintiff's] Speakers' Bureau with knowledge of this drug far beyond the information in the label. . . . [He] has substantially more knowledge of what conclusions to draw from the label."), *aff'd per curiam*, 476 F. App'x 746 (Fed. Cir. 2012).

[33] The term "on-label use" refers to a "use[] that [is] approved by the FDA." *See In re Plavix Mktg., Sales Practices & Prods. Liab. Litig.*, 123 F. Supp. 3d 584, 604 (D.N.J. 2015) ("[A] drug

Indication 1. [*See* PFOF ¶ 64 ("The treatment of DPN falls within Tapentadol ER's first indication . . . ."); 3/11 Tr. (Haeussler) at 125:17-23, 126:11-15.] However, to support this assertion, Plaintiffs do not point to Actavis's label but rather their own original NUCYNTA® ER label, which only contained Indication 1. [*See* PFOF ¶¶ 54, 59, 62, 66, 73, 221; 3/11 Tr. (Haeussler) at 116:22-117:1, 126:24-127:23; 3/14 p.m. Tr. (Brown) at 95:17-22, 80:6-81:5, 82:11-14.]

The Court does not find Plaintiffs' reliance on its own original NUCYNTA® ER label persuasive for two reasons. First, as discussed above, Indication 1 was supported in the original NUCYNTA® ER label by the very DPN study that Actavis has specifically carved out of its label. [PFOF ¶¶ 61-62; PTX-1499 at JN_NUCYNTA_0273457-59; 3/11 Tr. (Haeussler) at 121:17-122:16.] Second, Actavis has presented extensive evidence that when NUCYNTA® ER was only approved for Indication 1, DPN was an "off-label"[34] use that could not be promoted by Janssen. [DFOF ¶¶ 2538-44; 3/11 Tr. (Haeussler) at 140:16-24; DTX-1674_0001 ("[Indication 1] is only for moderate to severe chronic pain in adults. That is the only thing that can be said when discussing the indication. In the US, the commercial team is prohibited for promoting for a specific indication example for LBP or OA or DPN unless you have that as an indication statement."); DTX-1419_0008 ("While some are using tapentadol to treat chronic low back pain, many more are treating conditions off-label. [Such off-label c]onditions include DPN, . . . postherpetic neuralgia, ..."); DTX-1419_0025 ("Specifically, the [DPN] indication: Eases concerns for HCPs already or considering prescribing Nucynta for DPN and other neuropathic conditions off-label.").]

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prescribed for its on-label use—by definition—means that the prescription is medically reasonable for its intended purpose by virtue of the FDA approval process.").

[34] If a use is not "on-label," it is referred to as "off-label." Although a doctor may prescribe a drug for an off-label use, a pharmaceutical company may not promote its drug for off-label uses. *See* 21 U.S.C. § 331.

In fact, Janssen paid approximately $50 million dollars to conduct the study necessary to get approval for Indication 2 so that it would be able to promote NUCYNTA® ER to treat DPN [DFOF ¶ 2544; 3/11 Tr. (Haeussler) at 148:6-149:9], which is compelling evidence that NUCYNTA® ER was not previously indicated for DPN.

Defendants have also argued that Plaintiff's decision not to assert claims 3 and 6 of the '130 patent (which are directed to treatment of DPN) against Actavis suggests that Plaintiff does not believe Actavis's label promotes the product for treatment of DPN. [*See* 4/27 Sealed Tr. at 64:3-13, 65:7-66:10.] At the very least, the fact that Actavis has specifically carved out Indication 2 (and "actively and voluntarily removed any reference to" DPN) is evidence that Actavis does not specifically intend to encourage the use of the product for the treatment of DPN. *See Otsuka*, 99 F. Supp. 3d at 485.

ii. Inclusion of the CLBP study in the label is not evidence that Actavis intends for its product to be used to treat polyneuropathic pain

The only clinical study that appears in Actavis's label is the CLBP study that appeared in the original NUCYNTA® ER label as one of two studies supporting the approval of Indication 1. [DFOF ¶ 2561; DTX-1653.] In the context of the approval of Indication 1, that CLBP study appears to have been considered by the FDA, and in fact by Janssen itself, to be a study of nociceptive pain. [*See* DFOF ¶ 2527; 3/11 Tr. (Haeussler) at 116:22-24; 152:5-154:19; DTX-2007_0006 (emphasis added); *see also* DTX-2007_000107.] In light of this characterization, the Court does not find the presence of that study in Actavis's label to be evidence that Actavis specifically intends the drug to be used for polyneuropathic pain.

Specifically, in the FDA's feedback to Janssen about the two studies supporting Indication 1, the FDA stated that "the efficacy of Tapentadol ER in the treatment of chronic pain was established from two positive adequate and well-controlled trials (Studies 11 and 15) . . . ."

[DTX-2007_0007.] Study 11 was a study of patients with CLBP and Study 15 was a study of patients with DPN. [DTX-2007_000105.] As characterized by the FDA's Primary Clinical Reviewer, these two studies had "different populations (LBP and DPN), and different types of pain (nociceptive pain and neuropathic pain)." [DTX-2007_000107.] Accordingly, in its Medical Review, the FDA noted:

> Based on the Clinical Review of Dr. Eric Brodsky, dated 8/19/10, the efficacy of Tapentadol ER in the treatment of chronic pain was established from two positive adequate and well-controlled trials (Studies 11 and 15) with supportive evidence from Study 8. The two positive trials had . . . ***different populations (low back pain [LBP] and painful diabetic peripheral neuropathy [DPN]), and different types of pain (nociceptive and neuropathic)***, thereby providing heterogeneous designs and populations for study of Tapentadol ER.

[DFOF ¶ 2527; DTX-2007_0006 (emphasis added).] Thus, the FDA's characterization of the two studies was that: Study 11, which studied CLBP, was a study of nociceptive pain; and Study 15, which studied DPN, was a study of neuropathic pain. [*Id.*] Plaintiff's fact witness for issues related to regulatory approval of the NUCYNTA® products, Dr. Haeussler, confirmed that the FDA considered the CLBP study to be a study of nociceptive pain in the context of granting approval for Indication 1. [DFOF ¶ 2528; 3/11 Tr. (Haeussler) at 152:5-154:19.]

In addition to the FDA's and Janssen's characterizations of the CLBP study, Defendants presented scientific evidence that the study was of nociceptive pain. The study was conducted to investigate efficacy in subjects with moderate to severe chronic low back pain, but these patients were not screened for neuropathic pain before participating. [DFOF ¶ 2522; PTX-1186 at § 14.1; DTX-1660_0003; 3/14 p.m. Tr. (Brown) at 119:15-17.] The CLBP study was described in detail in a paper published in 2010 by Robert Bunyak, *et al.*, which stated that the CLBP study did not investigate efficacy of tapentadol ER for neuropathic pain. [DFOF ¶ 2524; DTX-1660 ("*Bunyak*").] Defendants presented evidence that, because the study only included information on

the effectiveness for CLBP in patients in the general population without establishing whether any of them had a neuropathic component, a physician likely would not make any assessment of whether Actavis's product was useful for neuropathic pain based on the CLBP study in Actavis's label. [DFOF ¶ 2566; 3/11 Tr. (Weinberger) at 189:3-6, 191:20-192:8.] Thus, this Court does not find the CLBP study in the label to be evidence of Actavis's intent to encourage the use of its product to treat polyneuropathic pain.

Further support for Actavis's position is found in the fact that the FDA appears generally to consider CLBP to be non-neuropathic. In a 2014 draft Guidance for Industry publication by the FDA regarding analgesic indications, the FDA stated that "[n]on-neuropathic pain conditions . . . include chronic low back pain . . . ." [DFOF ¶¶ 2534; DTX-2064_00010; *cf.* DFOF ¶ 2534; PTX-3004 at 18 (March 2016 statement by the Centers for Disease Control and Prevention ("CDC") that "muscular back pain" is nociceptive pain).] Dr. Buvanendran confirmed that CLBP is primarily a form of nociceptive pain.[35] [DFOF ¶ 2532; 3/21 Tr. (Buvanendran) at 42:6-8.]

The Court recognizes that Plaintiffs have presented evidence concerning the estimated percentage of CLBP patients who suffer from a neuropathic component. [*See, e.g.*, DFOF ¶ 2524; DTX-1660_0016.; DFOF ¶ 2525; DTX-1664_0006.] This estimated percentage varies in the literature, with some estimates ranging as high as 55%. [DFOF ¶ 2533; PTX-872 ("*Morlion*") ("approximately 20-55%")[36]; DTX-1662_0001 (estimate of 20-35%); DTX-1664_0002 (estimate

[35] Moreover, Dr. Buvanendran testified that to the extent CLBP patients suffer from a neuropathic component, it is overwhelmingly mononeuropathic in nature rather than polyneuropathic. [3/21 Tr. (Buvanendran) at 42:8-14.]

[36] Plaintiffs cite the *Morlion* reference for the proposition that "[u]p to at least 83% of CLBP patients have a polyneuropathic pain component." [*See* PFOF ¶ 225.] What *Morlion* actually states is that "approximately 20-55% of patients with chronic LBP have a >90% likelihood of a neuropathic pain component, and, in an additional 28% of patients, a neuropathic pain component is suspected." [PTX-872 at JN_NUCYNTA_1656869.] *Morlion* does not provide compelling evidence for the higher end of Plaintiffs' range.

of 37%).] However, Plaintiffs' evidence on this point is unpersuasive for the following reasons. First, it is noteworthy that Plaintiffs' evidence about CLBP does not appear to sufficiently distinguish between polyneuropathic pain (which would infringe) and mononeuropathic pain (which would not infringe). [*See* DFOF ¶ 2533.] Second, and more critically, the literature confirms that even CLBP patients who may be suffering from a neuropathic component are still suffering from pain that is primarily nociceptive. [*See* DFOF ¶ 2533; *Morlion* at JN_NUCYNTA_1656870 ("Overall, 80-90% of patients with LBP are thought to experience pain arising from a nociceptive mechanical cause.").] Ultimately, Plaintiffs' evidence estimated that pure neuropathic causes are thought to account for only 5-15% of low back pain and that number may be higher for chronic low back pain. [DFOF ¶ 2533; *Morlion* at JN_NUCYNTA_1656870.] Again, however, this estimate does not appear to account for CLBP patients suffering from mononeuropathic pain, treatment of which would not infringe the '130 patent.

At most, Plaintiffs' evidence suggests that CLBP patients, in the abstract, can have a neuropathic component to their pain. However, Defendants' evidence directly addressed the specific CLBP study in Actavis's label, demonstrating that it has been characterized as a study of nociceptive pain by Janssen and the FDA. [*See supra.*] Defendants have also raised doubts that a physician would consider prescribing a product for polyneuropathic pain based solely on the CLBP study in Actavis's label. [*See supra.*] Defendants presented evidence that, despite Plaintiffs' presentation of percentage estimates for neuropathic components, CLBP is generally considered to be nociceptive in nature. [*See supra.*] Finally, Actavis's act of removing the DPN indication and any reference to DPN from its label is evidence that Actavis does not intend for its product to be used to treat polyneuropathic pain. [*See supra.*] Thus, on the evidence in the record, Plaintiffs

have not demonstrated that the presence of the CLBP study in Actavis's label is evidence that Actavis specifically intends for its product to be used to treat polyneuropathic pain.

b. Actavis's tapentadol hydrochloride extended release product will not induce infringement of the '130 patent.

In light of the factual findings above, the Court starts with the legal premise that to find inducement, "[t]he label must encourage, recommend, or promote infringement." *Takeda*, 785 F.3d at 631. Descriptions of an infringing method are insufficient. *Id.* ("The question is not just whether instructions 'describ[e] the infringing mode,' but whether the 'instructions teach an infringing use of the device *such that* we are willing to infer from those instructions an affirmative intent to infringe the patent.'" (citation omitted)). Because Plaintiffs have not pointed to such evidence in Actavis's label, Plaintiffs have not met their burden.

Plaintiffs argue that the *Takeda* case (and other cases on which Defendants rely) is inapposite because it involved an off-label use of the drug, whereas in this case the infringing use of Actavis's product to treat polyneuropathic pain would allegedly be an on-label use. However, because Actavis's label contains only Indication 1 supported only by the CLBP study, the Court is not persuaded that treatment of polyneuropathic pain is an on-label use of Actavis's product in this case.[37] [*See supra* Section IV.D.i.1.a.i.] Accordingly, the Court does not find that Plaintiffs' distinction between on-label and off-label provides a convincing or helpful framework in this case.

Moreover, even assuming this is a case where the infringing use is on-label for Actavis's product, Plaintiffs cite no case law for the proposition that the mere fact that a use is on-label ends

[37] This can be contrasted with the Court's statement made in denying Roxane's Motion for Summary Judgment of Noninfringement of the '130 Patent that "Indication 2 [] is merely a subset of Indication 1 . . . ." [ECF No. 390.] In that context, the label at issue included both indications as well as two DPN studies, neither of which appears in the current carved out versions of Actavis's or Roxane's label.

the inducement inquiry. Indeed, Defendants cite the *Shire* case from this district, which stands for the opposite proposition—that a "permit[ted]" on-label use is not necessarily an encouraged use. *Shire*, 2014 U.S. Dist. LEXIS 85369, at *15-16. In *Shire*, the plaintiff held a patent to a method of treatment comprising administering a drug "with intake of food." *Id.* The defendants' proposed label stated that "the products may be taken 'with or without food.'" *Id.* As the court stated:

> The problem is that the statement that the medication may be taken with or without food cannot be reasonably understood to be an instruction to engage in an infringing use. As [the d]efendants contend, it is indifferent to which option is selected. At most, it may be understood to permit an infringing use, but permission is different from encouragement.

Id. at 16.

The *Shire* case is informative on the issue presented in this case. As the instruction in Actavis's label only instructs the user to administer the drug to treat severe chronic pain, which undisputedly includes nociceptive pain, it cannot reasonably be understood to be an instruction to engage in the infringing use of administering the drug to treat polyneuropathic pain. *See id.* at 15-16. Thus, even if the label permits administration for polyneuropathic pain, permission is different from encouragement. *Id.*

Plaintiffs rely heavily on the language of the Federal Circuit in *AstraZeneca LP v. Apotex, Inc.*, where the court stated:

> [T]he district court found that [the defendant] had the requisite specific intent to induce infringement because [the defendant] ***included instructions in its proposed label that will cause at least some users to infringe*** the asserted method claims."

633 F.3d, 1042, 1060 (Fed. Cir. 2010) (emphasis added). Plaintiffs contend that Actavis's label fits this description. However, even if "some users" may use Actavis's product to treat polyneuropathic pain in a way that infringes, as discussed above, the Court does not agree that Actavis's label "includes instructions . . . that will ***cause***" those users to infringe. *See id.* (emphasis

added). In *Apotex*, the court determined that following the label instruction to "titrat[e] down from the recommended starting doses ***would necessarily lead to [the infringing]*** once-daily usage." *See id.* at 1049 (emphasis added). Here, on the other hand, doctors can and likely will follow the instructions on Actavis's label to prescribe Actavis's product for noninfringing purposes, such as treating nociceptive and mononeuropathic pain. [*See infra* Section IV.D.ii (Contributory Infringement).] Furthermore, to the extent doctors prescribe Actavis's product for infringing polyneuropathic pain treatments, it will not be because they have been encouraged by Actavis's label to do so. *See Shire*, 2014 U.S. Dist. LEXIS 85369, at *15-16; *see also Takeda*, 785 F.3d at 632.

Plaintiffs have also directed the Court's attention to the recent decision from the District of Delaware in *GlaxoSmithKline LLC v. Teva Pharmaceuticals USA, Inc.*, No. 14-878, 2016 U.S. Dist. LEXIS 94438 (D. Del. July 20, 2016), where the magistrate judge addressed similar facts to this case—namely, inducement by a drug label indication that was alleged to overlap with a carved out indication. In that case, the magistrate judge explicitly rejected the defendant's argument that a finding of induced infringement should be legally precluded any time a defendant files a Section viii statement and carves out its label. *Id.* at *42-43. Instead, the magistrate judge determined at the motion to dismiss phase that, accepting all of the allegations in the complaint as true, the plaintiff had stated a claim for inducement that was plausible and should have the opportunity to present evidence of the defendant's specific intent to induce infringement through further stages of the case. *Id.* at *37-52.[38]

[38] The Court notes that in *GlaxoSmithKline*, the defendant had taken specific actions to promote the product, including issuing press releases and marketing the product as AB rated. *Id.* at *26-37. This may be contrasted with the instant case.

This Court agrees fully with the conclusion in *GlaxoSmithKline* that the mere fact that Actavis has carved out Indication 2 from its label does not preclude Plaintiff's claim for inducement as a matter of law. Indeed, that is why this case was not terminated at the motion to dismiss or summary judgment stages. [*See* Case No. 15-6797, ECF No. 55 and 56 (Opinion and Order denying Motion to Dismiss); Case No. 14-3941, ECF Nos. 195 and 196 (Opinion and Order denying motion for summary judgment of noninfringement).] Like the magistrate judge in *GlaxoSmithKline*, this Court declined to dismiss Plaintiffs' claims or grant summary judgment in favor of Defendants, thus allowing Plaintiffs the opportunity to put forth evidence at trial of Actavis's specific intent to encourage the use of their products for the treatment of polyneuropathic pain.[39] At this point, however, this case has advanced through trial and Plaintiffs had the burden of presenting evidence of that specific intent. As discussed above, Plaintiffs failed to meet that evidentiary burden.

Plaintiffs cite case law for the proposition that the label need not use the exact words in the patent to induce infringement. [*See* PCOL ¶ 559 (citing *In re Omeprazole Patent Litig.*, 258 F. Supp. 2d 221, 235 (S.D.N.Y. 2001); *L.A. Biomedical Res. Institute v. Eli Lilly & Co.*, No. 13-8567, 2014 U.S. Dist. LEXIS 185431 (C.D. Cal. May 12, 2014); *Bone Care Int'l, L.L.C. v. Roxane Labs., Inc.*, No. 09-285, 2012 U.S. Dist. LEXIS 80450 (D. Del. June 11, 2012)).] Specifically, Plaintiffs quote language from *Omeprazole* indicating that the "absence of direct instruction on infringement . . . does not foreclose finding of active inducement." [*Id.*] Plaintiffs' quote, however, is truncated

[39] In denying Actavis's Motion to Dismiss, this Court declined to "engage in specific fact-finding" as to the instructions in Actavis's label and allowed Plaintiff's declaratory judgment claim for inducement to proceed. [Case No. 15-6797, ECF No. 55 at 11-12.] Similarly, in denying Roxane's Motion for Summary Judgment of Noninfringement, the Court concluded that Plaintiffs' evidence of intent raised "questions of fact that Roxane may explore at trial." [Case No. 14-3941, ECF No. 195 at 11-12.]

and omits the end of the *Omeprazole* court's sentence: "where the intended use of products would be readily apparent to the customer." *Omeprazole*, 258 F. Supp. 2d at 235 (citing *Mendenhall v. Astec Indus., Inc.*, 887 F.2d 1094 (Fed. Cir. 1989)). This Court does not require "magic words" in the label for a finding of inducement. *See Omeprazole*, 258 F. Supp. 2d at 234-35. What is required, however, is a showing that Actavis intends its customers to use the product to treat polyneuropathic pain because that use is readily apparent to the customer from the label—as discussed above, Plaintiffs have failed to make such a showing.

Similarly, Plaintiffs cite *Bone Care* and *L.A. Biomedical*, where the courts found that even though the label did not use the exact terms of the patent, there was inducement. However, in those cases, the courts first determined that the use of the product to treat a symptom in a manner consistent with the label would directly result in the patented treatment of the underlying condition. *Bone Care*, 2012 U.S. Dist. LEXIS 80450, at *33; *L.A. Biomedical*, 2014 U.S. Dist. LEXIS 185431, at *14 ("Therefore, a once daily dosage of [the drug] to treat ED in these patients results directly in treatment of the underlying penile fibrosis and the performance of the patented method."). Here, by contrast, nociceptive pain and neuropathic pain are distinct types of pain. [*See* PFOF ¶¶ 81-91; 3/23 Tr. (Ossipov) at 160:4-14.] Noninfringing uses of Actavis's product to treat nociceptive pain or mononeuropathic pain can be entirely distinct from uses of the product to treat polyneuropathic pain. [*See id.*] Thus, Plaintiffs have not demonstrated that use of Actavis's product in a manner consistent with Actavis's label will result directly in the infringing treatment of polyneuropathic pain.

Lastly, during her testimony, Plaintiffs' expert (Dr. Brown) was asked the following question by Plaintiffs' counsel:

> What would the label look like if somebody wanted to avoid infringement of the '130 patent, in your opinion?

[3/15 Tr. (Brown) at 92:10-11.] Dr. Brown responded:

> I would put under limitations of use to prescribe this for everything but polyneuropathic pain.

[3/15 Tr. (Brown) at 92:12-13.] Dr. Brown's opinion on this matter, however, does not alter the law of inducement. As the Federal Circuit said in *Takeda*, "[t]his turns the legal test on its head." 785 F.3d at 632 n.4. It is Plaintiffs' burden to demonstrate by a preponderance of the evidence that Actavis's proposed label encourages infringement. *See id.* It is not Actavis's burden to demonstrate affirmative steps taken to make sure that others avoid infringement. *Id.*

In light of the evidence that has been presented and the relevant case law, this Court finds that Plaintiffs have failed to meet their burden of proving induced infringement by a preponderance of the evidence against Actavis.

2. Roxane

Similar to Actavis's label, Roxane's label carves out Indication 2, leaving only Indication 1:

> Tapentadol Extended-Release Tablets are an opioid agonist indicated for the management of:
>
> - moderate to severe chronic pain in adults
>
> when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

[PTO ¶ 102; DFOF ¶ 2550; DTX-1566.] Additionally, Roxane's label contains only the CLBP study but not the DPN studies. [PTO ¶ 102; DFOF ¶ 2549; DTX-2020; DTX-1566; DTX-1568.] Accordingly, regarding the indications and the clinical studies, the Court's conclusions regarding Roxane's inducement are identical to those described above with respect to Actavis. Roxane's label, however, contains two additional pieces of information to which Plaintiffs point as evidence

of Roxane's intent to encourage the use of its product for the treatment of polyneuropathic pain. The Court addresses those pieces of information as follows.

The first place where Roxane's label differs from Actavis's is that, even though Roxane's label only describes the CLBP study, it states that "the efficacy of Tapentadol ER was studied in five studies." [DFOF ¶ 2576; PTX-923.] Dr. Brown opined that a clinician would read this sentence and would then "pull the studies and [] would find the DPN." [DFOF ¶ 2576; 3/15 Tr. (Brown) at 25:19-26:24.] However, this theory of specific intent has been rejected by courts in this district. *See United Therapeutics*, 2014 U.S. Dist. LEXIS 121573, at *49-50 (rejecting the argument that "a scholarly scavenger hunt—which *may* be incited by a reference in [the defendant's] proposed label, which *may* be undertaken by some physicians, and *may* ultimately result in a discovery which leads some physicians [to directly infringe], despite [the defendant's] carve out—may constitute evidence of [the defendant's] intent to induce physicians to engage in infringing conduct" suffices for purposes of induced infringement); *see also Otsuka Pharm. Co., LTD. v. Torrent Pharm. Ltd.*, 99 F. Supp. 3d 461, 493 (D.N.J. 2015) (citing *United Therapeutics*, 2014 U.S. Dist. LEXIS 121573).

The second piece of additional information in Roxane's label is the disclaimer, which reads:

> *Information describing the use of Tapentadol Extended Release Tablets in patients with Neuropathic Pain Associated with Diabetic Peripheral Neuropathy is approved for Janssen Pharmaceuticals, Inc. However, due to Janssen Pharmaceuticals, Inc.'s marketing exclusivity rights, this drug is not labeled with that information.*

[PFOF ¶ 229; PTX-923 at ROXtap00087161.] Plaintiffs contend that this is evidence of intent because this "language would lead any reasonable prescriber to conclude that Roxane's generic product . . . safely and effectively treats DPN, but excludes a DPN indication for a non-medical reason: Janssen's 'market exclusivity.'" [Pls. Br. at 8.] Roxane argues the opposite extreme—

that this disclaimer is explicit evidence of its intent not to infringe. [Defs. Br. at 36-37.] Ultimately, the Court finds that this disclaimer cuts both ways and constitutes the sort of language that the Federal Circuit has said "cannot be combined with speculation about how physicians may act to find inducement." *Takeda*, 785 F.3d at 632. The Federal Circuit has indicated that the Court should not "look outside the label to understand the alleged implicit encouragement in the label." *Id.* at 634. While Roxane's disclaimer notes the infringing DPN use of the product, it states that the product is "***not*** labeled with that information"—*i.e.*, one would have to look outside the label to understand how to administer the product for that use. Thus, the disclaimer by itself is insufficient to encourage the use of Roxane's product to treat polyneuropathic pain.

In light of the conclusions drawn above with respect to Actavis, and the Court's conclusion that the additional information in Roxane's label does not evidence intent to induce infringement, the Court finds that Plaintiffs have failed to meet their burden of proving induced infringement by a preponderance of the evidence against Roxane.

3. Alkem

Unlike Roxane and Actavis, Alkem has not carved Indication 2 or the DPN studies out of its label. Rather, Alkem's proposed label provides that Alkem's product is indicated for management of neuropathic pain associated with DPN, which is a common type of polyneuropathic pain:

> Tapentadol extended release tablets are opioid agonist indicated for the management of:
>
> - pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
>
> - neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

[PFOF ¶¶ 204, 207; PTX-224 at ALK_TAP_36275; 3/14 p.m. Tr. (Brown) at 50:21-24.] Alkem's label also includes the two DPN studies that appear in the NUCYNTA® ER label. [PFOF ¶ 209; PTX-225 at ALK_TAP_36298-36301.]

Alkem is aware of the '130 patent and the scope of its claims covering treatment of polyneuropathic pain and DPN. [PFOF ¶ 205; PTX-220 at ALK_TAP_36173, 36178; 3/14 p.m. Tr. (Brown) at 62:8-22.] Plaintiffs presented evidence that Alkem's label, including Indication 2 for neuropathic pain associated with DPN, reflects Alkem's specific intent to instruct a physician to prescribe the product to treat DPN, which is a type of polyneuropathic pain. [3/14 p.m. Tr. (Brown) at 66:7-18.] Plaintiffs also pointed to the presence of DPN clinical studies in Alkem's label as further evidence of Alkem's specific intent to encourage the administration of its product to treat DPN. [3/14 p.m. Tr. (Brown) at 66:19-67:8.] In light of the evidence presented by Plaintiffs regarding Indication 2 and the DPN clinical studies, the Court finds that Alkem will knowingly encourage physicians, pharmacists, and patients to administer its tapentadol hydrochloride extended release product to treat DPN. [PCOL ¶ 569.] Alkem has not presented evidence that undercuts this finding. [*See* PFOF ¶ 202.] Accordingly, the Court finds that Plaintiff has met its burden of demonstrating by a preponderance of the evidence that Alkem will "knowingly induce[] infringement and possess[] specific intent to encourage another's [direct] infringement." *AstraZeneca*, 633 F.3d at 1056; *Takeda*, 785 F.3d at 630-31 ("Inducement can be found where there is [e]vidence of active steps taken to encourage direct infringement."). Thus, Alkem will induce infringement of claims 1, 2, 3, and 6 of the '130 patent because it knows and intends for its products to be used in a manner that infringes the patent.

ii. <u>Contributory Infringement under 35 U.S.C. § 271(c)</u>

To prove contributory infringement, Plaintiff must prove by a preponderance of the evidence that: (1) somebody (*e.g.*, physicians, patients, and pharmacists) will directly infringe the

'130 patent by administering Defendants' products to treat polyneuropathic pain; (2) Defendants have knowledge of the '130 patent; (3) Defendants' products have no substantial non-infringing uses; and (4) Defendants' products are a material part of the invention of the '130 patent. *See Fujitsu*, 620 F.3d at 1326. Here, the first factor is satisfied because Defendants do not appear to dispute the likelihood that their products will be administered by at least some physicians, patients, and pharmacists to treat polyneuropathic pain. [*See* PFOF ¶¶ 213, 230; 3/14 p.m. Tr. (Brown) at 61:5-13, 69:8-25, 84:6-22, 99:12-21.] As to the second factor, Defendants are aware of the '130 patent. [PTO ¶¶ 63, 90, 99.] Regarding the fourth factor, the invention of the '130 patent is treatment of polyneuropathic pain with tapentadol hydrochloride—thus, each Defendant's tapentadol hydrochloride product is a material part of the invention. [PFOF ¶ 231; 3/14 p.m. Tr. (Brown) at 91:16-24, 100:7-14.]

The evidence presented at trial focused largely on the third factor of contributory infringement—whether there are substantial non-infringing uses of Defendants' products. A non-infringing use is substantial if it is "not unusual, far-fetched, illusory, impractical, occasional, aberrant, or experimental." *Vita-Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317, 1327 (Fed. Cir. 2009). In the context of pharmaceutical products, a substantial non-infringing use must be one for which the product is authorized to be sold—*i.e.*, it must be on-label.[40] *Eli Lilly*, 435 F. App'x at 927. Thus, in this case, substantial noninfringing uses include uses for severe chronic pain that is not polyneuropathic. [3/14 p.m. Tr. (Brown) at 85:10-13.]

It is undisputed that non-infringing uses of Defendants' products exist—Dr. Brown admitted that treatment of severe chronic nociceptive pain and treatment of severe chronic mononeuropathic pain would both be noninfringing uses of the products. [DFOF ¶ 3006; 3/23 Tr.

[40] It should be noted that all three Defendants' products will contain Indication 1.

(Brown) at 59:13-20.] Dr. Brown also conceded that the labeling for Defendants' products instruct users to administer the products for pain that is not polyneuropathic. [DFOF ¶ 3005; 3/14 p.m. Tr. (Brown) at 129:22-25.] Therefore, to meet their burden on contributory infringement, Plaintiffs attempted to demonstrate that such non-infringing uses are not substantial—*i.e.*, that the majority of the on-label uses for Defendants' products will infringe the patents.

Plaintiffs argue that uses of Defendants' products to treat nociceptive and mononeuropathic pain would be rare and insubstantial. [*See* PFOF ¶¶ 232-33.] Dr. Brown testified that nociceptive pain is most often acute (rather than chronic) and typically is treated with as-needed medication (rather than around-the-clock chronic pain medication). [3/14 p.m. Tr. (Brown) at 70:17-22, 85:13-17.] Dr. Brown also testified that mononeuropathic pain, such as diabetic mononeuropathic pain, is rare as compared to polyneuropathic pain. [PFOF ¶ 233; 3/14 p.m. Tr. (Brown) at 70:23-71:1, 72:12-18, 85:18-20.] Therefore, Plaintiffs contend that most conditions that present severe chronic pain, and are thus on-label for Defendants' products, are polyneuropathic in nature—*i.e.*, the products do not have substantial non-infringing uses.

Defendants' experts, however, presented extensive evidence of substantial noninfringing uses for Defendants' products. Dr. Weinberger testified that he has, in his own practice, used tapentadol hydrochloride extended release tablets to treat pain that is not polyneuropathic. [DFOF ¶ 3009; 3/11 Tr. (Weinberger) at 204:8-13.] Dr. Buvanendran testified that in his practice he has used long-acting opioids to treat severe chronic pain conditions that are non-neuropathic. [DFOF ¶¶ 3013-3014; 3/21 Tr. (Buvanendran) at 47:1-6.] Such conditions include nociceptive conditions such as chronic non-healing ulcers, chronic ureter and kidney or bladder obstructions, osteoarthritis, and rheumatoid arthritis. [DFOF ¶¶ 3013-3014; 3/21 Tr. (Buvanendran) at 107:21-108:8, 111:22-112:21,] Dr. Weinberger and Dr. Buvanendran also presented a number of

conditions that they opined could be treated with Defendants' products that would be noninfringing because they are nociceptive or mononeuropathic. [PFOF ¶¶ 234-235; 3/11 Tr. (Weinberger) at 204:14-205:11; Weinberger Demonstrative at 18; 3/21 Tr. (Buvanendran) at 44:5-47:11, 106:23-107:6.] While Plaintiffs' expert, Dr. Brown, testified that many of the conditions identified by Dr. Weinberger and Dr. Buvanendran were acute pain conditions [PFOF ¶ 234; 3/14 p.m. Tr. (Brown) at 85:21-91:8], Dr. Brown conceded that treatment of rheumatoid arthritis and osteoarthritis would be two uses that would be noninfringing. [DFOF ¶ 3010; 3/11 Tr. (Weinberger) at 204:16-25; 3/14 p.m. Tr. (Brown) at 89:2-5.]

In discussing the noninfringing pain conditions identified by Defendants' experts, Plaintiffs contend that these pain conditions are very uncommon, such that they do not constitute "substantial" noninfringing uses. [*See* PFOF ¶¶ 246-248; 3/23 Tr. (Brown) at 9:9-10:8 (providing estimates of less than 5% for patients suffering from purely nociceptive or mononeuropathic components of the Defendants' identified conditions).] However, Dr. Buvandendran and Dr. Weinberger both testified that treating the conditions they identified with tapentadol hydrochloride extended release drugs would not be "unusual, far-fetched, illusory, impractical, occasional, aberrant, or experimental" uses of the drugs. *See Vita-Mix*, 581 F.3d at 1327. [*See* DFOF ¶ 3011; 3/11 Tr. (Weinberger) at 205:12-206:21.]

For the reasons identified above, Plaintiffs have failed to meet their burden of demonstrating that Defendants' products will contribute to infringement of the asserted claims of the '130 patent.

E. '130 PATENT – INVALIDITY

i. <u>Anticipation</u>

Defendants contend that the asserted claims of the '130 patent are invalid under 35 U.S.C. § 102(b) as anticipated by the '737 patent. [PTO ¶¶ 1456, 1304, 1321-1324.] To prove that

the '130 patent is anticipated, Defendants bear the burden of proving by clear and convincing evidence that the '737 patent discloses every element of the claimed invention, administering tapentadol hydrochloride to treat polyneuropathic pain.

Defendants contend that the '737 patent anticipates the claimed invention because it discloses tapentadol hydrochloride and describes it as being "suitable for the treatment of severe pain," which will necessarily include a subpopulation with polyneuropathic pain. [Defs. Br. at 50; DFOF ¶¶ 3502, 3504; '737 patent at 1:52-55; 3/21 Tr. (Buvanendran) at 78:8-79:2, 79:21-80:6.] On this issue, Defendants presented the testimony of Dr. Buvanendran. Plaintiffs respond that the '737 patent does not anticipate the asserted claims because it does not disclose, explicitly or inherently, the polyneuropathic pain element of the asserted claims. [Pls. Br. at 47-48; PFOF ¶¶ 503-507.] On this issue, Plaintiffs presented the testimony of Dr. Brown and Dr. Ossipov.

It is undisputed that the '737 patent does not explicitly mention polyneuropathic pain. Ultimately, the dispute on this issue is whether Defendants have met their burden of proving by clear and convincing evidence that the disclosure of "severe pain" in the '737 patent discloses, explicitly or inherently, the treatment of polyneuropathic pain. [DFOF ¶ 3502; 3/21 Tr. (Buvanendran) at 78:8-79:2.]

The question of "[w]hat a prior art reference discloses in an anticipation analysis is a factual determination . . ." *Tegal Corp. v. Tokyo Electron Am., Inc.*, 257 F.3d 1331, 1345-46 (Fed. Cir. 2001). Furthermore, "in order to anticipate, a prior art disclosure must also be enabling, such that one of ordinary skill in the art could practice the invention without undue experimentation." *Novo Nordisk Pharm., Inc. v. Bio-Technology Gen. Corp.*, 424 F.3d 1347, 1355 (Fed. Cir. 2005).

Defendants argue that "severe pain" in the '737 patent teaches the claimed polyneuropathic pain. [DFOF ¶¶ 3502, 3504; '737 patent at 1:52-55; 3/21 Tr. (Buvanendran) at 78:8-79:2, 79:21-

80:6.] On cross examination, Dr. Brown admitted that in an abstract sense, severe pain can include polyneuropathic pain, polyneuropathic pain has always been a form of severe pain, and some of the population of patients with severe pain would have polyneuropathic pain. [DFOF ¶¶ 3505-07; 3/23 Tr. (Brown) at 48:22-49:17.] Dr. Ossipov made similar admissions, outside the context of the '737 patent. [3/23 Tr. (Ossipov) at 214:8-220:16.]

Plaintiffs argue, however, that the disclosure of "pain" in the '737 patent is limited to nociceptive pain. [Pls. Br. at 47-48.] Plaintiffs emphasize that the '737 patent never mentions the word "polyneuropathic pain" or the treatment thereof. [PFOF ¶ 504; 3/23 Tr. (Brown) at 11:11-19; 3/21 Tr. (Buvanendran) at 79:21-23.] Dr. Buvanendran admitted that "the '737 patent does not explicitly or necessarily disclose polyneuropathic pain or the treatment [of] polyneuropathic pain . . . ." [PFOF ¶ 504; 3/21 Tr. (Buvanendran) at 118:17-20.]

Plaintiffs further point out that the context of the '737 patent makes clear that the word "pain" referred only to nociceptive pain. First, the only test data for pain treatment disclosed in the '737 patent is from the mouse writhing test, which is a purely nociceptive pain model. [PFOF ¶ 505; 3/23 Tr. (Brown) at 12:4-11; 3/23 Tr. (Ossipov) at 116:15-22, 120:19-121:4, 172:6-8, 238:6-22; 3/11 Tr. (Mogil) at 266:17-19, 298:19-23; 3/21 Tr. (Buvanendran) at 117:19-23.] And second, the state of the art prior to the filing of the '130 patent was such that when a physician "discussed opioids in regard to the treatment of severe pain at that time, [s/he] did think nociceptive pain." [PFOF ¶ 506; 3/23 Tr. (Brown) at 12:12-24; 3/23 Tr. (Ossipov) at 116:23-117:20.]

Dr. Brown and Dr. Ossipov both testified that the context of the '737 patent was essential to their understanding of what that patent meant by the word "pain," as distinct from their understanding of what "pain" means in an abstract sense. [3/23 Tr. (Brown) at 39:24:-40:3 ("Q. Now, Doctor, you'll agree that the '737 patent describes using tapentadol hydrochloride to treat

severe pain, correct? A. It uses it in the context of what I said earlier in regard to the writhing test and our understanding in 1994."), 86:21-87:23 ("[W]hen I said it in the entire grand scheme of the world, pain can include neuropathic and nociceptive pain, but when you're looking at the specific confines of the '737 patent, we're talking about severe pain in the context of a writhing test, which is a test of nociceptive pain, and we're talking about using an opioid analgesic to treat that pain, which is consistent with what I thought in 1997. So, again, in the context of the '737 patent, I again feel that it's a model of nociceptive pain. . . . [T]he writhing test is very important in the context here."); 3/23 Tr. (Ossipov) at 160:4-14 ("The ['737] patent only shows data for nociceptive pain, so that shows that you have compounds that are antinociceptive . . . . So, no, you can't make that jump from an antinociceptive agent in a writhing test to being effective in polyneuropathic pain. There's absolutely no connection. It's a completely different mechanism.").] Furthermore, Dr. Ossipov testified that in the absence of any context to specifically indicate neuropathic pain, when the term "pain" is used, a POSA would "default to nociceptive pain." [3/23 Tr. (Ossipov) at 226:25-227:4; *see also* 3/23 Tr. (Ossipov) at 221:22-223:1 ("It's not specified what type of pain. . . . But again, somebody in my field, in preclinical research, seeing pain at that time would be thinking of nociceptive pain.").]

Defendants contend that Dr. Brown "impermissibly" limited the meaning of the term "severe pain" in the '737 patent. [*See* DFOF ¶ 3508.] Defendants further argue that Plaintiffs' infringement position against Actavis and Roxane requires this Court to read the word "pain" in Indication 1 of the labels to include polyneuropathic pain and, thus, Plaintiffs should not be heard to argue that the word "pain" in the '737 patent is limited to only nociceptive pain. [*See* Defs. Br. at 53; DFOF ¶ 4014; 3/14 p.m. Tr. (Brown) at 103:11-104:9; 3/15 Tr. (Brown) at 72:24-73:4.] However, as discussed above, the Court has found that the word "pain" in the labels is insufficient

to demonstrate specific intent to encourage treatment of polyneuropathic pain. [*See supra.*] Moreover, the Court finds persuasive Dr. Ossipov's and Dr. Brown's testimony that a POSA would have understood the term "severe pain" in the '737 patent to be nociceptive pain.[41]

The Court further notes that the '737 patent does not appear to enable the practice of the asserted claims of the '130 patent—namely, administration of tapentadol hydrochloride for the treatment of polyneuropathic pain. There is no discussion of polyneuropathic pain in the '737 patent and there is no evidence provided regarding the efficacy of tapentadol hydrochloride for treatment of polyneuropathic pain or other considerations (*e.g.*, side effects) regarding its use. Accordingly, having not enabled the asserted claims, the '737 patent cannot anticipate the asserted claims. *See Novo Nordisk*, 424 F.3d at 1355.

Defendants bear the burden of proving anticipation by clear and convincing evidence. The Court finds that Defendants have not met their burden of proving that the '737 patent anticipates the asserted claims of the '130 patent.

ii. Obviousness-type Double Patenting

Defendants contend that the asserted claims of the '130 patent are invalid under the judicially-created doctrine of obviousness-type double patenting. [PTO ¶¶ 1458, 1426-1439.] To prove that the claims of the '130 patent are invalid for obviousness-type double patenting, Defendants bear the burden of proving by clear and convincing evidence that the asserted claims

[41] In sum, the interpretation of the word "pain" is at issue for both the infringement and validity issues of the '130 patent. In each instance, the Court interprets the word "pain" in the context of the document in which it appears and the relevant legal issue. In the context of evaluating induced infringement, the Court does not find that the word "pain" in Actavis's and Roxane's labels evidences intent to encourage use of the products for treatment of polyneuropathic pain. Here, in the context of evaluating anticipation, the Court is not clearly convinced that a POSA would have understood "pain" in the prior art '737 patent to include polyneuropathic pain because the context of the document indicates that the pain is nociceptive.

of the '130 patent are not patentably distinct from an earlier expiring patent claim that Plaintiff also owns. *Amgen*, 580 F.3d at 1374. In this case, Defendants contend that the asserted claims of the '130 patent are not patentably distinct from claim 117 of the '593 patent. [*See* DFOF ¶¶ 4006-4055.] On this issue, Defendants presented the testimony of Dr. Buvanendran.

Plaintiffs offer two alternative responses to Defendants' double patenting contentions. Plaintiffs first contend that, as a matter of law, the doctrine of obviousness-type double patenting cannot apply to claim 117 of the '593 patent. [*See* PCOL ¶ 706; PFOF ¶ 509.] Alternatively, Plaintiffs contend that the asserted claims of the '130 patent are patentably distinct from claim 117. [*See* PFOF ¶¶ 510-531.] On this issue, Plaintiffs presented the testimony of Dr. Brown.

1. Applicability of the doctrine of obviousness-type double patenting to claim 117

As a threshold issue, Plaintiffs contend that, as a matter of law, the doctrine of obviousness-type double patenting is not applicable in this case. Claim 117 in the '593 patent (*i.e.*, the earlier claim) was a claim added during the reissue prosecution of the '593 and did not issue until April 24, 2007, which was one month after the filing of the '130 patent. [*See* PFOF ¶ 509; 3/21 Tr. (Buvanendran) at 118:21-121:8.] Thus, Plaintiffs argue, claim 117 "did not exist at the time of filing of the '130 patent" and thus cannot serve as the "earlier" claim in the obviousness-type double patenting analysis. [*Id.*]

Plaintiffs' argument is inconsistent with the law and with the purpose of the obviousness-type double patenting doctrine. The Federal Circuit has explicitly stated that "the doctrine of obviousness-type double patenting continues to apply where two patents that claim the same invention have different expiration dates." *Abbvie*, 764 F.3d at 1374. In other words, it is the date the patent expires—rather than the date it is filed or issued—that determines whether the doctrine can be applied. *See id.* This interpretation is consistent with the purpose of the doctrine, which is to prevent a patent holder from extending the term of the monopoly by obtaining additional patent

claims that are not patentably distinct. *Id.*; *see also id.* at 1373 ("The ban on double patenting ensures that the public gets the benefit of the invention after the original period of monopoly expires.").

According to the Orange Book, the claims of the '593 patent (including claim 117) expire on August 5, 2022 and the claims of the '130 patent do not expire until September 22, 2028. [DFOF ¶ 4004.] Both the '593 patent and the '130 patent are commonly owned by the same entity, Grünenthal. [PFOF ¶ 4005; *see* '593 patent; '130 patent.] Accordingly, since claim 117 in the '593 patent is a claim in a patent that expires earlier than the asserted claims of the '130 patent, and both patents are owned by the same entity, claim 117 may be properly viewed as the "earlier" claim for purposes of the obviousness-type double patenting inquiry.

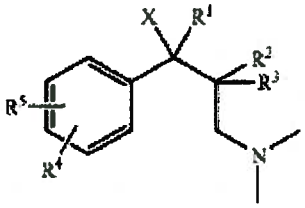
2. Application of the doctrine of obviousness-type double patenting

To evaluate obviousness-type double patenting, the Court must first identify the differences between the earlier claim (claim 117 of the '593 patent) and the later claim (claim 1 of the '130 patent). *Abbvie*, 764 F.3d at 1374. The Court must then determine whether those differences render the later claim patentably distinct from the earlier claim. *Id.*

a. The differences between the two claims

Claim 117 of the '593 patent depends from independent claim 8 of the '593 patent, and therefore includes all the elements of claim 8. *See* 35 U.S.C. § 112(d) "A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers."). Defendants demonstrated that the full claim 117 (including the limitations of claim 8) reads as follows:

> A method of treating a mammal suffering from pain, said method comprising administering to said mammal an effective analgesic amount of 1-phenyl-3-dimethyl-aminopropane compound corresponding to formula I



wherein the compound is (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylropyl-phenol hydrochloride (-21).

[DFOF ¶ 4008; *see* 3/21 Tr. (Buvanendran) at 51:8-13.] Dr. Buvanendran placed this rewritten claim 117 side-by-side with claim 1 of the '130 patent for purposes of comparison:

'593 Patent, Claim 117 (1994)	'130 Patent, Claim 1 (2007)
[Claim 8] **A method of treating a mammal suffering from pain,**	**A method of treating polyneuropathic pain in a subject suffering therefrom,**
said method comprising administering to said mammal an effective analgesic amount	**said method comprising administering to said subject an effective polyneuropathic pain inhibiting amount**
of a 1-phenyl-3-dimethyl-aminopropane compound ... **[Claim 117]** **wherein the compound is (–)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride (–21)**	**of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol or a pharmaceutically acceptable salt thereof**

[*See* 3/21 Tr. (Buvanendran) at 51:14-52:12; Buvanendran Demonstrative at 30.]

As demonstrated by the side-by-side comparison, when directly compared, there are three differences between claim 117 of the '593 patent and claim 1 of the '130 patent. [DFOF ¶ 4009; 3/21 Tr. (Buvanendran) at 51:14-52:12.] Two differences are that claim 117 of the '593 patent refers to treating a "mammal" with an "analgesic amount" while claim 1 of the '130 patent refers to treating a "subject" with a "pain inhibiting amount." [DFOF ¶ 4010; 3/21 Tr. (Buvanendran) at

51:19-52:1, 52:8-12.] It is undisputed that these differences do not render claim 1 of the '130 patent patentably distinct from claim 117 of the '593 patent. [*Id.*]

The third difference is that claim 117 of the '593 patent refers to treating "pain" while claim 1 of the '130 patent refers to treating "polyneuropathic pain." [DFOF ¶ 4010; 3/21 Tr. (Buvanendran) at 52:2-12.] The essence of the dispute on the issue of obviousness-type double patenting is whether this difference between "pain" and "polyneuropathic pain" renders claim 1 of the '130 patent patentably distinct from claim 117 of the '593 patent.

b. Whether the later claim is patentably distinct

i. Defendants' first argument – "pain" is an umbrella term

Defendants first contend that the term "pain" in claim 117 of the '593 patent is an umbrella term which includes both the concepts of nociceptive pain and neuropathic pain. [*See* DFOF ¶ 4011; 3/21 Tr. (Buvanendran) at 52:13-24.] This argument is similar to Defendants' position regarding anticipation of the '130 patent by the '737 patent—*i.e.*, that the term "pain" includes and teaches "polyneuropathic pain." With respect to anticipation, the Court has determined that, in light of the context provided by the '737 patent, a POSA would have understood the term "pain" as "nociceptive pain." [*See supra* Section IV.E.i.] As the disclosure of the '593 patent is essentially identical to the disclosure of the '737 patent, the Court's conclusion remains the same with respect to obviousness-type double patenting.

The Court notes that in the anticipation context above, the analysis was limited to what was disclosed within the four corners of the prior art '737 patent, *see Advanced Display*, 212 F.3d at 1282, whereas the obviousness inquiry allows Defendants to present evidence from other prior art references as to how a POSA would have understood the term "pain" at the time of the filing of

the '130 patent.[42] [*See* DFOF ¶¶ 4011-4021.] As such, Defendants argue that a POSA in 1994 would have understood the term "pain" to refer to a genus that includes the species of nociceptive pain (including somatic and visceral) and neuropathic pain (including mononeuropathic and polyneuropathic). [*See* DFOF ¶ 4019; 3/21 Tr. (Buvanendran) at 52:13-24.] Defendants point to prior art suggesting that the term "pain" referred to both nociceptive and neuropathic pain. [*See* PFOF ¶¶ 4015-4017; DTX-1576.] In a reference published in 1989, Dr. Donna L. Hammond discussed the nomenclature used to discuss pain, referring both to nociceptive pain and neuropathic pain. [DFOF ¶¶ 4015-16; DTX-1576_0004.] Dr. Brown and Dr. Ossipov have also conceded that, in the abstract sense, the term "pain" includes both nociceptive and neuropathic pain. [3/23 Tr. (Brown) at 86:21-23.]

Nevertheless, much like the Court's conclusion with respect to anticipation, the Court finds Defendants' evidence is limited to how Dr. Hammond, Dr. Brown, and Dr. Ossipov would have understood the meaning of the term "pain" in an abstract sense. That evidence is ancillary to the question of what "pain" means ***in claim 117 of the '593 patent.*** [*See supra* Section IV.E.i.] The Court concludes that Defendants' outside evidence does not outweigh the evidence presented as to the context of the '593 patent—namely, the nociceptive mouse writhing test that provides the only evidence of analgesia in the '593 patent disclosure. [*See* PFOF ¶ 505; 3/23 Tr. (Brown) at 12:4-11; 3/23 Tr. (Ossipov) at 116:15-22, 120:19-121:4, 172:6-8, 238:6-22; 3/11 Tr. (Mogil) at 266:17-19, 298:19-23; 3/21 Tr. (Buvanendran) at 117:19-21.] Accordingly, the Court finds that

[42] The parties essentially agree that a POSA with respect to the '130 patent would have had a working knowledge of, and experience in a field related to, neuropathic pain and treatment thereof. [PFOF ¶ 498; 3/21 Tr. (Buvanendran) at 30:3-17.] Defendants presented evidence that a POSA would have understood the term "pain" the same way in 1994 (at the time of the filing date of the '593 patent) and in 2007 (at the time of the filing date of the '130 patent). [DFOF ¶ 4013; 3/21 Tr. (Buvanendran) at 53:6-10.]

the term "pain" in claim 117 of the '593 patent is limited to nociceptive pain and therefore does not encompass all of the subject matter of the asserted claims of the '130 patent.

ii. Defendants' second argument – nociceptive pain renders obvious polyneuropathic pain

Defendants alternatively argue that even if the term "pain" in claim 117 of the '593 patent only refers to nociceptive pain, a POSA reading that claim in March 2007 (the filing date of the '130 patent) would have found it obvious to use the compound tapentadol hydrochloride to treat polyneuropathic pain. [*See* DFOF ¶ 4022; 3/21 Tr. (Buvanendran) at 59:17-23.] Defendants contend that a POSA would have known that tapentadol hydrochloride was an opioid derivative and by March 2007, there was substantial literature establishing that opioids were effective for treating polyneuropathic pain. [DFOF ¶¶ 4023-24; 3/21 Tr. (Buvanendran) at 59:24-60:9.]

Defendants presented evidence of a 2002 internal Grünenthal report in which Dr. Christoph wrote: "Thus, the old dogma of lacking efficacy of opioids in the treatment of neuropathic pain holds no longer true." [DFOF ¶ 4027; DTX-1030_0015; 3/14 a.m. Tr. (Christoph) at 101:19-23.] In that same report, Dr. Christoph noted that "several studies have proven efficacy of opioids in neuropathic pain conditions (Rowbotham et al., 1991; Dellemijn and Vanneste, 1997; Sindrup et al., 1999)." [DFOF ¶ 4027; DTX-1030_0015; 3/14 a.m. Tr. (Christoph) at 99:1-13.] Defendants also presented a 2003 internal Grünenthal report in which the inventors of the '130 patent wrote:

> Although there is a large consensus concerning the effectiveness of opioids in nociceptive pain, their efficacy in neuropathic pain was debatable until recent years (Portenoy, 1996; Dellmijn, 1999). However, several studies have proven efficacy of opioids in neuropathic pain condition (Dellmijn & Vanneste, 1997; Sindrup *et al*, 1999).

[DFOF ¶ 4026; PTX-454 at 14.]

In addition to internal Grünenthal documents, Defendants pointed to prior art studies investigating the efficacy of opioids in treating neuropathic pain. [*See* DFOF ¶¶ 4035-4047;

PTX-1141 (March 2005 study by Gilron et al. confirming the findings of earlier studies showing the efficacy of opioids in the treatment of neuropathic pain); 3/21 Tr. (Buvanendran) at 62:23-63:10; DTX-1609 (2004 treatment algorithm published by Namaka et al. showing opioids, including tramadol, as a second line treatment for neuropathic pain); 3/21 Tr. (Buvanendran) at 63:13-64:4; PTX-1131 (2005 treatment algorithm published by Finnerup discussing the use of opioids such as morphine, oxycodone, and tramadol for the treatment of polyneuropathic pain); DTX-1603 (2005 review article by Freeman studying the opioid oxycodone for treating diabetic neuropathy and describing efficacy of opioids, including tramadol, for treatment of polyneuropathic pain); DTX-1599 (2006 article by Baron reviewing more than 25 years of studies concerning the treatment of neuropathic pain, including opioids like tramadol, morphine, and oxycodone); 3/21 Tr. (Buvanendran) at 64:12-65:22.] Dr. Buvanendran testified that as a clinical practitioner he prescribed opioids in his practice to treat polyneuropathic pain. [DFOF ¶ 4048; 3/21 Tr. (Buvanendran) at 66:4-10.] Finally, Defendants presented evidence of studies that specifically investigated the efficacy of tramadol (*i.e.*, Grünenthal's predecessor drug and the drug from which tapentadol was derived) in treating polyneuropathic pain. [*See* DFOF ¶¶ 4028-4047; DTX-1605 (June 1998 study by Harati, et al. concluding that "tramadol was significantly more effective than placebo for treating the pain of diabetic neuropathy" and "[t]ramadol is an alternative to tricyclic drugs or anticonvulsants for treating the pain of diabetic neuropathy"); 3/23 Tr. (Brown) at 94:20-95:1; DTX-916 (2006 study by Hollingshead, et al. concluding that "tramadol is an effective treatment for neuropathic pain"); 3/21 Tr. (Buvanendran) at 62:11-14; DTX-1609; PTX-1131; DTX-1603; DTX-1599.]

Plaintiffs presented evidence, however, that the standard was not to prescribe opioids for neuropathic pain because neuropathic pain was generally considered to be unresponsive to opioids.

[PFOF ¶ 513; 3/23 Tr. (Brown) at 14:5-8.] Notwithstanding the discrete studies identified by Defendants above, Plaintiffs' evidence demonstrated that POSAs saw neuropathic pain as refractory to opioids (*i.e.*, either the opioid would be ineffective or would require very high doses to be effective). [PFOF ¶ 513; 3/23 Tr. (Brown) at 14:6-8, 15:4-11.] Because of this, opioids were known to show only limited effectiveness in treating neuropathic pain conditions because "they relatively quickly were reaching levels of side effects because you needed to—they needed to be dosed higher than in normal nociceptive pain conditions." [3/14 a.m. Tr. (Christoph) at 103:19-23; 3/23 Tr. (Brown) at 15:4-11.] Prescribing opioids at higher doses can cause serious problems in patients, including side effects (like nausea, vomiting, and constipation). [PFOF ¶ 514; 3/23 Tr. (Brown) at 15:12-25.] High doses of opioids can also cause destruction, dysfunction, or sensitivity of the normal nociceptive pain pathways, which can lead to conditions like hyperalgesia (where a person experiences pain at a different level and manner than a normal person would experience). [PFOF ¶¶ 514-15; 3/23 Tr. (Brown) at 15:15-16:10.]

Defendants contend that Dr. Brown's conclusion about the effectiveness of tramadol and other opioids for treating polyneuropathic pain was based only on her own clinical experience and not a review of the literature. [*See* DFOF ¶ 4034; 3/23 Tr. (Brown) at 20:16-18.] Defendants further contend that Dr. Brown improperly focused on side effects and quality of life to discount the published clinical evidence about efficacy of opioids for treating polyneuropathic pain. [*See* DFOF ¶ 4050.] The asserted claims in the '130 patent, however, are for methods of "*treating*" polyneuropathic pain. Plaintiffs presented evidence demonstrating that the effective treatment of polyneuropathic pain involves many considerations other than simply identifying a drug that exhibits efficacy in lowering a patient's pain score. [3/21 Tr. (Buvanendran) at 95:15-18; 3/23 Tr. (Brown) at 24:2-11.]

Plaintiffs also presented evidence of literature before, and even after, the 2007 filing date of the '130 patent suggesting that there was controversy surrounding the usefulness of opioids in treating neuropathic pain. [PFOF ¶¶ 519-530; DTX-1609 (Namaka et al. explained that "usefulness of narcotics [or opioids] in the treatment of chronic neuropathic pain is often debated and not very well studied"); DTX-1401 (2007 article by Dworkin et al. explaining that "[t]he management of patients with chronic [neuropathic pain] is complex and response to existing treatments is often inadequate. Even with well-established [neuropathic pain] medications, effectiveness is unpredictable, dosing can be complicated, analgesic onset is delayed, and side effects are common."); PTX-3002 (2011 article by Candiotti et al. describing the "use of opioids for the treatment of noncancer pain" as "particularly controversial"); PTX-3003 (2013 article by Dr. Buvanendran in which he stated that "[t]he use of opioids for the treatment of neuropathic pain remains controversial"); PTX-3004 (March 2016 Center for Disease Control and Prevention guidelines, which concluded: "No evidence shows a long-term benefit of opioids in pain and function versus no opioids for chronic pain" and "[e]xtensive evidence shows the possible harms of opioids."); PTX-1141 (Gilron stating that "available drugs to treat neuropathic pain have incomplete efficacy and dose-limiting adverse effects).]

In light of the conflicting evidence presented by the parties about the prior art teachings regarding opioid use to treat neuropathic pain, the Court finds that Defendants have not met their burden of demonstrating by clear and convincing evidence that a POSA would have had a reasonable expectation that tapentadol hydrochloride would be effective to treat polyneuropathic pain. Furthermore, even if Defendants had met their burden of demonstrating that a POSA would have expected efficacy (which they have not) Defendants have not rebutted Plaintiffs' evidence

that treatment of pain involves more than efficacy alone and a POSA would not have had an expectation of successfully *treating* polyneuropathic pain using tapentadol hydrochloride.

3. Prosecution history

In addition to their substantive arguments regarding obviousness, Plaintiffs contend that the arguments put forth by Defendants in this case were the same ones presented by the USPTO Examiner during the prosecution history of the '130 patent. [PFOF ¶¶ 500-501; PTX-1600 at GRT-NUC00043833-34, 43877-79.] Plaintiffs argue that despite having considered these arguments, the Examiner ultimately allowed the '130 patent claims and concluded that "the cited references do not teach []or provide adequate motivation to arrive at the instantly claimed methods" and that "the instant claims are seen to be novel and non-obvious over the teachings of the prior art." [PFOF ¶¶ 500-502; PTX-1600 at GRT-NUC00044296-97.]

Defendants contend that they are relying in this litigation on numerous prior art references that were not considered by the Examiner. [*See* DFOF ¶¶ 4029, 4032, 4035, 4040, 4042, 4044, 4046.] Moreover, Defendants contend that the prosecution history demonstrates that, even without considering the numerous references they rely on in this litigation, the Examiner first rejected the claims of the '130 patent as prima facie obvious over the '737 patent (which contains the same disclosure as the '593 patent at issue in the double-patenting inquiry). [*See* DFOF ¶¶ 4053-4055.] Defendants argue that Plaintiff did not contest the Examiner's determinations but rather rebutted the prima facie obviousness conclusion by submitting a declaration to the USPTO demonstrating unexpected results, which is a secondary consideration of nonobviousness. [*See* Defs. Br. at 55; DFOF ¶ 4053; PTX-1600 at GRT-NUC00043876-82, 43980-84, 44066-71, 44045-53.]

The Court notes that, while the Examiner's considerations and conclusions are instructive on the issue of invalidity, they must be viewed through the lens of the relevant standards of proof. It is well-settled that "[i]n civil litigation, a challenger who attacks the validity of patent claims

must overcome a presumption of validity with clear and convincing evidence that the patent is invalid." *In re Swanson*, 540 F.3d 1368, 1377 (Fed. Cir. 2008) (citing 35 U.S.C. § 282).

> In [US]PTO examinations . . . , the standard of proof—a preponderance of evidence—is substantially lower than in a civil case; there is no presumption of validity; and the examiner is not attacking the validity of the patent but is conducting a subjective examination of the claims in light of prior art.

Id. (internal citations and quotations omitted).

The Supreme Court has addressed the impact of the prosecution history on the standards and burdens of proving invalidity. *See generally Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91 (2011). In *i4i*, the Court affirmed that the "heavy burden of persuasion" borne by a patent challenger is unaltered by considerations of whether the patent examiner considered the evidence during prosecution. *Id.* at 102, 108-12.

Here, while the USPTO Examiner initially found the claims of the '130 patent prima facie obvious, that finding was based on a preponderance of the evidence standard rather than the relevant clear and convincing evidence standard applicable to this case. Furthermore, although Defendants have presented additional evidence not considered by the examiner about the meaning of "pain" and use of opioids to treat neuropathic pain, Plaintiffs have also put forth evidence counteracting these points.

In this litigation, the '130 patent claims are presumed valid and Defendants bear the burden of overcoming this presumption by presenting clear and convincing evidence of obviousness. In light of the conflicting evidence presented by the parties about the meaning of the term "pain" in the '593 patent as well as the prior art teachings regarding the controversy surrounding opioid use to treat neuropathic pain, Defendants have failed to meet their burden.

4. Secondary considerations of non-obviousness

Plaintiffs presented evidence of two secondary considerations of nonobviousness—unexpected results and long-felt need. [*See* PFOF ¶¶ 532-51.] Defendants contend that Plaintiffs' evidence was not legally probative. [*See* DFOF ¶¶ 4056-69.]

a. Unexpected results

Dr. Christoph testified about results that he considered unexpected when using tapentadol hydrochloride to treat polyneuropathic pain. First, Dr. Christoph discovered that tapentadol hydrochloride unexpectedly provided the benefit of treating mononeuropathic pain and polyneuropathic pain at a dose that did not inhibit normal nociceptive pain transmissions. [PFOF ¶¶ 533, 536; '130 patent at 16:62-66 ("In both pain models [tapentadol] produces a selective inhibition of the pathologically induced pain response, without at the same time influencing the normal pain response."); 3/14 a.m. Tr. (Christoph) at 40:15-41:8, 43:24-46:22; PTX-1600 at GRT-NUC44045-53.] This property was discovered using animal models redesigned or newly designed in Dr. Christoph's lab. [PFOF ¶ 534; 3/14 a.m. Tr. (Christoph) at 37:9-21.] Selective inhibition of neuropathic pain without affecting the nociceptive pathway beneficially allows for neuropathic pain treatment without impairing the normal protective mechanisms of nociceptive pain. [PFOF ¶ 535; 3/23 Tr. (Ossipov) at 117:21-118:23; 3/14 a.m. Tr. (Christoph) at 46:23-47:15.]

Second, Dr. Christoph discovered that tapentadol hydrochloride is more potent in the treatment of polyneuropathic pain than it is for mononeuropathic pain. [PFOF ¶ 540; 3/14 a.m. Tr. (Christoph) at 47:16-48:7; PTX-1600 at GRT-NUC44048-50.] By comparing the results from the redesigned animal models, Dr. Christoph discovered that the minimally effective dose of tapentadol hydrochloride was threefold less for polyneuropathic pain treatment as compared to mononeuropathic pain. [PFOF ¶ 540; 3/14 a.m. Tr. (Christoph) at 47:16-48:1.] Dr. Christoph also discovered that the maximally effective dose (*i.e.*, the dose needed to reach full antineuropathic

efficacy) of tapentadol hydrochloride was tenfold less for polyneuropathic pain as compared to mononeuropathic pain. [PFOF ¶ 540; 3/14 a.m. Tr. (Christoph) at 48:2-7.] This was surprising to Dr. Christoph because polyneuropathic pain is the more severe condition. [PFOF ¶ 540; 3/14 a.m. Tr. (Christoph) at 48:8-13.]

Third, Dr. Christoph discovered that in the STZ polyneuropathic pain model, tapentadol hydrochloride outperformed morphine. [PFOF ¶ 541; PTX-1600 at GRT-NUC44052.] Dr. Christoph found it "astonishing" that less tapentadol was required to achieve the same level of efficacy as morphine, especially because morphine is more potent than tapentadol in other pain models. [PFOF ¶ 541; 3/14 a.m. Tr. (Christoph) at 51:4-54:6.]

Fourth, Dr. Christoph also discovered that tapentadol hydrochloride possesses multiple layers of synergism, which allows lower dosages to be used to achieve desired effects and provides some explanation for the other unexpected properties tapentadol hydrochloride exhibits. [PFOF ¶ 542; 3/14 a.m. Tr. (Christoph) at 54:7-12, 62:23-63:21.] Dr. Christoph discovered an 'intrinsic' synergism between the multiple mechanisms of action of tapentadol hydrochloride in treating neuropathic pain, which he published in the Journal of Pharmacology and Experimental Therapeutics. [PFOF ¶ 543; 3/14 a.m. Tr. (Christoph) at 59:11-60:17; PTX-699.] He also discovered a 'site-site' synergy in the spinal and supraspinal levels (*i.e.*, administering tapentadol hydrochloride into these two locations results in a synergistic effect), a type of synergy which is relatively rare. [PFOF ¶ 543; 3/14 a.m. Tr. (Christoph) at 61:13-62:15.] Dr. Christoph also published these results. [PFOF ¶ 544; PTX-797; 3/14 a.m. Tr. (Christoph) at 60:18-61:12.]

Defendants mainly contend that Plaintiffs' evidence of unexpected results is not legally probative because Plaintiffs have not shown a comparison to tramadol, which Defendants contend is the closest prior art. [*See* DFOF ¶¶ 4056-4060.] *See In re Baxter Travenol Labs.*, 952 F.2d 388,

392 (Fed. Cir. 1991) ("[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art."). The Court does not agree. First, as much of Defendants' obviousness challenge was based on the prior art category of "opioids," the Court finds that Plaintiffs' evidence comparing tapentadol hydrochloride to other opioids (such as morphine) is legally probative. Second, Plaintiffs presented evidence suggesting that morphine, as the gold standard in opioid treatment, was a particularly good comparison [3/14 p.m. Tr. (Christoph) at 11:16-21; 3/23 Tr. (Brown) at 26:7-17] and that tramadol was not an appropriate reference point because the compounds were very different with different mechanisms of action and different potencies [PFOF ¶ 538; 3/14 a.m. Tr. (Christoph) at 86:8-87:1.]

Defendants further contend that Plaintiffs have not established what expectation a POSA would have had before attempting to use tapentadol hydrochloride to treat polyneuropathic pain. [*See* DFOF ¶ 4061.] However, for each category of unexpected result, Dr. Christoph testified about the nature of the result and why it was surprising. Ultimately, Plaintiffs' evidence demonstrated that tapentadol hydrochloride had unexpected properties that distinguished it from being "just another opioid." [PFOF ¶ 546; 3/23 Tr. (Brown) at 26:7-15.] Accordingly, the Court finds that Plaintiffs' evidence of unexpected results weighs in favor of a finding that the asserted claims of the '130 patent are nonobvious.

b. Long-felt need

Dr. Brown testified that before NUCYNTA® ER entered the market, there was a long-felt, unresolved need for a new opioid that could treat chronic pain with lower side effects, the most common of which are constipation, nausea, vomiting, sleepiness, and dizziness. [PFOF ¶ 548; 3/23 Tr. (Brown) at 26:22-27:5.] Plaintiffs' evidence demonstrated that lowering these side effects of traditional opioids could reduce the number of incidents of patients terminating their opioid treatment altogether. [PFOF ¶ 548; 3/23 Tr. (Brown) at 28:8-12; PTX-698.] Finally, Dr. Brown

testified, and Dr. Buvanendran has written in the past, that NUCYNTA® ER has been successful at lowering the side effects experienced by patients taking other extended release opioids. [PFOF ¶¶ 549-50; 3/23 Tr. (Brown) at 27:18-28:4; PTX-3005 at 61.] Thus, Plaintiffs have demonstrated that NUCYNTA® ER has satisfied a long-felt need in the market for an opioid with lower side effects.

5. The asserted claims of the '130 patent do not violate the doctrine of obviousness-type double patenting

Having reviewed the evidence presented, the Court finds that the asserted claims of the '130 patent are patentably distinct from claim 117 of the '593 patent and, thus, the asserted claims of the '130 patent do not violate the judicially-created doctrine of obviousness-type double patenting. Accordingly, Defendants have failed to meet their burden of proving by clear and convincing evidence that the asserted claims of the '130 patent are invalid.

F. DEPOMED WILL BE IRREPARABLY HARMED BY A GENERIC LAUNCH

i. Legal Principles

The Hatch-Waxman Act provides that for any act of infringement described in Section 271(e)(2) of the Patent Act:

> (A) the court shall order the effective date of any approval of the drug or veterinary biological product involved in the infringement to be a date which is not earlier than the date of the expiration of the patent which has been infringed,
> (B) injunctive relief may be granted against an infringer to prevent the commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of an approved drug, veterinary biological product, or biological product, [and]
> (C) damages or other monetary relief may be awarded against an infringer only if there has been commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of an approved drug, veterinary biological product, or biological product[.]

35 U.S.C. § 271(e)(4).

In general, to obtain injunctive relief "[a] plaintiff must demonstrate: (1) that it has suffered an irreparable injury; (2) that remedies available at law, such as monetary damages, are inadequate to compensate for that injury; (3) that, considering the balance of hardships between the plaintiff and defendant, a remedy in equity is warranted; and (4) that the public interest would not be disserved by a permanent injunction." *eBay Inc. v. MercExchange, L.L.C.*, 547 U.S. 388, 391 (2006). To satisfy the irreparable harm factor, a patentee must establish that: "1) that absent an injunction, it will suffer irreparable harm, and 2) that a sufficiently strong causal nexus relates the alleged harm to the alleged infringement." *Apple Inc. v. Samsung Elecs. Co.*, 695 F.3d 1370, 1374 (Fed. Cir. 2012). Evidence of price erosion, loss of market share, loss of profits, loss of research opportunities, and possible layoffs may constitute irreparable harm. *See Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1362 (Fed. Cir. 2008); *Robert Bosch LLC v. Pylon Mfg. Corp.*, 659 F.3d 1142, 1154 (Fed. Cir. 2011) (showing of lost market share and sales supported a finding of irreparable harm); *Purdue Pharma L.P. v. Boehringer Ingelheim GmbH*, 237 F.3d 1359, 1368 (Fed. Cir. 2001) (evidence of likelihood of price erosion and loss of market position caused by generic's entry to market supported finding of irreparable harm). "The phenomenon of price erosion in the pharmaceutical industry is well-known." *Hoffmann La Roche Inc. v. Cobalt Pharms. Inc.*, No. 07-4539, 2010 U.S. Dist. LEXIS 119432, *35 (D.N.J. Nov. 10, 2010). "Price erosion is most likely to occur in cases . . . in which no generic competitors have yet entered the marketplace, placing the patentee in an exclusive position." *Id.* at *38. "Direct competition in the same market is certainly one factor suggesting strongly the potential for irreparable harm without enforcement of the right to exclude." *Presidio Components, Inc. v. Am. Technical Ceramics Corp.*, 702 F.3d 1351, 1363 (Fed. Cir. 2012); *see also Trebro Mfg., Inc. v. FireFly Equip., LLC*, 748 F.3d 1159,

1171 (Fed. Cir. 2014) ("Trebro and FireFly are direct competitors selling competing products in this market. Thus, the record strongly shows a probability for irreparable harm.").

ii. Plaintiffs Have Met Their Burden

1. Irreparable harm

On April 2, 2015, Depomed acquired the exclusive U.S. rights to the NUCYNTA® products from Janssen for a contingency-free $1.05 billion cash payment. [PFOF ¶ 718; 3/9 Tr. (Anders) at 197:14-18; PTX1563 at DM_0000020.] The acquisition, which significantly exceeded Depomed's shareholder equity, represented a significant investment for Depomed. [PFOF ¶ 718; 3/9 Tr. (Anders) at 197:22-198:1; PTX1563 at DM_0000059.] In order to raise the capital necessary to outbid the other companies also vying for the rights to the NUCYNTA® products, Depomed took on approximately $920 million in debt, $575 million of which carries a minimum interest rate of 10.75% and is secured by substantially all of Depomed's assets. [PFOF ¶ 718; 3/9 Tr. (Anders) at 197:22-199:23; PTX1568 at DM_0000406-07; PTX1563 at DM_0000118.] The NUCYNTA® products became the flagship asset in Depomed's portfolio of pain and central nervous system specialty pharmaceuticals, and the NUCYNTA® products now account for approximately 60% of Depomed's revenues. [PFOF ¶ 720; 3/9 Tr. (Anders) at 179:24-180:1, 180:21-182:14; PTX-1559.] In making the decision to purchase the NUCYNTA® brand products, the proprietary nature of those products and the length of the exclusivity period afforded by the patents-in-suit were significant factors. [PFOF ¶ 719; 3/9 Tr. (Anders) at 188:25-189:23; PTX-829 at JN_NUCYNTA_1634430.]

If Defendants proceed to market with their proposed infringing generic NUCYNTA® products before the expiration of the patents-in-suit, these products would directly compete with NUCYNTA® in the United States, where Depomed currently has the exclusive rights to market and sell NUCYNTA®. Once Defendants' products enter the market, prescription volume for

NUCYNTA® will decline [3/9 Tr. (Anders) at 201:14-16], which will result in lost market share, lost revenue, and Depomed's business suffering. [PFOF ¶ 721; 3/9 Tr. (Anders) 200:12-201:20; PTX-1568 at DM_0000438-39.] *See Robert Bosch*, 659 F.3d at 1154 (finding that lost market share and price erosion can be irreparable harm). Significantly, Depomed asserts that the drop in revenue for NUCYNTA® means that it will be unable to fulfill the significant debt obligations it took on in order acquire the NUCYNTA® brand products from Janssen. [PFOF ¶ 722; 3/9 Tr. (Anders) at 197:22-201:23; PTX1568 at DM_0000406-07; PTX1563 at DM_0000118.]

The Court finds that if Defendants enter the market by launching their tapentadol hydrochloride products, it would threaten Depomed's business and cause extreme hardship. Thus, Depomed will be irreparably harmed without an injunction to prevent Defendants from launching their products.

2. Inadequate remedy at law

For substantially the same reasons that Depomed will be irreparably harmed by Defendants' launch, Depomed will not have an adequate remedy at law for the losses it will sustain. Direct competition with a low-cost generic version of NUCYNTA® ER will cause extreme hardship to Depomed operating under strict debt obligations. [*See infra.*] Monetary compensation cannot be quantified for the loss that Depomed will sustain by losing significant market share and revenue on its flagship product. *Novartis Consumer Health, Inc. v. Johnson & Johnson-Merck Consumer Pharms. Co.*, 290 F.3d 578, 596 (3d Cir. 2002); *Lazzaroni USA Corp. v. Steiner Foods*, 2006 U.S. Dist. LEXIS 20962, at *21 (D.N.J. Apr. 10, 2006) ("[L]oss of market share is the kind of harm for which there may be no adequate remedy at law." (internal quotation marks omitted)). There is no reason to believe that Defendants will stop infringing, or that the irreparable harm resulting from their infringement will otherwise cease, absent an injunction.

3. Balance of hardships

Defendants have not yet launched their products and will therefore not be forced to incur the costs of withdrawing the products from the market. Defendants did not call any fact witnesses to testify during trial. Thus, they presented no evidence about harm they will suffer if they are enjoined from launching their tapentadol hydrochloride products until the expiration of Plaintiffs' patents. However, as discussed, the harm that Depomed will suffer due to a low-cost generic competing with its flagship product (in which it invested $1.05 billion) is substantial and outweighs any harm Defendants might suffer by delaying their launch. Furthermore, any harm that Defendants may suffer from being enjoined was foreseeable and avoidable, as they were aware of the patents-in-suit covering NUCYNTA®, but chose to develop their infringing products anyway. [PFOF ¶ 723; PTO ¶¶ 58, 63, 73, 78, 90, 94, 99, 103-110.]

4. Public interest

Courts have long recognized the importance of the patent system in encouraging innovation, which provides incentive to innovative drug companies to invest in costly research and development activities. Among other things, pharmaceutical research requires the realization of profits from successful drugs to make up for the losses from drugs that never make it to market or prove unsuccessful for other reasons. *Eli Lilly & Co. v. Premo Pharm. Labs., Inc.*, 630 F.2d 120, 137 (3d Cir. 1980) ("In enacting the patent laws, Congress recognized that it is necessary to grant temporary monopolies on inventions in order to induce those skilled in the 'useful arts' to expend the time and money necessary to research and develop new products and to induce them 'to bring forth new knowledge.' This justification for sacrificing short-term price competition in order to foster creativity and improvement of products in long-run is particularly applicable to the pharmaceutical industry." (internal citation omitted)); *Sanofi-Aventis Deutschland GmbH v. Glenmark Pharms. Inc., USA*, 821 F. Supp. 2d 681, 696 (D.N.J. 2011) ("[The plaintiff] invested

significant resources with the expectation that it would be able to recoup its investment, and the patent system is designed to provide incentives for innovative drug companies to continue costly development efforts."). Not enforcing patent rights through injunctions may destroy confidence in the system and discourage investment in pharmaceutical research and development. The interests of a large portion of the public—those who have or will eventually develop conditions not adequately served by existing therapies—are served by a legal regime that protects investment in research and development. *Sanofi*, 821 F. Supp. 2d at 695-96 ("Importantly, the patent system provides incentive to the innovative drug companies to continue costly development efforts, and therefore there is a significant public interest in encouraging investment in drug development and protecting the exclusionary rights conveyed in valid pharmaceutical patents." (internal quotation marks omitted)). Thus, the public interest weighs in favor of an injunction.

V. CONCLUSION

For the foregoing reasons, the Court finds that Defendants have not met their burden of proving by clear and convincing evidence that the '593 patent, the '364 patent, or the '130 patent is invalid. Plaintiffs have met their burden of proving by a preponderance of the evidence that Alkem will induce infringement of the '130 patent. Plaintiffs have not met their burden of proving that Actavis or Roxane will induce infringement of the '130 patent. Plaintiffs have not met their burden of proving that any of the Defendants will contribute to infringement of the '130 patent.

This Opinion will be filed under temporary seal. The Opinion will be unsealed on Friday October 21, 2016 unless an appropriate motion to seal same (pursuant to Local Civil Rule 5.3(c)) is filed by October 14, 2016. An appropriate order accompanies this Opinion.

Dated: September 30, 2016

CLAIRE C. CECCHI, U.S.D.J.