IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

VANDA PHARMACEUTICALS INC. and AVENTISUB LLC,	)	
Plaintiffs,	)	
v.	)	C.A. No. 13-1973-GMS (consolidated)
ROXANE LABORATORIES, INC.,	)	**PUBLIC VERSION**
Defendant.	)	

DEFENDANT ROXANE'S PROPOSED
FINDINGS OF FACT AND CONCLUSIONS OF LAW

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TABLE OF CONTENTS

Page

I. INTRODUCTION 1

II. Background proposed findings of fact 1

A. The '610 Patent and the Level of Skill in the Art 1
B. The RE'198 Patent and the Level of Skill in the Art 1
C. The Proceedings and Roxane's Accused Product 2

III. Roxane does not infringe the '610 patent 2

A. Proposed Findings of Fact 2
1. Treatment of Schizophrenia with Iloperidone 2
2. Roxane's Label Does Not Encourage, Recommend, or Promote a Physician to Perform or Dose a Patient Based on a CYP2D6 Genotyping Test 3
3. The Prescribing Behaviors of All Testifying Experts Confirm that the Label Does Not Recommend CYP2D6 Genotyping 6
4. Other Objective Evidence Confirms that the Label Does Not Recommend CYP2D6 Genotyping 9
5. There are Substantial Non-Infringing Uses of Roxane's Proposed Iloperidone Tablets 10
6. Vanda Did Not Establish Roxane Intends to Induce or Contribute to Infringement 12
7. Vanda Presented No Meaningful Evidence Regarding the Asserted Dependent Claims 12
B. Proposed Conclusions of Law 13
1. Vanda Has Not Presented Evidence of Direct Infringement 13
2. Roxane Does Not Infringe Under § 271(c) 14
3. Roxane Does Not Induce Infringement Under § 271(b) 14

IV. The asserted claims of the '610 patent are Invalid as unpatentable under 35 u.s.c.§ 101 15

A. Proposed Findings of Fact 15
B. Proposed Conclusions of Law 19

V. The Asserted Claims of the '610 Patent are Obvious 22

A. Proposed Findings of Fact 22
B. Proposed Conclusions of Law 24

VI. The asserted claims of the '610 patent are invalid for lack of written description 25

A. Proposed Findings of Fact 25
B. Proposed Conclusions of Law 30

VII. Asserted Claim 3 of the RE'198 Patent is Obvious 31

A. Proposed Findings of Fact 31
B. Proposed Conclusions of Law 38

VIII. Conclusion 40

TABLE OF AUTHORITIES

Page(s)

CASES

ACCO Brands, Inc. v. ABA Locks Mfr. Co.,
501 F.3d 1307 (Fed. Cir. 2007) 14

Alice Corp. Pty. Ltd. v. CLS Bank Int'l,
134 S. Ct. 2347 (U.S. 2014) 20

Anton/Bauer, Inc. v. PAG, Ltd.,
329 F.3d 1343 (Fed. Cir. 2003) 14

Ariad Pharm., Inc. v. Eli Lilly & Co.,
560 F.3d 1366 (Fed. Cir. 2009) 30

Ass'n for Molecular Pathology v. Myriad Genetics, Inc.,
133 S.Ct. 2107 (2013) 17, 20, 21

Bayer Schering Pharma AG v. Barr Labs., Inc.,
575 F.3d 1341 (Fed. Cir. 2009) 24

BMS v. Teva,
752 F.3d 973 (Fed. Cir. 1985) 39

Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.,
752 F.3d 967 (Fed. Cir. 2014) 38

Daiichi Sankyo Co. v. Matrix Labs., Ltd.,
619 F.3d 1346 (Fed. Cir. 2010) 38

Dealertrack, Inc. v. Huber,
674 F.3d 1315 (Fed. Cir. 2012) 20

Diamond v. Diehr,
450 U. S. 175 (1981) 19

Endo Pharm., Inc. v. Actavis Inc.,
C.A. No. 14-1381-RGA, 2015 WL 7253674 (D. Del. Nov. 17, 2015) 21, 22

Genetic Techs. Ltd v. Merial L.L.C.,
No. 15-2012, 2016 WL 1393573 (Fed. Cir. Apr. 8, 2016) 21

Graham v. John Deere Co. of Kansas City,
383 U.S. 1 (1966) 24

TABLE OF AUTHORITIES

Page(s)

ICU Med., Inc. v. Alaris Med. Sys., Inc.,
558 F.3d 1368 (Fed. Cir. 2009) 30

In re Deuel,
51 F.3d 1552 (Fed. Cir. 1995) 39

Kim v. ConAgra Foods, Inc.,
465 F.3d 1312 (Fed. Cir. 2006) 14

KSR Int'l Co. v. Teleflex Inc.,
550 U.S. 398 (2007) 24

Lemelson v. United States,
752 F.2d 1538 (Fed. Cir. 2014) 14

Mayo Collaborative Services v. Prometheus Laboratories, Inc.,
132 S. Ct. 1289 (U.S. 2012) 17, 20, 21, 22

Merck & Co. v. Biocraft Labs., Inc.,
874 F.2d 804 (Fed. Cir. 1989) 25

Pfizer, Inc. v. Apotex, Inc.,
480 F.3d 1348 (Fed. Cir. 2007) 24

PIN/NIP, Inc. v. Platte Chem. Co.,
304 F.3d 1235 (Fed. Cir. 2002) 30

Purdue Pharma Prods. L.P. v. Par Pharm., Inc.,
642 F. Supp. 2d 329 (D. Del. 2009) 24

Takeda Pharm. U.S.A., Inc. v. West-Ward Pharm. Corp.,
785 F.3d 625 (Fed. Cir. 2015) 15

Vita-Mix Corp. v. Basic Holding, Inc.,
581 F.3d 1317 (Fed. Cir. 2009) 14

Warner-Lambert Co. v. Apotex Corp.,
316 F.3d 1348 (Fed. Cir. 2003) 13, 15

STATUTES

35 U.S.C. § 101 22

35 U.S.C. § 103 22

35 U.S.C. § 271(c) 14

TABLE OF AUTHORITIES

Page(s)

C.F.R. § 314.94(a)(8)(iv) 3

Experts Testifying On Behalf of Roxane

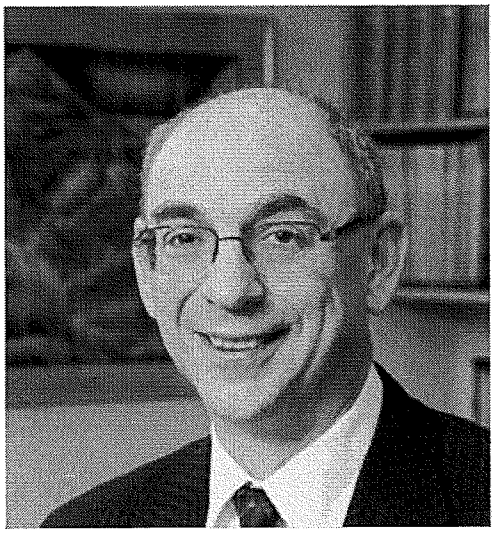
Dr. Neil Kaye



Dr. Kaye is a triple board-certified psychiatrist who focuses primarily on adult outpatients and specializes in psychopharmacology, neuropsychiatry, forensics, clinical drug research, and treatment of psychiatric disorders. He has evaluated and treated over 10,000 patients over thirty years, many of whom were diagnosed with schizophrenia. Dr. Kaye is a member of the American Psychiatric Association, the American Academy of Psychiatry and the Law, the Medical Society of Delaware (executive council), and the National Alliance of Mentally Ill for the State of Delaware (advisory board). He has served as a reviewer for the Journal of Clinical Psychiatry, the Journal of Neuropsychiatry and Clinical Neuroscience, and the Journal of Psychopharmacology, and has authored over one hundred articles in peer reviewed journals. Dr. Kaye has been named a distinguished fellow of the American Psychiatric Association, a top psychiatristby the Consumer Research Council, and a top doctor by Delaware Today. 379:1-382:18 (Kaye); JX-90.

The Court accepted Dr. Kaye as an expert in the fields of psychiatry and psychopharmacology and the treatment of psychiatric disorders, including schizophrenia. 382:20-383:1. Dr. Kaye testified regarding Vanda's failure to establish infringement of the '610 patent from the perspective of a psychiatrist who treats patients for schizophrenia, including the lack of evidence of direct infringement, his opinion that the label does not induce infringement, the substantial non-infringing uses for Roxane's iloperidone product, and the lack of evidence of intent to induce and/or contribute to direct infringement.

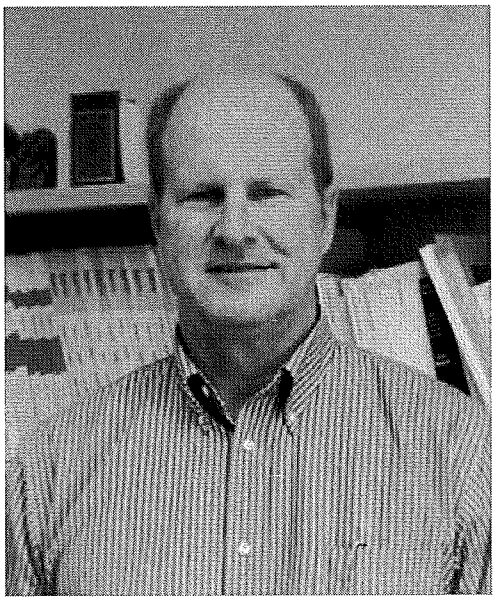
Dr. Mark Ratain



Dr. Ratain is the Leon Jacobsen Professor of Medicine at the University of Chicago. He is the founder and director of the Center for Personalized Therapeutics at the University of Chicago, and he serves as the chief hospital pharmacologist and Associate Director of Clinical Sciences. Dr. Ratain graduated from Harvard University in1976, and attended medical school at Yale University, followed by post-graduate training at Johns Hopkins hospital, and a three-year fellowship at the University of Chicago. He is board-certified in internal medicine, medical oncology, hematology, and clinical pharmacology. Dr. Ratain is a member of the American Society for Clinical Pharmacology and Therapeutics, the American College of Clinical Pharmacology, and the Association of American Physicians. He serves as the co-editor in chief of the Journal of Pharmacogenetics and Genomics. Dr. Ratain has researched in the field of pharamcogenetics and pharmacogenomics over the past twenty years. He has published over 400 articles, many of which relate to CYP2D6 genotyping and the effects of that genotype on the drug tamoxifen. He has received a number of major awards in the field of clinical pharmacology, including awards from the American Society of Clinical Pharmacology and Therapeutics, the American Association of Pharmaceutical Scientists, and the Pharmaceutical Manufacturers' Association Foundation. 488:5-491:19 (Ratain); JX-92.

The Court accepted Dr. Ratain as an expert in the fields of pharmacogenetics and clinical pharmacology. 491:20-25. Dr. Ratain provided testimony regarding Vanda's failure to establish infringement of the '610 patent from the perspective of a clinical pharmacologist and expert in pharmacogenomics, focusing on the substantial noninfringing uses for Roxane's iloperidone tablets. Dr. Ratain also testified regarding the level of a person of ordinary skill in the art of the '610 patent and the invalidity of the asserted claims of the '610 patent under 35 U.S.C. §§ 101, 103, and 112.

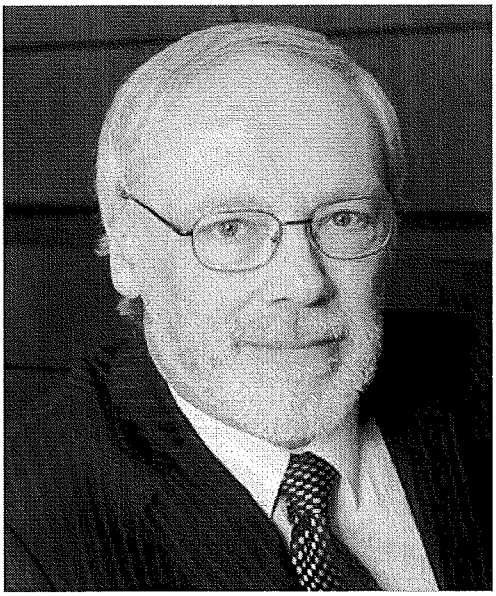
Dr. Charles McCulloch



Dr. McCulloch is a Professor of Biostatistics at the University of California San Francisco School of Medicine. Prior to joining UCSF, Dr. McCulloch worked at Cornell University as a Professor of Biological Statistics, head of the biometrics unit, chair of the Department of Statistical Science, and director of graduate studies. Dr. McCulloch holds a Bachelor's degree and a Master's degree in mathematical sciences from Johns Hopkins University, and a Master's Degree and Ph.D. in statistics from Cornell University. He has published over 300 peer-reviewed publications and five textbooks, including publications he has coauthored in the fields of genetics, pharmacology, and psychiatry. Dr. McCulloch also served as a member and chairperson of the National Institutes of Health study section on biostatistical methods and research design. 625:20-629:18 (McCulloch); JX-91.

The Court accepted Dr. McCulloch as an expet in statistic, biostatistics, statistical analysis of scientific data, and study design. 629:18-24. Dr. McCulloch provided testimony regarding the data and study design disclosed in the '610 patent, and whether the information in the specification provides support for the asserted claims.

Dr. Bruce Sargent



Dr. Sargent has worked and conducted research in the field of drug discovery and development since 1975, when he received his B.A. and Master's deree in natural sciences from the University of Cambridge. He holds a Ph.D. from the University of Manchester. After obtaining his Ph.D., Dr. Sargent worked for Boots Pharmaceuticals, which became Knoll Pharmaceuticals. Dr. Sargent's first leadership responsibility at these companies was in the area of antipsychotics, and he continued to work with antipsychotics throughout his time at Boots and Knoll. Dr. Sargent then joined Albany Molecular Research as an assistant director in 2001, and by 2011, he led all drug discovery activities and supervised approximately 350 research scientists. Dr. Sargent has spent approximately 35 years working in the field of CNS disorders, and approximately 30 years working on antipsychotic drug development. He is a member of the American Chemical Society, a former board member for the New York Biotechnology Association, and a Fellow of the Royal Society of Chemistry. Dr. Sargent has authored approximately 50 scientific papers and is an inventor on approximately a dozen U.S. patents, the majority of which are in the CNS field. 652:19-658:14 (Sargent); JX-93.

The Court accepted Dr. Sargent as an expert in the discovery, design, and development of pharmaceutical compounds with a particular emphasis in antipsychotics. 658:15-21. Dr. Sargent provided testimony regarding the invalidity of the RE'198 patent.

I. INTRODUCTION

Defendant Roxane requests judgment in its favor on the asserted claims of U.S. Patent Nos. 8,856,610 (the "'610 patent") and RE 39,198 (the "'198 patent").

II. BACKGROUND PROPOSED FINDINGS OF FACT

A. The '610 Patent and the Level of Skill in the Art

1. The '610 patent is entitled to a priority date no earlier than September 30, 2004. UF ¶ 11; JX-1 at 1.

2. A person of ordinary skill in the art of the '610 patent at the time of the invention would have a degree in medicine, pharmacy, pharmacology, or a related field and practical experience in the field of psychiatry and/or clinical pharmacology, including pharmacogenomics. A person of ordinary skill in the art would have familiarity with interpreting research findings (including statistical results) and/or adjusting drug dosages based on a patient's drug metabolism and/or laboratory test results. *See* 512:3-513:19 (Ratain). A board-certified or board-eligible psychiatrist would satisfy this definition so long as the psychiatrist has familiarity with adjusting drug doses based on a patient's metabolism and/or access to a person with experience in pharmacogenomics. 513:20-514:2 (Ratain). Similarly, a clinical pharmacologist with experience in pharmacogenomics would satisfy this definition so long as that person has access to psychiatrists. *Id.*

B. The RE'198 Patent and the Level of Skill in the Art

3. The RE'198 patent" is entitled to a priority date no earlier than May 19, 1989. UF ¶ 6; JX-2 at 1.

4. The level of ordinary skill in the art to which the RE'198 patent pertains would include a medicinal or pharmaceutical chemist involved in research and development of pharmaceuticals

who had knowledge and experience in the design and synthesis of potential drug candidates, as well as some experience with the design and synthesis of antipsychotic drugs. *See* 676:7-17 (Sargent). Such a person would have a masters, Ph.D., or medical degree, and meaningful experience in this area. *Id.*; *see* 821:5-13 (Bartlett; "I think we pretty much all agree on that").

C. The Proceedings and Roxane's Accused Product

5. Roxane filed Abbreviated New Drug Application No. 20-5480 (the "Roxane ANDA") seeking FDA approval to sell generic iloperidone tablets in 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg strengths prior to the expiration of the RE'198 patent. UF ¶ 29.

6. The '610 Patent issued on November 19, 2013. UF ¶ 10. Vanda asserted infringement on June 16, 2014 under 35 U.S.C. § 271 (a), (b), (c), and (e). (C.A. No. 1:14-cv-757, D.I. 1.) When Vanda filed suit, the '610 patent was not listed in the Orange Book. UF ¶ 28. REDACTED

REDACTED

REDACTED. *See infra* ¶ 28.

7. On or about January 15, 2015, Vanda listed the '610 Patent in the Orange Book after acquiring the Fanapt NDA from Novartis. U.F. ¶ 28; *see also* 134:22-24 (Polymeropoulos).

8. On May 6, 2015, Roxane sent Vanda a Notice Letter providing Roxane's basis for asserting noninfringement and invalidity of the '610 patent and describing why it lacks any intent to encourage any acts of infringement. 148:4-149:13 (Polymeropoulos); DTX-342.

III. ROXANE DOES NOT INFRINGE THE '610 PATENT

A. Proposed Findings of Fact

1. Treatment of Schizophrenia with Iloperidone

9. When treating a patient with schizophrenia, a psychiatrist's primary concern is achieving efficacy. 384:10-385:21 (Kaye). Schizophrenia is a serious condition associated with high rates of morbidity. A psychiatrist's goal is to effectively treat the patient as quickly as possible. *Id.*

10. Genotyping cannot predict a patient's response to any particular dose of a drug such as iloperidone. 390:17-391:20 (Kaye). Instead, physicians rely on their clinical experience and titrate the drug to efficacy in order to use the lowest possible dose of a drug that can control symptoms. 391:21-392:21; DTX-11, at 13-14.

2. Roxane's Label Does Not Encourage, Recommend, or Promote a Physician to Perform or Dose a Patient Based on a CYP2D6 Genotyping Test

11. As a generic drug manufacturer, Roxane does not market its products to physicians but sells its drugs to wholesalers. 420:9-421:2 (Kaye). Vanda's sole basis for asserting inducement is Roxane's proposed label that it has submitted to the FDA, which is, in all relevant respects, required by statute to be identical to the Fanapt label. *See* 21 C.F.R. § 314.94(a)(8)(iv).

12. Roxane's iloperidone tablets are indicated for the treatment of schizophrenia in adults. The recommended target dose is 12 to 24 mg/day administered twice daily. JX-11, at 1, 4. The label further instructs prescribers to "consider the ability of Iloperidone Tablets to prolong the QT interval and the use of other drugs first." *Id.* at 1. With respect to QT interval prolongation, the label provides that "[p]atients should be advised to consult their physician immediately if they feel faint, lose consciousness or have heart palpitations." *Id.* at 24.

13. Roxane's proposed label directs physicians to titrate to efficacy. JX-11, at 1, 4. The highlights of the prescribing information provides a target dose of 12 to 24 mg daily, and mandate a titration schedule to achieve 12 mg/day no faster than day four. 398:16-401:1 (Kaye); JX-11, at 1. The label likewise states that iloperidone *must* be titrated slowly, mandating that "patients need to be titrated to an effective dose." 401:5-403:1 (Kaye); JX-11, at 4. Titration does not require any information regarding a patient's genotype, and iloperidone was prescribed using titration long before genotyping tests were widely available. 403:13-404:7 (Kaye).

14. Roxane's label also contains no reference to limiting CYP2D6 poor metabolizers to 12

mg/day or less, and no instruction that extensive metabolizers should receive greater than 12 mg/day. 401:2-403:20 (Kaye); JX-11, at 4-5. Vanda at trial relied primarily on two sentences in the pharmacokinetics section of the label: "PMs of CYP2D6 have higher exposure to iloperidone compared with EMs and PMs should have their dose reduced by one-half. Laboratory tests are available to identify CYP2D6 PMs." 230:17-231:13 (Preskorn), 404:8-406:3 (Kaye); JX-11, at 4-5, 21. But as Dr. Kaye explained (i) a physician will follow the mandatory language in the label and titrate to efficacy regardless of metabolizer status, and (ii) a physician following the label would read this statement as providing information to the physician that, in titrating to efficacy, an effective dose might be lower for poor metabolizers. 401:2-405:7 (Kaye). The cited label language does not encourage, recommend, or promote a physician to prescribe iloperidone in a manner recited in the claims. 404:23-405:12 (Kaye).

15. The first statement that poor metabolizers have higher iloperidone exposure and should have their dose reduced by one-half does not specifically refer to CYP2D6 genotypic poor metabolizers as opposed to phenotypic poor metabolizers. 406:12-410:17 (Kaye). Dr. Kaye explained that the most common way to determine whether a patient is a poor metabolizer is to review the patient's history. 408:2-21 (Kaye); DTX-18, at 7. Roxane's proposed label does not recommend conducting a CYP2D6 genotyping assay or other laboratory test as opposed to obtaining information from a patient's history as Dr. Kaye described.

16. The label itself describes metabolizer status by reference to serum levels of iloperidone—a measure of phenotype —not by reference to any allele or genetic variant. 407:13-408:1 (Kaye); JX-11, at 21. Dr. Kaye explained that phenotyping is more clinically helpful than CYP2D6 genotyping, because it directly measures what the physician is trying to assess. 412:11-413:16 (Kaye). Dr. Preskorn admitted in a paper that he would measure patients'

iloperidone serum levels in accordance with good medical practice, not that he would perform a CYP2D6 genotyping test. 285:14-287:12 (Preskorn); JX-36, at 7.

17. The second statement— "laboratory tests are available"— neither refers to CYP2D6 genotyping nor recommends that it be performed. 257:4-258:6 (Preskorn), 407:13-406:11 (Kaye), 503:22-504:3 (Ratain); JX-11, at 21. Roxane's proposed label contains no reference to genotyping or alleles, either explicitly or by inference. 406:12-20 (Kaye). Poor metabolizers can be identified by laboratory tests that determine a patient's phenotype, such as measuring iloperidone concentrations or administering dextromethorphan. 144:13-146:5 (Polymeropoulos), 211:14-215:7 (Kricka), 285:14-289:8 (Preskorn), 409:13-410:17, 411:17-413:16, 419:10-12 (Kaye); DTX-19, at 2; DTX-20, at 4; DTX-356; DTX-501; DTX-502; JX-36, at 7. The '610 patent admits that these phenotype tests are effective. 999:2-11 (Guengerich). Further, the plain meaning of the subject language is merely informative and not a recommendation. 257:4-258:6 (Preskorn).

18. By contrast, other drug labels (including those for Nuedexta, Pimozide, Tetrabenazine, and Abacavir) do contain explicit language specifying genotyping and indicating that genotyping is recommended. 263:25-268:3 (Preskorn), 406:21-407:12 (Kaye), 505:19-507:7 (Ratain); DTX-351, at 5; DTX-29, at 16; DTX-503, at 11; DTX-25, at 2 Thus, the FDA plainly knows how to specify when genotyping is recommended. No such language appears in the Roxane proposed label. 406:4-407:12 (Kaye); JX-11, at 4-5, 21.

19. Finally, nowhere does Roxane's proposed label recommend taking a biological sample for purposes of CYP2D6 genotyping. 406:17-20 (Kaye). The label elsewhere does recommend taking a biological sample for monitoring blood potassium levels in certain patients, 255:15-256:25 (Preskorn), 504:10-19 (Ratain); JX-11, at 6, but never for genotyping.

3. The Prescribing Behaviors of All Testifying Experts Confirm that the Label Does Not Recommend CYP2D6 Genotyping

20. Defendant's expert Dr. Kaye testified to the absence of any evidence that physicians have practiced any of the asserted claims. 394:9-398:3 (Kaye). Dr. Kaye explained that he had never genotyped a patient in connection with prescribing iloperidone. 381:21-382:4 (Kaye). He further explained that a physician would not genotype a patient in order to determine what dose of a drug to use, because "genotyping does not predict efficacy or dose response." 390:17-392:7 (Kaye). Instead, Dr. Kaye, who has evaluated and treated more than 10,000 patients and treats patients with schizophrenia on a daily basis, 379:14-17, 381:1-5 (Kaye), explained that in accordance with the label's titration requirement, physicians always titrate to efficacy rather than rely on genotyping. 394:9-398:3, 400:6-403:20 (Kaye); *see supra* ¶¶ 13-14.

21. Dr. Kaye specifically inquired of his colleagues at two conferences as to whether they genotyped their patients in connection with administering iloperidone, and none of the other psychiatrists had ever genotyped a patient in connection with prescribing iloperidone, nor did they know such a test could be done. 395:25-398:3, 413:24-414:12 (Kaye).

22. Plaintiffs' expert, Dr. Preskorn, admitted that he has never practiced any claim of the '610 patent, that none of his residents had ever done so, and that no physicians he interviewed on the subject had ever practiced the claims. 243:3-244:1, 244:19-245:25, 289:23-291:19 (Preskorn). Dr. Preskorn testified for Vanda on infringement, but his testimony was entirely conclusory and was based on no *actual* knowledge of any physician practicing the claimed method or other objective evidence in support of his claims. Dr. Preskorn conceded on cross-examination that he was forced to retract portions of his expert report that had asserted that he (and physicians at his direction) had actually practiced claims of the '610 patent. 242:22-245:25 (Preskorn). In fact, Dr. Preskorn had never genotyped a patient in a clinical setting, although he

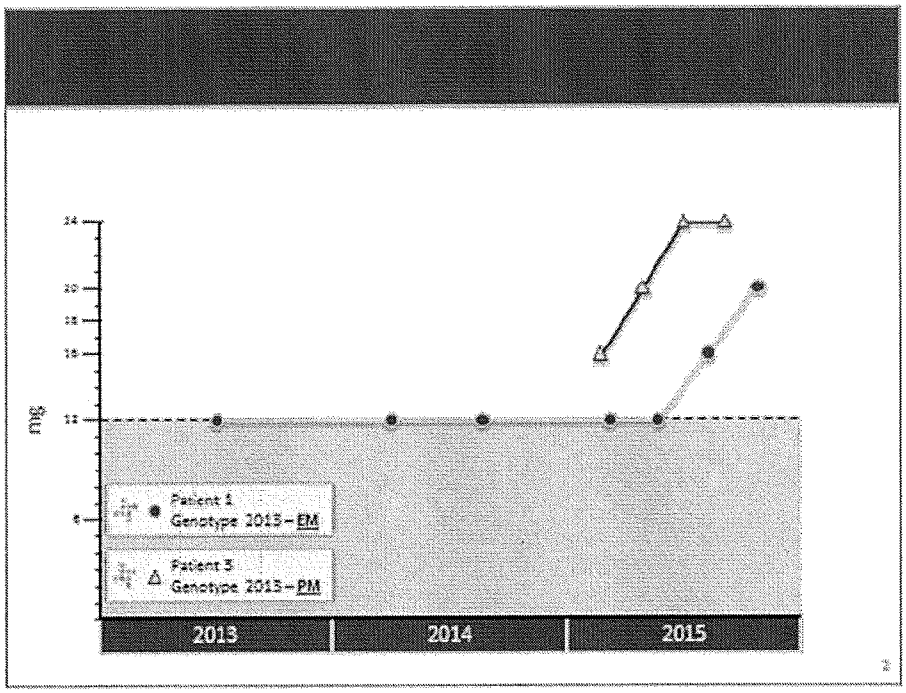
had phenotyped patients. 289:1-17 (Preskorn). Dr. Preskorn published articles detailing his use of therapeutic dose monitoring (a form of phenotyping that involves adjusting a dose based on plasma levels). 282:1-284:18 (Preskorn); *e.g.*, DTX-355, at 3.

23. Plaintiffs' expert regarding genotyping tests, Dr. Kricka likewise admitted he had spoken to no prescribing physicians regarding whether a prescriber could determine a patient's CYP2D6 status without genotyping. 209:19-210:6, 211:1-13 (Kricka). Inventor Dr. Wolfgang confirmed that he had no personal knowledge of any physician ever practicing the claimed method. 477:20-478:2 (Wolfgang).

24. The prescribing practice of Plaintiffs' expert, Dr. Alva, confirms Dr. Kaye's testimony that physicians titrate to efficacy rather than dosing based on CYP2D6 genotype. Dr. Alva acknowledged that genotyping may not predict a patient's clinical response. 312:2-11 (Alva). Accordingly, Dr. Alva testified that his typical practice is to start a patient at a target dose of 12 mg/day and monitor the patient's reaction, regardless of whether the patient had been genotyped, was an extensive metabolizer, or was a poor metabolizer. 320:17-321:13 (Alva). Both in post-marketing iloperidone trials and in his clinical practice, Dr. Alva acknowledged that titrating to efficacy could result in prescribing iloperidone at a level of more than 12 mg/day for a CYP2D6 poor metabolizer—a practice Dr. Alva testified was consistent with the iloperidone labeling. 315:6-319:23 (Alva); DTX-344, at 2. Similarly, an extensive metabolizer could receive 12 mg/day or less of iloperidone, consistent with the labeling. 320:17-321:13 (Alva).

25. Dr. Alva's patient records demonstrate that he titrates to efficacy rather than using genotyping to make dosing decisions. 322:11-326:17, 329:8-336:12 (Alva), 396:16-398:3 (Kaye); DTX-299. Dr. Alva genotyped only four of the eighteen patients whom Dr. Alva treated with iloperidone, and for none of them did he practice the claimed method. 325:17-326:17,

331:23-332:14, 334:23-335:14, 335:21-336:4 (Alva), 395:25-398:3 (Kaye). One of the four was a poor metabolizer, and every dose Dr. Alva prescribed to that patient after the genotyping test was outside the claimed method: 16 mg/day, later increased to 20 mg/day, and then 24 mg/day. 329:8-331:5 (Alva); DTX-299, at 91, 99, 103, 109. Further, following the label instruction to titrate to efficacy, Dr. Alva continued to administer 12 mg/day of iloperidone to a patient for approximately at least a year and a half after genotyping the patient as an extensive metabolizer. 322:11-326:4 (Alva). When he eventually increased the dose above 12 mg/day, he did so not because of the patient's genotype status, but because "his symptoms required an increase in the dose." 340:9-12 (Alva). Dr. Alva's prescribing practices with respect to these two patients are illustrated below:



325:15-326:7, 329:14-331:21 (Alva). Likewise, Dr. Alva prescribed an initial target dose of 24 mg/day to a patient who was never genotyped. 332:15-333:5 (Alva). Dr. Alva's treatment of the patients he described at trial is summarized below:

Total Patients = 18; Total Genotyped = 4		
Genotype	**Initial Target Dose**	**Maximum Dose**
EM	12 mg/day	20 mg/day
PM	16 mg/day	24 mg/day
N/A	24 mg/day	24 mg/day

326:8-17, 331:23-332:6, 334:23-335:20 (Alva).

4. Other Objective Evidence Confirms that the Label Does Not Recommend CYP2D6 Genotyping

26. Objective evidence confirms that the label does not recommend CYP2D6 genotyping. 413:17-417:25 (Kaye). For example, Vanda represented to European regulators that iloperidone had been used for three years in the U.S. "in the absence of CYP2D6 genotyping." 139:11-141:23 (Polymeropoulos), 275:20-276:24 (Preskorn), 414:13-415:19 (Kaye); DTX-10. Likewise, internal Vanda correspondence shows that Vanda did not intend to require genotyping prior to treatment with iloperidone. 152:14-154:5 (Polymeropoulos); DTX-36, at 2.

27. Dr. Weiden, a consultant for Vanda, member of Vanda's Schizophrenia Advisory Board, and spoke on Vanda's behalf to the FDA, published an article explaining that "[t]here are no recommendations [in the label] to test patients for genetic variants that result in poor metabolism of CYP2D6." DTX-35, at 2; *see also* 154:20-160:22 (Polymeropoulos), 415:21-416:4 (Kaye); DTX-500. While Vanda now contends that the label *restricts* Iloperidone use at a dose above 12 mg/day to patients who have been determined by genotyping not to be poor metabolizers, Vanda represented to the EMA that "the Prescribing Information for iloperidone in the United States has ***no restrictions***." DTX-10, at 10 (emphasis added); 280:4-17 (Preskorn).

28. Likewise, as the NDA holder at the time the '610 patent issued, Novartis had a financial incentive to list the '610 patent in the Orange Book but refused to do so. 135:8-19 (Polymeropoulos). At the time, Novartis had an active sales force, and Dr. Polymeropoulos admitted that Novartis was in a better position than Vanda to know how physicians interpreted

the label. 136:6-139:4 (Polymeropoulos). Novartis never took a license to the patent during the period it was promoting and selling iloperidone. 142:21-143:11 (Polymeropoulos).

29. Dr. Kaye explained that numerous statements by Novartis confirmed his understanding of the label. 417:10-25 (Kaye); DTX-32, ¶¶ 48-50. REDACTED

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30. PharmGKB is an organization that summarizes expert consensus based on clinical evidence and peer-reviewed literature regarding genomics. 268:10-269:14 (Preskorn). PharmGKB classified iloperidone as "actionable," meaning the label "does not require or recommend genetic testing." 509:22-510:7 (Ratain); DTX-109, at 4; DTX-353, at 1. Vivot similarly comprehensively reviewed relevant FDA labels and determined that the iloperidone label does ***not*** "recommend" genetic testing. 272:6-275:19 (Preskorn); DTX-27, at 1.

31. Further, numerous third-party payers refuse to cover CYP2D6 testing for iloperidone patients on the grounds that it is considered investigational. 493:19-498:23 (Ratain); DTX-15, at 1-2; DTX-92, at 4-5; DTX-98, at 4. Payers do reimburse when the label contains a recommendation for genetic testing. 498:13-23, 506:22-507:7 (Ratain).

5. There are Substantial Non-Infringing Uses of Roxane's Proposed Iloperidone Tablets

32. The most common practice for prescribing iloperidone is to titrate to efficacy without a genotyping test, which is fully consistent with the approved labeling. 400:6-405:12, 418:15-419:2 (Kaye), 492:23-24, 498:4-8 (Ratain). Often patients may receive doses outside the ranges in the patent claims as a result of that titration. 419:5-12, 312:2-313:10, 317:24-318:12, 319:14-

23, 320:22-321:13 (Kaye). By contrast, the '610 patent claims treating patients with certain doses *based on* genetic test results. 77:3-9 (Polymeropoulos).

33. Physicians also rely on phenotyping or methods of ascertaining CYP2D6 status other than genotyping. 419:10-12 (Kaye). The '610 patent specification describes, but does not claim, phenotyping tests. 144:13-146:5 (Polymeropoulos). The original application contained claims to phenotyping, Vanda did not pursue those claims. 146:6-147:20 (Polymeropoulos); DTX-368, at 31. Phenotyping is consistent with the approved labeling but outside the scope of the claims. 280:18-284:18 (Preskorn), 407:13-410:17, 419:10-12 (Kaye); DTX-355, at 3.

34. The label language regarding dose reductions refers only to homozygous poor metabolizers, not to intermediate metabolizers or heterozygotes. 207:8-20, 208:19-209:18 (Kricka), 501:18-503:12 (Ratain). Specifically, the label defines CYP2D6 poor metabolizers as lacking capacity to metabolize CYP2D6 substrates, and distinguishes them from intermediate metabolizers and heterozygotes. 502:10-14 (Ratain). Because an intermediate metabolizer is not a poor metabolizer as described in the label, the Roxane label language does not suggest or recommend any reduction in dose for those patients. 248:7-250:2, 251:11-14 (Preskorn). But the patent claims do include intermediate metabolizers as poor metabolizers and mandate a dose reduction for those patients. *Id.*

35. Likewise, a heterozygote is not a poor metabolizer as defined by the label, and the Roxane label language does not suggest or recommend any reduction in dose for those patients. 247:11-14, 249:2-6 (Preskorn), 502:7-503:2 (Ratain). These heterozygotes make up approximately 30 percent of the population, while poor metabolizers are approximately seven percent. 503:9-12 (Ratain). But the patent claims define CYP2D6 poor metabolizers to include heterozygotes. 250:3-19 (Preskorn), 502:21-503:12 (Ratain).

36. The patent claims require that extensive metabolizers receive an Iloperidone dose "**greater than** 12 mg/day." JX-1 at 11 (emphasis added). But as Dr. Preskorn admitted—and his demonstrative vividly showed—the Roxane labeling recommends dosing those patients **at** 12 mg/day, since that dosage is within the target therapeutic dose of 12-24 mg/day. 228:2-16 ("[I]n individuals who are not CYP2D6 poor metabolizers, they will use the recommended dosing range of 12 to 24 milligrams per day.") (Preskorn). Dr. Alva's testimony shows that this use of Roxane's proposed product is more prevalent than any supposed infringing uses—the most common target dose is 12 mg/day, including for extensive metabolizers. 320:17-321:13 (Alva).

6. Vanda Did Not Establish Roxane Intends to Induce or Contribute to Infringement

37. Plaintiffs' witnesses presented no testimony that Roxane intends to induce infringement. Drs. Kaye and Ratain confirmed that they were aware of no such evidence. 420:5-8 (Kaye).

38. In its notice letter dated May 6, 2015, Roxane informed Vanda that Roxane would not induce infringement because, *inter alia*, its proposed label does not recommend CYP2D6 genotyping and because phenotyping laboratory tests are available to identify CYP2D6 poor metabolizers. 147:21-149:10 (Polymeropoulos); DTX-342, at 4. The statements in Roxane's Notice Letter are consistent with literature describing the fact that the iloperidone label does not recommend CYP2D6 genotyping. 159:17-160:22 (Polymeropoulos).

7. Vanda Presented No Meaningful Evidence Regarding the Asserted Dependent Claims

39. Dr. Preskorn's testimony regarding the asserted dependent claims was entirely conclusory. 189:19-193:12, 236:21-240:23 (Preskorn). When testifying about claim 2, Dr. Preskorn merely stated that the claimed steps were standard steps in a DNA sequencing analysis, but he did not testify that Roxane's label in any way encourages a physician to follow those steps. 189:19-193:12 (Preskorn). Similarly, with respect to claims 3-6 and 11, Dr. Preskorn

merely testified that the CYP2D6 genotyping tests that he was familiar with test for the alleles at issue, but again, he provided no testimony that Roxane's label encourages a physician to test for those specific alleles. 236:21-237:15 (Preskorn).

40. The same is true for claim 7, which recites the administration of 6 milligrams or less of iloperidone twice per day to poor metabolizer, and claims 8, 12, and 16, which recite a *specific* dose of exactly 6 milligrams twice per day to a poor metabolizer. Dr. Preskorn merely stated in conclusory fashion that a prescriber following the label would prescribe a maximum dose of 12 mg per day to a poor metabolizer, noting that the label states that iloperidone should be given twice per day. 237:16-239:5, 239:24-240:7, 240:13-17 (Preskorn). As noted above, however, Vanda presented no evidence of any physician ever dosing a poor metabolizer at 12 milligrams per day or less. *See supra* ¶¶ 20-22. Indeed, Dr. Alva has administered patients a single daily dose of iloperidone. 323:24-324:6, 324:17-19, 324:24-325:1 (Alva). Further, as described above, physicians titrate to efficacy, and Vanda provided no evidence that physicians in practice prescribe a maximum of 12 milligrams per day to a poor metabolizer. With respect to claims 8, 12, and 16, Dr. Preskorn further testified only that 12 milligrams per day was the *maximum* dose, and he presented no testimony whatsoever that the label encourages physicians to prescribe this *specific dose*. 238:24-239:5, 239:24-240:7, 240:13-17 (Preskorn)

B. Proposed Conclusions of Law

41. The patentee has the burden of proving infringement by a preponderance of the evidence. *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1364 (Fed. Cir. 2003).

1. Vanda Has Not Presented Evidence of Direct Infringement

42. Vanda has presented no evidence of any physician practicing the claims of the '610 patent. (FOF ¶ 20-24). Instead, it offers only its conclusory, unsupported testimony of Dr. Preskorn (FOF ¶¶ 22-23), which is insufficient as a matter of law. *Kim v. ConAgra Foods, Inc.*,

465 F.3d 1312, 1319-20 (Fed. Cir. 2006) (granting JMOL of non-infringement based on conclusory nature of expert's testimony); *Lemelson v. United States*, 752 F.2d 1538, 1551 ("We give no weight to the series of conclusory statements offered by [Plaintiff's] expert witness."). Absent any evidence of direct infringement, Vanda cannot establish contributory or induced infringement. *ACCO Brands, Inc. v. ABA Locks Mfr. Co.*, 501 F.3d 1307, 1313 (Fed. Cir. 2007); *Anton/Bauer, Inc. v. PAG, Ltd.*, 329 F.3d 1343, 1343, 1349 (Fed. Cir. 2003).

2. Roxane Does Not Infringe Under § 271(c)

43. To establish contributory infringement, Vanda must show that Roxane will sell a product "knowing it to be 'especially made or especially adapted for use in an infringement of [a patented method] and *not* a staple article or commodity of commerce *suitable for substantial non-infringing use*.'" *Vita-Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317, 1327 (Fed. Cir. 2009) (emphasis in original) (quoting 35 U.S.C. § 271(c)). Vanda has not met its burden.

44. Vanda presented no evidence that Roxane's proposed product is especially adapted for use in infringing the '610 patent, nor has it presented any testimony that the knowledge requirement is satisfied.

45. Further, as described in paragraphs 32-36 above, numerous substantial non infringing uses are entirely consistent with Roxane's proposed iloperidone label. The testimony at trial established that the noninfringing uses constitute the vast majority of prescriptions, and thus are not "unusual, far-fetched, illusory, impractical, occasional, aberrant, or experimental." *Vita-Mix Corp,.* 581 F.3d at 1327. Roxane does not contribute to the infringement of the '610 patent.

3. Roxane Does Not Induce Infringement Under § 271(b)

a. Roxane Does Not Encourage, Recommend, or Promote Infringement

46. Vanda's sole basis for asserting inducement is vague, informational language in Roxane's

proposed iloperidone label. But Vanda must do more than show that the label merely describes an allegedly infringing use—it must prove that the label "encourage[s], recommend[s], or promote[s] infringement." *Takeda Pharm. U.S.A., Inc. v. West-Ward Pharm. Corp.*, 785 F.3d 625, 631 (Fed. Cir. 2015) ("*Takeda II*"); *see also id* at 632 ("[V]ague label language cannot be combined with speculation about how physicians may act to find inducement.").

47. As set forth in paragraphs 11-19 above, Roxane's proposed label does not encourage, recommend, or promote a physician to perform the claimed method.

b. **Vanda Has Not Established Intent to Induce Infringement**

48. As set forth in paragraphs 37-38 above, Vanda produced no evidence that Roxane intends to induce infringement. Further, the objective reasonableness of Roxane's interpretation—confirmed by independent sources— undermines any assertions of intent. (*See supra* ¶¶ 26-31).

49. Further, as set forth in paragraphs 32-36 above, numerous substantial noninfringing uses exist for the '610 patent. "Where there are many uses for a product, . . . [the court is] not in a position to infer or not infer intent on the part [of the defendant] without any direct evidence." *Warner-Lambert Co.,* 316 F.3d at 1365. Thus, "where a product has substantial noninfringing uses, intent to induce infringement cannot be inferred even when the defendant has actual knowledge that some users of its product may be infringing the patent." *Id.*; *see also Takeda Pharm. USA, Inc. v. West-Ward Pharm. Corp.*, 72 F. Supp. 3d 539, 543-44 (D. Del. 2014), *affirmed by Takeda II.* The numerous noninfringing uses for Roxane's product undermine any inference that Roxane intends to induce infringement of the '610 patent.

IV. THE ASSERTED CLAIMS OF THE '610 PATENT ARE INVALID AS UNPATENTABLE UNDER 35 U.S.C.§ 101

A. Proposed Findings of Fact

50. Although Vanda previously opposed resolving this issue on summary judgment by

asserting that "[t]he Court will hear conflicting fact and expert testimony about these issues" (D.I. 140, at 1), Vanda presented no expert testimony disagreeing with Roxane's evidence that the asserted '610 patent claims are directed to a law of nature and offered no testimony whatsoever directed to § 101.

51. Each of the asserted '610 patent claims is directed to using CYP2D6 genotyping to determine the appropriate dose of iloperidone to treat a patient with schizophrenia. 516:1-20 (Ratain). Each asserted '610 patent claim recites the limitation "obtaining . . . a biological sample" which requires obtaining genetic material. JX-1 at 17:1-18:58. The '610 patent specification describes the CYP2D6 gene as polymorphic and highly complex with over 70 known allelic variants. JX-1 at 4:64-5:6; 517:17-518:5 (Ratain). Accordingly, a patient's CYP2D6 genetic sequence is a law of nature and that genetic sequence determines whether the patient is a poor metabolizer as defined in the patent. 517:20-518:9 (Ratain).

52. The asserted '610 patent claims recite a law of nature in two respects. Initially, the claims recite a relationship between genetic polymorphisms in CYP2D6 and the extent to which that person metabolizes iloperidone through CYP2D6. 519:1-14 (Ratain). The '610 patent itself describes the invention in terms of this relationship:

> The present invention describes an association between genetic polymorphisms in the CYP2D6 locus, corresponding increases in the concentrations of iloperidone or its metabolites, and the effect of such increases in concentrations on corrected QT (QTc) duration relative to baseline.

JX-1 at 2:34-38.

53. Second, the claims recite obtaining a biological sample (a law of nature), analyzing it for genetic subtype (another law of nature), and adjusting the dose based on genetic status. 516:10-521:5 (Ratain); JX-1, at 11. A patient's genetic status, as revealed by their biological sample, is a law of nature pursuant to the *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.,* 133 S.Ct.

2107 (2013) line of authority. 518:6-23 (Ratain).

54. The relationship claimed in the '610 patent is analogous to the pharmacological relationship that the Supreme Court found unpatentable in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289, 1296-97 (U.S. 2012). There, the Supreme Court concluded that patent claims describing the relationship between the ways in which thiopurine compounds are metabolized by the body simply described a law of nature. *Id.*; *see also* 520:6-23 (Ratain). The asserted '610 patent claims parallel those at issue in *Mayo*. 521:3-5 (Ratain).

55. During prosecution, the Patent Examiner found the pending claims to be directed to a law of nature and allowed them to issue only after specific doses were added to the claims. 521:6-21 (Ratain); JX-94, at 21; JX-20, at 2; DTX-82, at 2. But as Dr. Ratain testified, the dose adjustment limitations are routine and conventional activity. 521:6-522:10 (Ratain).

56. Claim 1 has three basic components: an administering step (i.e., adjusting dose), a determining step (i.e., performing the genotyping test), and a wherein clause (i.e., reciting the desired outcome of the method). 516:21-517:10 (Ratain). None of Vanda's experts testified that genotyping and adjusting drug dosage add anything more than routine and conventional activity. Vanda's expert Dr. Roth conceded that as a practicing physician, he frequently would adjust drug dose to address a patient's side effects. 935:19-23; 936:16-20 (Roth).

57. The administering step requires adjusting the dose to either (a) 12 mg/day or less for CYP2D6 poor metabolizers or (b) more than 12 mg/day for non-CYP2D6 poor metabolizers. Adjusting drug dose is routine and conventional activity. 521:22-522:8 (Ratain). Dr. Ratain testified that common sense, fundamental medical training, FDA Guidance, and other literature support his opinion that adjusting drug dose is routine and conventional activity. 522:11-525:10 (Ratain); DTX-79, at 43-44; JX-79, at 151; DTX-122, at 2; DTX-118, at 1, 3-4; DTX-76, at 5-6,

8. Common sense dictates that if one takes too much of a drug and experiences a side effect, then one should reduce the dose of the drug. 522:18-523:1 (Ratain).

58. Adjusting dose to avoid side effects, i.e., toxicity, is taught as standard dose titration in medical school. 522:18-523:19 (Ratain). For example, the standard medical textbook Goodman and Gilman teaches the basic principle of medicine that "subsequent adjustments may be aided in some instances by measurement of drug concentrations ***but must ultimately be based on whether the regimen is efficacious either without adverse effects or at an acceptable level of toxicity***." 523:6-19 (Ratain); DTX-79 at 43-44 (emphasis added).

59. Peer-reviewed literature further establishes that dose adjustment is routine and conventional. It is well-described in the literature that poor metabolizers of CYP2D6 often require dose reductions of drugs. 523:20-525:4 (Ratain).

60. For example, the prior-art reference Kirchheiner states that for the tricyclics, dose reductions around 50 percent were generally recommended for CYP2D6 poor metabolizers. 523:20-524:9 (Ratain); DTX-122 at 2; UF ¶ 66. Dr. Guengerich admitted that Kirchheiner suggested dose adjustments. 993:20-994:13 (Guengerich). Table II of Shah taught that poor metabolizers often have 2 to 5-fold increase in drug exposure ("AUC") which implies that such individuals often require dose reduction of 50 percent or more. 524:10-23 (Ratain); JX-79 at 151. Shah was published prior to September 30, 2004. JX-79, at 1.

61. FDA's 1997 and 1999 Guidances further establish that dose adjustments are routine. Those documents encouraged NDA applicants to investigate the impact of CYP2D6 for drug metabolism. 525:5-10; 533:6-17 (Ratain); *see also* DTX-76 and DTX-118. The 1997 Guidance stated: "[w]hen a genetic polymorphism affects an important metabolic route of elimination, large dosing adjustments may be necessary to achieve the safe and effective use of the drug."

DTX-118 at 1. It also explained how to evaluate the appropriate dosing adjustment:

> Identifying metabolic differences in patient groups based on genetic polymorphisms, or on other readily identifiable factors such as age, race, and gender, could help guide the design of dosimetry studies for such populations groups. This kind of information also will provide improved dosing recommendations in product labeling, facilitating the safe and effective use of a drug by allowing prescribers to anticipate necessary dose adjustments.

DTX-118 at 3; 985:9-986:10 (Guengerich), 525:5-10 (Ratain). The Guidance specified CYP2D6 polymorphisms in particular. DTX-76, at 5-6, 8.

62. Dr. Ratain testified that while exact dose reduction may not necessarily be ascertained without doing studies, the studies to determine the correct dose adjustment were routine. 524:24-525:4 (Ratain). Indeed, FDA typically requires such studies during the drug approval process. *See* 534:6-11 (Ratain); DTX-118 at 1, 3-4.

63. '610 patent claims 8 and 16, specifying dose of 6 mg iloperidone twice daily, are not patentably distinct from claim 1. Neither this dose nor the dosage range of claim 1 requires anything other than conventional activity. 525:11-526:1 (Ratain).

64. Further, the genotyping procedure specified in the asserted claims was completely routine when the application was filed in September 2004, as the patent specification acknowledges. 517:11-16, 530:15-22 (Ratain); JX-1 at 1:62-2:11. No witness suggested otherwise.

65. Dr. Ratain testified that after considering the subject matter of the asserted claims as a whole and in ordered combination, he concluded that the subject matter was nothing more than a law of nature with the addition of the result of wholly routine experimentation. 516:16-20, 526:14-24 (Ratain). No witness rebutted Dr. Ratain's opinion.

B. Proposed Conclusions of Law

66. Laws of nature are not patentable. *Diamond v. Diehr*, 450 U. S. 175, 185 (1981). "If a law of nature is not patentable, then neither is a process reciting a law of nature, unless that

process has additional features that provide practice assurance that the process is more than a drafting effort designed to monopolize the law of nature itself. A patent, for example, could not simply recite a law of nature and then add the instruction 'apply the law.'" *Mayo,* 132 S. Ct. at 1297.

67. The ultimate question of patent eligibility under § 101 is an issue of law. *Dealertrack, Inc. v. Huber*, 674 F.3d 1315, 1333 (Fed. Cir. 2012). Determining patentability under §101 requires a two-step inquiry. First, a court must "determine whether the claims at issue are directed to one of those patent-ineligible concepts." *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2355 (U.S. 2014). If the claims are directed toward patent-ineligible subject matter, the court must then "consider the elements of each claim both individually and 'as an ordered combination' to determine whether the additional elements 'transform the nature of the claim' into a patent-eligible application." *Id.*

68. Claims that recite "relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a [] drug will prove ineffective or cause harm" are not patentable under 35 U.S.C. ¶ 101. *Mayo*, 132 S. Ct. at 1296-97. Genetic status and genetic mutations are unquestionably unpatentable laws of nature. *See Myriad*, 133 S.Ct. 2107 (2013).

69. Vanda opposed Roxane's request for summary judgment briefing, asserting that at trial it would proffer expert testimony that there is no law of nature and that the claimed steps are not routine and conventional. *See, e.g.,* D.I. 148 at 1 n.1. Vanda offered no such testimony. Thus, as detailed in Roxane's request for summary judgment briefing, *see* D.I. 133, 142, and for the reasons adduced by Roxane at trial, the asserted '610 patent claims are invalid.

70. The asserted claims are directed to detection of genetic status and genetic material. Genetic sequences are inherently a law of nature and are not patentable because, *inter alia*, the

ostensible inventors "did not create or alter any of the genetic information" and such material "existed in nature before [they] found" it. *Myriad*, 133 S.Ct. at 2116. Genetic testing claims similar to those at issue in *Mayo* have been repeatedly found to recite laws of nature. *Genetic Techs. Ltd v. Merial L.L.C.*, No. 15-2012, 2016 WL 1393573, at *5-6 (Fed. Cir. Apr. 8, 2016).

71. The asserted claims are also directed to the relationship between mutations in a patient's CYP2D6 gene and the likelihood of elevated iloperidone in a patient's bloodstream and the correlated benefit of lowering the iloperidone dose for that subpopulation. This is a law of nature. This relationship is akin to the ones found patent ineligible by the Supreme Court in *Mayo*, and by the Federal Circuit in *Ariosa* and *Genetic Technologies*. *See id.* at *5; *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371 (Fed. Cir. 2015).

72. The '610 patent acknowledges that the claimed invention relates to a law of nature. *See supra* ¶¶ 52-53. That characterization is relevant to the determination of whether the asserted claims do in fact recite a law of nature. *Endo Pharm., Inc. v. Actavis Inc.*, C.A. No. 14-1381-RGA, 2015 WL 7253674, at *3 (D. Del. Nov. 17, 2015).

73. The asserted '610 patent claims are not rendered patentable by reciting limitations requiring dose adjustment to avoid the particular side effect of QTc prolongation. The Supreme Court in *Mayo* previously determined that adjusting the dose of a drug to reduce the risk of a side effect is routine and conventional activity. *Mayo*, 132 S. Ct. at 1297-98. Such subject matter is patent ineligible:

> In *Mayo*, the Supreme Court considered method claims that likewise required analysis of a biological sample (the blood of a patient being treated with a thiopurine drug) and in which the focus of the claimed advance over the prior art was allegedly newly discovered information about human biology: the likelihood that a patient could suffer toxic side effects from particular doses of the drug.

Genetic Techs., 2016 WL 1393573, at *5. In an analogous case, Judge Andrews rejected the argument that specifying a lower dose of the drug either rendered the claims patentable or

distinguished the claims from *Mayo*. *Endo*, 2015 WL 7253674, at *1, 3. And here, Dr. Ratain's unrebutted testimony establishes that determining the appropriate dose reduction is nothing more than routine and conventional activity.

74. Nor does the requirement of a genotyping test render the claim patent-eligible. It is undisputed that the recited genotyping test was routine and conventional before September 30, 2004. JX-1 at 1:62-64; 12:21-56.

75. When taken separately or in ordered combination, the claim limitations do not render the claimed subject matter patent-eligible.

V. THE ASSERTED CLAIMS OF THE '610 PATENT ARE OBVIOUS

A. Proposed Findings of Fact

76. Many of the facts relevant to the inquiry under 35 U.S.C. § 101 are relevant to the inquiry under 35 U.S.C. § 103. 526:25-527:8 (Ratain).

77. As the '610 patent concedes, before September 30, 2004, CYP2D6 was well-studied, with more than 70 different known variants. 984:6-16 (Guengerich). The literature also disclosed that a certain population were CYP2D6 poor metabolizers, and described how to genotype for CYP2D6 variants. 528:10-13; 530:4-22 (Ratain); JX-1 at 1:53-2:11.

78. Before the critical date, iloperidone was known to be useful. JX-1 at 1:36-47. It was in advanced clinical trials and was described in published articles as an important new antipsychotic drug. 528:2-9; 529:6-530:3 (Ratain); DTX-53 at 291-293. The literature also reported that iloperidone caused QTc prolongation. *Id.*; *see also* JX-1 at 1:49-52; DTX-53, at 291. Dr. Polymeropoulos' declaration concedes that as of the filing date, iloperidone was known to treat schizophrenia and was known to be associated with QTc prolongation. 120:20-121:17 (Polymeropoulos); DTX-73, at 2.

79. Specifically, CYP2D6 was known to be important to the metabolism of iloperidone. The

prior-art Mutlib reference taught that iloperidone had completed Phase II clinical trials as a potential atypical antipsychotic with a low propensity to cause extrapyramidal side effects. 528:14-529:3; JX-68 at Abstract and 1285; U.F. ¶ 77. Mutlib taught that CYP2D6 was important in the metabolism of iloperidone. 530:23-531:13 (Ratain).

80. Mutlib reported the results of a study of the metabolism of iloperidone in human liver microsomes to define its metabolic pathways. 531:14-20; JX-68, Abstract. Mutlib disclosed that metabolites 2 and 4 were formed by CYP3A4 and by the polymorph CYP2D6, respectively. 531:21-23 (Ratain); JX-68, Abstract. Mutlib "clearly indicated that CYP2D6 is primarily responsible for the production of the major *in vitro* human microsomal metabolite 4. By comparison with those factors known to alter the *in vivo* metabolism of the prototype CYP2D6 and CYP3A4 substrates, certain predictions concerning the regulation of iloperidone metabolism in humans may be made." 532:1-21 (Ratain); JX-68 at 1292. A person skilled in the art would have understood from Mutlib that CYP2D6 was important for iloperidone metabolism and that further studies would quantitatively show its role. 532:6-25 (Ratain). Dr. Guengerich admitted that Mutlib provided reasonable evidence that CYP2D6 played a major role in the metabolism of iloperidone. 979:20-982:25 (Guengerich); *see also* JX-68, at 2; DTX-51, at 8.

81. The 1997 FDA guidance would have motivated a skilled artisan to study iloperidone pharmacokinetics in relation to CYP2D6 metabolism and genotype, and to determine the quantitative importance of CYP2D6 for iloperidone metabolism. 533:1-24 (Ratain); DTX-118; *see also supra* ¶ 57. As Vanda has conceded, before the critical date, FDA would have required clinical pharmacology studies to examine how the drug is metabolized. 115:9-16 (Polymeropoulos), 977:24-979:4 (Guengerich); 533:1-24 (Ratain); DTX-76 and DTX-118.

82. A skilled artisan performing the study recommended in the FDA Guidance would have

learned quantitatively the difference between CYP2D6 poor metabolizers and individuals that are not poor metabolizers. 533:25-534:5. As of September 2004, these types of studies would be performed for any drug for which CYP2D6 was an important metabolic route of elimination. 534:6-11 (Ratain). This process is exactly what Novartis did in its iloperidone clinical program. 534:12-16 (Ratain); *see* ¶¶ 94-95, *infra*.

B. Proposed Conclusions of Law

83. Obviousness is a question of law based on underlying facts. *Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1346 (Fed. Cir. 2009). "Section 103(a) forbids issuance of a patent when the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007) (citation and quotation marks omitted).

84. The obviousness analysis requires that "the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved." *Id.* (quoting *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966)).

85. The obviousness analysis is not limited to the problem that the patentee was trying to solve; "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *KSR*, 550 U.S. at 420.

86. "When the prior art provides the means of making the invention and predicts the results, and the patentee merely verifies the expectation through 'routine testing,' the claims are obvious." *Purdue Pharma Prods. L.P. v. Par Pharm., Inc.*, 642 F. Supp. 2d 329, 368 (D. Del. 2009) (citing *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1367 (Fed. Cir. 2007)). A patent is

obvious where the experimentation needed to arrive at the claimed subject matter was "'nothing more than routine' application of a well-known problem-solving strategy." *Pfizer*, 480 F.3d at 1368-69 (citing *Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 809 (Fed. Cir. 1989)).

87. Claims 1-9, 11-13, and 16 of the '610 patent would have been obvious to a person of ordinary skill in the art as of September 30, 2004. The prior art taught that (1) iloperidone was useful to treat schizophrenia and schizoaffective disorders, (2) iloperidone was known to pose a risk of QTc prolongation, (3) various CYP2D6 genotypes existed, some of which were associated with the CYP2D6 poor metabolizer phenotype, and (4) CYP2D6 genotyping assays were available. Mutlib further taught that CYP2D6 was an important factor in the metabolism of iloperidone. A person of ordinary skill in the art would have understood from Mutlib that one should assess the quantitative impact of CYP2D6 on iloperidone metabolism. Accordingly, FDA Guidance would have motivated a person of ordinary skill in the art to perform routine clinical studies to determine what dosing adjustments, if any, were necessary to accommodate CYP2D6 poor metabolism.

88. A study to confirm that a poor metabolizer should receive one-half of the typical dose would have been entirely routine as of 2004, and in fact was part of Novartis' routine development work for Iloperidone. The subject matter of the asserted claims therefore is the obvious result of wholly routine experimentation and therefore invalid as obvious.

89. Plaintiffs have not offered sufficient evidence of secondary indicia to render claims 1-9, 11-13, and 16 of the '610 patent nonobvious.

VI. THE ASSERTED CLAIMS OF THE '610 PATENT ARE INVALID FOR LACK OF WRITTEN DESCRIPTION

A. Proposed Findings of Fact

90. Each of the asserted '610 patent claims recites a limitation requiring administration of 12

mg/day or less to subjects determined by a genotyping assay to be a CYP2D6 poor metabolizer. The stated goal is to reduce QTc prolongation, and Plaintiffs have relied on that purported benefit in asserting non-obviousness of the claimed invention. The data in the patent do not support the asserted claims, all of which involve this threshold of a 12 mg dose per day. 630:4-9; 631:11-632:11 (McCulloch); 535:20-536:2 (Ratain).

91. The '610 patent includes no disclosure of administering 12 mg/day or less to a subject having a CYP2D6 poor metabolizer genotype, let alone in order to reduce the risk of QTc prolongation.

92. In the study that provided the data in the '610 patent specification (the "2328 study," JX-28), there was no adjustment of dose based on genotype. 477:5-15 (Wolfgang). Moreover, not a single patient in that study received a dose of 12 mg/day or less, which the asserted claims require to purportedly reduce the risk of QTc prolongation. Thus, the 2328 study as set forth in the specification is not an embodiment. 477:16-19 (Wolfgang).

93. Dr. Ratain testified that the data in the patent do not support the limitation requiring a dose of 12 mg/day or less for CYP2D6 poor metabolizers. 536:3-537:3 (Ratain).

94. The dose reduction in the label was supported by different data that were not included in the '610 patent specification—data from Novartis Study 0104 conducted in the 1998-1999 time frame. 537:4-17 (Ratain); *see* 99:12-14, 132:5-134:13 (Polymeropoulos); DTX-73, at 5-7; DTX-225, at 34, 35.

95. The 0104 study specifically took healthy volunteers that were genotyped to be either CYP2D6 extensive metabolizers or CYP2D6 poor metabolizers and gave them a single 3 mg dose of iloperidone. 537:4-17 (Ratain); DTX-225, at 34, 35. Novartis observed that the poor metabolizers had poorer metabolism of iloperidone that the extensive metabolizers. *Id.*

Specifically, the 0104 study showed that poor metabolizers have about a 43% reduction in iloperidone clearance compared to extensive metabolizers. 537:18-538:8 (Ratain); JX-18 at 23-24. Dr. Polymeropoulos conceded that the foregoing data is the data that supports the claimed subject matter of reducing the dose of iloperidone by about half to a poor metabolizer and that the data which supports that notion is ***not*** included in the specification. 132:5-134:13 (Polymeropoulos); DTX-73, at 5-7. Dr. Ratain agreed. 536:3-538:8, 541:14-22 (Ratain).

96. Tables 6 and 7 are the only tables that have information on dosage, QTc prolongation, and poor metabolizer genotypes, which are the same categories of information recited in the asserted claims. 632:16-633:4; 637:2-12 (McCulloch); 540:19-20 (Ratain). Thus, Tables 6 and 7 provide the only data pertinent to the inquiry as to whether the 12 mg/day threshold value in the claims is supported by the specification. 632:16-21 (McCulloch).

97. To support the claims, the CYP2D6 poor metabolizers would have had to have shown worse QTc prolongation results than CYP2D6 non-poor metabolizers, but this is not the case in the 8 mg b.i.d. column or the 12 mg b.i.d. column in Table 6. 635:15-637:1 (McCulloch); 480:2-22 (Wolfgang). In fact, the data show that the poor metabolizers had less QTc prolongation than the non-poor metabolizers, which is the opposite of what would support the claims. *Id.*

98. Moreover, the data in Tables 6 and 7 show inconsistent trends across the dosages studied. As the dose is lowered, the genotypic group having the best QTc prolongation results varies. Accordingly, the data does not demonstrate a trend to support the conclusion that poor metabolizers have greater QTc prolongation than extensive metabolizers. 635:15-637:1; 637:2-12 (McCulloch). Neither Table 6 nor 7 (nor any other data in the specification) compares the relative risk *across dose* for poor metabolizers. In fact, Tables 6 and 7 show no benefit to poor metabolizers in reducing dose. The only individuals the patent classified as poor metabolizers

had *no change* in QTc prolongation, and therefore there is nothing that would allow a person of ordinary skill in the art to conclude that reducing the dose to below 12 mg/day would benefit those individuals. 1001:16-1003:17 (Guengerich).

99. Further, neither Table 6 nor 7 shows any risk of QTc prolongation that is of clinical concern. Regulatory guidelines suggest that QTc prolongation greater 500 milliseconds in aggregate and changes greater than or equal to 60 milliseconds are of clinical concern. 481:22-482:9 (Wolfgang); JX-28, at 88.

100. Tables 6 and 7 do not show any aggregate QTc prolongation that is in excess of 500 milliseconds or any relative QTc prolongation greater than 60 milliseconds. 481:16-483:6 (Wolfgang), 540:15-541:1 (Ratain). There is no data in the patent that show any aggregate QTc prolongation that is in excess of 500 ms or any relative QTc prolongation greater than 60 ms. 481:16-484:8 (Wolfgang).

101. The sample sizes in Tables 6 and 7 are small, which make it important to do a formal statistical analysis which should include a calculation of a p-value. 633:21-634:5; 637:2-12 (McCulloch). No p-values are reported for Tables 6 and 7, which suggests that the data may not be reliable. 634:15-22, 637:2-12 (McCulloch). The specification confirms this, stating that the results "should be viewed with caution since the number of observations is small" and "[g]iven the small number of observations and the unbalanced [sic] in regards to genotype design of the study, a confirmatory prospective study may be required before any further interpretation of this data is warranted." 634:23-635:14 (McCulloch); JX-1 at 9:24-30. The data in the remaining tables, Tables 2-5 and 8-9, cannot be used to draw a reliable conclusion about QTc prolongation, dose, and genotype based on some indirect relationship. 640:17-645:22 (McCulloch).

102. The 2328 study did not evaluate a 12 mg/day dose. 638:1-12 (McCulloch); 541:7-13

(Ratain). Although other higher doses were studied in the 2328 study, the data provided in the specification do not permit reliable extrapolation about the relationship between genotype of QTc prolongation at the 12 mg per day threshold. 637:13-23 (McCulloch); 541:14-17 (Ratain).

103. Given the few data points in the study disclosed in the specification, one would need information about the relationship, which could be linear or non-linear, between QTc prolongation and the different doses in order to model that relationship to determine what happens with respect to QTc prolongation at 12 mg/day. 638:13-639:5 (McCulloch). But the specification provides no information about the form or shape of the relationship between QTc prolongation and the different iloperidone doses. 639:6-10 (McCulloch).

104. Without having information about the form or shape of the relationship, extrapolation is not possible based on the data disclosed in the specification, which is limited to 16 mg/day and 24 mg/day, because depending on whether the relationship is non-linear or linear, one could get quite different results for the QTc measurements at 12 mg/day. 639:11-640:16 (McCulloch).

105. Prior to May 24, 2010, none of the pending claims in the application for the '610 patent suggested a specific dose of iloperidone for poor metabolizers. 538:9-540:14 (Ratain).

106. On May 24th, 2010, FDA sent a letter to Novartis requesting a change in the iloperidone labeling. 539:4-10 (Ratain); JX-20. One of the requested changes was to include the following language: "Similarly, PMs of CYP2D6 have higher exposure to iloperidone compared with EMs and PMs should have their dose reduced by one-half. Laboratory tests are available to identify CYP2D6 PMs." JX-20, at 2 (emphasis reflects new label language).

107. The pending claims were then amended in an attempt to be consistent with FDA's requested label change. 539:21-25 (Ratain); DTX-82, at 2, 7.

108. There is no support in the original claims or in the original specification for this dose

reduction from 24 to 12 mg/day. 540:4-14 (Ratain). "This dose reduction seems to be motivated by the fact that FDA figured out that poor metabolizers should have a dose reduction from 24 to 12, and then the inventors amended the claims." *Id.*

B. Proposed Conclusions of Law

109. Invalidity for failure to meet the written description requirement of § 112 is a question of fact. *PIN/NIP, Inc. v. Platte Chem. Co.*, 304 F.3d 1235, 1243 (Fed. Cir. 2002). To comply with the written description requirement, the specification must describe "the invention, with all its claimed limitations." *ICU Med., Inc. v. Alaris Med. Sys.*, Inc., 558 F.3d 1368, 1379 (Fed. Cir. 2009) (citation omitted).

110. To satisfy the written description requirement, the patentee must "convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and demonstrate that by disclosure in the specification of the patent." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 560 F.3d 1366, 1371-72 (Fed. Cir. 2009).

111. As set forth in paragraphs 90-108 above, the asserted '610 patent claims are invalid for lack of written description. The specification does not show that as of the filing date, the patentees were in possession of the claimed administration of a dose of 12 mg or less to genotypically poor metabolizers, nor has it described any benefit of reduced QTc prolongation of such a dose. The study included in the specification did not evaluate doses of less than 16 mg/day. Nor is there a description of the method as claimed—obtaining the results of a CYP2D6 genotype assay, and based on those results, giving poor metabolizers 12 mg/day or less, and giving extensive metabolizers more than 12 mg/day. During prosecution, the claims were amended to recite the claimed dosing limitations limitation only after the FDA made the sponsor revise its label. Therefore, a skilled artisan viewing the '610 patent specification would not have understood the named inventors to have possessed what they claimed to have invented.

VII. ASSERTED CLAIM 3 OF THE RE'198 PATENT IS OBVIOUS

A. Proposed Findings of Fact

112. By 1989, the first compounds discovered to treat schizophrenia had come to be called "typical" antipsychotic agents. 671:9-15 (Sargent). While effective, this class of drugs exhibited undesirable side effects called extrapyramidal symptoms ("EPS"), such as movement disorders. *Id.* By contrast, an "atypical" antipsychotic was understood to be "a compound that lacks or essentially lacks" these EPS. 671:19-22 (Sargent); 822:13-14 (Bartlett); 891:11-892:24 (Roth). Also, many compounds existed whose typicality or atypicality was unknown, because they had never been evaluated in the clinic. *See* 671:24-672:2 (Sargent). By 1989, skilled artisans were uniformly motivated to synthesize new compounds with a goal of atypical properties. *See* 672:18-22 (Sargent); 822:5-14 (Bartlett); 893:24-894:2 (Roth).

113. In 1989, antipsychotic drug discovery typically involved pursuing new chemical compounds by a structural analog approach—that is, by "selecting a lead compound, or more typically several lead compounds, as a starting point for which one would then make analogs, modifications of that molecule," with the goal of creating a compound with the desired activity. 660:13-17 (Sargent); *see also* 809:6-18 (Strupczewski); 822:15-823:7 (Bartlett).

114. A lead compound is a prior-art compound that would be a natural choice for further development efforts—preferably one that exhibits the desired primary activity (i.e., antipsychotic effect), and possesses other promising structural or biological features. 661:19-662:19 (Sargent). The presence of unwanted side effects in a lead is not typically a concern, provided "you believe there is potential to remove them" (662:20-663:5 (Sargent)) because "you are planning to get rid of [them] as you develop a lead compound." 706:21-707:2 (Sargent).[1]

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[1] For example, clozapine had severe toxicities and nonetheless was regularly used as a lead

115. To select lead compounds, researchers often consulted the published literature. *See* 661:23-662:5 (Sargent). A particularly popular literature source was the Annual Reports in Medicinal Chemistry, "the most widely read review article in medicinal chemistry." 689:7-690:7 (Sargent). Medicinal chemists would have had ready access to compounds reported throughout many years of Annual Reports. *See* 690:9-22

116. Having selected one or more lead compounds, medicinal chemists synthesized structural analogs of each lead, with the goal of preserving the basic biological activity of the lead compound while also adjusting its other properties. *See* 663:9-19 (Sargent). Although a large number of possible modifications are theoretically possible (*see, e.g.*, 825:25-829:20 (Bartlett)), medicinal chemists applied well-known tools and approaches to "rapidly … eliminate irrelevant areas of the molecule and focus on those that are important." 664:20-23 (Sargent). Dr. Sargent testified that he expected the medicinal chemists he himself supervised to have certain "tools at their fingertips," including "bioisosteric replacement." 665:3-11 (Sargent).

117. Bioisosteric replacement refers to replacing an entire functional group of a molecule with another group that mimics the group's activity. *See* 665:3-7 (Sargent); 779:24-780:4 (Strupczewski). Two groups may be bioisosteric with respect to antipsychotic activity, but not to other activities the molecule may have. As Dr. Sargent explained, replacing a group with its known bioisostere preserves the primary biological activity of the compound (e.g., antipsychotic activity), but does not necessarily preserve other activities, including side effects or lack thereof (e.g., atypicality). *See* 667:2-10 (Sargent). Bioisosteric relationships are discovered empirically, through replacements on multiple molecules, before becoming recognized as bioisosteres in the field. *See* 667:11-668:7 (Sargent). Dr. Sargent explained that "[i]f you have the ability in your

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compound until it fell out of favor in the mid-1980s. *See* 672:10-12 (Sargent; clozapine toxicity); 675:1-11 (Sargent; clozapine as a lead); 753:24-754:6 (Sargent).

antipsychotic lead compound to employ a bioisostere, it is low hanging fruit. It is one of the first things you would try." 668:19-21 (Sargent); *see also* 840:9-11 (Bartlett), 923:13-17 (Roth).

118. The structural analogs generated during antipsychotic drug discovery were tested for the desired activity profile. *See* 660:13-17 (Sargent). Typically, animal assays were used. *See* 669:8-12 (Sargent). A common test for antipsychotic activity at the time was the climbing mouse assay. *See* 669:13-16 (Sargent); DTX-280. Earlier tests included the fighting mouse assay. *See* 670:9-18 (Sargent).

119. Two notable atypical antipsychotic agents were known in the field in 1989: clozapine and risperidone. *See* 672:3-14 (Sargent). Clozapine was the original (and for many years, the only) atypical antipsychotic drug, but was plagued by "some really nasty toxicities, which was driving people to find replacements for it." 672:5-12; 685:10-11 (Sargent); *see also* 767:16-20 (Strupczewski). Despite these side effects, clozapine itself initially was a promising lead compound. *See* 672:25-673:12; 675:1- 3 (Sargent). But this approach ultimately proved unsuccessful, and by 1989 researchers had largely abandoned clozapine as a lead. *See id.*; *see also* 741:15-21 (Sargent). Between 1985 and 1990 only two new variants of clozapine appeared in the Annual Reports. *See* 675:4-25 (Sargent).

120. By 1989, experience with clozapine analogs had demonstrated that even seemingly minor structural modifications to clozapine completely abolished its atypical properties. *See* 673:24-674:20 (Sargent); 732:25-733: 8 (Sargent). As such, by 1989, "[t]hat left us with going back to using typical compounds as leads." 675:21-25 (Sargent); *see also* 733:9-16 (Sargent).

121. Risperidone, which emerged in 1986, would have motivated one of ordinary skill to pursue similar compounds as leads because it showed atypical antipsychotic activity. *See* DTX-157; *see also* DTX-158; 672:13-14, 685:12-14 (Sargent); 731:9-732:11 (Sargent; "big news" that

"sent ripples out"); 741:22-25 (Sargent); 796:23-797:22 (Strupczewski); 815:2-7 (Strupczewski); 847:12-21, 848:14-18, 860:14-17, 867:15-17 (Bartlett); 932:3-20 (Roth). Notably, risperidone "had a very different sort of chemical structure" from clozapine, so researchers had "something different to look at." 685:12-16 (Sargent). Specifically, skilled artisans would have recognized that risperidone was structurally related to the cyclic butyrophenone class of compounds, except that where a butyrophenone would contain a benzoyl group, risperidone contained a benzisoxazole group. *See* 683:8-684:17 (Sargent) (butyrophenones), 685:17-686:21 (Sargent); *see also* 741:22-742:13 (Sargent); 827:14-18 (Bartlett: Strupczewski 1985 included cyclic variants "in the class of butyrophenones"), 863:5-11 (Bartlett).

122. Inspired by risperidone, one of ordinary skill would have sought a lead compound from (i) known antipsychotics (*see* 687:16-24 (Sargent)), (ii) butyrophenones, particularly cyclic butyrophenones that most closely resemble risperidone (687:16-688:2 (Sargent)), and (iii) compounds that contained (or could be engineered to contain) a benzisoxazole group. *See* 686:23-688:2 (Sargent); *see also* 863:21-864:3 (Bartlett).

123. The Annual Reports in the preceding 20-odd years reported just 37 butyrophenone antipsychotic agents (691:1-9 (Sargent)), only *six* of which were cyclic butyrophenones—the type most structurally similar to risperidone. *See* 691:20-22 (Sargent); *see also* 756:8-17 (Sargent). This group of cyclic butyrophenones includes Compound A and Compound B, which were identified as promising antipsychotics in three Duncan publications and subsequently reported in Johnson 1974 and several times in the Annual Reports. *See* 691:10-22 (Sargent); *see also* DTX-142 at 2, DTX-143 at 1:52-72, JX-40 at 4, JX-66, DTX-242 at 1-2, DTX-246 at 4.

124. Skilled artisans would have been aware of Compound A. *See* 846:21-847:7 (Bartlett). Compound A was known in 1989 to be a cyclic a butyrophenone that possessed antipsychotic

activity. *See* 925:13-22 (Roth); 863:12-20 (Bartlett); *see also* 692:19-693:17 (Sargent); 697:2-7 (Sargent); 747:6-10 (Sargent); DTX-142 at 2, DTX-143 at 1:52-72, JX-40 at 4, JX-66, DTX-242 at 1-2, DTX-246 at 4. Butyrophenones were popular targets for antipsychotic investigation: Dr. Bartlett testified that "the butyrophenones and related compounds are mentioned in every single annual report as the third class of compounds which one looks at." 836:3-6 (Bartlett).

125. Compound A contains a 4-fluoro-benzoyl group. *See* 688:10-15, 697:8-20 (Sargent). Compound A, and the related Compound B, were repeatedly identified as being the most promising from among dozens of candidate "major tranquilizers," a term synonymous with antipsychotics. *See* 693:8-695:20 (Sargent); *see also* DTX-142 at 2 (selecting Compounds A and B, there called 4 and 5, from 42 candidate compounds); DTX-143 at 1:52-72 (same); JX-40 at 4 (selecting Compounds A and B, there called 10 and 21, from 57 candidate compounds); 842:24-843:1 (Bartlett; "I agree that within the Duncan reference, Compound A is top dog"); *see also* DTX-132 at 1 (discussing terminology); 670:19-671:4 (Sargent) (discussing nomenclature); 773:19-774:2 (Strupczewski); 825:16-18 (Bartlett; "this was a major tranquilizer. My understanding is this was used as a traditional neuroleptic compound"). In 1974, Johnson "confirmed and highlighted Compound A as a potential antipsychotic." 696:9-10 (Sargent); *see also* JX-66. Compound B also had shown promise of atypicality. *See* 755:9-11 (Sargent); 760:19-761:9 (Sargent redirect). And both compounds were featured multiple times in the Annual Reports: Compound A was featured twice, in 1971 (DTX-242 at 1-2, as "Compound 5") and also in 1975, where it was listed as "Possessing Antipsychotic Activity" (DTX-246 at 4, as "Compound 10"), whereas Compound B was listed on five separate occasions. *See* 691:16-19, 696:12-25 (Sargent); *see also* 834:17-835:3 (Bartlett). By 1989, one of ordinary skill also would have known that patent protection on Compound A had expired, and that it had never entered

clinical trials. *See* 706:16-20 (Sargent).

126. One of ordinary skill in 1989 would have been motivated to select Compound A as a lead compound in the search for an atypical antipsychotic drug. *See* 708:9-11, 709:2-11, 710:7-10 (Sargent).

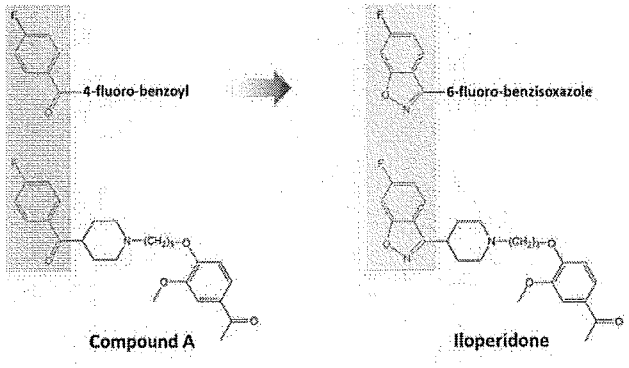
127. In 1985 Strupczewski, subsequently a named inventor on the RE'198 patent, published a structure-activity relationship ("SAR") study in the Journal of Medicinal Chemistry., "the most important journal in the field." 698:2-18, 704:7-14 (Sargent); *see also* JX-26; 777:19-778:2 (Strupczewski); 847:8-11 (Bartlett); 927:24-928:3 (Roth). In this work, Strupczewski took "several groups of butyrophenone compounds and made the benzisoxazole derivatives of them," and "repeatedly show[ed] that you can replace a benzoyl group with a benzisoxazole group in the field of antipsychotics." 698:9-18 (Sargent); *see also* 778:21-25 (Strupczewski); 854:13-16 (Bartlett) (Strupczewski 1985 presents "a classic structure activity relationship"). Strupczewski reported that his benzisoxazole replacements retained—and in some cases improved upon—antipsychotic activity. *See* 700:9-16; 704:24-705:3 (Sargent); JX-26 at 763-765 (results), 768 (climbing mouse assay). For example, Strupczewski 1985 reported that the benzisoxazole replacement of the antipsychotic cyclic butyrophenone compound HP291—namely, Compound 8b—was considerably more potent in the climbing mouse assay. *See* 700:21-701:20 (Sargent); JX-26 at 764; 852:4-12 (Bartlett) (benzisoxazole replacement "increased the potency of those compounds").

128. Strupczewski 1985 explicitly "demonstrated that the benzoyl and the benzisoxazol[-]3-yl groups are bioisosteric." 698:9-18 (Sargent); JX-26 at 766 ("[T]he benzoyl and 1,2-benzisoxazol-3-yl groups are bioisosteric"); 840:21-841:8 (Bartlett); DTX-147 (Shutske 1982) and JX-51 at 23 (1984 Annual Reports); 780:9-21 (Strupczewski).

129. Strupczewski 1985 also reported that among benzisoxazole replacements, "a fluorine in the 6-position of the benzisoxazole nucleus results in maximum activity." JX-26 at 766; 702:17-703:1, 705:4-6 (Sargent); 814:6-14 (Strupczewski); 852:22-853:6 (Bartlett).

130. Strupczewski 1985 performed a benzoyl-to-benzisoxazole replacement on four of the six prior-art cyclic butyrophenones—including a replacement of Duncan's Compound B to yield Strupczewski 1985 Compound 10b—but did not report the equivalent substitution to Compound A. *See* 703:3-25, 701:22-702:6 (Sargent); JX-26 at 766 n.8 (citing JX-40); 782:10-15 (Strupczewski); 785:14-19 (Strupczewski, testifying that "if one took [Compound B] and made the benzoyl to benzisoxazole substitution described in [his] paper" one would "end up with the Compound in Table 6"); 703:3-22 (Sargent); JX-26 at 765 (Compound 10b).

131. The *only* difference between the prior art lead compound (Compound A) and the claimed compound (iloperidone) is the replacement of the 4-fluoro-benzoyl group of Compound A with a 6-fluoro-benzisoxazole:



See 697:8-20 (Sargent); 704:1-6 (Sargent); 812:7-11 (Strupczewski). As described above, this precise replacement was taught as being bioisosteric in Strupczewski 1985. Dr. Bartlett conceded during cross-examination that "the difference between the claimed subject matter and Compound A was disclosed in Mr. Strupczewski's paper." 851:16-19 (Bartlett); *see also* JX-26; 785:14-19 (Strupczewski).

132. Asserted claim 3 of the RE'198 patent does not claim any activity whatsoever for iloperidone; it claims only the chemical compound itself or a pharmaceutically acceptable addition salt thereof by "whatever form you got." 874:7-13 (Bartlett); *see also* 849:4-9 (Bartlett); JX-2 at 112:44-47; 679:13-16 (Sargent). The RE'198 patent reports results of the climbing mouse assay indicating antipsychotic activity, but there is no suggestion (or test data that might indicate) that iloperidone has atypical antipsychotic activity. 680:17-24 (Sargent), 681:13-682:3 (Sargent) ("You need a different test in order to do that"); 850:2-5, 874:7-13 (Bartlett); 930:11-15 (Roth).

B. Proposed Conclusions of Law

133. In the context of ostensibly novel chemical compounds, the obviousness inquiry may involve one or more lead compounds. A lead compound is a compound in the prior art that would be "a natural choice for further development efforts." *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 974 (Fed. Cir. 2014) (citation omitted). "'[K]nowledge in the art of the functional properties and limitations of the prior art compounds' are also important to this analysis." *Id.* at 974 (*quoting Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010)). "The motivation to modify that lead compound can come from any number of sources and need not necessarily be explicit in the art." *Id.* at 973. It is sufficient to show that the claimed and prior art compounds possess a "sufficiently close relationship . . . to create an expectation," in light of the totality of the prior art, that the new compound will have "similar properties" to the prior art compound. *Id.* (citation omitted). "Whether a lead compound and a claimed compound have a sufficiently close relationship frequently turns on their 'structural similarities and differences.'" *Id.* (citation omitted). "Normally a *prima facie* case of obviousness is based upon structural similarity, *i.e.*, an established structural relationship between a prior art compound and the claimed compound." *In re Deuel*, 51 F.3d 1552, 1558

(Fed. Cir. 1995).

134. One of ordinary skill in 1989 would have been motivated to select Compound A as a lead compound in the search for an atypical antipsychotic drug. The 1988 publication of risperidone's atypical antipsychotic activity in the clinic caused tremendous excitement in the field, and would have motivated one of ordinary skill to pursue similar compounds as leads. *See supra* at ¶ 121. Inspired by risperidone,[2] one of ordinary skill would have sought a lead compound that was (i) a known antipsychotic, (ii) a butyrophenone, particularly a cyclic butyrophenone, and (iii) either contained or could be engineered to contain a benzisoxazole. *See supra* at ¶ 122. Compound A, a cyclic butyrophenone generally known by 1988 to have antipsychotic activity, meets all these criteria and was "a natural choice for further development efforts." *BMS v. Teva*, 752 F.3d at 973 (citation omitted); *see also supra* at ¶ 124-125.

135. The prior art also directed one of ordinary skill to Compound A. For instance, Compound A and Compound B had repeatedly been singled out in the art as particularly promising antipsychotic candidates, and both had been profiled multiple times in the Annual Reports in Medicinal Chemistry. *See supra* at ¶ 125.

136. Further adding to its appeal, Compound A was off-patent by 1989 and had never been marketed or put into clinical trials. *See supra* at ¶ 125.

137. Skilled artisans would have evaluated many other potential candidates besides Compound A. This is normal and expected, because "the selection of a lead compound necessarily leads a medicinal chemist to choose one or two or three from hundreds." *See* 870:22-871:23 (Bartlett). Also, the presence of possible side effects generally would not deter one of ordinary skill from selecting a particular lead. *See supra* at ¶ 114.

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[2] Strupczewski first synthesized iloperidone mere weeks after the publication of risperidone's atypicality. *See* 799:1-10 (Strupczewski); 868:14-869:21 (Bartlett)

138. Starting with Compound A , the precise benzoyl-to-benzisoxazole replacement that yields iloperidone is obvious. The *only* difference between the prior art (Compound A) and the claim at issue (iloperidone) is the replacement of the 4-fluoro-benzoyl with a 6-fluoro-benzisoxazole, "an infinitesimally small switch" and one explicitly taught in the prior art. 710:1-18 (Sargent).

139. Strupczewski 1985 taught that the benzisoxazole group was bioisosteric with the benzoyl in the antipsychotic context, that this replacement could improve antipsychotic activity, and in particular that the 6-fluoro substituent on the benzisoxazole conferred the most potent antipsychotic activity. *See supra* at ¶¶ 127-128. Thus, one of ordinary skill would have been motivated to make Strupczewski 1985's benzoyl-to-benzisoxazole replacement with a reasonable expectation that doing so could yield a compound "with the characteristics of Compound A, but maybe enhanced activity." 858:13-24 (Bartlett); *see also* 710:11-18 (Sargent). Strupczewski first synthesized iloperidone mere weeks after the publication of risperidone's atypicality. *See* 799:4-9 (Strupczewski); 868:14-869:21 (Bartlett).

140. Notably, Strupczewski 1985 did not teach that the benzoyl-to-benzisoxazole substitution would confer *atypicality,* and it did not need to, as atypicality is neither demonstrated nor claimed in the RE'198 patent. *See* supra at ¶ 132.

141. In sum, claim 3 of the RE'198 patent is obvious because one of ordinary skill in 1989 would have selected Compound A as a lead compound and made the 4-fluoro-benzoyl-to-6-fluoro-benzisoxazole replacement explicitly taught in Strupczewski 1985, which yields iloperidone.

VIII. CONCLUSION

142. Accordingly, Roxane does not infringe the asserted claims of the '610 patent, and the asserted claims of the '610 patent and asserted claim 3 of the RE'198 patent are invalid for the reasons stated above.

Respectfully submitted,

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