

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

**IN RE: OZEMPIC (SEMAGLUTIDE)
PATENT LITIGATION**

No. 22-md-3038-CFC

**NOVO NORDISK INC. AND NOVO
NORDISK A/S,**

Plaintiffs/Counterclaim Defendants,

v.

**RIO BIOPHARMACEUTICALS INC., et
al.,**

C.A. No. 22-294-CFC

Defendants/Counterclaim Plaintiffs.

**NOVO NORDISK INC. and NOVO
NORDISK A/S,**

No. 22-cv-1040-CFC

Plaintiffs/Counterclaim Defendants,

v.

MYLAN PHARMACEUTICALS INC.,

Defendant/Counterclaim Plaintiff.

**OPENING EXPERT REPORT OF WILLIAM J. JUSKO, PH.D.
REGARDING INVALIDITY OF U.S. PATENT NO. 10,335,462**

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TABLE OF ABBREVIATIONS

Full Name of Cited Reference	Abbreviation
U.S. Patent App. Pub. No. 2011/0166321	'321 publication
U.S. Patent No. 10,335,462 (NN-OZEM-000000071-95)	'462 patent
Prosecution History for U.S. Patent No. 10,335,462 (NN-OZEM-000003820-4446)	'462 patent prosecution history
U.S. Patent App. Pub. No. 2004/0102486	'486 publication
U.S. Patent No. 5,512,549	'549 patent
U.S. Patent No. 8,114,833 (SEMA(JDG)_0000447-68)	'833 patent
Bell, <i>Hamster Preproglucagon Contains the Sequence of Glucagon and Two Related Peptides</i> , 302 NATURE 716 (1983)	Bell
Bhansali, <i>Historical Overview of Incretin Based Therapies</i> , 58 J. ASSOC. OF PHYSICIANS OF INDIA 10 (2010) (SEMA(JDG)_0000014-18)	Bhansali
Blonde, <i>Comparison of Liraglutide Versus Other Incretin-Related Anti-Hyperglycaemic Agents</i> , 14 (suppl. 2) DIABETES, OBESITY & METABOLISM 20 (2012)	Blonde
<i>ClinicalTrials.gov Background</i> , CLINICALTRIALS.GOV, https://clinicaltrials.gov/ct2/about-site/background (last visited Mar. 15, 2024)	ClinicalTrials.gov Background
Drab, <i>Incretin-Based Therapies for Type 2 Diabetes Mellitus: Current Status and Future Prospects</i> , 30 PHARMACOTHERAPY 609 (2010)	Drab
FDA Guidance for Industry, <i>Exposure-Response Relationships - Study Design, Data, Analysis, and Regulatory Applications</i> (Apr. 2003)	FDA Exposure Response 2003
Garber, <i>Efficacy of Metformin in Type II Diabetes: Results of a Double-Blind, Placebo-Controlled, Dose-Response Trial</i> , 102 AM. J. MED. 491 (1997)	Garber

TABLE OF ABBREVIATIONS
(continued)

Full Name of Cited Reference	Abbreviation
<i>Award: ClinicalTrials.gov</i> , https://ash.harvard.edu/news/clinicaltrials.gov (last visited Mar. 15, 2024)	Harvard Award
Holst, <i>Truncated Glucagon-like Peptide I, an Insulin-Releasing Hormone from the Distal Gut</i> , 211 (2) FEBS LETTERS 169 (1987)	Holst
<i>International Conference on Harmonisation; Dose-Response Information to Support Drug Registration; Guideline; Availability</i> , 59 Fed. Reg. 55972 (Nov. 9, 1994)	ICH 1994
EMA, <i>ICH Topic S 7 A Safety Pharmacology Studies for Human Pharmaceuticals</i> (June 2001)	ICH 2001
Kirillova, <i>Results and Outcome Reporting in ClinicalTrials.gov, What Makes it Happen?</i> , 7(6) PLoS ONE 1 (2012)	Kirillova
Knudsen, <i>Glucagon-like Peptide-1: The Basis of a New Class of Treatment for Type 2 Diabetes</i> , 47 J. MED. CHEMISTRY 4128 (2004)	Knudsen 2004
Knudsen, <i>Liraglutide: The Therapeutic Promise from Animal Models</i> , 64(suppl 167) INT J CLIN PRACT 4 (2010)	Knudsen 2010b
Landersdorfer, <i>Pharmacokinetic/Pharmacodynamic Modelling in Diabetes Mellitus</i> , 47(7) CLIN PHARMACOKINET 417 (2008)	Landersdorfer 2008
Landersdorfer, <i>Mechanism-Based Population Pharmacokinetic Modelling in Diabetes: Vildagliptin as a Tight Binding Inhibitor and Substrate of Dipeptidyl Peptidase IV</i> , 73 Br J Clin Pharmacol 391 (2011)	Landersdorfer 2011a
Landersdorfer, <i>Mechanism-Based Population Modelling of the Effects of Vildagliptin on GLP-1, Glucose and Insulin in Patients with Type 2 Diabetes</i> , 73 BR J CLIN PHARMACOL 373 (2011)	Landersdorfer 2011b
Lovshin, <i>Incretin-Based Therapies for Type 2 Diabetes Mellitus</i> , 5 NATURE REVIEWS ENDOCRINOLOGY 262 (2009) (SEMA(JDG)_0002250-58)	Lovshin 2009

TABLE OF ABBREVIATIONS
(continued)

Full Name of Cited Reference	Abbreviation
Lund, <i>Emerging GLP-1 Receptor Agonists</i> , 16 EXPERT OPINION ON EMERGING DRUGS 607 (2011)	Lund
Madsbad, <i>An Overview of Once-Weekly Glucagon-Like Peptide-1 Receptor Agonists - Available Efficacy and Safety Data and Perspectives for the Future</i> , 13 DIABETES, OBESITY & METABOLISM 394 (2011) (SEMA(JDG)_0002439-52)	Madsbad 2011
Mojsov, <i>Insulintropin: Glucagon-like Peptide I (7-37) Co-encoded in the Glucagon Gene is a Potent Simulator of Insulin Release in the Perfused Rat Pancreas</i> , 79 J. CLIN. INVEST. 616 (1987)	Mojsov
Møller, <i>Mechanism-Based Population Modelling for Assessment of L-Cell Function Based on Total GLP-1 Response Following an Oral Glucose Tolerance Test</i> , 38 J. PHARMACOKINET PHARMACODYN 713 (2011)	Moller
Monami, <i>Effects of Glucagon-Like Peptide-1 Receptor Agonists on Body Weight: A Meta-Analysis</i> , 2012 EXPERIMENTAL DIABETES RSCH. 1 (2012)	Monami
Murphy, <i>Review of the Safety and Efficacy of Exenatide Once Weekly for the Treatment of Type 2 Diabetes Mellitus</i> , 46 ANN PHARMACOTHER 812 (2012)	Murphy
Clinical Trial No. NCT00696657 (Internet Archive)	NCT00696657
Clinical Trial No. NCT00851773 (Internet Archive)	NCT00851773
Rohatagi, <i>Model-Based Development of a PPARγ Agonist, Rivoglitazone, to Aid Dose Selection and Optimize Clinical Trial Designs</i> , 48 J. CLIN. PHARM. 1420 (2008)	Rohatagi
Seino, <i>Dose-Dependent Improvement in Glycemia with Once-Daily Liraglutide without Hypoglycemia or Weight Gain: A Double-Blind, Randomized, Controlled Trial in Japanese Patients with Type 2 Diabetes</i> , 81 DIABETES RSCH. & CLINICAL PRACTICE 161 (2008)	Seino
Shargel, APPLIED BIOPHARMACEUTICS & PHARMACOKINETICS (5th ed. 2005)	Shargel

TABLE OF ABBREVIATIONS
(continued)

Full Name of Cited Reference	Abbreviation
Tamimi, <i>Drug Development: From Concept to Marketing!</i> , 113 NEPHRON CLIN PRACT C125 (2009)	Tamimi
Tasneem, <i>The Database for Aggregate Analysis of ClinicalTrials.gov (AACT) and Subsequent Regrouping by Clinical Specialty</i> , 7(3) PLoS ONE 1(2012)	Tasneem
<i>Victoza</i> , PHYSICIANS' DESK REFERENCE (65th ed. 2010)	Victoza label
International Patent App. Pub. No. WO 2011/058193	WO '193
International Patent App. Pub. No. WO 2011/073328	WO '328
International Patent App. Pub. No. WO 2011/138421 (SEMA(JDG)_0002087-158)	WO '421
International Patent App. Pub. No. WO 91/11457	WO '457
International Patent App. Pub. No. WO 2006/097537 (SEMA(JDG)_0002453-528)	WO '537
Yun, <i>Pharmacokinetic and Pharmacodynamic Modelling of the Effects of Glimepiride on Insulin Secretion and Glucose Lowering in Healthy Humans</i> , 31 J. CLIN. PHARM. & THER. 469 (2006)	Yun
Zarin, <i>The ClinicalTrials.gov Results Database—Update and Key Issues</i> , 364 NEW ENGL. J. MED. 852 (2011)	Zarin

1. My name is William J. Jusko, Ph.D. I have been retained by Mylan Pharmaceuticals Inc., Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc., Rio Biopharmaceuticals Inc. and EMS S/A; Sun Pharmaceutical Industries Ltd. and Sun Pharmaceutical Industries, Inc.; and Zydus Worldwide DMCC, Zydus Pharmaceuticals (USA) Inc., and Zydus Lifesciences Limited (collectively, the "defendants"). I understand that Novo Nordisk Inc. and Novo Nordisk A/S (collectively, "Novo Nordisk" or "Plaintiffs") have asserted that the defendants infringe claims 1, 3-5, and 7 of U.S. Patent No. 10,335,462 ("’462 patent"). I have been asked to express my opinions regarding the validity of certain asserted claims of the ’462 patent.

I. QUALIFICATIONS AND BACKGROUND

A. EDUCATION AND EXPERIENCE

2. I am a Professor of Pharmaceutical Sciences at the University of Buffalo School of Pharmacy and Pharmaceutical Sciences. My specialty and research focus broadly include Pharmacokinetics, Pharmacodynamics, Pharmacogenomics, and Pharmacometrics.

3. My research interests also include theoretical, basic, and clinical aspects of the pharmacokinetics and pharmacodynamics of various immunosuppressive agents including corticosteroids, as well as drugs used to treat diabetes, inflammation, and cancer.

4. I have characterized the effects of diverse drugs in cells, tissues, animals, and human subjects and have evolved advanced pharmacokinetic/pharmacodynamic (“PK/PD”) models for rapidly acting as well as cascade-type processes. I also have developed mechanism-based pharmacokinetic, pharmacodynamic, and disease progression models and computational methods describing the action of various drugs and utilized mathematical models of drug action to determine optimal dosage regimens for diverse drugs.

5. I have worked as a consultant for the Food and Drug Administration (FDA) Clinical Pharmacology Advisory Committee, the National Institutes of Health (NIH) Pharmacology Study Section, the Council for International Exchange of Scholars, and for many pharmaceutical companies.

6. From 2001 to 2016, I served as chair of the University of Buffalo Department of Pharmaceutical Sciences. More than 100 students and fellows have completed research training under my guidance.

7. I have published more than 670 research articles and serve on the editorial boards of numerous academic journals, including formerly being the editor-in-chief for the Journal of Pharmacokinetics and Pharmacodynamics.

8. I received a Bachelor of Pharmacy in 1965 from State University of New York at Buffalo. I remained at State University of New York (SUNY) at Buffalo where I completed my Ph.D. in Pharmaceutical Sciences in 1969.

9. I began my academic career in 1969 as an Assistant Professor of Pharmacology at the Boston University School of Medicine, where I remained for years.

10. I have been a faculty member at the University of Buffalo since 1972. From 1972 to 1974, I was an Assistant Professor of Pharmaceutics at the University of Buffalo.

11. I remained at the University of Buffalo from 1974 to present, where I transitioned through several roles including as the Director of the Doctor of Pharmacy Program, Vice-Chairman of the Department of Pharmacy, Professor of Pharmaceutical Sciences, Chair of Pharmaceutical Sciences, and Director of the Center of Excellence in Pharmacokinetics and Pharmacodynamics. I am now currently a SUNY Distinguished Professor in Pharmaceutical Sciences.

12. My expertise has been recognized by my peers. I received the 2020 Distinguished Pharmaceutical Scientist Award from the American Association of Pharmaceutical Sciences (“AAPS”). The Distinguished Pharmaceutical Scientist Award is the AAPS’s most esteemed honor and is a lifetime achievement that recognizes an individual who has made substantial contributions to the research and advancement of pharmaceutical sciences.

13. I received the 2019 Lewis B. Sheiner Lecturer Award from the International Society of Pharmacometrics (“ISoP”); the 2018 Oscar B. Hunter

Career Award in Therapeutics from the American Society for Clinical Pharmacology and Therapeutics; a coveted MERIT (Method to Extend Research in Time) Award from the NIH; and several other awards.

14. I have appreciable experience in studying the pharmaceutical and pharmacological properties of drugs used to treat diabetes. My *curriculum vitae* (“CV”) lists at least 31 such publications with 21 involving the study of antidiabetic drugs or the diabetes disease conditions in animal models (diabetic rats) and 10 pertaining to the study of antidiabetic drugs in healthy or diabetic humans. Part of this work was supported by the Pfizer Company when I directed my Department’s participation in the UB/Pfizer Strategic Alliance in PK/PD with millions of dollars of support from the company.

15. I am also an inventor on a patent application assigned to SmithKline Beecham Corporation in which I assisted in the development of their antidiabetic drug, Avandia (rosiglitazone) and helped to describe the Exposure/Response (PK/PD) relationships between plasma drug concentrations, lowering of glucose, and lowering of glycated hemoglobin (HbA_{1c}) concentrations in blood in type 2 diabetic patients. See ’486 publication. This drug was approved by the FDA as the first-in-class known as “insulin sensitizers” that help the uptake of glucose by transporters into tissues. I later helped the Daiichi Sankyo Company in developing

rivoglitazone, a drug in the same class with similar effects. *See* Rohatagi. We generated Exposure/Response relationships for a range of doses in these studies.

16. I have particularly relevant experiences pertaining to glucagon-like peptide-1 (“GLP-1”)-related mechanisms in diabetes, some of which I discuss in more detail below. I also have considerable experience in designing studies (including dosing studies) and assessing pharmacokinetic and pharmacodynamic data from phase I, II, and III clinical trials. This includes clinical trials for the antidiabetic drugs rosiglitazone, rivoglitazone, pramlintide, vildagliptin, inhaled insulin and others.

17. I am currently a consultant for ReveraGen BioPharma, Inc. advising on dosing in their clinical trials and performing data analyses for their steroid vamorolone in treating adolescent males with Duchenne muscular dystrophy.

18. A copy of my CV, attached as Exhibit A, provides a more comprehensive review of my work and describes my qualifications in greater detail, including a list of all publications that I authored during my career.

B. PRIOR TESTIMONY

19. In the past four years, I have testified in the following proceedings:

- *Kellington v. Bayer*, 5:14-CV-00002 (W.D. VA), 2:14-CV-00036-WMA;
- *Hospira Inc. v. Genentech, Inc.*, IPR2017-00805 (PTAB);

- *KVK-Tech, Inc. v. Shire PLC*, IPR2018-00290, IPR2018-00293 (PTAB);
- *Novartis AG v. Apotex Inc.*, Civil Action No. 15-6934 (SRC)(CLW);
- *Tris Pharma, Inc. v. Teva Pharmaceuticals USA, Inc.*, 2-20-cv-05212 (D.N.J.);
- *Novartis Pharmaceuticals Corp. v. Dr. Reddy's Labs. Inc.*, C.A. No. 21-1106 (D. Del.);
- *Mylan Pharmaceuticals Inc. v. Novo Nordisk A/S*, IPR2023-00724 (P.T.A.B.).

C. BASIS FOR OPINIONS AND MATERIALS CONSIDERED

20. A list of the materials I considered, in addition to my experience, education, and training, to provide the opinions contained in this report is attached as Exhibit B.

D. RETENTION AND COMPENSATION

21. I have been retained by counsel for the defendants as a technical expert to provide certain of my opinions regarding the '462 patent. I receive \$800 per hour for this work. No part of my compensation is dependent upon my opinions given or the outcome of this proceeding. I have no affiliations with Novo Nordisk Inc. or Novo Nordisk A/S, or any affiliates presently known to me, or the named inventor on the '462 patent.

II. LEGAL STANDARDS

22. In preparing and forming my opinions set forth in this report, I have been informed by counsel of the relevant legal principles. I applied my understanding of those principles in forming my opinions. My understanding of those principles is summarized below.¹ I took these principles into account when forming my opinions in this proceeding.

23. I understand that my opinions regarding invalidity are presented from the viewpoint of a person of ordinary skill in the art (“POSA” or “skilled artisan”) in the field of technology of the patent as of the patent’s priority date. In this report, my opinions are premised on the perspective of a POSA at the time of the earliest claimed priority date listed on the face of the ’462 patent, July 1, 2012. *See* ’462 patent at cover page. To the extent that Novo Nordisk later asserts that the asserted

¹ In performing my analysis and reaching my opinions and conclusions, I have been informed of and have been advised to apply various legal principles relating to invalidity, which I set forth herein. In setting forth these legal standards, it is not my intention to testify about the law. I only provide my understanding of the law, as explained to me by counsel, as a context for the opinions and conclusions I am providing.

claims are entitled to an earlier priority or invention date, I reserve the right to supplement this report.

24. I have been informed that the defendants bear the burden of proving invalidity by clear and convincing evidence. I have been told that this means the Court, considering the evidence, must have an abiding conviction that it is highly probable that the asserted claims are invalid.

25. I understand that for a patent claim to be invalid as anticipated, a prior art reference must disclose each element of the claim expressly and/or inherently as arranged in the claim.

26. Counsel has informed me that the concept of patent obviousness involves four factual inquiries: (1) the scope and content of the prior art; (2) the differences between the claimed invention and the prior art; (3) the level of ordinary skill in the art; and (4) secondary considerations of non-obviousness.

27. It is my understanding from counsel that when there is some recognized reason to solve a problem, and there are a finite number of identified, predictable and known solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If such an approach leads to the expected success, it is likely not the product of innovation but of ordinary skill and common sense. It is my understanding that any need or problem known in the field of endeavor at the time of invention or addressed by the patent can provide a reason

for combining prior art elements to arrive at the claimed subject matter. I understand that only a reasonable expectation of success is necessary to show obviousness.

III. PERSON OF ORDINARY SKILL IN THE ART

28. In my opinion, the following definition of a person of ordinary skill in the art (“POSA” or “skilled artisan”) applies to the claims of the ’462 patent. If the Court adopts, or the parties agree to, a different definition of a POSA I reserve the right to amend and/or supplement my opinions on invalidity.

29. A POSA here would have had (1) an M.D., a Pharm. D., or a Ph.D. in pharmacy, chemical engineering, bioengineering, chemistry, or related discipline; (2) at least two years of experience in protein or peptide therapeutic development and/or manufacturing or diabetes treatments; and/or (3) experience with the development, design, manufacture, formulation, or administration of therapeutic agents, and the literature concerning protein or peptide formulation and design, or diabetes treatments.

30. Alternatively, the POSA would be (1) a highly skilled scientist lacking an M.D., Pharm. D., or Ph.D., but would have (2) more than five years of experience in the area of protein or peptide therapeutic development and/or manufacturing or diabetes treatments; and/or (3) experience with the development, design, manufacture, formulation, or administration of therapeutic agents for diabetes, and

the literature concerning protein or peptide formulation and design, or diabetes treatments.

31. A POSA would have understood the prior art references referred to herein and would have the capability to draw inferences. It is understood that, to the extent necessary, a POSA may collaborate with one or more other POSAs for one or more aspects with which the other POSA may have expertise, experience, and/or knowledge. Additionally, a POSA could have had a lower level of formal education than what I describe here if the person has a higher degree of experience.

32. I understand that Novo Nordisk proposed that a person of ordinary skill in the art would have, among other possible qualifications, an M.D., Ph.D. or equivalent degree in Pharmacology, Pharmaceutics, Biopharmaceutics, or a related field, and 3-5 years of experience conducting clinical research in the field of diabetes treatments, including the design of dosing regimens and dosage forms for type 2 diabetes treatments, or 3-5 years of research or industry experience relating to developing pharmaceutical formulations.

33. As shown by my qualifications provided in my CV and as explained in this report, I met the qualifications of a POSA for purposes of the '462 patent regardless of which party's definition is adopted.

34. Regardless of which party's definition is adopted for a POSA, my opinions would not change.

IV. BRIEF SUMMARY OF OPINIONS

35. In my opinion, WO '421 anticipates claims 1 and 3 of the '462 patent.

36. In my opinion, Lovshin 2009 anticipates claims 1 and 3 of the '462 patent.

37. In my opinion, NCT00696657 anticipates claims 1 and 3 of the '462 patent.

38. In my opinion, claims 1, 3-5, and 7 of the '462 patent would have been obvious over WO '421, NCT00696657, WO '537 and/or Lovshin 2009, optionally in view of one or more of the '833 patent and Madsbad 2011.

39. In my opinion, claims 1, 3-5, and 7 of the '462 patent would have been obvious over WO '421 alone or in view of the '833 patent.

40. In my opinion, claims 1, 3-5, and 7 of the '462 patent would have been obvious over WO '537 in view of Lovshin 2009.

41. I understand that the defendants' expert Dr. Paul Dalby is submitting an expert report with his opinions about why claims 4, 5, and 7 of the '462 patent, directed to formulation-related elements, are obvious over the prior art. I defer to Dr. Dalby's opinion regarding obviousness with respect to claims 4, 5, and 7 of the '462 patent.

42. I understand that experts retained by Novo Nordisk may provide opinions regarding alleged secondary considerations of nonobviousness of the

asserted '462 patent claims. I reserve the right to address any secondary considerations that Novo Nordisk's experts may provide.

V. THE '462 PATENT

A. THE SPECIFICATION AND CLAIMS OF THE '462 PATENT

43. I have read the '462 patent, titled "Use of Long-Acting GLP-1 Peptides," and reviewed the relevant portions of the prosecution history of the '462 patent. The '462 patent issued from U.S. Patent Application No. 15/656,042 ("'042 Application"), filed July 21, 2017, which is a continuation of U.S. Application No. 14/409,493, filed as PCT/EP2013/063004, filed June 21, 2013, and claims priority to Provisional Application No. 61/708,162, filed October 1, 2012, and Provisional Application No. 61/694,837, filed August 30, 2012, and European patent 12174535, filed July 1, 2012, and European patent 12186781, filed October 1, 2012. '462 patent at cover page. The '462 patent lists Christine Bjoern Jensen as the sole inventor and Novo Nordisk A/S as the Assignee. *Id.*

44. The '462 patent has one independent claim and nine dependent claims.

45. Independent claim 1 recites "[a]method for treating type 2 diabetes, comprising administering semaglutide once weekly in an amount of 1.0 mg to a subject in need thereof."

46. Claim 2 recites, "[t]he method according to claim 1, wherein the semaglutide is administered by parenteral administration."

47. Claim 3 recites, “[t]he method according to claim 2, wherein the solution² is administered by subcutaneous injection.”

48. Claim 4 recites, “[t]he method according to claim 1, wherein the semaglutide is administered in the form of an isotonic aqueous solution comprising phosphate buffer at a pH in the range of 7.0-9.0.”

49. Claim 5 recites, “[t]he method according to claim 4, wherein the solution further comprises propylene glycol and phenol.”

50. Claim 6 recites, “[t]he method according to claim 4, wherein the pH is 7.4.”

51. Claim 7 recites, “[t]he method according to claim 6, wherein the solution further comprises propylene glycol and phenol.”

52. Claim 8 recites, “[t]he method according to claim 4, wherein the phosphate buffer is a sodium dihydrogen phosphate buffer.”

53. Claim 9 recites, “[t]he method according to claim 1, wherein the semaglutide is administered by subcutaneous injection in the form of an isotonic aqueous solution comprising at a sodium dihydrogen phosphate buffer at a pH in the

² I note that although claim 3 recites, “[t]he method according to claim 2 [which depends from claim 1], wherein the solution is administered by subcutaneous injection,” neither claim 2 nor claim 1 recites “a solution.”

range of 7.0-9.0, and wherein the solution further comprises propylene glycol and phenol.”

54. Claim 10 recites, “[t]he method according to claim 9, wherein the pH is 7.4.”

B. THE PROSECUTION HISTORY OF THE ’462 PATENT

55. The ’042 Application that issued as the ’462 patent was filed on July 21, 2017 and included independent claim 1, which recited:

1. A method for

a) reduction of HbA1c;

b) treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes; or

c) treatment of obesity, reducing body weight and/or food intake, or inducing satiety;

wherein said method comprises administration of a GLP-1 agonist to a subject in need thereof, wherein said GLP-1 agonist

i) has a half-life of at least 72 hours;

ii) is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week; and

iii) is administered once weekly or less often.

See '462 patent prosecution history, 2017-07-21 Specification as filed at 38 (NN-OZEM-000003828).

56. On July 23, 2018, the Examiner issued a Non-final Office Action, rejecting the claims for, among other rejections, anticipation. Claims 1-10 were rejected as being anticipated by Clinical Trials NCT00696657 (NCT00696657) as evidenced by Lau, Madsbad 2011 as evidenced by the Eperzan assessment report, and Madsbad 2011 as evidenced by the Trulicity assessment report, and claims 1-8 and 10 were rejected as anticipated by Kim as evidenced by Bydureon NDA. See '462 patent prosecution history, 2018-07-23 Non-Final Office Action at 5-8 (NN-OZEM-000004354-57).

57. In response, the Applicant made the following amendments to claim 1:

1. (Currently Amended) A method for treating type 2 diabetes, comprising administering semaglutide once weekly in an amount of 1.0 mg to a subject in need thereof

~~a) reduction of HbA1c;~~

~~b) treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes; or~~

~~c) treatment of obesity, reducing body weight and/or food intake, or inducing satiety;~~

~~wherein said method comprises administration of a GLP-1 agonist to a subject in need thereof,~~

~~wherein said GLP-1 agonist~~

~~i) has a half life of at least 72 hours;~~

~~ii) is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week; and~~

~~iii) is administered once weekly or less often.~~

See '462 patent prosecution history, 2019-01-23 Amendment and Reply Under 37 CFR 1.111 at 2 (NN-OZEM-000004384).

58. On March 6, 2019, the Examiner issued a Notice of Allowance stating in the Reasons for Allowance:

The '657 clinical trial compared semaglutide and liraglutide in treatment of type 2 diabetic patients. The semaglutide or liraglutide was used as on add-on therapy to type 2 diabetic patients already taking metformin. Efficacy of treatment was further assessed by a reduction in HbA1c levels. Patients in the Arm Labels D and E of the clinical trial were administered 0.8 mg once weekly by subcutaneous injection. However, the reference does not teach or disclose a higher amount of 1 mg semaglutide.

See '462 patent prosecution history, 2019-03-06 Notice of Allowability at 4-5 (NN-OZEM-000004402-403).

VI. CLAIM CONSTRUCTION

59. I understand from counsel that the claims of a patent generally are to be construed to have their plain and ordinary meaning as understood by a POSA considering the patent specification and prosecution file history. I further understand that it is proper for patentees to act as their own lexicographers and define and use claim terms in ways specific to their patent.

60. I have been informed that the Court issued its claim construction order on July 25, 2023. D.I. 148 in No. 22-md-3038.

61. I understand the Court found the preamble, “[a] method for treating type 2 diabetes,” of claim 1 of the ’462 patent to be an express limitation of claims 1-10. The Court further found that the preamble, “[a] method for treating type 2 diabetes,” means that “the claimed administration is for the purpose of care and management of a patient with Type 2 diabetes” or “the claimed administration is intended to care for and manage a patient with Type 2 diabetes.” *Id.* at 2-3. I also understand that the Court construed the preamble so that it does not require any particular degree or minimum threshold of efficacy for the claimed method for treating type 2 diabetes.

62. I understand the Court adopted the following agreed upon constructions:

- “once weekly in an amount of 1.0 mg” of claim 1 has its plain and ordinary meaning, which is “one administration per week in an amount of 1.0 mg”; and
- “solution” of claims 3, 4, 5, and 7 has its plain and ordinary meaning, which is “a solution comprising semaglutide.”

Id. at 8.

63. I have applied these constructions in forming my opinions in this report.

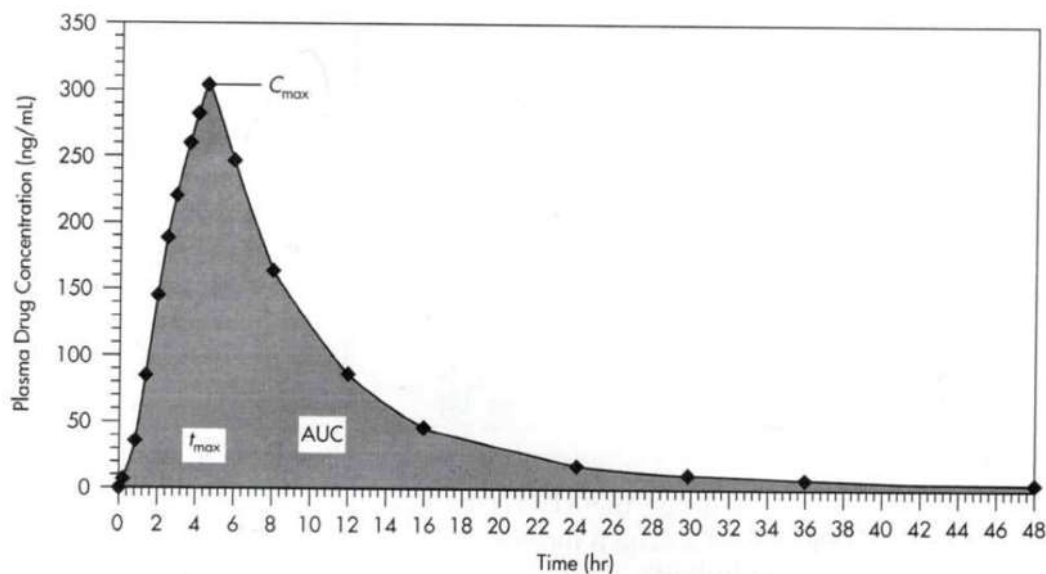
VII. BACKGROUND

A. PHARMACOKINETICS AND PHARMACODYNAMICS

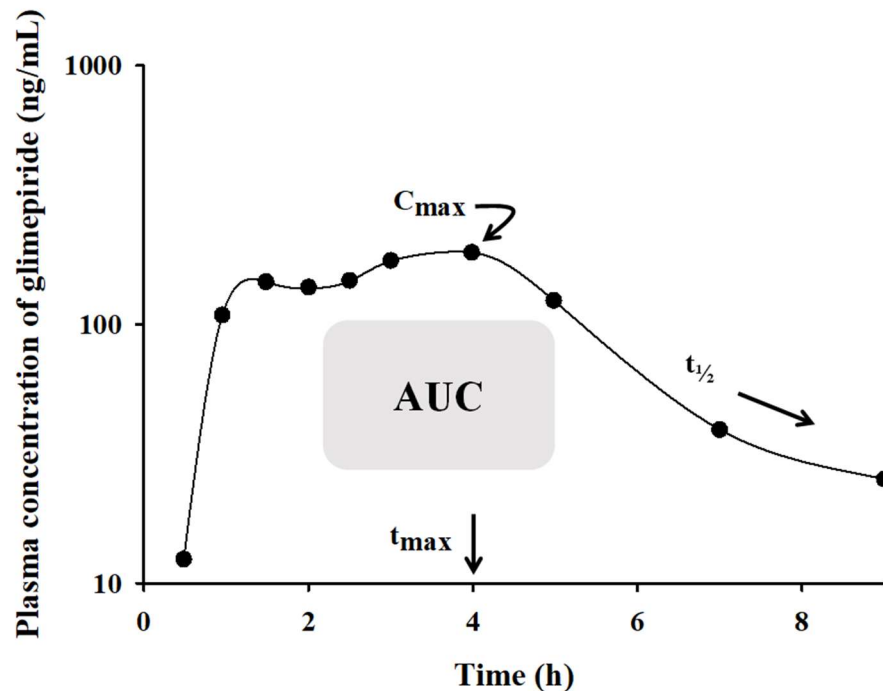
64. Pharmacokinetics (“PK”) and pharmacodynamics (“PD”) are two branches of pharmacology directed to the study of how a drug interacts with the body. Pharmacokinetics is the description of how the body affects the handling of drugs. Pharmacokinetics describes the time course and factors affecting drug absorption from the site of administration (e.g., gastrointestinal tract, subcutaneous tissue), distribution to various tissues, and elimination by metabolism, renal excretion, and biliary excretion. *See* Shargel at 3. Characterizing the distribution and elimination of a drug is an important prerequisite for determination or modification of dosing regimens for patients. *Id.* The study of pharmacokinetics involves both experimental approaches, e.g., analytical methods for the measurement of drugs and metabolites in animals and humans, and theoretical approaches, development of

pharmacokinetic models that quantitate and/or predict drug disposition after drug administration. *Id.*

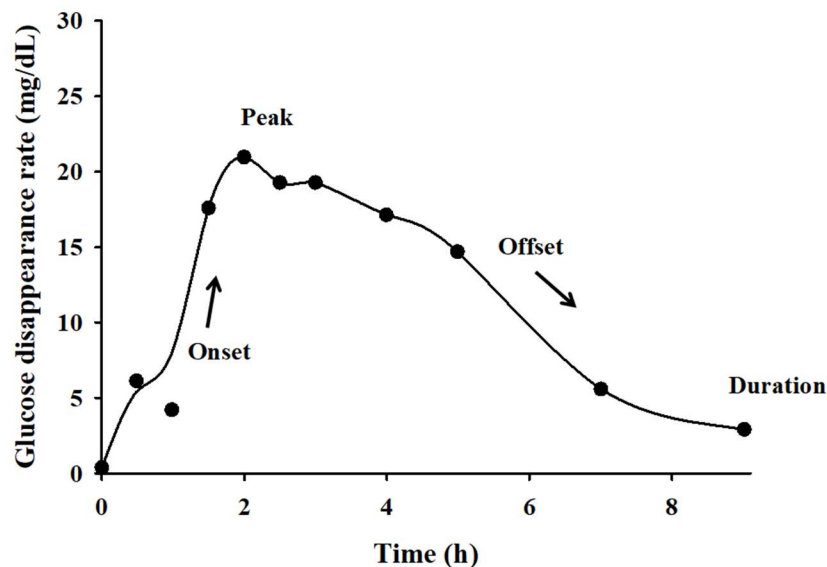
65. The simplest expression of pharmacokinetics is the “exposure” of the drug, namely the relationship between plasma (blood) concentrations and time where parameters such as $C_{\max}$ (maximum concentration), $t_{\max}$ (time of maximum concentration), AUC (Area Under the Concentration-Time Curve), and $t_{1/2}$ (half-life) are described and measured, such as the graph set forth below. *Id.* at 461, Figure 15-1.



66. For example, the graph shown below is adapted from Figure 2 of Yun, showing such properties for the antidiabetic drug glimepiride (Amaryl®) in healthy human subjects after administration of a single 2 mg oral dose. *See Yun at Fig 2.*

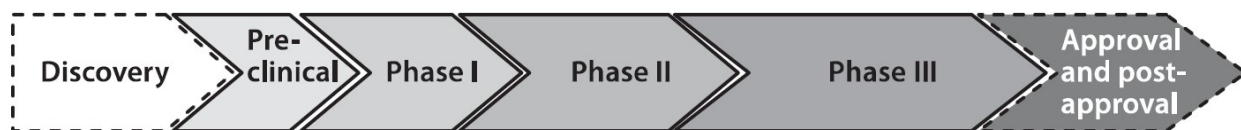


67. Pharmacodynamics is the description of how the drug affects the body, and refers to the relationship between the drug concentration in blood or at the site of action and the pharmacologic response. *See* Shargel at 4. It describes the time course and factors affecting the onset, peak, and duration of drug responses after single and multiple doses of a drug. While such responses are determined by many factors and exhibit many time courses, the simplest of graphs would show these phases in tandem with a pharmacokinetic profile (i.e., PK/PD), such as shown above. The graph below demonstrating these properties is adapted from Figure 6 of Yun, and shows the effects of administration of a single 2 mg dose of glimepiride on utilization of glucose in healthy human subjects. *See* Yun at Fig 6.



B. DRUG DEVELOPMENT – CLINICAL TRIAL DESIGN

68. The process of designing a drug is long-term and expensive, involving different phases of drug development, starting with discovery, preclinical studies including basic research, laboratory experiments and animal studies before moving to human clinical studies (phase I-IV studies). *See* Tamimi at c125-26, Fig. 1 (see schematic below reproduced from Fig. 1 of Tamimi).



69. Before a drug can be tested in humans, the United States Food and Drug Administration (FDA) and other regulatory agencies require that preclinical studies be performed to predict that the drug can be safely given to humans. *See* Knudsen 2010b at 4; Tamimi at c127. Preclinical studies involve obtaining functional

biochemical properties such as receptor binding and pharmacokinetic testing *in vitro* and pharmacodynamic and pharmacokinetic testing *in vitro* and *in vivo* of the drug, including studies in animal models to explore the drug's mechanistic effects on different tissues and organs. *See* Tamimi at c127; Knudsen 2010b at 4. Next, a suitable formulation is developed for the drug and the drug is “progressed through the required toxicology testing (including genotoxicity, safety pharmacology in all biological systems, single and multiple dose toxicity and toxicokinetic studies) to enable the first in human and subsequent clinical studies.” Tamimi at c127; *see* ICH 2001 at 5-8 (“The effects of a test substance on the functions listed in the safety pharmacology core battery should be investigated prior to first administration in humans.”). Prerequisites for filing a drug approval request include reproductive toxicology in male and female animals and long-term carcinogenicity testing. *Id.* Thus, by the time a drug reaches the phase to be evaluated in humans, an extensive body of data will have been generated to understand its therapeutic potential and minimize risks. *See* Tamimi at c127; Knudsen 2010b at 4.

70. After the preclinical testing is satisfied, there are four phases for evaluating new drugs, phases I-IV. Phase I studies usually include a small number of healthy subjects, with the purpose to evaluate the safety, tolerability, pharmacodynamic and pharmacokinetic effects of the drug. *See* Tamimi at c127. A range of doses are investigated in a phase I study, including a minimum dose

extending to maximum tolerated dosages. All phase I-IV studies require approval from ethics committees and the relevant regulatory agency. *Id.* Additional phase I studies can be conducted throughout any of the other phases of development. *Id.*

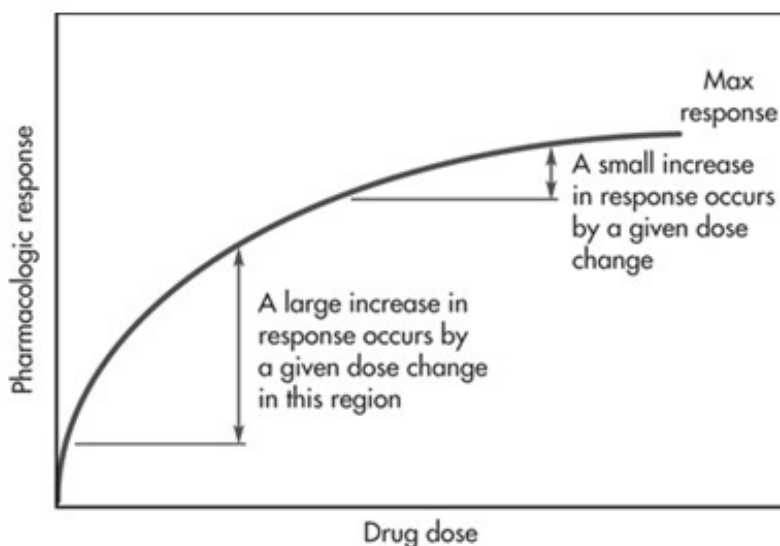
71. Following establishment of the drug's safety, pharmacokinetics, and dose selection in healthy volunteers in a phase I study, the efficacy and safety of the drug is next investigated in persons who have the disease/condition the drug is intended to treat in one or more phase II studies. Tamimi at c128. Phase II studies can be divided into phase IIa and phase IIb, or can be combined into one large study, which can include several hundred patients. *Id.* Phase II studies define the minimally effective or non-effective dose and assist in selecting the optimal doses, based on clinical efficacy and safety, to pursue in the much larger phase III study. *Id.* A range of doses from suboptimal to maximally effective doses are typically investigated in the phase II study to help determine optimal doses, which are doses with an acceptable balance of beneficial effects and undesired effects. *Id.*; *see also, e.g.*, ICH 1994 at 55973 (“What is most helpful in choosing the starting dose of a drug is knowing the shape and location of the population (group) average dose-response curve for both desirable and undesirable effects. Selection of dose is best based on that information, together with a judgment about the relative importance of desirable and undesirable effects.”), 55974 (“It is important to choose as wide a range of doses as is compatible with practicality and patient safety to discern clinically meaningful

differences.”), 55976 (“Depending on circumstances (the disease, the drug’s toxicity), the starting dose may range from a low dose with some useful effect to a dose that is at or near the full-effect dose.”); FDA Exposure Response 2003 at 2, 4 (“The dose-response study is a particularly informative design, allowing observations of benefits and risks at different doses and therefore providing an ability to weigh the benefits and risks when choosing doses. The dose-response study can help ensure that excessive doses (beyond those that add to efficacy) are not used, offering some protection against unexpected and unrecognized dose-related toxicity.”).

72. Both the FDA and other international regulatory bodies (including from Europe and Japan) encourage the determination of “Exposure/Response” during the development of new drugs. *See* FDA Exposure Response 2003 at 2 (“Exposure-response information is at the heart of any determination of the safety and effectiveness of drugs. That is, a drug can be determined to be safe and effective only when the relationship of beneficial and adverse effects to a defined exposure is known.”); ICH 1994 at 55972-74, 55976. This involves the assessment of both pharmacokinetics and pharmacodynamics over a range of doses in seeking to understand what doses are optimal and the rates of undesired effects in human subjects and how to best use the drug in patients. *Tamimi* at c127-28; FDA Exposure Response 2003 at 4; ICH 1994 at 55972-74, 55976. The results of such studies in

the phase I or phase II assessment of PK/PD often yield pharmacodynamic parameters such as the $E_{\max}$ (maximum effect of the drug) and EC_{50} (drug concentration producing one-half of the $E_{\max}$). *See* Shargel at 578, Figs. 19-1, 19-2.

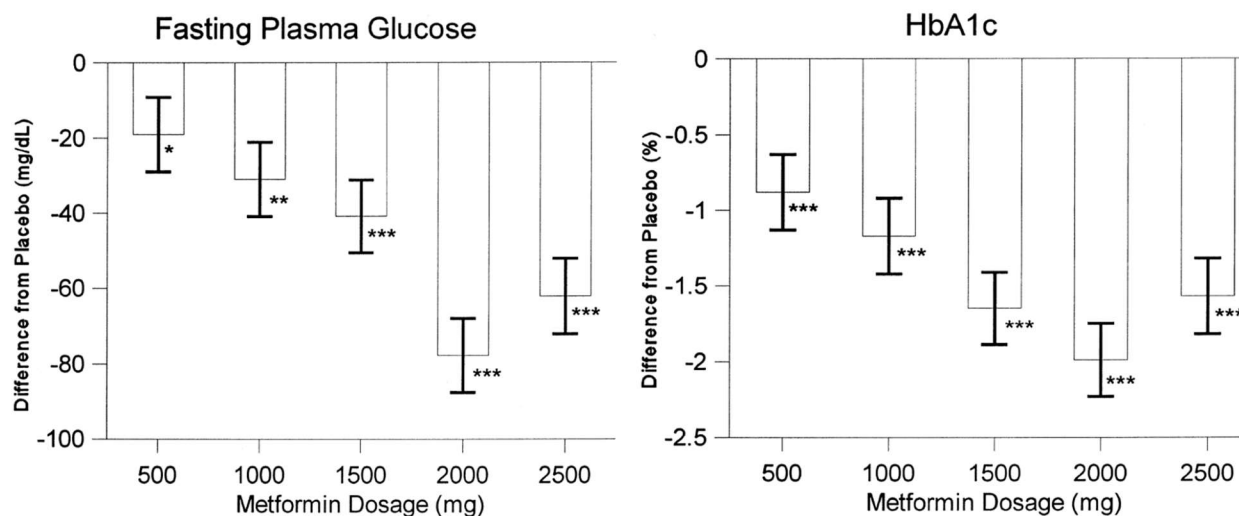
73. The pharmacologic effect of a drug depends on the dose and the pharmacokinetics of the drug. *See* Shargel at 577. As the dose of the drug increases, the concentration at the receptor or target site increases, and the pharmacologic response (effect) increases up to a maximum effect. A plot of the pharmacologic effect to dose on a linear scale generally results in a hyperbolic curve with maximum pharmacologic effect ($E_{\max}$) at the plateau on the dose-response curve, as shown in the figure below (reproduced from Figure 19-1 of Shargel). *Id.* at 577-78.



74. Typically, the optimal dose is often the smallest dose providing the near maximal treatment effect (i.e., the lowest dose near or on the plateau) because higher doses usually result in higher adverse event rates. To best understand the

Exposure/Response of a drug, phase II studies typically investigate a range of doses including lower doses and higher doses that are predicted to be on the dose-response curve plateau. *See* FDA Exposure Response 2003 at 4; ICH 1994 at 55972-74, 55976.

75. An example of a phase II dose-response study in which the efficacy of a range of dosages of a drug were investigated was the phase II double-blind, placebo controlled, dose response trial testing various doses of metformin as compared with placebo in patients with type 2 diabetes. *See* Garber at 491-92. The dose-response bar graphs from this study provided below illustrate the responses (consisting of lowering of fasting plasma glucose and glycated hemoglobin, HbA_{1c}) versus a range of doses of metformin, which is typical for a phase II dose-response study. *See id.* at 495, Fig. 1.



76. As shown in the bar graphs above, the metformin doses administered to patients with type 2 diabetes ranged from low doses (500 mg) to much higher doses (2000 mg and 2500 mg), with the maximum efficacy of metformin observed at 2000 mg, not 2500 mg. *See id.* at 495, Fig. 1. The highest dose of metformin administered, 2500 mg, would fall well onto the plateau of the dose-response curve.

77. If the drug shows promising efficacy in a successful phase II study, then larger phase III studies can be performed to confirm the clinical doses, timing, and frequency prior to registration. Tamimi at c128. Typically, a minimum of two phase III studies are performed, involving up to several thousand patients. *Id.* Finally, once successful phase III studies are completed, the data are compiled and submitted to the appropriate regulatory agency. *Id.* at c129. Phase IV studies include post-marketing or safety surveillance trials. *Id.* at c129-30.

C. PHARMACOKINETICS AND PHARMACODYNAMICS RELATED TO GLP-1 AND SEMAGLUTIDE

78. Type 1 diabetes is characterized by the body's inability to produce insulin, whereas type 2 diabetes involves a genetic susceptibility resulting in insulin deficiency and an excessive glucagon secretion. Landersdorfer 2008 at 418; Madsbad 2011 at 394. There are a diversity of drugs, hormones, and mediators that can affect glucose, which can be used or modulated to treat diabetes. In 2008, I

published a review of mathematical (PK/PD) methods and models for several such anti-diabetic drug effects. *See Landersdorfer 2008.*

1. GLP-1

79. In the early 1980s, two peptides, glucagon-like peptide 1 (“GLP-1”) and glucagon-like peptide 2 (“GLP-2”), related to the hormone glucagon were identified. *See generally Bell.* GLP-1 is a 30 amino acid peptide produced and secreted from intestinal enteroendocrine L cells after meal ingestion. Lund at 607. GLP-1 binds to GLP-1 receptors (GLP-1R) expressed on pancreatic beta cells resulting in the stimulation of insulin secretion, suppression of glucagon secretion, slowing of gastric emptying, and (likely by binding to GLP-1R in the brain) inducing a feeling of satiety thereby reducing food intake. *Id.* at 607-08. Owing to these benefits, pharmacological strategies based on GLP-1 based therapies were pursued for the treatment of type 2 diabetes. *Id.* at 608. I supervised the mathematical analysis of GLP-1 profiles obtained by Novo Nordisk from type 2 diabetic subjects after an oral glucose tolerance test and developed a PK/PD model to describe the production and loss of GLP-1 in plasma over 4 hours. *See Moller.*

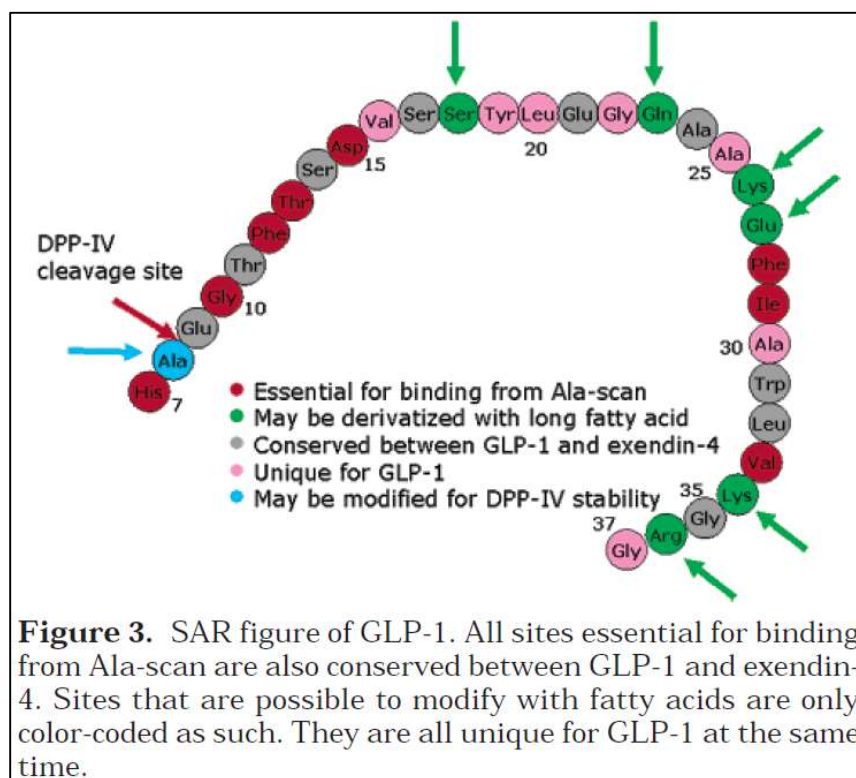
80. GLP-1 has a short half-life owing to rapid degradation by the enzyme dipeptidyl peptidase IV (DPP-4) found in plasma and tissues. *See Lovshin 2009* at 263. One method of treating diabetes was to administer inhibitors of DPP-4 (known as incretin enhancers) and thereby extend the action of naturally secreted GLP-1.

Before the earliest claimed priority date, there were at least six known DPP-4 inhibitors, including sitagliptin, vildagliptin, alogliptin, saxagliptin, linagliptin, and dutogliptin. *See* Lovshin 2009 at 263, Table 1 (listing DPP-4 inhibitors). I assisted in developing a PK/PD Exposure/Response model for vildagliptin (Galvus[®]), used to assess the pharmacokinetics and actions of vildagliptin at different doses. *See* Landersdorfer 2011a; Landersdorfer 2011b.

2. GLP-1 derivatives

81. Further studies related to GLP-1 found that the body naturally synthesizes truncated forms of the GLP-1 peptide, including GLP-1 (7-37). *See, e.g.*, Mojsov; Holst. In addition to inhibiting the secretion of glucagon, a hormone that raises blood glucose, GLP-1 (7-37) was found to have an insulintropic (stimulating insulin secretion) effect. Mojsov at 616-18; Holst at 172-74. In the early and mid-1990s, GLP-1 derivatives (including derivatives of GLP-1 (7-37)) were being developed that possessed improved pharmacological properties. *See, e.g.*, '549 patent at Abstract, 1:9-11, 2:27-32, 3:9-11, 25-30; WO '457 at 2:24-29, 3:2-7. Thus, GLP-1 and certain of its truncated forms (e.g., GLP-1 (7-37)) were known by skilled artisans to be potential therapeutic agents for the treatment of type 2 diabetes, owing to their ability to stimulate insulin, inhibit glucagon, and ultimately lower blood glucose levels.

82. Exendin-4 is a GLP-1 analog, isolated from the venom of Gila monsters, that shares 53% sequence identity with GLP-1 and binds to GLP-1 receptors (GLP-1Rs) but has the advantage of greater stability against DPP-4 and thus prolonged pharmacokinetics. *See* Knudsen 2004 at 4129-130. The figure below (reproduced from Figure 3 of Knudsen 2004) summarizes the understanding gained from GLP-1 and exendin-4 studies, including the DPP-IV cleavage site and amino acid residues essential for binding the GLP-1 receptor. Knudsen 2004 at 4130, Fig. 3. As shown in the figure below, the amino acids essential for binding are His7, Gly10, Phe12, Thr13, Asp15, Phe28, Ile29, and Val33. Knudsen 2004 at 4130, Fig. 3.



83. Further research into the use of GLP-1 and its derivatives ultimately resulted in FDA approval of several GLP-1R agonists such as exenatide and liraglutide to treat type 2 diabetes. *See* Lovshin 2009 at 263; Victoza label. Exenatide is synthetic exendin-4, which was approved by the FDA in 2005 for the treatment of type 2 diabetes. *See* Lovshin 2009 at 263. Exenatide initially was administered subcutaneously twice daily for treatment of type 2 diabetes, but was subsequently formulated for slow release so that it needed to only be administered once weekly. *Id.* As disclosed in Lovshin 2009, “the success of exenatide accelerated the development of new GLP-1R agonists with pharmacokinetic properties optimized for once-daily or once-weekly administration.” *Id.* at 264.

84. As disclosed in the prior art, a benefit of once weekly dosing for GLP-1 receptor agonists in development was that it could “improve compliance, and ... offer an improved throughout-the-day glycemic control compared with the currently available GLP-1R agonists (exenatide and liraglutide).” Lund at 611. Knudsen disclosed, “[n]ausea may best be avoided by a long half-life because a long half-life gives the smallest needed excursions in plasma concentrations.” Knudsen 2004 at 4131.

a. Liraglutide

85. Liraglutide is “an analog of human GLP-1 and acts as a GLP-1 receptor agonist,” and is the active ingredient in Victoza[®]. Victoza label at 2671. Liraglutide

“is made by attaching a C-16 fatty acid (palmitic acid) with a glutamic acid spacer on [a] lysine residue at position 26 of the peptide precursor.” *Id.* at 2671. The amino acid sequence of liraglutide is shown below:

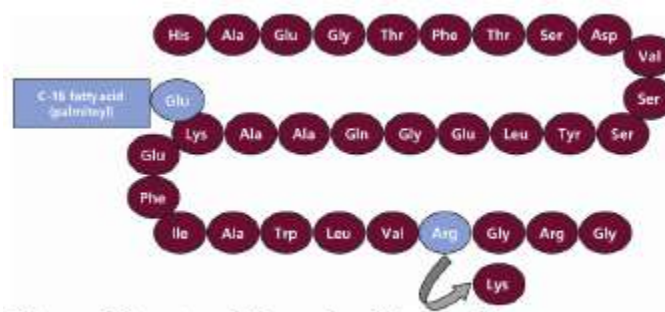


Figure 1 Structural Formula of liraglutide

*Id.*³

86. The single-letter abbreviation of the amino acid sequence of liraglutide, above, is:

HAEGTFTSDVSSYLEGQAAKEFIAWLVRGRG

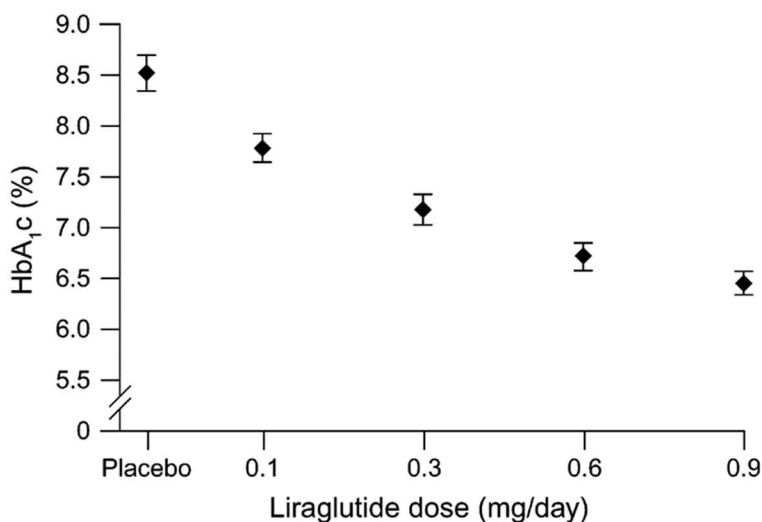
87. The amino acid residues shown to be essential in GLP-1 for GLP-1 receptor binding are also present in liraglutide. *See* Knudsen 2004 at 4130, Fig. 3.

88. Before the earliest priority date, skilled artisans would have known that liraglutide was the subject of numerous clinical studies and publications describing its effectiveness and was studied alone or alongside other diabetes therapies. *See,*

³ This figure appears in the Victoza label, however, for purposes of readability this figure is from the electronic version of the Victoza label found at Drugs@FDA website

(https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/022341s037s038lbl.pdf (last accessed March 19, 2024)).

e.g., Blonde; Lund; Madsbad 2011; Murphy. The development of liraglutide included studies of the pharmacokinetics and glucose lowering in animal models and then Phase I and Phase II dose-ranging studies in healthy subjects and type 2 diabetic patients. *See* Knudsen 2010b; Madsbad 2011. Liraglutide exhibits consistent dose/response profiles for lowering HbA_{1c} as might be expected for any agent that functions as a GLP-1 agonist. The graph shown below from Figure 1 of Seino provides one of the earliest Dose/Response profiles published for liraglutide showing lowering of HbA_{1c} after 14 weeks of once-daily treatment of type 2 diabetic patients. *See* Seino at 164, Fig. 1.



89. The narrow error bars (representing the standard error) indicate that variability was modest at each dose level and that higher doses produced stronger effects than lower doses, reflecting a clear dose-response relationship for HbA_{1c}. *See id.* at 166 (“A clear dose response relationship for HbA_{1c} was shown in this study.”).

Moreover, as shown above, liraglutide showed the classic sigmoidal dose/response profile for lowering HbA1c. As reported in Seino, “[a]ll doses of liraglutide tested showed a degree of efficacy.” *Id.* While it was not clear whether a plateau was reached, the progression of increasing responses with higher doses offered confidence that the properties of this GLP-1 agonist within the incretin system were well-understood. For example, there was no loss of efficacy during chronic exposure from possible antibodies to liraglutide. *Id.* at 164. By the time that the Victoza label was approved, liraglutide had been studied at higher doses than 0.9 mg/day, such as 1.2 mg/day and 1.8 mg/day. Victoza label at 2672-673, Table 4.

90. Liraglutide was approved in 2010 as Victoza[®] “as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.” Victoza label at 2668. Drab disclosed that “as with exenatide, the most common adverse effect of liraglutide is nausea.” Drab at 618. Drab disclosed that during the phase III trials, “the frequency of nausea with liraglutide ranged from 10.5% when combined with a sulfonylurea to 40% with a thiazolidinedione.” *Id.* “In comparison, the frequency of nausea and/or vomiting reported with metformin is approximately 25%. As with exenatide, nausea with liraglutide can be limited by gradual dosage titration.” *Id.*

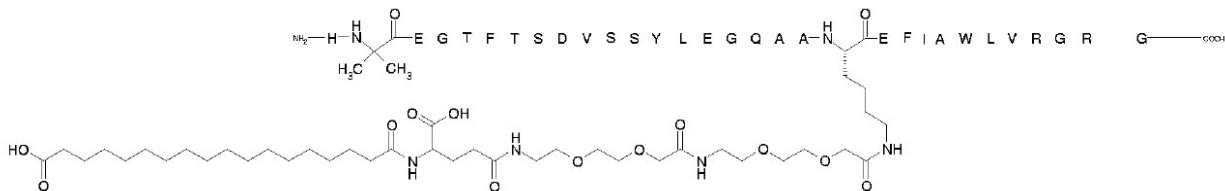
91. As disclosed on the Victoza label, liraglutide was to be subcutaneously “[a]dminister[ed] once daily at any time of day, independently of meals.” *Id.* After

one week of dosing at 0.6 mg daily, the dose of Victoza[®] was increased to 1.2 mg daily for long-term treatment, an amount that could be “increased to 1.8 mg” if the lower dose “[did] not result in acceptable glycemic control.” *Id.* This demonstrates that 1.2 mg was not the maximum effective or maximum tolerated dose, and that a reasonably large increase (50%) produced a greater effect with acceptable tolerance. *See id.* at Table 4, Fig. 3.

b. Semaglutide

92. Prior to the earliest alleged priority date, skilled artisans were investigating another GLP-1 derivative receptor agonist, semaglutide, which was also sometimes referred to as NN9535. *See* WO '193 at 34:18 (“semaglutide/NN9535 (Novo Nordisk)"); *see also* Lund at 610, Table 1 (“Semaglutide (NN9535) Novo Nordisk”); Lovshin 2009 at 263, Table 1.

93. Example 4 of WO '537 disclosed the structure of semaglutide (N-ε²⁶-[2-(2-[2-(2-[2-(2-[4-(17-Carboxyheptadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Aib8,Arg34]GLP-1-(7-37)peptide):



WO '537 at 47:4-22 (Example 4); *see also* '321 publication at [0010] (“WO 06/097537 discloses a number of GLP-1 derivatives including semaglutide (Example 4), a mono-acylated GLP-1 derivative for once weekly administration which is under development by Novo Nordisk A/S.”).

94. Thus, a skilled artisan would have known the primary amino acid sequence of semaglutide. In single letter abbreviation, that amino acid sequence is:

H[A]EGTFTSDVSSYLEGQAAKEFIAWLVRGRG

See WO '537 at 47:4-22 (Example 4) (where “[A]” represents a modified amino acid).

95. Like liraglutide, the amino acid residues shown to be essential in GLP-1 for GLP-1 receptor binding are also present in semaglutide. *See* Knudsen 2004 at 4130, Fig. 3.

96. Thus, before the priority date, a skilled artisan would have known that liraglutide and semaglutide were in the same therapeutic category of GLP-1 receptor agonists and share nearly identical primary amino acid sequences, differing only at the modified [A] position in semaglutide.

D. SEMAGLUTIDE CLINICAL TRIALS

97. Before the priority date, it was well-known that semaglutide was a once weekly GLP-1 receptor agonist used to treat diabetes. *See* Lund at Fig. 1; Lovshin 2009 at 263, Table 1; Bhansali at 13 (“Semaglutide (NN9535) is a once-weekly

human GLP-1 analogue that is being developed by Novo Nordisk for the treatment of type 2 diabetes.”); WO ’537 at 22:24-23:3; 47:4-22; WO ’421 at 43:9-10, claim 17. Skilled artisans would have known semaglutide was being investigated in in phase I and II clinical studies. *See* Lund at Fig. 1; Lovshin 2009 at 263, Table 1. For example, Lund disclosed that multiple trials involving semaglutide were completed or in process:

So far, three Phase I studies looking at pharmacokinetics and safety of semaglutide (NCT00813020, NCT00833716 and NCT00851773), and one Phase II randomized-controlled clinical trial comparing semaglutide with placebo and liraglutide have been completed (NCT00696657). At the end of March 2011, a Phase I study looking at the influence of the pharmacokinetics of an oral contraceptive combination drug after administration of semaglutide was initiated (NCT01324505).

Lund at 613-14.

98. A skilled artisan would have been aware that the dose range being investigated in clinical trials for semaglutide was 0.1-1.6 mg once weekly. Lovshin 2009 at 263, Table 1; WO ’421 at 43:13. Indeed, the phase II study, NCT00696657 (“NCT00696657”), titled “Investigation of Safety and Efficacy of Five Doses of Semaglutide Versus Placebo and Open-label Liraglutide, as Add on Therapy, in Subjects Diagnosed With Type 2 Diabetes Currently Treated With Metformin or

Controlled With Diet and Exercise A 12 Week Multi-centre, Multi National, Double-blind, Placebo-controlled, Randomised, Nine Armed Parallel Group, Dose Finding Trial,” and sponsored by Novo Nordisk, was investigating such doses. NCT00696657 at 15-16. NCT00696657 was a 12-week study that began in June 2008 and was completed in February 2009. *Id.* at 15.

99. The “Purpose” section of NCT00696657 disclosed:

This trial was conducted in Europe, Asia and Africa. Study participants were randomised evenly to treatment with semaglutide (0.1 mg QW - 1.6 mg QW, 6 treatment arms, placebo or liraglutide (1.2 mg QD, or 1.8 mg QD). Treatment allocation to semaglutide or placebo was double-blind, whereas liraglutide treatment was administered open-label. Primary efficacy parameter was HbA1c and the treatment duration was 12 weeks.

Id. at 15.

100. NCT00696657 had six Experimental arms (A-F), which included once weekly subcutaneous (s.c.) injections of 0.1 mg, 0.2 mg, 0.4 mg, and 0.8 mg, 0.8 mg (with titration), and 1.6 mg (with titration) semaglutide. *Id.* at 15-16. NCT00696657 also had six Placebo Comparator arms (G1-G6), which included once weekly subcutaneous injections of placebo versions of 0.1 mg, 0.2 mg, 0.4 mg, and 0.8 mg, 0.8 mg (with titration), and 1.6 mg semaglutide (with titration) and two Experimental

arms (H and I), which included once daily subcutaneous injections of 1.2 mg and 1.8 mg liraglutide, respectively. *Id.* at 16.

101. A skilled artisan would have also been aware of the Phase I study, NCT00851773 (“NCT00851773”), titled “A Randomised, Double Blind, Placebo-controlled, Parallel-group, Multiple Doses, Dose Escalation Study to Assess the Safety, Tolerability, and Pharmacokinetics Profiles of NN9535 in Healthy Male Japanese and Caucasian Subjects After Weekly Subcutaneous Injections,” also sponsored by Novo Nordisk. NCT00851773 at 7; Lund at 613-14. The phase I NCT00851773 was an 8-week study that began in February 2009, the same month the phase II NCT00696657 was completed, and was completed in October 2009. NCT00851773 at 7.

102. The “Purpose” section of NCT00851773 disclosed:

This trial is conducted in Europe. The aim of this clinical trial is to assess and compare the safety and tolerability, as assessed by adverse events after multiple subcutaneous doses of NN9535 in healthy male Japanese and Caucasian subjects.

Id.

103. There are several versions of the NCT00851773 protocol that were publicly available. The 2009 NCT00851773 version had seven Experimental arms (A-G), which included once weekly subcutaneous injections of semaglutide at 0.1

mg (arm A); 0.2 mg (arm B); 0.4 mg (arm C); 0.8 (with titration) (arm D); 0.8 mg (arm E); 1.6 mg (with titration) (arm F); and “[d]ose to be determined based on safety and tolerability of previous dose steps” (with titration) (arm G). *Id.* at 11-12. For arm G, the protocol further stated “[t]his dose-aim is optional and will only be implemented if the 0.8 mg is tolerated but the 1.6 mg is not.” *Id.* at 11.

104. 2009 NCT00851773 also included seven Placebo Comparator arms (H1-H7), which included once weekly subcutaneous injections of placebo versions of 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg (with titration), 0.8 mg, 1.6 mg semaglutide (with titration), and dose to be determined based on safety and tolerability of previous dose steps (with titration). *Id.* at 11-12.

105. The 2010 NCT00851773 version had five Experimental arms (A-E), which included once weekly subcutaneous injections of semaglutide at 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg (with titration), and 1.2 mg (with titration). *Id.* at 7-8. Thus, the Experimental arms testing the 0.8 mg dose and the 1.6 mg dose (with titration) were removed from the trial. 2010 NCT00851773 also had five Placebo Comparator arms (F1-F5), which included once weekly subcutaneous injections of placebo versions of 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg (with titration), and 1.2 mg semaglutide (with titration). *Id.* Similarly, the Placebo arms that were the placebo versions of the 0.8 mg and the 1.6 mg semaglutide (with titration) doses were removed from the trial.

106. Based on NCT00696657 and 2009 NCT00851773, skilled artisans would have been aware that the 0.8 mg semaglutide dose was to be tested both with and without titration, and the 1.6 mg dose was being tested only with titration. A POSA would understand from this that Novo Nordisk had reservations about the tolerability of the 1.6 mg dose in 2009, because this dose was only being tested with titration in NCT00696657 and 2009 NCT00851773, whereas the 0.8 mg dose was being tested with and without titration.

107. Based on the disclosures of NCT00696657 and 2010 NCT00851773, skilled artisans would have also been aware that the dosing regimen between the earlier NCT00696657 study and the later NCT00851773 study were different. Whereas the highest dose tested in NCT00696657 was 1.6 mg semaglutide, the highest dose tested in 2010 NCT00851773 was only 1.2 mg semaglutide.

108. Thus, before the earliest claimed priority date of the '462 patent, skilled artisans would have been aware that Novo Nordisk was actively investigating once weekly doses of semaglutide, had reservations about the tolerability of the 1.2 mg and 1.6 mg doses, and was homing in on the optimal doses of semaglutide, to treat diabetes.

VIII. SCOPE AND CONTENT OF THE PRIOR ART

109. Set forth below are prior art references supporting my expert opinions on invalidity of claims 1, 3-5, and 7 of the '462 patent. All the references I cite in

this document would have been known, and publicly available, to a POSA as of the relevant priority date.

110. The prior art disclosures identified in this expert report would have been understood by a POSA in light of the background knowledge that he or she would have had by the applicable priority dates of the '462 patent. Thus, to the extent I list or describe a reference below but do not rely on it as a ground for arguing invalidity, that prior art should be understood to form part of the background knowledge of a POSA, and to support that person's motivation to combine the prior art with a reasonable expectation of success. Further, to the extent I cite a reference for just one or several of its teachings, I reserve the right to rely on that reference for any other aspect of its teaching.

111. For every item of prior art recited here, I reserve the right, as necessary, to establish that the subject matter I describe has an earlier effective date or date of first publication than indicated here. In addition to the references specifically recited in this report, I rely generally on the knowledge of a POSA at the time of invention, including, without limitation, the knowledge described generally in this report (i.e., without referring to a specific document).

A. WO '421

112. International Patent Application Publication No. WO 2011/138421 ("WO '421") titled "Combination Therapy" was published on November 10, 2011,

before the earliest claimed priority date of the '462 patent. WO '421 at cover page. The international application that published as WO '421, PCT/EP2011/057256, was filed on May 5, 2011. WO '421 claims priority to two European patent applications, 10162036.7, filed May 5, 2010 and 11155154.5, filed February 21, 2011. *Id.* Boehringer Ingelheim International GMBH is listed as the applicant and Thomas Klein, Rolf Grempler, and Michael Mark are listed as inventors. *Id.*

113. WO '421 disclosed:

The present invention relates to methods for treating and/or preventing metabolic diseases, especially type 2 diabetes mellitus, obesity and/or conditions related thereto (e.g. diabetic complications) comprising the combined administration of a GLP-1 receptor agonist (e.g. exogenous GLP-1 or a GLP-1 analogue) and a certain DPP-4 inhibitor, to pharmaceutical compositions and combinations comprising such active components, and to certain therapeutic uses thereof.

Id. at 1:4-9.

114. WO '421 also disclosed, “[n]on-oral (typically injected) antidiabetic drugs conventionally used in therapy (such as e.g. first- or second-line, and/or mono- or (initial or add-on) combination therapy) include, without being restricted thereto, GLP-1 or GLP-1 analogues, and insulin or insulin analogues.” *Id.* at 5:19-21.

115. WO '421 disclosed “[p]referred examples of GLP-1 receptor agonists (GLP-1 analogues) of this invention are exenatide, exenatide LAR [i.e., long-acting release formulation], liraglutide, taspoglutide, semaglutide, albiglutide, lixisenatide and dulaglutide.” *Id.* at 33:20-22.

116. Claim 17 of WO '421 recites:

A GLP-1 receptor agonist selected from exenatide, exenatide LAR, liraglutide, taspoglutide, semaglutide, albiglutide, lixisenatide and dulaglutide, for use in a method of treating type 2 diabetes, obesity or both, said method comprising administration (e.g. separate, sequential or simultaneous administration) of the GLP-1 receptor agonist and a DPP-4 inhibitor which is preferably linagliptin.

Id. at 64:27-31.

117. WO '421 disclosed that “[t]he GLP-1 receptor agonist is typically administered by subcutaneous injection, e.g. ranging from thrice daily, twice daily, once daily to once weekly injection. Suitable doses and dosage forms of the GLP-1 receptor agonist may be determined by a person skilled in the art.” *Id.* at 43:1-3. WO '421 disclosed that “[s]emaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg)” and “[l]iraglutide is administered once daily by subcutaneous injection (Victoza, 0.5-3 mg, particularly 0.5 mg to 2 mg, specific dosage strengths are 0.6 mg, 0.9 mg, 1.2 mg or 1.8 mg).” *Id.* at 43:9-10, 13.

B. LOVSHIN 2009

118. “Incretin-Based Therapies for Type 2 Diabetes Mellitus” (“Lovshin 2009”) is the title of a review article authored by Julie A. Lovshin and Daniel J. Drucker. Lovshin 2009 was published in 2009, before the earliest claimed priority date of the ’462 patent. Lovshin 2009 at 262.

119. Lovshin 2009 disclosed:

Incretin-based drugs, such as glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase 4 inhibitors, are now routinely used to treat type 2 diabetes mellitus. These agents regulate glucose metabolism through multiple mechanisms, their use is associated with low rates of hypoglycemia, and they either do not affect body weight (dipeptidyl peptidase 4 inhibitors), or promote weight loss (glucagon-like peptide-1 receptor agonists). The success of exenatide and sitagliptin, the first therapies in their respective drug classes to be based on incretins, has fostered the development of multiple new agents that are currently in late stages of clinical development or awaiting approval. This Review highlights our current understanding of the mechanisms of action of incretin-based drugs, with an emphasis on the emerging clinical profile of new agents.

Id. at 262.

120. Lovshin 2009 stated “[h]erein, we review the data from clinical trials that have assessed GLP-1R agonists and DPP-4 inhibitors (Table 1) and highlight emerging incretin-based therapies that are in the late stages of clinical testing.” *Id.*

Table 1 of Lovshin 2009 disclosed that NN9535, also known by skilled artisans as semaglutide,⁴ was being investigated at a dose of “0.1-1.6 mg once weekly.” *Id.* at 263, Table 1 (reproduced below).

Table 1 Incretin-based therapies		
Agent	Dose	Status
<i>GLP-1R agonists (subcutaneous injection)</i>		
Exenatide	5–10 µg twice daily	A
Liraglutide	1.2–1.8 mg once daily	F
AVA0010	5–30 µg once or twice daily	I
Exenatide QW	2 mg once weekly	I
Taspoglutide	20–30 mg once weekly	I
Albiglutide	30–50 mg once weekly	I
CJC-1134-PC	1.5–3 mg once or twice weekly	I
NN9535	0.1–1.6 mg once weekly	I
LY2189265	0.25–3 mg once weekly	I
LY2428757	0.5–17.6 mg once weekly	I
<i>DPP-4 inhibitors (oral)</i>		
Sitagliptin	25–100 mg once daily	A
Vildagliptin	50 mg twice daily	A
Alogliptin	12.5–25 mg once daily	F
Saxagliptin	5–10 mg once daily	F
Linagliptin	2.5–5 mg once daily	I
Dutogliptin	200–400 mg once daily	I
Abbreviations: QW, once weekly; A, approved; F, filed for regulatory approval; I, being investigated.		

Id. at 263, Table 1.

⁴ See WO '193 at 34:18 (“semaglutide/NN9535 (Novo Nordisk)”); *see also* Lund at 610, Table 1 (“Semaglutide (NN9535) Novo Nordisk”).

121. Lovshin 2009 also disclosed, “multiple once-weekly GLP-1 therapies are under active clinical investigation in phase I-II studies (NN9535, LY2199265, and a pegylated GLP-1 molecule, LY2428757; see Table 1).” *Id.* at 266.

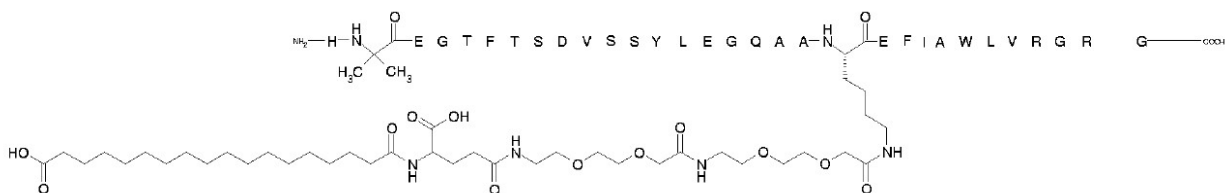
C. WO ’537

122. International Patent Application Publication No. WO 2006/097537 A2 (“WO ’537”) is titled “Acylated GLP-1 Compounds,” and was published on September 21, 2006, before the earliest claimed priority date of the ’462 patent. WO ’537 at cover page. Novo Nordisk A/S is listed as the applicant of WO ’537 and Jesper Lau, Florencio Zaragoza Dörwald, Henrik Stephensen, Paw Bloch, Thomas Kruse Hansen, and Kjeld Madsen are listed as inventors. *Id.*

123. WO ’537 disclosed “[p]rotracted GLP-1 compounds and therapeutic uses thereof” (*id.* at cover page (abstract)) and that “[t]he invention relates to the field of therapeutic peptides, i.e. to new protracted GLP-1 compounds.” *Id.* at 1:5-6; *see also id.* at 4:1-3 (“The term ‘GLP-1 peptide’ as used herein means GLP-1 (7-37) (SEQ ID No 1), a GLP-1 (7-37) analogue, a GLP-1 (7-37) derivative or a derivative of a GLP-1 (7-37) analogue. In one embodiment the GLP-1 peptide is an insulintropic agent.”).

124. Example 4 of WO ’537 disclosed the structure of semaglutide (N-ε²⁶-[2-(2-[2-(2-[2-(2-[4-(17-Carboxyheptadecanoylamino)-4(S)-

carboxybutyrylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Aib8,Arg 34]GLP-1-(7-37)peptide):



Id. at 47:4-8. Claim 28 of WO '537 also disclosed semaglutide. *Id.* at 72:17-74:10.

125. WO '537 disclosed that modified GLP-1 peptides such as semaglutide could be used in “a medicament for the treatment or prevention of hyperglycemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes, [or] obesity,” or “for delaying or preventing disease progression in type 2 diabetes.” *Id.* at 22:24-23:3. WO '537 further discloses that formulations can be prepared a variety of different concentrations, such as from 0.1 mg/mL to 25 mg/mL. *Id.* at 24:11-13. WO '537 also explains that such a composition “may be administered to a patient in need of such treatment.” *Id.* at 32:32-33.

126. WO '537 disclosed once weekly administration of GLP-1 peptides, including semaglutide. “One aspect of this invention is to prepare GLP-1 analogues/derivatives with extended plasma half-lives that are suitable for once weekly administration.” *Id.* at 59:24-25. WO '537 also disclosed: “Thus, there is a need to develop new GLP-1 compounds which can be administered less than once daily, e.g. once every second or third day preferably once weekly, while retaining an

acceptable clinical profile.” *Id.* at 1:31-33. WO ’537 also disclosed screening of once weekly GLP-1 analogues. *Id.* at 59:28-32.

127. The ’462 patent admits that WO ’537 disclosed once weekly administration of semaglutide. ’462 patent at 9:43-45 (“WO 06/097537 discloses semaglutide (Example 4), a mono-acylated GLP-1 agonist for once weekly administration.”).

128. WO ’537 disclosed that the disclosed formulations could be administered parenterally, such as by subcutaneous injection. *Id.* at 34:15-16 (“Parenteral administration may be performed by subcutaneous, intramuscular, intraperitoneal or intravenous injection by means of a syringe, optionally a pen-like syringe.”).

D. SEMAGLUTIDE CLINICAL TRIALS

1. NCT00696657

129. Clinical Trial No. NCT00696657 (“NCT00696657”) is titled “A Randomised Controlled Clinical Trial in Type 2 Diabetes Comparing Semaglutide to Placebo and Liraglutide” and described on clinicaltrials.gov. NCT00696657 at 15. According to the version of NCT00696657 captured by the Wayback Machine on June 25, 2011, certain of its details were first received by ClinicalTrials.gov on June 2011, 2008, and certain details of NCT00696657 were “Last Updated on March 16, 2011.” *Id.* Novo Nordisk was the sponsor of NCT00696657. *Id.* Christine B. Jensen,

M.D., Ph.D., of Novo Nordisk is listed as the study director for NCT00696657. *Id.* at 17. Christine Bjoern Jensen is also a named inventor of the '462 patent. '462 patent at cover page.

130. The official title of NCT00696657 is “Investigation of Safety and Efficacy of Five Doses of Semaglutide Versus Placebo and Open-label Liraglutide, as Add on Therapy, in Subjects Diagnosed With Type 2 Diabetes Currently Treated With Metformin or Controlled With Diet and Exercise A 12 Week Multi-centre, Multi National, Double-blind, Placebo-controlled, Randomised, Nine Armed Parallel Group, Dose Finding Trial.” NCT00696657 at 15. The Purpose section of NCT00696657 states:

This trial was conducted in Europe, Asia and Africa. Study participants were randomised evenly to treatment with semaglutide (0.1 mg QW - 1.6 mg QW, 6 treatment arms, placebo or liraglutide (1.2 mg QD, or 1.8 mg QD). Treatment allocation to semaglutide or placebo was double-blind, whereas liraglutide treatment was administered open-label. Primary efficacy parameter was HbA_{1c} and the treatment duration was 12 weeks.

Id. at 15.

131. NCT00696657 listed an enrollment of 415 patients. *Id.* at 15. The primary outcome measures listed for NCT00696657 was HbA_{1c} level after 12 weeks treatment. *Id.* at 15. Secondary outcome measures in NCT00696657 included,

among others, the percentage of subjects with adverse events or with hypoglycaemic episode. *Id.* at 15.

132. NCT00696657 had six experimental arms in the clinical trial (A-F), which included subcutaneous injections of semaglutide, once weekly, at doses of 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, 0.8 mg (with titration), and 1.6 mg (with titration). *Id.* at 15-16. Skilled artisans would have understood that “with titration” meant that the recited dose amount was reached by starting from a lower dose amount and then increasing the dose until reaching the final level. Thus, in NCT00696657, the 0.8 mg dose was tested with and without titration, whereas the 1.6 mg dose was tested only with titration.

133. NCT00696657 also included six Placebo Comparator arms (G1-G6) and two Experimental arms (H and I), which included subcutaneous injections once daily of 1.2 and 1.8 mg of liraglutide. *Id.* at 16.

2. NCT00851773

134. Clinical Trial No. NCT00851773 (“NCT00851773”) is titled “Safety, Tolerability, and Profile of Action of Drug in the Body of NN9535 in Healthy Male Japanese and Caucasian Subject” and was listed and described on clinicaltrials.gov. *See* NCT00851773 at 7. According to the version of NCT00851773 captured by the Wayback Machine on October 22, 2011, the details of NCT00851773 were “Last Updated on July 15, 2010” (“2010 NCT00851773”). *Id.* Novo Nordisk was the

sponsor of NCT00851773. *Id.* Jean Lynge, MSc, PhD, of Novo Nordisk is listed as the study director for NCT00851773. *Id.* at 8. NCT00851773 disclosed that the start date of the study was February 2009 and that the competition date was August 2009. *Id.* at 7.

135. The Purpose of NCT00851773 disclosed:

This trial is conducted in Europe. The aim of this clinical trial is to assess and compare the safety and tolerability, as assessed by adverse events after multiple subcutaneous doses of NN9535 in healthy male Japanese and Caucasian subjects.

Id. at 7.

136. NCT00851773 listed an enrollment of 84 patients. *Id.* at 7. The primary outcome measures listed for NCT00851773 was adverse events at all scheduled visits following screening. *Id.* Secondary outcome measures in NCT00851773 included, among others, the frequency of hypoglycaemic episodes and vital signs. *Id.*

137. A version of NCT00851773 captured by the Wayback Machine on September 11, 2009 that states it was “Last Updated on August 26, 2009” (“2009 NCT00851773”) disclosed that the NCT00851773 protocol included seven Experimental arms (A-G), which included once weekly subcutaneous injections of semaglutide (NN9535) for eight weeks at the following doses:

- (A) 0.1 mg once weekly,
- (B) 0.2 mg once weekly,
- (C) 0.4 mg once weekly,
- (D) 0.4 mg once weekly for 1 week, 0.8 mg once weekly for 7 weeks,
- (E) 0.8 mg once weekly,
- (F) 0.4 mg once weekly for 1 week, 0.8 mg once weekly for 1 week, 1.6 mg once weekly for 6 weeks, and
- (G) 0.4 mg once weekly for 1 week, 0.8 mg once weekly for 1 week, followed by once weekly injections for 6 weeks. Dose to be determined based on safety and tolerability of previous dose steps. This dose is optional and will be implemented if the 0.8 mg is tolerated but the 1.6 mg is not.

Id. at 11.

138. The later version of NCT00851773 updated on July 15, 2010 (“2010 NCT00851773”), included five Experimental arms (A-E), which included once weekly subcutaneous injections of semaglutide (NN9535) for eight weeks at the following doses:

- (A) 0.1 mg once weekly,
- (B) 0.2 mg once weekly,
- (C) 0.4 mg once weekly,
- (D) 0.4 mg once weekly for 1 week, 0.8 mg once weekly for 7 weeks,

(E) 0.4 mg once weekly for 1 week, 0.8 mg once weekly for 1 week, 1.2 mg once weekly for 6 weeks.

Id. at 7.

139. 2010 NCT00851773 also included five Placebo Comparator arms (F1-F5). *Id.* at 7-8.

140. Thus, in the earlier protocol from 2009 NCT00851773, there were seven Experimental arms and the highest dose tested was 1.6 mg semaglutide (titrated), compared with the later updated 2010 NCT00851773 protocol that only included five Experimental arms with the highest dose tested being 1.2 mg semaglutide. *Compare id.* at 11 with *id.* at 7.

3. Public Availability of ClinicalTrials.gov

141. I understand that a prior art reference is proven to be a “printed publication” upon a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, can locate it. I understand that for an electronic publication, including an online database or Internet publication, to be considered a prior art printed publication, the publication must have been accessible to persons concerned with the art to which the document

relates. I also understand that documents obtained via the Wayback Machine⁵ are presumed to be publicly accessible at the date and time provided in the time stamp.

⁵ As described in the U.S. Patent Office's Manual of Patenting Examining Procedure (MPEP), I understand the Wayback Machine is a digital library maintained by the Internet Archive for viewing information on archived digital Internet webpages. *See* MPEP § 2128.II.E ("Printed Publications" as Prior Art) ("The Wayback Machine® is a digital library maintained by the Internet Archive (a non-profit organization) for viewing information on archived digital Internet webpages. Simply, the Wayback Machine® uses software programs, known as crawlers, to surf the Internet and automatically store copies of Web objects (Web pages, images, videos, etc.), preserving these objects as they exist at the point and time of capture. These Web objects are stored as Web captures with the capture time/date in the form of a time stamp and the URL of the original website of capture. Accordingly, the Wayback Machine® provides the ability to view and browse Internet information that may no longer be available on the original website. ... Prior art obtained via the Wayback Machine® sets forth a *prima facie* case that the art was publicly accessible at the date and time provided in the time stamp."). Available at: <https://www.uspto.gov/web/offices/pac/mpep/s2128.html> (last accessed March 19, 2024).

142. NCT00696657 and NCT00851773 are archived versions of pages from the ClinicalTrials.gov website, as stored on the Wayback Machine website. These documents would have been available on the ClinicalTrials.gov website before the priority date and would have been easily located by a POSA using the robust search tools then available on the ClinicalTrials.gov website.

143. ClinicalTrials.gov is a website that “provides patients, their family members, health care professionals, researchers, and the public with easy access to information on publicly and privately supported clinical studies on a wide range of diseases and conditions.” ClinicalTrials.gov Background at 1. ClinicalTrials.gov is maintained by the National Library of Medicine (“NLM”) at the National Institutes of Health (“NIH”). *Id.* In my opinion, the NIH is one of the most reliable sources of information in the medical field. POSAs would understand that information provided by the NIH, including through the ClinicalTrials.gov website, was reliable, trustworthy, and accurate.

144. It is my understanding that “ClinicalTrials.gov was created as a result of the Food and Drug Administration Modernization Act of 1997 (“FDAMA”).” *See* ClinicalTrials.gov Background at 2; *see also* 42 U.S.C. § 282(i) (“Data bank of information on clinical trials for drugs for serious or life-threatening diseases and conditions”). I understand that “FDAMA required the U.S. Department of Health and Human Services (HHS), through NIH, to establish a registry of clinical trials

information for both federally and privately funded trials conducted under investigational new drug applications to test the effectiveness of experimental drugs for serious or life-threatening diseases or conditions.” *Id.* I understand that “NIH and the Food and Drug Administration (FDA) worked together to develop the site, which was made available to the public in February 2000.” *Id.*

145. In 2004, ClinicalTrials.gov was awarded the *Innovation in American Government Award* from Harvard’s Kennedy School (“Harvard”). Harvard Award at 1. Harvard noted that before ClinicalTrials.gov came online, “those wishing to find information on diseases and treatment options often find themselves sifting through too many websites with too much information and too little plain language.” *Id.* at 1-2. Harvard stated:

[u]ntil 2000, this problem was particularly pressing for those who wished to find information on clinical trials of medical treatments. Not only were medical care providers unable to access information on clinical trials in an efficient manner, but patients were often unable to access it at all, depriving them of both information and the opportunity to seek experimental treatment through trial participation. In response, Congress passed the Food and Drug Modernization Act of 1997, mandating the creation of a centralized, publicly accessible registry for federally and privately funded trials ‘of experimental interventions for serious or life-threatening diseases and conditions.

Id. at 1. Harvard further noted that “ClinicalTrials.gov was designed to be a centralized, standardized, and current resource for those seeking information on clinical studies.” *Id.* at 2. Harvard explained that

[t]he site was also designed to be as widely accessible and comprehensible as possible, in keeping with the goals of the 1997 legislation. The data for each trial are standardized and presented in a clear, easy-to-read format. Users can run specific key-word searches or browse by condition, sponsor, or geographical location, making it easy to navigate the site’s vast amount of information. Furthermore, knowledge of medical terminology is not presumed; the database indexes lay terms so that a search for “heart attack” will retrieve the same information as a search for “myocardial infarction.” The site also contains a glossary of terms and answers to frequently asked questions about clinical trials.

Id. at 2-3. Harvard went on to state:

ClinicalTrials.gov has developed a successful model for the creation and maintenance of a system that processes and presents large amounts of specialized information to a wide range of users. The site now contains records from trials in all 50 states and more than 90 countries and it has logged over 75 million hits since its launch. In April 2002, *Time* magazine named ClinicalTrials.gov as the country’s best overall online health resource. The technology and processes developed by the ClinicalTrials team have proven to be effective and promise to

play an important role in the future management and dissemination of critical medical information.

Id. at 3.

146. The importance of ClinicalTrials.gov as a research tool was widely recognized in the prior art. *See* Zarin at 853 (“The ClinicalTrials.gov trial registry was launched more than a decade ago. Since that time, it has been evolving in response to various policy initiatives. The registry now contains information on more than 100,000 clinical studies and has emerged as a key element of many public health policy initiatives aimed at improving the clinical research enterprise.”); Kirillova.

147. Searching ClinicalTrials.gov did not require registration, subscription fees, or personal identification. ClinicalTrials.gov Background at 2. The ability of POSAs to search, navigate and locate information of interest was unambiguously demonstrated in the prior art medical literature. For example, in Monami, a 2012 article in Experimental Diabetes Research, researchers conducted a meta-analysis of clinical trials on humans reported through December 15, 2011, using GLP-1 receptor agonists, including exenatide, liraglutide, albiglutide, semaglutide, and lixisenatide. Monami at 2. Data sources for the trial included, inter alia, “a search of <http://www.clinicaltrials.gov/> website.” Further, “[r]esults of those trials were retrieved, if available, on <http://www.novonordisk-trials.com/> or <http://www.clinicaltrials.org/>.” *Id.* (emphasis added). Thus, Monami made clear that,

at the priority date, researchers were able to access ClinicalTrials.gov and to locate and obtain information on clinical trials. *See also* Tasneem at 3 (“A dataset comprising 96,346 clinical studies was downloaded from ClinicalTrials.gov in XML format on September 27, 2010. We chose ClinicalTrials.gov for our study because it is the largest database of its kind and because it covers the full range of clinical conditions, includes a broad group of trial sponsors, and has a regulatory mandate.”).

148. Thus, as of the priority date, POSAs knew that ClinicalTrials.gov contained valuable and readily accessible information on clinical trials. A POSA interested in clinical trials involving GLP-1 receptor agonists would have easily found NCT00696657 and NCT00851773 on the ClinicalTrials.gov website. Indeed, in my own experience before and around the priority date, I routinely accessed the ClinicalTrials.gov website, utilized its search tools, and reviewed and analyzed the information on the site. In my experience, as reflected in the prior art, the ClinicalTrials.gov website was readily accessible and easily navigable to POSAs as of the priority date.

E. KNUDSEN 2004

149. “Glucagon-like Peptide-1: The Basis of a New Class of Treatment for Type 2 Diabetes” (“Knudsen 2004”) is the title of a journal article authored by Lotte Bjerre Knudsen at Novo Nordisk, published in 2004, before the earliest claimed priority date of the ’462 patent. Knudsen 2004 at 4128.

150. Knudsen 2004 disclosed the amino acid sequences of GLP-1 and exendin-4. *Id.* at 4130, Fig. 1. Knudsen also disclosed the structures of liraglutide and exenatide. *Id.* at Fig. 2. Figure 3 of Knudsen 2004 disclosed the structure-activity relationship (SAR) of GLP-1 including the sites essential for binding to the GLP-1 receptor. *Id.* at Fig. 3.

151. Knudsen 2004 described how “the efficacy of a GLP-1-like drug will be dependent on the duration of action of the compound or the formulation even though some of the long-term benefits of GLP-1 compounds, like increasing β -cell mass, may not require constantly elevated GLP-1 levels,” and stated “that long-term efficacy can be obtained without major gastrointestinal side effects.” *Id.* at 4128-29. Knudsen disclosed, “[n]ausea may best be avoided by a long half-life because a long half-life gives the smallest needed excursions in plasma concentrations.” *Id.* at 4131.

F. LUND

152. “Emerging GLP-1 Receptor Agonists” (“Lund”) is the title of a review article authored by Asger Lund, Filip K. Knop, and Tina Vilsbøll, which was

published online on September 9, 2011,⁶ before the earliest claimed priority date of the '462 patent. Lund at 607.

153. Lund provided “an overview of the clinical data on the currently available GLP-1R agonists used for treatment of type 2 diabetes, exenatide and liraglutide, as well as the emerging GLP-1R agonists including the long-acting compounds.” *Id.* at Abstract. Lund disclosed, “[t]he long-acting GLP-1R agonists in late development may improve the effects of GLP-1 even further with optimized pharmacokinetic profiles resulting in fewer side effects. Meta-analyses have shown promising effects on cardiovascular disease.” *Id.* at 607.

154. Figure 1 of Lund (reproduced below) disclosed a list of GLP-1 receptor agonists, “GLP-1-based” and “Exendin-4-based,” for subcutaneous injection:

⁶ My opinion that the claims of the '462 patent are anticipated and obvious does not require the disclosures of Lund. Lund merely confirms the other prior art set forth in this report.

GLP-1 receptor agonists for sc injection			
GLP-1-based		Exendin-4-based	
Daily	Weekly	Daily	Weekly
Liraglutide	Albiglutide	Exenatide	Exenatide-LAR
	Dulaglutide	Lixisenatide	CJC-1134-PC
	Semaglutide		

Id. at 609, Fig. 1.

155. Table 1 of Lund (reproduced below) disclosed an overview of the existing and emerging GLP-1R agonists and their state of development and ongoing trials:

Compound	Company	Formulation	Status of development	Ongoing trials
Exenatide	Eli Lilly/Amylin Pharmaceuticals, Inc.	Twice-daily	Launched	Combination with insulin/obesity + CVD
Liraglutide	Novo Nordisk	Once-daily	Launched	Combination with insulin/obesity + CVD
Exenatide once-weekly	Eli Lilly/Amylin Pharmaceutical, Inc./Alkermes, Inc.	Once-weekly	Expected 2011	Combination with insulin/obesity
Lixisenatide	Zealand Pharma A/S/Sanofi-Aventis	Once-daily	Expected 2011	Phase III, GetGoal
CJC-1134-PC	ConjuChem	Once-weekly	Phase I/II	Phase I/II
Albiglutide	GlaxoSmithKline	Once-weekly	Expected 2012	Phase III, Harmony
Dulaglutide (LY2189265)	Eli Lilly	Once-weekly	Expected 2013	Phase III, Award
Semaglutide (NN9535)	Novo Nordisk	Once-weekly	Phase II	On hold

CVD: Cardiovascular disease; GLP-1R: Glucagon-like peptide-1 receptor.

Id. at 610, Table 1.

156. Table 2 of Lund (reproduced below) disclosed the amino acid structures of GLP-1 and the GLP-1R agonists on the market or in late clinical development:

Name	Structure
Native GLP-1	His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg
Liraglutide	His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Arg-Gly-Arg-Gly Glu-C16 fatty acid
Albiglutide	(His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg) ₂ - linked to human albumin
Exenatide	His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser
Lixisenatide	His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser-Lys-Lys-Lys-Lys-Lys
CJC-1134-PC	His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-C13H19O6N3 (linker molecule)

GLP-1: Glucagon-like peptide-1; GLP-1R: Glucagon-like peptide-1 receptor.

Id. at 610, Table 2.

157. Lund also disclosed a summary of the GLP-1 receptor agonists including exenatide once weekly, lixisenatide, CJC-1134-PC, albiglutide, dulaglutide, and semaglutide. *Id.* at 611-14.

158. Lund disclosed that “[s]emaglutide (NN9535) is a long-acting GLP-1R agonist planned for once-weekly [subcutaneous] injections, based on the GLP-1 backbone, in preparation by Novo Nordisk, Bagsværd, Copenhagen, Denmark.” *Id.* at 613. Lund also disclosed:

So far, three Phase I studies looking at pharmacokinetics and safety of semaglutide (NCT00813020, NCT00833716 and NCT00851773), and one Phase II randomized-controlled clinical trial comparing semaglutide with placebo and liraglutide have been completed (NCT00696657). At the end of March 2011, a Phase I study looking at the influence of the pharmacokinetics of an oral contraceptive

combination drug after administration of semaglutide was initiated (NCT01324505).

Id. at 613-14.

G. SEINO

159. “Dose-dependent improvement in glycemia with once-daily liraglutide without hypoglycemia or weight gain: A double blind, randomized, controlled trial in Japanese patients with type 2 diabetes” (“Seino”) is the title of a journal article authored by Y. Seino, M.F. Rasmussen, M. Zdravkovic, K. Kaku. Seino at 161. Seino was published May 20, 2008, before the earliest claimed priority date of the ’462 patent. *Id.*

160. Seino disclosed “[i]n this study, we investigated efficacy and safety from a dose response perspective with four doses of liraglutide and placebo in Japanese patients with type 2 diabetes.” *Id.* at 166. The study was “a multicenter, double blind, randomized, parallel group phase 2 trial to evaluate the dose response relationship on glycemic control of four doses of liraglutide and placebo in Japanese subjects with type 2 diabetes.” *Id.* at 162. Seino disclosed “[t]he primary efficacy endpoint was HbA_{1c} after 14 weeks of treatment, with other measures of glycemic control (fasting plasma glucose (FPG), postprandial plasma glucose (PPG), self monitored plasma glucose profile) as secondary endpoints.” *Id.* “Patients were randomized at the end of the run in period to liraglutide or placebo in four cohorts,

each planned to contain 50 patients; in each cohort a planned 40 patients received one of four liraglutide doses (0.1 mg/day; 0.3 mg/day; 0.6 mg/day or 0.9 mg/day) and 10 received placebo. Liraglutide doses in the 0.6 and 0.9 mg/day cohorts were increased from a starting dose of 0.3 [to] 0.6 mg/day after 1 week and, in the 0.9 mg/day cohort, by a further 0.3 mg/day after 2 weeks.” *Id.*

161. Regarding the results of the study, Seino stated: “[w]e demonstrated significantly dose dependent improvements in key parameters of glycemia HbA_{1c}, FPG, PPG, seven point self monitored plasma glucose and beta cell function following 14 weeks’ treatment with liraglutide.” *Id.* Seino reported “[a] clear dose response relationship for HbA_{1c} was shown in this study.” *Id.* “All doses of liraglutide tested showed a degree of efficacy, with a plateau of dose response at 0.9 mg/day. A dose of 0.9 mg/day appears to be highly effective and, of the doses tested, offers the optimal efficacy/tolerability balance in Japanese patients with type 2 diabetes.” *Id.* Seino disclosed that “there was no treatment related development of liraglutide antibodies during the trial.” *Id.* Figure 1 of Seino shows the dose-response for HbA_{1c} with increasing doses of liraglutide. *Id.* at 164. The data in Figure 1 are the means $\pm$ standard error (S.E.) for HbA_{1c} after 14 weeks. *Id.*

H. VICTOZA LABEL

162. The Victoza® label, issued January 2010, provides the prescribing information of Victoza®, approved by FDA in 2010 (“Victoza label”). *See* Victoza label at 2675.

163. The Victoza label disclosed, “Victoza is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.” *Id.* at 2668. “Victoza contains liraglutide, an analog of human GLP-1” that “acts as a GLP-1 receptor agonist.” *Id.* at 2671.

164. The Victoza label disclosed that liraglutide was “made by attaching a C-16 fatty acid (palmitic acid) with a glutamic acid spacer on the remaining lysine residue at position 26 of the peptide precursor.” *Id.* at 2671.

165. The Victoza label disclosed:

Liraglutide is an acylated human Glucagon-Like Peptide-1 (GLP-1) receptor agonist with 97% amino acid sequence homology to endogenous human GLP-1(7-37). GLP-1(7-37) represents <20% of total circulating endogenous GLP-1. Like GLP-1(7-37), liraglutide activates the GLP-1 receptor, a membrane-bound cell-surface receptor coupled to adenylyl cyclase by the stimulatory G-protein, Gs, in pancreatic beta cells. Liraglutide increases intracellular cyclic AMP (cAMP) leading to insulin release in the presence of elevated glucose concentrations. This insulin secretion subsides as blood glucose

concentrations decrease and approach euglycemia. Liraglutide also decreases glucagon secretion in a glucose-dependent manner. The mechanism of blood glucose lowering also involves a delay in gastric emptying.

Id. at 2671-72.

166. The Victoza label disclosed:

GLP-1(7-37) has a half-life of 1.5-2 minutes due to degradation by the ubiquitous endogenous enzymes, dipeptidyl peptidase IV (DPP-IV) and neutral endopeptidases (NEP). Unlike native GLP-1, liraglutide is stable against metabolic degradation by both peptidases and has a plasma half-life of 13 hours after subcutaneous administration. The pharmacokinetic profile of liraglutide, which makes it suitable for once daily administration, is a result of self-association that delays absorption, plasma protein binding and stability against metabolic degradation by DPP-IV and NEP.

Id. at 2672.

167. The Victoza label also disclosed the following regimen:

- Administer once daily at any time of day, independently of meals (2).
- Inject subcutaneously in the abdomen, thigh or upper arm (2).
- The injection site and timing can be changed without dose adjustment (2).

- Initiate at 0.6 mg per day for one week. This dose is intended to reduce gastrointestinal symptoms during initial titration, and is not effective for glycemic control. After one week, increase the dose to 1.2 mg. If the 1.2 mg dose does not result in acceptable glycemic control, the dose can be increased to 1.8 mg (2).
- When initiating Victoza, consider reducing the dose of concomitantly-administered insulin secretagogues to reduce the risk of hypoglycemia (2).

Id. at 2668.

168. The Victoza label disclosed that Victoza was available as a “[s]olution for subcutaneous injection,” in a “pre-filled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg.” *Id.* at 2668.

I. SHARGEL

169. “Applied Biopharmaceutics and Pharmacokinetics” (“Shargel”) is the title of a book edited by Leon Shargel, Ph.D., RPh, Susanna Wu-Pong, Ph.D., RPh, and Andrew B.C. Yu, Ph.D., RPh, which was published in 2005, before the earliest claimed priority date of the ’462 patent. *See* Shargel.

170. Shargel disclosed that “[p]harmacokinetics is the science of the kinetics of drug absorption, distribution, and elimination (ie, excretion and metabolism).” *Id.*

at 3. Shargel disclosed “[c]haracterization of drug disposition is an important prerequisite for determination or modification of dosing regimens for patients.” *Id.* “The study of pharmacokinetics involves both experimental and theoretical approaches.” *Id.* Shargel disclosed “[p]harmacodynamics refers to the relationship between the drug concentration at the site of action (receptor) and pharmacologic response, including biochemical and physiologic effects that influence the interaction of drug with the receptor.” *Id.* at 4.

171. Shargel provided a schematic of a plasma drug concentration-time curve showing parameters such as $C_{\max}$ (maximum concentration), $t_{\max}$ (time of maximum), and AUC (Area Under the Curve). *Id.* at 461, Figure 15-1. Shargel disclosed “[t]he onset, intensity, and duration of the pharmacologic effect depend on the dose and the pharmacokinetics of the drug.” *See id.* at 577. Shargel continued, “[a]s the dose of the drug increases, the concentration at the receptor site increases, and the pharmacologic response (effect) increases up to a maximum effect. A plot of the pharmacologic effect to dose on a linear scale generally results in a hyperbolic curve with maximum pharmacologic effect ($E_{\max}$) at the plateau on the dose-response curve.” *Id.* at 577-78, Fig. 19-1.

J. TAMIMI

172. “Drug Development: From Concept to Marketing!” (“Tamimi”) is the title of a minireview authored by Nihad A.M. Tamimi and Peter Ellis, which was

published in 2009, before the earliest claimed priority date of the '462 patent. Tamimi at c125.

173. Tamimi provided a summary of the development of a drug, including discovery, pre-clinical studies, phase I-III studies, approval, and post approval. *See id.* at c125-31, Fig. 1. Tamimi disclosed that “[d]rug development is a long, expensive and highly regulated process.” *Id.* at c130. Tamimi disclosed that after compounds have been screened and positively selected, “functional biochemical and pharmacological testing in vitro, followed by pharmacodynamic and pharmacokinetic testing in vitro and in vivo” is performed. *Id.* at c127. Tamimi disclosed a suitable formulation is then developed for the drug and the drug is “progressed through the required toxicology testing (including genotoxicity, safety pharmacology in all biological systems, single and multiple dose toxicity and toxicokinetic studies) to enable the first in human and subsequent clinical studies.” *Id.*

174. Tamimi also disclosed, “[c]linical phases of drug development include phase I in healthy volunteers to assess primarily pharmacokinetics, safety and toleration, phase II in a cohort of patients with the target disease to establish efficacy and dose-response relationship and large-scale phase III studies to confirm safety and efficacy.” *Id.* at c125. Tamimi disclosed “[p]hase I studies require approval from an ethics committee and the relevant regulatory agency.” *Id.* at c127. “Phase I studies

usually start with single sub-pharmacological doses which are escalated gradually and followed by multiple doses.” *Id.* Tamimi disclosed “[s]topping rules to dose escalation include severe adverse events, clinically significant ECG abnormalities and clinically significant laboratory abnormalities.” *Id.* “Phase I studies require approval from an ethics committee and the relevant regulatory agency.” *Id.* “Other phase I studies to support drug development are conducted throughout phase II and II of development.” *Id.* Regarding phase II studies, Tamimi disclosed “[o]nce the drug’s safety, pharmacokinetics and dose selection has been established in healthy volunteers, the next step is to investigate the efficacy and safety of the drug in the target population.” *Id.* at c128. Tamimi disclosed that phase II studies are usually divided into phase IIa and phase IIb but occasionally they are combined. *Id.* “Phase IIb follows on from the proof of concept in which several dose levels are tested in the target population (dose-ranging studies) to define the minimally effective or non-effective dose and to decide the optimal dose, based on clinical efficacy and safety, to take to the next stage.” *Id.* Tamimi disclosed that phase III studies are “the final stage of drug development prior to registration and will confirm the clinical doses, frequency of timing of administration for approval.” *Id.*

K. FDA Exposure Response 2003

175. “Guidance for Industry, *Exposure-Response Relationships – Study Design, Data, Analysis, and Regulatory Applications*” was provided by the Food and

Drug Administration (FDA) of the U.S. Department of Health and Human Services in April 2003, before the earliest claimed priority date of the '462 patent. *See* FDA Exposure Response 2003.

176. FDA Exposure Response 2003 stated that “[e]xposure-response information is at the heart of any determination of the safety and effectiveness of drugs. That is, a drug can be determined to be safe and effective only when the relationship of beneficial and adverse effects to a defined exposure is known.” *Id.* at 2. FDA Exposure Response 2003 further stated “[t]he dose-response study is a particularly informative design, allowing observations of benefits and risks at different doses and therefore providing an ability to weigh the benefits and risks when choosing doses. The dose-response study can help ensure that excessive doses (beyond those that add to efficacy) are not used, offering some protection against unexpected and unrecognized dose-related toxicity.” *Id.* at 4. FDA Exposure Response 2003 stated:

For the purposes of this guidance, we are using the broad term *exposure* to refer to dose (drug input to the body) and various measures of acute or integrated drug concentrations in plasma and other biological fluid (e.g., C_{max}, C_{min}, C_{ss}, AUC). Similarly, *response* refers to a direct measure of the pharmacologic effect of the drug. Response includes a broad range of endpoints or biomarkers ranging from the clinically remote biomarkers (e.g., receptor occupancy) to a presumed mechanistic effect (e.g., ACE inhibition), to a potential or accepted

surrogate (e.g., effects on blood pressure, lipids, or cardiac output), and to the full range of short-term or long-term clinical effects related to either efficacy or safety.

Id. at 2.

L. ICH 1994

177. “International Conference on Harmonisation; Dose-Response Information to Support Drug Registration; Guideline; Availability” (“ICH 1994”) is the title of a notice published in the Federal Register on November 9, 1994, before the earliest claimed priority date of the ’462 patent. ICH 1994.

178. ICH 1994 disclosed that “[t]he Food and Drug Administration (FDA) is publishing a final guideline entitled ‘Dose-Response Information To Support Drug Registration.’” *Id.* at 55972. ICH 1994 stated “[t]his guideline was prepared by the Efficacy Expert Working Group of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).” ICH 1994 explained:

The guideline describes why dose-response information is useful and how it should be obtained in the course of drug development. This information can help identify an appropriate starting dose as well as how to adjust dosage to the needs of a particular patient. It can also identify the maximum dosage beyond which any added benefits to the patient would be unlikely or would produce unacceptable side effects. This guideline is intended to help ensure that dose response information

to support drug registration is generated according to sound scientific principles.

Id. at 55972.

179. ICH 1994 disclosed that “ICH is concerned with harmonization of technical requirements for the registration of pharmaceutical products among three regions: The European Union, Japan, and the United States.” *Id.*

180. ICH 1994 provided the text of the final guideline titled “Dose-Response Information to Support Drug Registration.” *Id.* Under a heading titled “Purpose of Dose-Response Information,” the final guideline stated:

Knowledge of the relationships among dose, drug concentration in blood, and clinical response (effectiveness and undesirable effects) is important for the safe and effective use of drugs in individual patients. This information can help identify an appropriate starting dose, the best way to adjust dosage to the needs of a particular patient, and a dose beyond which increases would unlikely to provide added benefit or would produce unacceptable side effects.

Id. at 55972.

181. The final guideline continued:

Historically, drugs have often been initially marketed at what were later recognized as excessive doses (i.e., doses well onto the plateau of the dose-response curve for the desired effect), sometimes with adverse consequences (e.g., hypokalemia and other metabolic disturbances with

thiazide-type diuretics in hypertension). This situation has been improved by attempts to find the smallest dose with a discernible useful effect or a maximum dose beyond which no further beneficial effect is seen, but practical study designs do not exist to allow for precise determination of these doses.

Id. at 55973.

182. Under a heading titled “Use of Dose-Response Information in Choosing Doses,” the final guideline disclosed:

What is most helpful in choosing the starting dose of a drug is knowing the shape and location of the population (group) average dose-response curve for both desirable and undesirable effects. Selection of dose is best based on that information, together with a judgment about the relative importance of desirable and undesirable effects.

Id. at 55973.

183. Under a heading titled “Study Designs for Assessing Dose Response,” the final guideline stated “[i]t is important to choose as wide a range of doses as is compatible with practicality and patient safety to discern clinically meaningful differences.” *Id.* at 55974.

184. Under a heading titled “Guidance and Advice,” the final guideline stated “[d]epending on circumstances (the disease, the drug’s toxicity), the starting

dose may range from a low dose with some useful effect to a dose that is at or near the full-effect dose.” *Id.* at 55976.

M. KNUDSEN 2010B

185. “Liraglutide: The Therapeutic Promise from Animal Models” (“Knudsen 2010b”) is the title of a review paper authored by Lotte Bjerre Knudsen at Novo Nordisk A/S, published in October 2010, before the earliest claimed priority date of the ’462 patent. Knudsen 2010b at 4.

186. Knudsen 2010b disclosed “[p]reclinical work is a necessary precursor to human studies: assessment of toxicity in a preclinical setting is a legal requirement, but preclinical studies also gather important preliminary data on pharmacokinetics and pharmacodynamics.” *Id.* Knudsen 2010b also disclosed “[a] large body of data in any preclinical programme is generated from *in vitro* investigations; however, normal animals and animal models of the disease state allow us to examine the effects of a new drug on the complex interplay of metabolic processes.” *Id.*

N. BHANSALI

187. “Historical Overview of Incretin Based Therapies” (“Bhansali”) is the title of an article authored by A. Bhansali, D. Maji, PV Rao, S. Banerjee, and H. Humar, which was published in 2010, before the earliest claimed priority date of the ’462 patent. Bhansali at 10.

188. Bhansali taught that GLP-1 is an incretin hormone playing a role in the “physiological responses is activated following meal intake, providing neural and endocrine signals regulating the digestion, absorption and assimilation of ingested nutrients.” Bhansali at 10. Bhansali disclosed that “[e]xanatide is the first GLP-1 receptor agonist that has been approved for use as an adjunctive therapy to improve glycaemic control in patients with type 2 diabetes[.]” *Id.*

189. Bhansali described the known regulatory approval and treatment effectiveness of liraglutide at that time:

Liraglutide is the first once-daily human GLP-1 analogue. In July 2009, Victoza® (liraglutide) was approved by the European Medicines Agency (EMA) in the treatment of type 2 diabetes mellitus to achieve glycaemic control. In January 2010, the U.S. Food and Drug Association (FDA) approved Victoza® as an adjunct therapy to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus. It has been shown in different trials that at suggested therapeutic doses of 1.2 mg and 1.8 mg, liraglutide can lower glycated haemoglobin A1c (HbA_{1c}) by 1.0-1.5% points as mono- or combination therapy in approximately two-thirds of subjects. GLP-1 receptor agonist showed a greater effect than the DPP-4 inhibitor in reducing postprandial glucose (PPG) concentrations, a more potent effect in increasing insulin secretion and decreasing postprandial glucagon secretion, a relatively greater effect in reducing caloric intake, and it decreased the rate of gastric emptying.

Id. at 10.

190. Bhansali stated:

GLP-1 receptors are expressed in the gastrointestinal tract, endocrine pancreas (α and β cells), lung, kidneys, heart and several areas of the brain (hypothalamus, nucleus of the solitary tract, area postrema).

* * *

It is shown that GLP-1(7-36) is a more potent insulin secretagogue than [gastric inhibitory polypeptide, GIP] *in vitro*. It has been shown in both preclinical and human studies that, *in vivo*, GLP-1 can stimulate insulin secretion in a glucose-dependent manner. Other biological effects, which include inhibiting glucagon secretion, decelerating gastric emptying and reducing food intake with GLP-1, were also demonstrated.

* * *

Interestingly, GLP-1 may also have other beneficial effects that are independent from its effects on glucose metabolism. Animal studies showed that GLP-1 protected myocardial cells from ischemic and reperfusion injury, prevented endothelial dysfunction, promoted endothelium in dependent artery relaxation and increased diuresis and natriuresis. In subjects with type 2 diabetes, studies showed that GLP-1 reduced systolic blood pressure (SBP) and decreased plasma concentrations of triglyceride and plasminogen activator inhibitor

(PAI-1) and brain natriuretic peptide (BNP), which are considered biomarkers of cardiovascular diseases.

Id. at 11 (footnotes removed).

191. Bhansali disclosed: “Because of the short plasma half-life of native GLP-1, there is a need to develop long-acting derivatives to make GLP-1 treatment clinically relevant.” *Id.* at 11.

192. Bhansali taught that exenatide, a synthetic GLP-1 receptor agonist, was developed as a twice-daily treatment option “to improve glycaemic control in patients with type 2 diabetes.” *Id.* at 12. Bhansali stated that clinical trial results with exenatide indicated that it “stimulated insulin secretion in a glucose-dependent manner, [] suppressed glucagon secretion, slowed gastric emptying[,] reduced food intake in patients with type 2 diabetes[, and] improved long-term glycaemic control.” *Id.*

193. Bhansali disclosed that the “most common adverse effects” in patients receiving exenatide “were nausea and vomiting,” but that those were “significantly reduced with step-wise dose escalation of exenatide.” *Id.* at 12.

194. Bhansali disclosed that liraglutide was known and it is “a once-daily human GLP-1 analogue, which has been developed by Novo Nordisk.” *Id.* at 12. Liraglutide was known to be an analog of human GLP-1 where “lysine at position 34 of human native GLP-1 is substituted by arginine, and a palmitic acid chain (C-

16) is attached to an ϵ -amino group of lysine at position 26 via glutamate spacer,” with an overall “97% amino acid homology with the human GLP-1 peptide.” *Id.* Bhansali stated that liraglutide was approved as Victoza® in July 2009 in Europe and in January 2010 in the United States, in each case to improve or achieve glycemic control in patients with type 2 diabetes mellitus. *Id.* In several phase 3 trials, and at the suggested therapeutic doses of 1.2 mg and 1.8 mg once daily, “liraglutide lowered HbA_{1c} by 1.0-1.5% in approximately two-thirds of patients when administered as monotherapy or in combination with other oral antidiabetic drugs.” Bhansali at 12-13.

195. As with exenatide, “[l]iraglutide was generally well tolerated,” and “[t]he most common adverse events with liraglutide treatment were related to the gastrointestinal system,” with nausea “the most frequently reported side effect.” *Id.* at 13. These adverse events were reported to be “mostly mild and occurred during the initial period of treatment.” *Id.*

196. Bhansali stated that liraglutide was superior to exenatide in diabetes-related treatment effect: “liraglutide reduced mean HbA_{1c} significantly more than exenatide with a difference of 0.33%. More patients achieved a HbA_{1c} value of less than 7% in the liraglutide group than exenatide (54% vs. 43%). Both drugs resulted in similar weight loss, and were well tolerated, but nausea was less persistent and

minor hypoglycaemia less frequent with liraglutide than with exenatide (Table 3).”

Id. at 13.

197. Bhansali further disclosed that semaglutide (also identified as NN9535) was in active development as a promising treatment for Type 2 diabetes:

Semaglutide (NN9535) is a once-weekly human GLP-1 analogue that is being developed by Novo Nordisk for the treatment of type 2 diabetes. Semaglutide lowers blood glucose through stimulating release of insulin and lowers body weight. The phase 2 programme with more than 400 people was completed in 2009. Novo Nordisk is also developing an oral GLP-1 (NN9924) to increase the convenience of GLP-1 treatment of type 2 diabetes. It is more resistant to enzymatic degradation, and its first phase 1 clinical trial started January 2010.

Id. at 13.

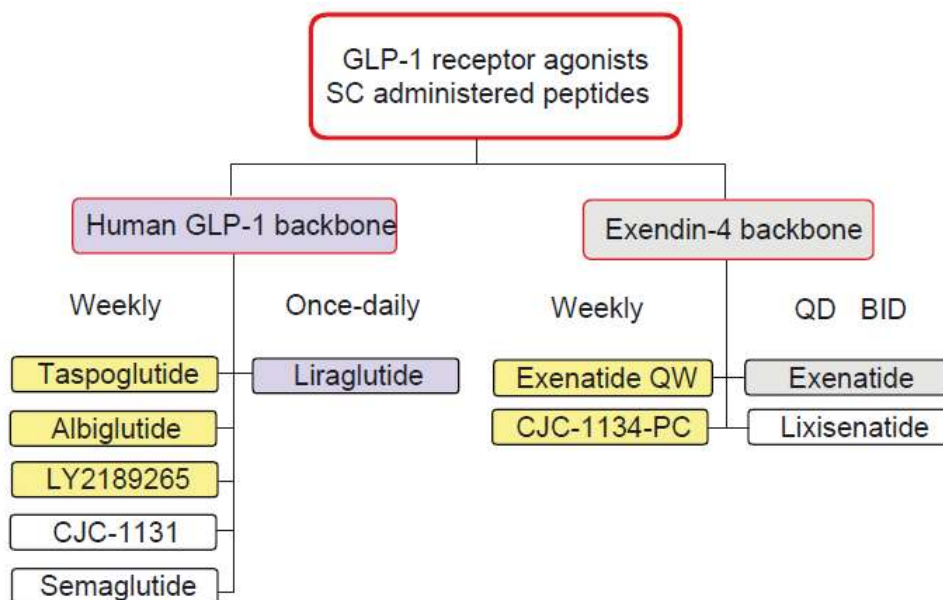
O. MADSBAD 2011

198. “An Overview of Once-Weekly Glucagon-Like Peptide-1 Receptor Agonists—Available Efficacy and Safety Data and Perspectives for the Future” (“Madsbad 2011”) is the title of a review article authored by Sten Madsbad and coauthors, published on January 5, 2011, before the earliest claimed priority date of the ’462 patent.

199. Madsbad 2011 provided an overview of once-weekly GLP-1 agonists for treatment of type-2 diabetes. Madsbad 2011 stated “[a] greater reduction in haemoglobin A1c (HbA1c) and fasting plasma glucose was found with the once-

weekly GLP-1 receptor agonists compared with exenatide BID.” Madsbad 2011 at Abstract. Madsbad 2011 further taught that “gastrointestinal side effects were less with the once-weekly agonists compared with exenatide BID.” *Id.* Madsbad 2011 concluded that the “once-weekly GLP-1 receptor analogues are promising candidates for the treatment of type 2 diabetes.” *Id.*

200. Madsbad 2011 disclosed dosing regimens for several GLP-1 receptor agonists, including semaglutide, which is administered by subcutaneous (sc) injection:



Id. at 395.

201. Madsbad 2011 disclosed that “[i]ncretin-based therapies, such as the injectable glucagon-like peptide-1 (GLP-1) receptor agonists and orally administered dipeptidyl peptidase-4 (DPP-4) inhibitors, have recently been

introduced into clinical practice. . . . Several once-weekly GLP-1 receptor agonists are in phase 3 development.” *Id.* at 394.

P. ’833 PATENT

202. U.S. Patent No. 8,114,833 (“’833 patent”) is titled “Propylene Glycol-Containing Peptide Formulations which are Optimal for Production and for Use in Injection Devices.” ’833 patent at cover page. The ’833 patent issued on February 14, 2012. *Id.* The ’833 patent lists Novo Nordisk A/S as the assignee and the inventors are listed as Tina Bjeldskov Pedersen, Claude Bonde, and Dorthe Kot Engelund. *Id.* I understand that the ’833 patent is prior art to the claims of the ’462 patent.

203. The ’833 patent disclosed:

[I]n a preferred embodiment, the formulations of the invention are to be administered parenterally to a patient in need thereof. Parenteral administration may be performed by subcutaneous, intramuscular or intravenous injection by means of a syringe, optionally a pen-like syringe.

’833 patent at 13:45-50.

204. The ’833 patent further disclosed:

[I]t is understood that depending on the peptide or peptides included in the formulations of the invention, the formulations may be used in methods of treatment of diseases or conditions for which use of the peptide is indicated. One skilled in the art would understand that when

used in such methods of treatment, the formulations would have to be administered in amount effective to treat the condition or disease for which the peptide was being administered where an “effective amount” or an “amount . . . effective” is understood to mean a dosage which is sufficient in order for the treatment of the patient with the disease or condition to be treated to be effective compared to treatment without the administered dosage. . It is to be understood that “an effective amount” is the effective dose to be determined by a qualified practitioner, who may titrate dosages to achieve the desired response. Factors for consideration of dose will include potency, bioavailability, desired pharmacokinetic/pharmacodynamic profiles, the condition or disease to be treated (e.g. diabetes, obesity, weight loss, gastric ulcers), patient-related factors (e.g. weight, health, age, etc.) presence of co-administered medications (e.g. insulin), time of administration, or other factors known to a medical practitioner.

’833 patent at 13:60-14:15.

Q. ADDITIONAL PRIOR ART AND REFERENCES

205. In addition to the references discussed above and throughout this report, I utilize the knowledge and expertise of a POSA. Also, in this report I cite to references in addition to those recited and summarized above, including to provide background on the state of the art at the priority date. All references, whether summarized above or not, that were publicly available prior to the priority date of the ’462 patent are within the scope of the prior art.

IX. INVALIDITY OF THE '462 PATENT

A. CLAIMS 1 AND 3 OF THE '462 PATENT ARE ANTICIPATED BY WO '421, LOVSHIN 2009, OR NCT00696657

1. WO '421 Anticipated Claims 1 and 3 of the '462 Patent

206. As described below, in my opinion, claims 1 and 3 of the '462 patent are invalid as anticipated by WO '421.

a. Teachings of WO '421

207. The teachings of WO '421 are detailed above in paragraphs 112-117.

b. WO '421 anticipated claim 1

208. Independent claim 1 recites “[a]method for treating type 2 diabetes, comprising administering semaglutide once weekly in an amount of 1.0 mg to a subject in need thereof.” In my opinion, WO '421 taught each element of claim 1 of the '462 patent.

209. *First*, WO '421 disclosed the preamble of claim 1 of the '462 patent, which the Court found was limiting but did not require any particular degree or minimum threshold of efficacy. *See* Section VI above.

210. The specification of WO '421 stated that “[t]he present invention relates to methods for treating and/or preventing metabolic diseases, especially type 2 diabetes mellitus.” WO '421 at 1:4-5. WO '421 also disclosed that “[p]referred examples of GLP-1 receptor agonists (GLP-1 analogues) of this invention are

exenatide, exenatide LAR, liraglutide, taspoglutide, semaglutide, albiglutide, lixisenatide and dulaglutide.” *Id.* at 33:20-22 (emphasis added).

211. Further, claim 17 of WO ’421 recites:

A GLP-1 receptor agonist selected from exenatide, exenatide LAR, liraglutide, taspoglutide, ***semaglutide***, albiglutide, lixisenatide and dulaglutide, ***for use in a method of treating type 2 diabetes***, obesity or both, said method comprising administration (e.g. separate, sequential or simultaneous administration) of the GLP-1 receptor agonist and a DPP-4 inhibitor which is preferably linagliptin.

Id. at 64:27-31 (emphasis added). Thus, the specification and claim 17 of WO ’421 taught the preamble, “[a]method for treating type 2 diabetes.”

212. *Second*, WO ’421 also disclosed the element “comprising administration of semaglutide” of claim 1. It is my understanding from counsel that the term “comprising” means that the claim limitations that follow the term “comprising” must be present in an embodiment of the claims, but that the term is “open,” meaning that additional limitations may also be present in an embodiment of the claims. Therefore, while claim 1 of the ’462 patent must include “administering semaglutide once weekly in an amount of 1.0 mg to a subject in need

thereof,” claim 1 also allows for administration of semaglutide in combination with another drug, including before, after, or with other drugs.

213. The specification of WO ’421 disclosed “a method for treating and/or preventing metabolic diseases, especially type 2 diabetes mellitus . . . comprising the combined (e.g., simultaneous, *separate* or sequential) administration of an effective amount of a GLP-1 receptor agonist . . . and . . . an effective amount of a DPP-4 inhibitor.” WO ’421 at 10:14-20 (emphasis added). WO ’421 taught that “[p]referred examples of GLP-1 receptor agonists . . . are . . . semaglutide.” *Id.* at 33:20-22.

214. In addition, claim 17 of WO ’421 recited “semaglutide . . . for use in a method of treating type 2 diabetes . . . said method comprising administration (e.g., *separate*, sequential or simultaneous administration) of the [semaglutide] and a DPP-4 inhibitor.” *Id.* at 64:26-31 (emphasis added). Further, WO ’421 disclosed that administration of the combination therapy of a GLP-1 receptor agonist and DPP-4 “may refer to first line, second line or third line therapy, or initial or add-on combination therapy or replacement therapy.” *Id.* at 36:22-24. WO ’421 also disclosed that administration of the combination therapy may occur by administering the active components as separate formulations “simultaneously, *separately*, sequentially, or chronologically staggered.” *Id.* at 36:2-24 (emphasis added).

215. In my opinion, skilled artisans would understand these disclosures to include administration of *semaglutide* alone, including as a separate course of

treatment. Thus, both the specification and claim 17 of WO '421 disclosed the element “comprising administration of semaglutide.”

216. Moreover, because the scope of “[a]method for *treating* type 2 diabetes, *comprising* administering semaglutide” in claim 1 of the '462 patent may include administering semaglutide before, after, or with other drugs, the specification and claim 17 of WO '421 disclosed the element “comprising administration of semaglutide” of claim 1.

217. *Third*, WO '421 also disclosed the element “once weekly in an amount of 1.0 mg.” In particular, the specification of WO '421 disclosed that “[s]emaglutide is administered once weekly by subcutaneous injection (0.1 to 1.6 mg).” *Id.* at 43:14. In my opinion, a skilled artisan would have understood that the disclosed range included a discrete number of dosing steps, proceeding in increments of no less than 0.1 mg. For example, skilled artisans would have known that the related GLP-1 receptor agonist, liraglutide, was administered in doses of 0.6 mg increments, including 0.6 mg, 1.2 mg, and 1.8 mg. *See* Victoza label at 2668. Further, skilled artisans would have known that weekly semaglutide doses of 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, and 1.6 mg were being tested in Novo Nordisk’s phase II clinical study (*see* NCT00696657 at 15-16) and weekly semaglutide doses of 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, and 1.2 mg were being tested in Novo Nordisk’s phase I clinical study

(*see* NCT00851773 at 7).⁷ Therefore, a POSA would have pursued dosing increments of no less than 0.1 mg/dose and would have immediately envisioned all the options in that range at the smallest reasonable step size, which would include at most a group of just 16 doses (i.e., 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.5 mg, 0.6 mg, 0.7 mg, 0.8 mg, 0.9 mg, 1.0 mg, 1.1 mg, 1.2 mg, 1.3 mg, 1.4 mg, 1.5 mg, and 1.6 mg).

218. Moreover, skilled artisans would have been aware of Novo Nordisk's phase I and phase II clinical trials testing once weekly doses ranging from 0.1-1.6 mg semaglutide. *See* NCT00696657 at 15-16; NCT00851773 at 7. Similar to the liraglutide phase II study about which Seino reported that "[a]ll doses [liraglutide 0.1 mg/day, 0.3 mg/day, 0.6 mg/day, and 0.9 mg/day] tested showed a degree of efficacy" (Seino at 166), skilled artisans would similarly expect that all of the once weekly doses of semaglutide tested in NCT00696657 and NCT00851773 would exhibit some degree of efficacy.⁸

⁷ My ultimate opinions that claims 1 and 3 would have been anticipated do not require the disclosure of the NCT00851773. This disclosure only confirms that claims 1 and 3 would have been anticipated.

⁸ Although it is my opinion that skilled artisans would have understood a 1.0 mg dose of semaglutide to be effective, this goes further than the Court's claim construction requires because the Court's construction does not require any particular degree or minimum threshold of efficacy. *See* Section VI above.

219. Thus, WO '421 disclosed the element “once weekly in an amount of 1.0 mg” of claim 1.

220. Moreover, because claim 17 of WO '421 recited “[a] GLP-1 receptor agonist selected from . . . semaglutide . . . for use in a method of treating type 2 diabetes . . . said method comprising administration . . . of the GLP-1 receptor agonist,” a POSA would immediately envision using the once weekly dose of “0.1 to 1.6 mg” semaglutide disclosed in WO '421 for administration for at least the same reasons as described above. Thus, claim 17 of WO '421 also disclosed the element “once weekly in an amount of 1.0 mg” of claim 1.

221. *Fourth*, WO '421 disclosed the element “to a subject in need thereof.” Throughout the disclosure, WO '421 taught that the therapy should be for the treatment of diabetes in a human patient. *See., e.g.*, WO '421 at 36:3-5. WO '421 also disclosed that therapies “may be used in [drug] naïve patients,” or “patients with advanced or late stage type 2 diabetes” or “patients ineligible for metformin” or “patients having...renal disease [or] ... dysfunction.” *Id.* at 8:35-10:7. Thus, WO '421 disclosed the element “to a subject in need thereof” of claim 1.

222. Claim 17 of WO '421 also disclosed “to a subject in need thereof” *because* a skilled artisan would have the understanding that “administration of the GLP-1 receptor agonist” (semaglutide) “for use in a method of treating type 2

diabetes” would necessarily be for the purposes of administering to a human patient to treat type 2 diabetes.

223. Thus, for the aforementioned reasons, both the specification and claim 17 of WO '421 anticipated claim 1 of the '462 patent.

c. WO '421 anticipated claim 3

224. In my opinion, WO '421 anticipated claim 3 of the '462 patent. Claim 2 depends from claim 1 and recites, “[t]he method according to claim 1, wherein the semaglutide is administered by parenteral administration.” Claim 3 depends from claim 2 and recites, “[t]he method according to claim 2, wherein the solution is administered by subcutaneous injection.”

225. WO '421 disclosed “[s]emaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg).” WO '421 at 35:23-36:5, 43:13. In my opinion, skilled artisans would have known that a subcutaneous injection is necessarily a solution.

226. The specification of WO '421 and claim 17 of WO '421 therefore anticipated claim 3 of the '462 patent.

2. Lovshin 2009 Anticipated Claims 1 and 3 of the '462 Patent

227. As described below, in my opinion, claims 1 and 3 of the '462 patent are invalid as anticipated by Lovshin 2009.

a. Teachings of Lovshin 2009

228. The teachings of Lovshin 2009 are detailed above in paragraphs 118-121.

b. Lovshin 2009 anticipated claim 1

229. Independent claim 1 recites “[a]method for treating type 2 diabetes, comprising administering semaglutide once weekly in an amount of 1.0 mg to a subject in need thereof.” In my opinion, Lovshin 2009 taught each element of claim 1 of the ’462 patent.

230. *First*, Lovshin 2009 disclosed the preamble of claim 1 of the ’462 patent, which the Court found was limiting but did not require any particular degree or minimum threshold of efficacy. *See* Section VI above. Lovshin 2009 disclosed “[i]ncretin-based drugs, such as glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase 4 inhibitors, are now routinely used to treat type 2 diabetes mellitus.” Lovshin 2009 at Abstract. *Lovshin* 2009 also disclosed, “multiple once-weekly GLP-1 therapies are under active clinical investigation in phase I-II studies (NN9535, LY2199265, and a pegylated GLP-1 molecule, LY2428757; see Table 1).” *Id.* at 266.

231. Thus, Lovshin 2009 taught the preamble, “[a]method for treating type 2 diabetes.”

232. *Second*, Lovshin 2009 also disclosed the element “comprising administration of semaglutide” of claim 1. Lovshin 2009 disclosed, “multiple once-weekly GLP-1 therapies are under active clinical investigation in phase I-II studies (NN9535, LY2199265, and a pegylated GLP-1 molecule, LY2428757; see Table 1).” *Id.* at 266. A POSA would have known that NN9535 was semaglutide.⁹ Moreover, if semaglutide was being investigated in phase I-II studies, a POSA would have known that this involved administering semaglutide to subjects in the phase I-II studies. Thus, Lovshin 2009 disclosed the element “comprising administration of semaglutide” of claim 1.

233. *Third*, Lovshin 2009 also disclosed the element “once weekly in an amount of 1.0 mg.” In particular, Table 1 of Lovshin 2009 disclosed that NN9535 (semaglutide) was being investigated at a dose of “0.1-1.6 mg once weekly.” *Id.* at 263, Table 1. In my opinion, a skilled artisan would have understood that the disclosed range included a discrete number of dosing steps, proceeding in increments of no less than 0.1 mg. For example, skilled artisans would have known that the

⁹ See WO '193 at 34:18 (“semaglutide/NN9535 (Novo Nordisk)”); *see also* Lund at 610, Table 1 (“Semaglutide (NN9535) Novo Nordisk”); Bhansali at 13 (“Semaglutide (NN9535) is a once-weekly human GLP-1 analogue that is being developed by Novo Nordisk for the treatment of type 2 diabetes.”).

related GLP-1 receptor agonist, liraglutide, was administered in doses of 0.6 mg, 1.2 mg, and 1.8 mg. *See* Victoza label at 2668. Further, skilled artisans would have known that weekly semaglutide doses of 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, and 1.6 mg were being tested in Novo Nordisk's phase II clinical study (*see* NCT00696657 at 15-16) and weekly semaglutide doses of 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, and 1.2 mg were being tested in Novo Nordisk's phase I clinical study (*see* NCT00851773¹⁰ at 7). Therefore, a POSA would have pursued dosing increments of no less than 0.1 mg/dose and would have immediately envisioned all the options in that range at the smallest reasonable step size, which would include at most a group of just 16 doses (i.e., 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.5 mg, 0.6 mg, 0.7 mg, 0.8 mg, 0.9 mg, 1.0 mg, 1.1 mg, 1.2 mg, 1.3 mg, 1.4 mg, 1.5 mg, and 1.6 mg).

234. Moreover, skilled artisans would have been aware of Novo Nordisk's phase I and phase II clinical trials testing once weekly doses ranging from 0.1-1.6 mg semaglutide. *See* NCT00696657 at 15-16; NCT00851773 at 7. Similar to the liraglutide phase II study disclosed in Seino in which "[a]ll doses [liraglutide 0.1 mg/day, 0.3 mg/day, 0.6 mg/day, and 0.9 mg/day] tested showed a degree of efficacy" (Seino at 166), skilled artisans would similarly expect that all once weekly

¹⁰ My ultimate opinions that claims 1 and 3 of the '462 patent would have been anticipated do not require the disclosure of the NCT00851773. This disclosure only confirms that claims 1 and 3 of the '462 patent would have been anticipated.

doses of semaglutide tested in NCT00696657 and NCT00851773 would exhibit some degree of efficacy.¹¹

235. Thus, Lovshin 2009 disclosed the element “once weekly in an amount of 1.0 mg” of claim 1.

236. *Fourth*, Lovshin 2009 disclosed the element “to a subject in need thereof.” Lovshin 2009 disclosed, “multiple once-weekly GLP-1 therapies are under active clinical investigation in phase I-II studies (NN9535, LY2199265, and a pegylated GLP-1 molecule, LY2428757; see Table 1).” Lovshin 2009 at 266. If semaglutide was being investigated in phase I-II studies, a POSA would have known that this involved administering semaglutide to subjects in the phase I-II studies. Thus, Lovshin 2009 disclosed the element “to a subject in need thereof” of claim 1.

237. Thus, for the aforementioned reasons, Lovshin 2009 anticipated claim 1 of the ’462 patent.

c. Lovshin 2009 anticipated claim 3

238. In my opinion, Lovshin 2009 anticipated claim 3 of the ’462 patent. Claim 2 depends from claim 1 and recites, “[t]he method according to claim 1, wherein the semaglutide is administered by parenteral administration.” Claim 3

¹¹ Although it is my opinion that skilled artisans would have understood a 1.0 mg dose of semaglutide to be effective, this goes further than the Court’s claim construction requires because the Court’s construction does not require any particular degree or minimum threshold of efficacy. *See* Section VI above.

depends from *claim 2* and recites, “[t]he method according to claim 2, wherein the solution is administered by subcutaneous injection.”

239. Lovshin 2009 disclosed that the dose *of* NN9535 (semaglutide) to be administered to a patient is “0.1–1.6 mg once weekly,” given by “subcutaneous injection” to treat type 2 diabetes. Lovshin 2009 at 263. In my opinion, skilled artisans would have known that a subcutaneous injection is necessarily a solution.

240. Lovshin 2009 therefore anticipated claim 3 of the ’462 patent.

3. NCT00696657 Anticipated Claims 1 and 3 of the ’462 Patent

241. As described below, in my opinion, claims 1 and 3 of the ’462 patent are invalid as anticipated by NCT00696657.

a. Teachings of NCT00696657

242. The teachings of NCT00696657 are detailed above in paragraphs 129-133.

b. NCT00696657 anticipated claim 1

243. Independent claim 1 recites “[a]method for treating type 2 diabetes, comprising administering semaglutide once weekly in an amount of 1.0 mg to a subject in need thereof.” In my opinion, NCT00696657 taught each element of claim 1 of the ’462 patent.

244. *First*, NCT00696657 disclosed the preamble of claim 1 of the '462 patent, which the Court found was limiting but did not require any particular degree or minimum threshold of efficacy. *See* Section VI above.

245. The Purpose section of NCT00696657 disclosed:

Study participants were randomised evenly to treatment with semaglutide (0.1 mg QW - 1.6 mg QW, 6 treatment arms, placebo or liraglutide (1.2 mg QD, or 1.8 mg QD). Treatment allocation to semaglutide or placebo was double-blind, whereas liraglutide treatment was administered open-label. Primary efficacy parameter was HbA1c and the treatment duration was 12 weeks.

NCT00696657 at 15.

246. Thus, NCT00696657 disclosed the preamble of claim 1.

247. *Second*, NCT00696657 also disclosed the element “comprising administration of semaglutide” of claim 1. As discussed above, NCT00696657 disclosed that “[s]tudy participants were randomised evenly to treatment with semaglutide.” *Id.* at 15. Thus, NCT00696657 disclosed the element “comprising administration of semaglutide.”

248. *Third*, NCT00696657 also disclosed the element “once weekly in an amount of 1.0 mg.” NCT00696657 had six Experimental arms in the clinical trial (A-F), which included subcutaneous injections of semaglutide, once weekly, at doses of 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, 0.8 mg (with titration), and 1.6 mg (with

titration). *Id.* at 15-16. Skilled artisans would have understood that “with titration” meant that the recited dose amount was reached by starting from a lower dose amount and then increasing the dose until reaching the final level.

249. In my opinion, skilled artisans would have immediately envisioned a dose of 1.0 mg semaglutide administered once weekly for use in the claimed method of treatment based on the disclosure of NCT00696657. That the 0.8 mg dose was tested in NCT00696657 with and without titration and the 1.6 mg dose was tested only with titration would have suggested to skilled artisans that the focus for semaglutide dosing was below 1.6 mg. In particular, the skilled artisan would have understood that Novo Nordisk may be apprehensive of the tolerability of 1.6 mg considering it was only being tested with titration, whereas, the 0.8 mg dose was being tested with and without titration, which suggests that the 0.8 mg dose could be tolerated without titration, and therefore doses lower than 1.6 mg and closer to the 0.8 mg dose would have a better balance between efficacy and side effects. As such, skilled artisans would have immediately envisioned the 1.0 mg semaglutide once weekly dose.

250. That skilled artisans would have immediately envisioned the 1.0 mg semaglutide dose is further confirmed because skilled artisans would have understood that the disclosed doses in NCT00696657 included a discrete number of dosing steps, proceeding in increments of no less than 0.1 mg (i.e., 0.1, 0.2, 0.4, 0.8,

1.6 mg doses). Moreover, skilled artisans would have known that the related GLP-1 receptor agonist, liraglutide, was administered in doses of 0.6 mg increments, including 0.6 mg, 1.2 mg, and 1.8 mg. *See* Victoza label at 2668. Thus, skilled artisans would have immediately envisioned all of the options in the range of doses at the smallest reasonable step size between 0.8 mg to 1.6 mg, which would include at most a group of just seven doses (i.e., 0.9 mg, 1.0 mg, 1.1 mg, 1.2 mg, 1.3 mg, 1.4 mg, and 1.5 mg).

251. Further, similar to the liraglutide phase II study disclosed in Seino in which “[a]ll doses [liraglutide 0.1 mg/day, 0.3 mg/day, 0.6 mg/day, and 0.9 mg/day] tested showed a degree of efficacy” (Seino at 166), skilled artisans would similarly expect that all once weekly doses of semaglutide tested in NCT00696657 would exhibit some degree of efficacy.¹²

252. Thus, NCT00696657 disclosed the element “once weekly in an amount of 1.0 mg.”

253. *Fourth*, NCT00696657 disclosed the element “to a subject in need thereof.” NCT00696657 disclosed that the trial was investigating treatment of

¹² Although it is my opinion that skilled artisans would have understood a 1.0 mg dose of semaglutide to be effective, this goes further than the Court’s claim construction requires because the Court’s construction does not require any particular degree or minimum threshold of efficacy. *See* Section VI above.

patients with type 2 diabetes. Thus, NCT00696657 disclosed the element “to a subject in need thereof.”

254. Thus, for the aforementioned reasons, NCT00696657 anticipated claim 1 of the '462 patent.

c. NCT00696657 anticipated claim 3

255. In my opinion, NCT00696657 anticipated claim 3 of the '462 patent. Claim 2 depends from claim 1 and recites, “[t]he method according to claim 1, wherein the semaglutide is administered by parenteral administration.” Claim 3 depends from claim 2 and recites, “[t]he method according to claim 2, wherein the solution is administered by subcutaneous injection.”

256. NCT00696657 disclosed that semaglutide was administered by subcutaneous administration. NCT00696657 at 15-16. NCT00696657 therefore anticipated claim 3 of the '462 patent.

B. CLAIMS 1, 3-5, AND 7 OF THE '462 PATENT WOULD HAVE BEEN OBVIOUS

1. Claims 1, 3-5, and 7 of the '462 Patent Would Have Been Obvious Over WO '421, NCT00696657, WO '537 and/or Lovshin 2009, Optionally in View of One or More of the '833 Patent and Madsbad 2011

257. As described below, in my opinion claims 1, 3-5, and 7 of the '462 patent would have been obvious over WO '421, NCT00696657, WO '537 and/or Lovshin 2009, optionally in view of one or more of the '833 patent and Madsbad

2011. It is my understanding that the defendants' formulation expert, Dr. Dalby, is submitting an expert report and providing an opinion that claims 4, 5, and 7 of the '462 patent would have been obvious over WO '421, NCT00696657, WO '537 and/or Lovshin 2009, optionally in view of one or more of the '833 patent and Madsbad 2011.

a. Claim 1 would have been obvious

258. Independent claim 1 recites “[a]method for treating type 2 diabetes, comprising administering semaglutide once weekly in an amount of 1.0 mg to a subject in need thereof.” In my opinion, claim 1 of the '462 patent would have been obvious over WO '421, NCT00696657, WO '537 and/or Lovshin 2009, optionally in view of one or more of the '833 patent and Madsbad 2011.

(i) Teachings of WO '421

259. The teachings of WO '421 are detailed above in paragraphs 112-117.

(ii) Teachings of NCT00696657

260. The teachings of NCT00696657 are detailed above in paragraphs 129-133.

(iii) Teachings of WO '537

261. The teachings of WO '537 are detailed above in paragraphs 122-127.

(iv) Teachings of Lovshin 2009

262. The teachings of Lovshin 2009 are detailed above in paragraphs 118-121.

(v) Teachings of the '833 patent

263. The teachings of the '833 patent are detailed above in paragraphs 202-204.

(vi) Teachings of Madsbad 2011

264. The teachings of Madsbad 2011 are detailed above in paragraphs 198-201.

(vii) Skilled artisans would have been motivated to pursue, with a reasonable expectation of success, the treatment of type 2 diabetes with a once weekly 1.0 mg dose of semaglutide

265. In my opinion, in view of the state of the art and a skilled artisan's general knowledge before July 1, 2012, in particular, WO '421, NCT00696657, WO '537 and/or Lovshin 2009, optionally in view of one or more of the '833 patent and Madsbad 2011, skilled artisans would have been motivated to optimize the once weekly dose of semaglutide to treat type 2 diabetes patients with a once weekly 1.0 mg dose of semaglutide and would have had a reasonable expectation of success in doing so.

266. To begin, as the Court found, the preamble "[a] method for treating type 2 diabetes" means that "the claimed administration is for the purpose of care and

management of a patient with Type 2 diabetes” or “the claimed administration is intended to care for and manage a patient with Type 2 diabetes.” D.I. 148 at 2-3. I understand that the Court construed the preamble so that it does not require any particular degree or minimum threshold of efficacy.

267. As taught in the art, skilled artisans would have known that GLP-1 analogues, such as semaglutide, could be therapeutically useful for treating type 2 diabetes, as a once weekly dosing regimen. For example, WO '421 disclosed “methods for treating and/or preventing metabolic diseases, especially type 2 diabetes mellitus, obesity and/or conditions related thereto (e.g. diabetic complications) comprising the combined administration of a GLP-1 receptor agonist (e.g. exogenous GLP-1 or a GLP-1 analogue) and a certain DPP-4 inhibitor.” WO '421 at 1:4-7. WO '421 further disclosed that “[p]referred examples of GLP-1 receptor agonists (GLP-1 analogues) of this invention are exenatide, exenatide LAR, liraglutide, taspoglutide, *semaglutide*, albiglutide, lixisenatide and dulaglutide,” each of which was disclosed to have “significant sequence identity to GLP-1.” *Id.* at 33:20-26 (emphasis added). WO '421 disclosed that “[s]emaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg).” *Id.* at 43:13.

268. WO '537 disclosed “[a]n embodiment provides the use of a [GLP-1] compound according to any one of the embodiments . . . for the preparation of a medicament for the treatment or prevention of hyperglycemia, type 2 diabetes,

impaired glucose tolerance, type 1 diabetes, obesity,” or “for delaying or preventing disease progression in type 2 diabetes.” WO ’537 at 22:24-23:3; *see also id.* at 37:34-36. WO ’537 specifically disclosed the structure of semaglutide and once weekly administration. WO ’537 at 47:4-8, 59:24-25 (“One aspect of this invention is to prepare GLP-1 analogues/derivatives with extended plasma half-lives that are suitable for once weekly administration.”); 59:28-32. The ’462 patent admits that WO ’537 disclosed once weekly administration of semaglutide. ’462 patent at 9:43-45 (“WO 06/097537 discloses semaglutide (Example 4), a mono-acylated GLP-1 agonist for once weekly administration.”). WO ’537 also disclosed that formulations can be prepared a variety of different concentrations “from 0.1 mg/ml to 25 mg/ml.” *Id.* at 24:11-13.

269. Lovshin 2009 disclosed that “[i]ncretin-based drugs, such as glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase 4 inhibitors, are now routinely used to treat type 2 diabetes mellitus.” Lovshin 2009 at 262.

270. Madsbad 2011 disclosed that the “once-weekly GLP-1 receptor analogues are promising candidates for the treatment of type 2 diabetes.” Madsbad 2011 at 394. Madsbad 2011 also disclosed that various GLP-1 receptor agonists, such as semaglutide, had once weekly subcutaneous dosing regimens. *Id.* at 395, Fig. 1. Madsbad 2011 further taught that “[i]ncretin-based therapies, such as the injectable glucagon-like peptide-1 (GLP-1) receptor agonists and orally

administered dipeptidyl peptidase-4 (DPP-4) inhibitors, have recently been introduced into clinical practice. . . . Several once-weekly GLP-1 receptor agonists are in phase 3 development.” *Id.* at 394.

271. Skilled artisans also would have known that Novo Nordisk was actively investigating semaglutide in phase I and phase II studies in once weekly dosing regimens. For example, in 2009, Lovshin 2009 disclosed that semaglutide was under clinical investigation in phase I-II studies. Lovshin 2009 at 263 (Table 1), 266. In 2011, Lund confirmed this disclosing, “[s]o far, three Phase I studies looking at pharmacokinetics and safety of semaglutide (NCT00813020, NCT00833716 and NCT00851773), and one Phase II randomized-controlled clinical trial comparing semaglutide with placebo and liraglutide have been completed (NCT00696657).” Lund at 613-14; *see also id.* at Table 1.

272. Skilled artisans would have known that Novo Nordisk was investigating a dose range of between 0.1-1.6 mg semaglutide once weekly to treat type 2 diabetes in a phase II study. *See* NCT00696657 at 15-16. Skilled artisans would also have been aware that the 0.8 mg dose was tested in NCT00696657 with and without titration and the 1.6 mg dose was tested only with titration. *Id.*

273. A POSA would have understood these to be disclosures of ranges of semaglutide doses including 1.0 mg once weekly. Alternatively, the dosage range

disclosed by WO '421, NCT00696657, and Lovshin 2009, and the use of WO '537 in a once weekly regimen, rendered the claimed 1.0 mg dosage obvious.

274. In my opinion, based on the disclosures in the art of the ranges of semaglutide doses including 1.0 mg once weekly, skilled artisans would have engaged in routine optimization to determine an effective dose of semaglutide that produces minimal side effects, which were well-known to be caused by GLP-1 receptor agonists, such as semaglutide. Moreover, skilled artisans would have been motivated to use once weekly semaglutide as a treatment for type 2 diabetes, because it allows for reduction in frequency of injections and improved compliance. Lund at 611. Skilled artisans would have a reasonable expectation of success of practicing the claimed “method for treating type 2 diabetes” with a 1.0 mg dose because a POSA would expect the 1.0 mg to have some efficacy. As I noted above, I understand that the Court construed the preamble so that it does not require any particular degree or minimum threshold of efficacy. My conclusion from the prior art therefore applies to the method for treating type 2 diabetes as the Court has interpreted that term (i.e., as not requiring any minimum degree of efficacy) and additionally goes beyond what the Court’s interpretation requires in terms of efficacy. That is, in my opinion, the prior art would motivate skilled artisans to use a once-weekly 1.0 mg semaglutide dose with a reasonable expectation that it would

provide significantly more than a minimal level of efficacy in treating type 2 diabetes.

275. In my opinion, by routine testing of the disclosed range of doses of semaglutide, a POSA would have been motivated with a reasonable expectation of success to use a weekly dose of 1.0 mg semaglutide by subcutaneous injection to treat type 2 diabetes. The '462 patent admits that identifying the claimed 1.0 mg dose of semaglutide in a method for treating type 2 diabetes would have been obvious to achieve using routine experimentation:

[A]n “effective amount” of a GLP-1 agonist as used herein means an amount sufficient to cure, alleviate, or partially arrest the clinical manifestations of a given disease or state and its complications. An amount adequate to accomplish this is defined as “effective amount”. Effective amounts for each purpose will depend on the severity of the disease or injury as well as the weight and general state of the subject. *It will be understood that determining an appropriate dosage may be achieved using routine experimentation, by constructing a matrix of values and testing different points in the matrix, which is all within the ordinary skills of a trained physician or veterinary [sic].*

'462 patent at 5:4-15 (emphasis added).

276. The ability of a POSA to determine an optimal dosage from a range is reinforced by the '833 patent, which discloses:

[I]t is understood that depending on the peptide or peptides included in the formulations of the invention, the formulations may be used in methods of treatment of diseases or conditions for which use of the peptide is indicated. . . . It is to be understood that “an effective amount” is the effective dose to be determined by a qualified practitioner, who may titrate dosages to achieve the desired response. Factors for

consideration of dose will include potency, bioavailability, desired pharmacokinetic/pharmacodynamic profiles, the condition or disease to be treated (e.g. *diabetes*, obesity, weight loss, gastric ulcers), patient-related factors (e.g. weight, health, age, etc.) presence of co-administered medications (e.g. insulin), time of administration, or other factors known to a medical practitioner.

'833 patent at 13:60-14:15 (emphasis added).

277. The skilled artisan would have understood that the doses tested in Novo Nordisk's phase I and II studies had already been tested in preclinical models and would be safe for human administration. Moreover, the skilled artisan would have understood that the doses tested in phase I and phase II studies would have been subject to the scrutiny of a human subjects institutional review board before testing began. The skilled artisan would have understood that for the studies to proceed, there was a scientific rationale and support for those doses being both safe and efficacious in human patients. *See supra* paragraphs 68-77; Tamimi at c127; Knudsen 2010b at 4; ICH 2001 at 5-8.

278. As discussed above, by the priority date of July 1, 2012, a skilled artisan would have been aware of the doses that Novo Nordisk chose to test in the phase I and phase II dose ranging studies. In particular, a skilled artisan would have been aware that the completed NCT00696657 phase II randomized-controlled clinical trial comparing semaglutide with placebo and liraglutide included six experimental arms (A-F), that consisted of subcutaneous injection once weekly doses of semaglutide at 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, 0.8 mg with titration, and 1.6 mg

with titration. NCT00696657 at 15-16. That these were the doses tested in the phase II dose-ranging study by Novo Nordisk provides confirmation that a skilled artisan would have been motivated to optimize the once weekly dose of semaglutide to treat type 2 diabetes patients with a 1.0 mg weekly dose.

279. Further, skilled artisans would also have been aware that in the NCT00696657 study, the 0.8 mg dose was tested with and without titration and the 1.6 mg dose was tested only with titration. *See* NCT00696657 at 15-16. That the 0.8 mg dose was tested in NCT00696657 with and without titration and the 1.6 mg dose was tested only with titration would have suggested to skilled artisans that the focus for semaglutide dosing was below 1.6 mg, dosed once weekly, and a skilled artisan would have been motivated to optimize the dose in that range to 1.0 mg. Moreover, the skilled artisan would have been motivated to use a dose between 0.8 mg and 1.6 mg, such as 1.0 mg, because the skilled artisan would have understood that Novo Nordisk may be apprehensive of the tolerability of 1.6 mg considering it was only being tested with titration, whereas, the 0.8 mg dose was being tested with and without titration, which suggests doses lower than 1.6 mg and closer to 0.8 mg, such as 1.0 mg, would have a better balance between efficacy and side effects.

280. Skilled artisans would also have also been aware that Novo Nordisk was originally investigating a dose range of 0.1-1.6 mg semaglutide once weekly in the phase I 2009 NCT00851773 study, similar to NCT00696657. *See* NCT00851773

at 11-12 (2009 NCT00851773). Also disclosed in the 2009 NCT00851773 protocol was that the 0.8 mg dose was tested with and without titration, whereas the 1.6 dose was tested only with titration. *Id.* at 11. There was also an optional dose to be “determined based on safety and tolerability of previous dose steps” that will “only be implemented if the 0.8 mg is tolerated but the 1.6 mg is not.” *Id.* Similar to NCT00696657, that the 0.8 mg dose was tested in 2009 NCT00851773 with and without titration and the 1.6 mg dose was tested only with titration would have suggested to skilled artisans that the focus for semaglutide dosing was below 1.6 mg, dosed once weekly, and a skilled artisan would have been motivated to optimize the dose in that range to 1.0 mg. Thus, this further confirms the skilled artisan would have been motivated to use a dose between 0.8 mg and 1.6 mg, such as 1.0 mg because the skilled artisan would have understood that Novo Nordisk may be apprehensive of the tolerability of 1.6 mg considering it was only being tested with titration, whereas, the 0.8 mg dose was being tested with and without titration, which suggests doses lower than 1.6 mg and closer to 0.8 mg, such as 1.0 mg, would have a better balance between efficacy and side effects.

281. Skilled artisans would also have also been aware that in a later protocol for 2010 NCT00851773, Novo Nordisk dropped the 1.6 mg dose and investigated a dose range of 0.1-1.2 mg semaglutide once weekly. *See* NCT00851773 at 7-8 (2010 NCT00851773).

282. In my opinion, a skilled artisan would have been motivated to pursue a 1.0 mg weekly dose of semaglutide as a treatment for type 2 diabetes because it would be understood that certain doses being tested in phase I and II studies within the 0.1-1.6 mg range would be more effective than others. A skilled artisan would understand that the phase I and II studies would be dose-ranging studies, in which Novo Nordisk would have selected doses to test to provide a dose-response curve to determine the suboptimal doses and the optimal doses, the most effective doses with the least side effects. *See* Tamimi at c127-28; FDA Exposure Response 2003 at 4; ICH 1994 at 55972-74, 55976; Shargel at 577-78, Figs. 19-1 and 19-2.

283. In my opinion, a skilled artisan would reasonably expect that the doses on the lower end of the range (e.g., ~0.1 mg doses) would have some efficacy but would be suboptimal doses (*see* Seino at 166 (“[a]ll doses of liraglutide tested showed a degree of efficacy)), in contrast to doses on the higher end of the range (e.g., ~1.6 mg doses), which would likely be found on the plateau of the dose ranging curve, providing the maximum beneficial effect. *See* Shargel at 577-78, Figs. 19-1 and 19-2.

284. Based on the doses that Novo Nordisk selected to test in the NCT00696657 phase II study, 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, and 1.6 mg semaglutide, a skilled artisan would have had a reasonable expectation of success that doses of at least between 0.8 to 1.6 mg semaglutide, such as 1.0 mg, would be

effective as a method for treating type 2 diabetes. And as discussed above, the Court found, the preamble, “[a] method for treating type 2 diabetes,” did not require any particular degree or minimum threshold of efficacy. *See* Section VI above. My opinion that the 1.0 mg semaglutide dose would be effective thus goes further than the Court’s claim construction requires.

285. As discussed above, a skilled artisan would have been aware that the purpose of a phase II study would be to evaluate a variety of doses, including suboptimal doses and maximum effective doses to provide a dose-response curve and determine the optimal doses. Further, a skilled artisan would also understand that prior to undergoing any phase I or phase II human studies, Novo Nordisk would have collected a substantial amount of pre-clinical data (i.e., *in vitro* and in healthy and diseased animal models) related to the pharmacokinetics and pharmacodynamics of semaglutide. *See, e.g.*, Knudsen 2010b at 4. Thus, a skilled artisan would have understood that the doses selected in Novo Nordisk’s dose-ranging study were supported by a breadth of internal preclinical studies and knowledge about semaglutide. *See supra* paragraphs 68-77.

286. In my opinion, a skilled artisan would have further understood that the lower doses, such as 0.1 mg, 0.2 mg, and 0.4 mg, would have been selected by Novo Nordisk to provide information about the suboptimal semaglutide doses on the dose-response curve. In my opinion, these doses on the lower end of the range would still

provide some degree of efficacy but would be suboptimal doses (*see* Seino at 166 (“[a]ll doses of liraglutide tested showed a degree of efficacy)). A skilled artisan would have also understood that higher doses, such as the 0.8 mg and 1.6 mg doses, were chosen by Novo Nordisk to evaluate the maximum response of semaglutide on the dose-response curve. Moreover, a skilled artisan would have reasonably expected that the 1.6 mg dose was chosen as a dose expected to be on the plateau of the dose-response curve, such that it would provide a maximum effect. *See* Shargel at 577-78, Figs. 19-1 and 19-2. Thus, a skilled artisan would have been motivated to optimize the weekly dose of semaglutide to between 0.8 mg and 1.6 mg and would have understood that the disclosed range included a discrete number of dosing steps, typically proceeding in 0.1 mg increments. A skilled artisan would have been motivated to try a 1.0 mg dose with a reasonable expectation that it would be effective in treating type-2 diabetes because it would have been one of seven 0.1 mg dose increments to test between 0.8 mg to 1.6 mg.

287. Moreover, a skilled artisan would be further motivated to optimize to a 1.0 mg dose within the 0.8 mg to 1.6 mg range because the 1.6 mg dose, would likely result in unwanted side effects, such as gastrointestinal problems. That the 0.8 mg dose was tested in NCT00696657 with and without titration and the 1.6 mg dose was tested only with titration would have suggested to skilled artisans that Novo Nordisk had reservations about the tolerability of the 1.6 mg dose considering it was only

being tested with titration, whereas, the 0.8 mg dose was being tested with and without titration, which suggests that this dose would have a better balance between efficacy and side effects. Indeed, other GLP-1-receptor agonists, such as the similarly structured, liraglutide, produced gastrointestinal problems at higher doses. *See, e.g.*, Victoza label at 2668 (allowing for titration of liraglutide from 0.6 to 1.2 mg dose “to reduce gastrointestinal symptoms during initial titration.”). Thus, a skilled artisan would be motivated look to optimize to a dose below the highest 1.6 mg dose tested in the phase II study, to provide effective treatment without unwanted side effects.

288. Indeed, the NCT00851773¹³ phase I study, assessing the safety and tolerability of semaglutide, further confirms that a skilled artisan would be motivated to optimize to a weekly dose such as 1.0 mg semaglutide. Similar to the NCT00696657 phase II study, the 2009 NCT00851773 protocol indicated that the 0.8 mg dose was tested with and without titration and the 1.6 mg dose was tested only with titration. NCT00696657 at 7-8. That the 1.6 mg dose was only tested with titration would have suggested to a skilled artisan that Novo Nordisk had

¹³ My ultimate opinions that claims 1 and 3 would have been obvious do not require the disclosure of the NCT00851773 study. This disclosure only confirms that claims 1 and 3 would have been obvious.

reservations about the tolerability of the 1.6 mg dose, which would have further provided motivation to optimize using a dose lower than 1.6 mg.

289. Moreover, in the later version of NCT00851773 (2010 NCT00851773), the highest dose tested was 1.2 mg, not 1.6 mg semaglutide. By the earliest alleged priority date of July 1, 2012, a skilled artisan would have known that the NCT00696657 phase II study was completed in February 2009 (NCT00696657 at 15), which was the same month that the NCT00851773 phase I study was just starting. *See* NCT00851773 at 7 (disclosing a “Study Start Date” of “February 2009.”).

290. A skilled artisan would have known that the highest doses tested in 2010 NCT00851773 phase I study differed from the highest doses tested in the NCT00696657 phase II study. In particular, instead of testing the same once weekly doses that were tested in the NCT00696657 phase II study, i.e., 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, and 1.6 mg semaglutide, the 2010 NCT00851773 phase I study instead tested 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, and 1.2 mg semaglutide once weekly, effectively reducing the 1.6 mg semaglutide dose, the highest dose tested in the phase II study, to 1.2 mg semaglutide. *Compare* NCT00696657 at 15-16 with NCT00851773 at 7 (2010 NCT00851773). In my opinion, a skilled artisan would have understood that this change from using a 1.6 mg dose to using a lower 1.2 mg

dose means that Novo Nordisk was fine tuning its clinical protocol, perhaps based on data collected from the earlier performed NCT00696657 phase II study.

291. In my opinion, this would further narrow the range of potential doses from between 0.8 mg to 1.2 mg semaglutide providing even further reasonable expectation that a once weekly 1.0 mg semaglutide dose would be successful for treating type 2 diabetes.

292. Moreover, because liraglutide was shown to exhibit the classic, sigmoidal dose/response profile for lowering HbA_{1c}, (*see* Seino at 164, Fig. 1), and because semaglutide is also a GLP-1 agonist with a similar structure and mechanism of action, a skilled artisan would have a strong scientific basis to expect a similar dose response relationship for lowering HbA_{1c}. The animal and human studies with liraglutide, the basic understanding of the pharmacokinetics and pharmacodynamics of GLP-1 receptor agonists, and the appreciation that several other agents were in development for once weekly dosing (e.g., Lovshin 2009 at Table 1) would have led a skilled artisan to expect consistency in responses between liraglutide and semaglutide on lowering glucose and HbA_{1c} in diabetic patients leading to progressive reductions of these biomarkers from lower to higher doses until reaching a plateau. In my opinion, these disclosures further supported the skilled artisan's reasonable expectation that a once weekly 1.0 mg semaglutide dose would be successful as "[a] method for treating type 2 diabetes."

293. Accordingly, claim 1 of the '462 patent would have been obvious to a skilled artisan over WO '421, NCT00696657, WO '537 and/or Lovshin 2009, optionally in view of one or more of the '833 patent and Madsbad 2011.

b. Claim 3 would have been obvious

294. In my opinion, claim 3 of the '462 patent would have been obvious over WO '421, NCT00696657, WO '537 and/or Lovshin 2009, optionally in view of one or more of the '833 patent and Madsbad 2011. Claim 2 depends from claim 1 and recites, “[t]he method according to claim 1, wherein the semaglutide is administered by parenteral administration.” Claim 3 depends from claim 2 and recites, “[t]he method according to claim 2, wherein the solution is administered by subcutaneous injection.”

295. NCT00696657 disclosed that semaglutide in the phase II trial was administered as a subcutaneous injection. *See* NCT00696657 at 15-16.

296. The '833 patent disclosed:

[I]n a preferred embodiment, the formulations of the invention are to be administered parenterally to a patient in need thereof. Parenteral administration may be performed by subcutaneous, intramuscular or intravenous injection by means of a syringe, optionally a pen-like syringe.

'833 patent at 13:45-50.

297. Madsbad 2011 disclosed that semaglutide is administered by subcutaneous (sc) injection. Madsbad 2011 at 395, Fig. 1.

298. WO '537 further disclosed that “[p]arenteral administration may be performed by subcutaneous, intramuscular, intraperitoneal or intravenous injection by means of a syringe, optionally a pen-like syringe.” WO '537 at 34:15-16; *see also* WO '537 at 34:3-4 (“Even more preferably, are controlled release and sustained release systems administered subcutaneous.”)

299. WO '421 disclosed that “[s]emaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg).” WO '421 at 43:13.

300. In my opinion, skilled artisans would have known that a subcutaneous injection is necessarily a solution.

301. Accordingly, claim 3 of the '462 patent would have been obvious to a skilled artisan over WO '421, NCT00696657, WO '537 and/or Lovshin 2009, optionally in view of one or more of the '833 patent and Madsbad 2011.

c. Claims 4, 5, and 7 would have been obvious over WO '421, NCT00696657, WO '537 and/or Lovshin 2009 in combination with the '833 patent, optionally in view of Madsbad 2011

302. As I described above, it is my opinion that claims 1 and 3 of the '462 patent would have been obvious over WO '421, NCT00696657, WO '537 and/or Lovshin 2009, optionally in view of one or more of the '833 patent and Madsbad 2011. It is my understanding that the defendants' formulation expert, Dr. Dalby, is submitting an expert report and providing an opinion that claims 4, 5, and 7 of the

'462 patent would have been obvious over WO '421, NCT00696657, WO '537 and/or Lovshin 2009, optionally in view of one or more of the '833 patent and Madsbad 2011. It is therefore my opinion that claims 4, 5, and 7 of the '462 patent would have been obvious over WO '421, NCT00696657, WO '537 and/or Lovshin 2009, optionally in view of one or more of the '833 patent and Madsbad 2011 for the reasons discussed above and for the reasons discussed by Dr. Dalby.

2. Claims 1, 3-5, and 7 of the '462 Patent Would Have Been Obvious Over WO '421 Alone or in View of the '833 Patent

303. As described below, in my opinion claims 1, 3-5, and 7 of the '462 patent would have been obvious over WO '421 alone or in view of the '833 patent.

a. Claim 1 would have been obvious over WO '421

304. Independent claim 1 recites “[a]method for treating type 2 diabetes, comprising administering semaglutide once weekly in an amount of 1.0 mg to a subject in need thereof.” In my opinion, claim 1 of the '462 patent would have been obvious over WO '421.

(i) Teachings of WO '421

305. The teachings of WO '421 are detailed above in paragraphs 112-117.

(ii) Skilled artisans would have been motivated to pursue, with a reasonable expectation of success, the treatment of type 2 diabetes with a once weekly 1.0 mg dose of semaglutide

306. In my opinion, in view of the state of the art and a skilled artisan's general knowledge before July 1, 2012, in particular, WO '421, skilled artisans would have been motivated to optimize the once weekly dose of semaglutide to treat type 2 diabetes patients with a once weekly 1.0 mg dose of semaglutide and would have had a reasonable expectation of success in doing so.

307. To begin, as the Court found, the preamble "[a] method for treating type 2 diabetes" means that "the claimed administration is for the purpose of care and management of a patient with Type 2 diabetes" or "the claimed administration is intended to care for and manage a patient with Type 2 diabetes." D.I. 148 at 2-3. I understand that the Court construed the preamble so that it does not require any particular degree or minimum threshold of efficacy.

308. Based on the teachings of WO '421, skilled artisans would have known that WO '421 disclosed methods for treating and/or preventing type 2 diabetes by administering a GLP-1 receptor agonist, such as semaglutide. *See, e.g.*, WO '421 at 1:4-9, 33:20-22 ("Preferred examples of GLP-1 receptor agonists (GLP-1 analogues) of this invention are exenatide, exenatide LAR, liraglutide, taspoglutide, semaglutide, albiglutide, lixisenatide and dulaglutide.") (emphasis added), claim 17.

309. Moreover, a skilled artisan would have known from WO '421 that “[s]emaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg).” *Id.* at 43:13. As a result, skilled artisans would have engaged in routine optimization to determine an effective dose of semaglutide that produces minimal side effects, which were well-known to be caused by GLP-1 receptor agonists, such as semaglutide. Skilled artisans would have further been motivated to use once weekly semaglutide as a treatment for type 2 diabetes, because it allows for reduction in frequency of injections and improved compliance. Lund at 611.

310. In my opinion, by routine testing of the disclosed range of doses of semaglutide, a POSA would have been motivated with a reasonable expectation of success to use a weekly dose of 1.0 mg semaglutide by subcutaneous injection to treat type 2 diabetes. The '462 patent admits that identifying the claimed 1.0 mg dose of semaglutide in a method for treating type 2 diabetes would have been obvious to achieve using routine experimentation:

[A]n “effective amount” of a GLP-1 agonist as used herein means an amount sufficient to cure, alleviate, or partially arrest the clinical manifestations of a given disease or state and its complications. An amount adequate to accomplish this is defined as “effective amount”. Effective amounts for each purpose will depend on the severity of the disease or injury as well as the weight and general state of the subject. *It will be understood that determining an appropriate dosage may be achieved using routine experimentation, by constructing a matrix of values and testing different points in the matrix, which is all within the ordinary skills of a trained physician or veterinary [sic].*

'462 patent at 5:4-15 (emphasis added).

311. Skilled artisans would have been motivated to look to the teachings in the art with respect to using semaglutide to treat type 2 diabetes. As taught in the art, Novo Nordisk was actively investigating semaglutide in phase I and phase II studies. For example, in 2009, Lovshin 2009 disclosed that semaglutide was under clinical investigation in phase I-II studies. Lovshin 2009 at 266. In 2011, Lund confirmed this disclosing, “[s]o far, three Phase I studies looking at pharmacokinetics and safety of semaglutide (NCT00813020, NCT00833716 and NCT00851773), and one Phase II randomized-controlled clinical trial comparing semaglutide with placebo and liraglutide have been completed (NCT00696657).” Lund at 613-14; *see also id.* at Table 1.

312. A skilled artisan would also have known that the dose range being investigated by Novo Nordisk was a once weekly dose of between 0.1-1.6 mg semaglutide, the same dose range disclosed in WO '421. Lovshin 2009 at 263, Table 1; WO '421 at 43:13. In my opinion, a skilled artisan would have been motivated to pursue a 1.0 mg weekly dose of semaglutide as a treatment for type 2 diabetes because it would be understood that certain doses being tested in phase I and II studies within the 0.1-1.6 mg range would be more effective than others. A skilled artisan would understand that the phase I and II studies would be dose-ranging studies, in which Novo Nordisk would have selected doses to test to provide a dose-

response curve to determine the suboptimal doses and the optimal doses, the most effective doses with the least side effects. *See* Tamimi at c127-28; FDA Exposure Response 2003 at 4; ICH 1994 at 55972-74, 55976; Shargel at 577-78, Figs. 19-1 and 19-2.

313. The skilled artisan would have understood that the doses (or exposures) tested in phase I and II studies had already been tested in preclinical models and would be safe for human administration. Moreover, the skilled artisan would have understood that the doses tested in phase I and phase II studies would have been subject to the scrutiny of a human subjects institutional review board before testing began. The skilled artisan would have understood that for the studies to proceed, there was a scientific rationale and support for those doses being both safe and efficacious in human patients. *See supra* paragraphs 68-77; Tamimi at c127; Knudsen 2010b at 4; ICH 2001 at 5-8.

314. In my opinion, a skilled artisan would reasonably expect that the doses on the lower end of the range (e.g., ~0.1 mg doses) would have some efficacy but would be suboptimal doses (*see* Seino at 166 (“[a]ll doses of liraglutide tested showed a degree of efficacy)), in contrast to doses on the higher end of the range (e.g., ~1.6 mg doses), which would likely be found on the plateau of the dose ranging curve, providing the maximum effect. *See* Shargel at 577-78, Figs. 19-1 and 19-2.

315. Based on the doses that Novo Nordisk selected to test in the NCT00696657 phase II study, 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, and 1.6 mg semaglutide, a skilled artisan would have had a reasonable expectation of success that doses of at least between 0.8 to 1.6 mg semaglutide, such as 1.0 mg, would be effective as a method for treating type 2 diabetes. As I noted above, I understand that the Court construed the preamble so that it does not require any particular degree or minimum threshold of efficacy. My conclusion from the prior art therefore applies to the method for treating type 2 diabetes as the Court has interpreted that term (i.e., as not requiring any minimum degree of efficacy) and additionally goes beyond what the Court's interpretation requires in terms of efficacy. That is, in my opinion the prior art would motivate skilled artisans to use a once-weekly 1.0 mg semaglutide dose with a reasonable expectation that it would provide significantly more than a minimal level of efficacy in treating type 2 diabetes.

316. Indeed, by the priority date of July 1, 2012, a skilled artisan would have been aware of the doses that Novo Nordisk chose to test in the phase I and phase II dose ranging studies and the skilled artisan would be motivated with a reasonable expectation of success to optimize the weekly dose to 1.0 mg for treating type 2 diabetes.

317. In particular, a skilled artisan would have been aware that the completed NCT00696657 phase II randomized-controlled clinical trial comparing

semaglutide with placebo and liraglutide included six experimental arms (A-F), that consisted of subcutaneous injection once weekly doses of semaglutide at 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, 0.8 mg with titration, and 1.6 mg with titration. NCT00696657 at 15-16. That these were the doses tested in the phase II dose-ranging study by Novo Nordisk provides confirmation that a skilled artisan would have been motivated to optimize the once weekly dose of semaglutide to treat type 2 diabetes patients with a 1.0 mg weekly dose of semaglutide and would have had a reasonable expectation of success in doing so.

318. Based on the doses that Novo Nordisk selected to test in the NCT00696657 phase II study, 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, and 1.6 mg semaglutide, a skilled artisan would have had a reasonable expectation of success that doses of at least between 0.8 to 1.6 mg semaglutide, such as 1.0 mg, would be effective in treating type 2 diabetes. As discussed above, a skilled artisan would have been aware that the purpose of a phase II study would be to evaluate a variety of doses, including suboptimal doses and maximum effective doses to provide a dose-response curve and determine the optimal doses. Further, a skilled artisan would also understand that prior to undergoing any phase I or phase II human studies, Novo Nordisk would have collected a substantial amount of pre-clinical data (i.e., *in vitro* and healthy and diseased animal models) related to the pharmacokinetics and pharmacodynamics of semaglutide. See Tamimi at c127; Knudsen 2010b at 4. Thus,

a skilled artisan would have understood that the doses selected in Novo Nordisk's dose-ranging study were supported by a breadth of internal preclinical studies and knowledge about semaglutide.

319. In my opinion, a skilled artisan would have further understood that the lower doses, such as 0.1, 0.2, and 0.4 mg, would have been selected by Novo Nordisk to provide information about the suboptimal semaglutide doses on the dose-response curve. In my opinion, these doses on the lower end of the range would still provide some degree of efficacy but would be suboptimal doses (see Seino at 166 (“[a]ll doses of liraglutide tested showed a degree of efficacy)). A skilled artisan would have also understood that higher doses, such as the 0.8 mg and 1.6 mg doses, were chosen by Novo Nordisk to evaluate the maximum response of semaglutide on the dose-response curve. Moreover, a skilled artisan would have reasonably expected that the 1.6 mg dose was chosen as a dose expected to be on the plateau of the dose-response curve, such that it would provide a maximum effect. *See* Shargel at 577-78, Figs. 19-1 and 19-2. Thus, a skilled artisan would have been motivated to optimize the weekly dose of semaglutide to between 0.8 mg and 1.6 mg and would have understood that the disclosed range included a discrete number of dosing steps, typically proceeding in 0.1 mg increments. A skilled artisan would have been motivated to try a 1.0 mg dose with a reasonable expectation that it would be

effective in treating type-2 diabetes because it would have been one of seven 0.1 mg dose increments to test between 0.8 mg to 1.6 mg.

320. Moreover, a skilled artisan would be further motivated to optimize to a 1.0 mg dose within the 0.8 mg to 1.6 mg range because the 1.6 mg dose would likely result in unwanted side effects, such as gastrointestinal problems. That the 0.8 mg dose was tested in NCT00696657 with and without titration and the 1.6 mg dose was tested only with titration would have suggested to skilled artisans that Novo Nordisk had reservations about the tolerability of the 1.6 mg dose considering it was only being tested with titration, whereas, the 0.8 mg dose was being tested with and without titration, which suggests that this dose would have a better balance between efficacy and side effects. Indeed, other GLP-1-receptor agonists, such as the similarly structured, liraglutide, produced gastrointestinal problems at higher doses. *See, e.g.*, Victoza label at 2668 (allowing for titration of liraglutide from 0.6 to 1.2 mg dose “to reduce gastrointestinal symptoms during initial titration.”). Thus, a skilled artisan would be motivated to look to optimize to a dose below the highest 1.6 mg dose tested in the phase II study, to provide effective treatment without unwanted side effects.

321. Indeed, the NCT00851773¹⁴ phase I study, assessing the safety and tolerability of semaglutide, further confirms that skilled artisans would be motivated to optimize to a weekly dose such as 1.0 mg semaglutide. Similar to the NCT00696657 phase II study, the 2009 NCT00851773 protocol indicated that the 0.8 mg dose was tested with and without titration and the 1.6 mg dose was tested only with titration. NCT00696657 at 7-8. As discussed above, that the 1.6 mg dose was only tested with titration would have suggested to a skilled artisan that Novo Nordisk had reservations about the tolerability of the 1.6 mg dose, which would have further provided motivation to optimize using a dose lower than 1.6 mg.

322. Moreover, in the later version of NCT00851773 (2010 NCT00851773), the highest dose tested was 1.2 mg, not 1.6 mg semaglutide. By the earliest alleged priority date of July 1, 2012, a skilled artisan would have known that the NCT00696657 phase II study was completed in February 2009 (NCT00696657 at 15), which was the same month that the NCT00851773 phase I study was just starting. *See* NCT00851773 at 7 (disclosing a “Study Start Date” of “February 2009.”).

¹⁴ My ultimate opinions that claims 1 and 3 would have been obvious do not require the disclosure of the NCT00851773 study. This disclosure only confirms that claims 1 and 3 would have been obvious.

323. A skilled artisan would have known that the highest doses tested in the 2010 NCT00851773 phase I study differed from the highest doses tested in the NCT00696657 phase II study. In particular, instead of testing the same once weekly doses that were tested in the NCT00696657 phase II study, i.e., 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, and 1.6 mg semaglutide, the 2010 NCT00851773 phase I study instead tested 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, and 1.2 mg semaglutide once weekly, effectively reducing the 1.6 mg semaglutide dose, the highest dose tested in the phase II study, to 1.2 mg semaglutide. Compare NCT00696657 at 15-16 with NCT00851773 at 7 (2010 NCT00851773). In my opinion, a skilled artisan would have understood that this change from using a 1.6 mg dose to using a 1.2 mg dose means that Novo Nordisk was fine tuning its clinical protocol, perhaps based on data collected from the earlier performed NCT00696657 phase II study.

324. In my opinion, this would further narrow the range of potential doses from between 0.8 mg to 1.2 mg semaglutide providing even further reasonable expectation that the once weekly 1.0 mg semaglutide dose would be successful for treating type 2 diabetes.

325. Moreover, because liraglutide was shown to exhibit the classic sigmoidal dose/response profile for lowering HbA_{1c}, (see Seino at 164, Fig. 1), and because semaglutide is also a GLP-1 agonist with a similar structure and mechanism of action, a skilled artisan would have a strong scientific basis to expect a similar

dose response relationship with semaglutide for lowering HbA_{1c}. The animal and human studies with liraglutide, the basic understanding of the pharmacokinetics and pharmacodynamics of GLP-1 receptor agonists, and the appreciation that several other agents were in development for once weekly dosing (e.g., Lovshin 2009 at Table 1) would have led a skilled artisan to expect consistency in responses between liraglutide and semaglutide on lowering glucose and HbA_{1c} in diabetic patients leading to progressive reductions of these biomarkers from lower to higher doses until reaching a plateau. In my opinion, these disclosures further supported the skilled artisan's reasonable expectation that a once weekly 1.0 mg semaglutide dose would be successful as "[a] method for treating type 2 diabetes."

326. Accordingly, claim 1 of the '462 patent would have been obvious to a skilled artisan over WO '421.

b. Claim 3 would have been obvious over WO '421

327. In my opinion, claim 3 of the '462 patent would have been obvious over WO '421. Claim 2 depends from claim 1 and recites, "[t]he method according to claim 1, wherein the semaglutide is administered by parenteral administration." Claim 3 depends from claim 2 and recites, "[t]he method according to claim 2, wherein the solution is administered by subcutaneous injection."

328. WO '421 disclosed that "[s]emaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg)" to treat type 2 diabetes. WO '421 at 42:13. In

my opinion, skilled artisans would have known that a subcutaneous injection is necessarily a solution.

329. Accordingly, claim 3 of the '462 patent would have been obvious to a skilled artisan over WO '421.

c. Claims 4, 5, and 7 would have been obvious over WO '421 alone or in view of the '838 patent

330. As I described above, it is my opinion that claims 1 and 3 of the '462 patent would have been obvious over WO '421. It is my understanding that the defendants' formulation expert, Dr. Dalby, is submitting an expert report and providing an opinion that claims 4, 5, and 7 of the '462 patent would have been obvious over WO '421 alone or in view of the '838 patent. It is therefore my opinion that claims 4, 5, and 7 of the '462 patent would have been obvious over WO '421 alone or in view of the '838 patent for the reasons discussed above and for the reasons discussed by Dr. Dalby.

3. Claims 1, 3-5, and 7 of the '462 Patent Would Have Been Obvious Over WO '537 in View of Lovshin 2009

331. As described below, in my opinion claims 1, 3-5, and 7 of the '462 patent would have been obvious over WO '537 in view of Lovshin 2009. It is my understanding that the defendants' formulation expert, Dr. Dalby, is submitting an expert report and providing an opinion that claims 4, 5, and 7 of the '462 patent would have been obvious over WO '537 in view of Lovshin 2009.

a. Claim 1 would have been obvious over WO '537 in view of Lovshin 2009

332. Independent claim 1 recites “[a]method for treating type 2 diabetes, comprising administering semaglutide once weekly in an amount of 1.0 mg to a subject in need thereof.” In my opinion, claim 1 of the '462 patent would have been obvious over WO '537 in view of Lovshin 2009.

(i) Teachings of WO '537 and Lovshin 2009

333. The teachings of WO '537 are detailed above in paragraphs 122-127.

334. The teachings of Lovshin 2009 are detailed above in paragraphs 118-121.

(ii) Skilled artisans would have been motivated to pursue, with a reasonable expectation of success, the treatment of type 2 diabetes with a once weekly 1.0 mg dose of semaglutide

335. In my opinion, in view of the state of the art and a skilled artisan's general knowledge before July 1, 2012, in particular, WO '537 in combination with Lovshin 2009, skilled artisans would have been motivated to optimize the once weekly dose of semaglutide to treat type 2 diabetes patients with a once weekly 1.0 mg dose of semaglutide and would have had a reasonable expectation of success in doing so.

336. To begin, as the Court found, the preamble “[a] method for treating type 2 diabetes” means that “the claimed administration is for the purpose of care and

management of a patient with Type 2 diabetes” or “the claimed administration is intended to care for and manage a patient with Type 2 diabetes.” D.I. 148 at 2-3. I understand that the Court construed the preamble so that it does not require any particular degree or minimum threshold of efficacy.

337. Based on the teachings of WO '537, a skilled artisan would have known that semaglutide could be used for once weekly administration to treat type 2 diabetes. WO '537 disclosed that semaglutide could be used in “a medicament for the treatment or prevention of hyperglycemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes, [or] obesity,” or “for delaying or preventing disease progression in type 2 diabetes.” WO '537 at 22:24-23:3; *see also id.* at 37:34-36. WO '537 specifically disclosed the structure of semaglutide and once weekly administration. WO '537 at 47:4-8 (Example 4 disclosing the structure of semaglutide); *see also id.* at 72:17-74:10 (Claim 28 disclosing semaglutide); 59:24-25 (“One aspect of this invention is to prepare GLP-1 analogues/derivatives with extended plasma half-lives that are suitable for once weekly administration.”); 59:28-32. Indeed, the '462 patent admits that WO '537 disclosed once weekly administration of semaglutide. '462 patent at 9:43-45 (“WO 06/097537 discloses semaglutide (Example 4), a mono-acylated GLP-1 agonist for once weekly administration.”).

338. WO '537 also disclosed that formulations can be prepared a variety of different concentrations “from 0.1 mg/ml to 25 mg/ml.” *Id.* at 24:11-13. WO '537 also disclosed that the disclosed formulations could be administered parenterally, such as by subcutaneous injection. *Id.* at 34:15-16 (“Parenteral administration may be performed by subcutaneous, intramuscular, intraperitoneal or intravenous injection by means of a syringe, optionally a pen-like syringe.”).

339. Skilled artisans would have been motivated to look to teachings in the art with respect to using semaglutide to treat type 2 diabetes. As taught in the art, Novo Nordisk was actively investigating semaglutide in phase I and phase II studies. For example, in 2009, Lovshin 2009 disclosed that semaglutide was under clinical investigation in phase I-II studies. Lovshin 2009 at 266. In 2011, Lund confirmed this disclosing, “[s]o far, three Phase I studies looking at pharmacokinetics and safety of semaglutide (NCT00813020, NCT00833716 and NCT00851773), and one Phase II randomized-controlled clinical trial comparing semaglutide with placebo and liraglutide have been completed (NCT00696657).” Lund at 613-14; *see also id.* at Table 1.

340. A skilled artisan would also have known from Lovshin 2009 that the dose range being investigated by Novo Nordisk was a once weekly dose of between 0.1-1.6 mg semaglutide. Lovshin 2009 at 263, Table 1. In my opinion, a skilled artisan would have been motivated to pursue a 1.0 mg weekly dose of semaglutide

as a treatment for type 2 diabetes because it would be understood that certain doses being tested in phase I and II studies within the 0.1-1.6 mg range would be more effective than others. A skilled artisan would understand that the phase I and II studies would be dose-ranging studies, in which Novo Nordisk would have selected doses to test to provide a dose-response curve to determine the suboptimal doses and the optimal doses, the most effective doses with the least side effects. *See* Tamimi at c127-28; FDA Exposure Response 2003 at 4; ICH 1994 at 55972-74, 55976; Shargel at 577-78, Figs. 19-1 and 19-2.

341. As a result, skilled artisans would have engaged in routine optimization to determine an effective dose of semaglutide that produces minimal side effects, which were well-known to be caused by GLP-1 receptor agonists, such as semaglutide. Skilled artisans would have been motivated to use once weekly semaglutide as a treatment for type 2 diabetes because it allows for reduction in frequency of injections and improved compliance. Lund at 611.

342. In my opinion, by routine testing of the disclosed range of doses of semaglutide, a POSA would have been motivated with a reasonable expectation of success to use a weekly dose of 1.0 mg semaglutide by subcutaneous injection to treat type 2 diabetes. The '462 patent admits that identifying the claimed 1.0 mg dose of semaglutide in a method for treating type 2 diabetes would have been obvious to achieve using routine experimentation:

[A]n “effective amount” of a GLP-1 agonist as used herein means an amount sufficient to cure, alleviate, or partially arrest the clinical manifestations of a given disease or state and its complications. An amount adequate to accomplish this is defined as “effective amount”. Effective amounts for each purpose will depend on the severity of the disease or injury as well as the weight and general state of the subject. *It will be understood that determining an appropriate dosage may be achieved using routine experimentation, by constructing a matrix of values and testing different points in the matrix, which is all within the ordinary skills of a trained physician or veterinary [sic].*

’462 patent at 5:4-15 (emphasis added).

343. The skilled artisan would have understood that the doses (or exposures) tested in phase I and II studies had already been tested in preclinical models and would be safe for human administration. Moreover, the skilled artisan would have understood that the doses tested in phase I and phase II studies would have been subject to the scrutiny of a human subjects institutional review board before testing began. The skilled artisan would have understood that for the studies to proceed, there was a scientific rationale and support for those doses being both safe and efficacious in human patients. *See supra* paragraphs 68-77; Tamimi at c127; Knudsen 2010b at 4; ICH 2001 at 5-8.

344. In my opinion, a skilled artisan would reasonably expect that the doses on the lower end of the range (e.g., ~0.1 mg doses) would have some efficacy but would be suboptimal doses (*see* Seino at 166 (“[a]ll doses of liraglutide tested showed a degree of efficacy)), in contrast to doses on the higher end of the range

(e.g., ~1.6 mg doses), which would likely be found on the plateau of the dose ranging curve, providing the maximum beneficial effect. *See* Shargel at 577-78, Figs. 19-1 and 19-2.

345. Indeed, by the priority date of July 1, 2012, a skilled artisan would have been aware of the doses that Novo Nordisk chose to test in the phase I and phase II dose ranging studies, which would confirm that a skilled artisan would be motivated with a reasonable expectation of success to optimize the weekly dose to 1.0 mg for treating type 2 diabetes.

346. In particular, a skilled artisan would have been aware that the completed NCT00696657 phase II randomized-controlled clinical trial comparing semaglutide with placebo and liraglutide included six experimental arms (A-F), that consisted of subcutaneous injection once weekly doses of semaglutide at 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, 0.8 mg with titration, and 1.6 mg with titration. NCT00696657 at 15-16. That these were the doses tested in the phase II dose-ranging study by Novo Nordisk provides further confirmation that a skilled artisan would have been motivated to optimize the once weekly dose of semaglutide to treat type 2 diabetes patients with a 1.0 mg weekly dose of semaglutide and would have had a reasonable expectation of success in doing so.

347. Based on the doses that Novo Nordisk selected to test in the NCT00696657 phase II study, 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, and 1.6 mg

semaglutide, a skilled artisan would have had a reasonable expectation of success that doses of at least between 0.8 to 1.6 mg semaglutide, such as 1.0 mg, would be effective in treating type 2 diabetes. As I noted above, I understand that the Court construed the preamble so that it does not require any particular degree or minimum threshold of efficacy. My conclusion from the prior art therefore applies to the method for treating type 2 diabetes as the Court has interpreted that term (i.e., as not requiring any minimum degree of efficacy) and additionally goes beyond what the Court's interpretation requires in terms of efficacy. That is, in my opinion the prior art would motivate skilled artisans to use a once-weekly 1.0 mg semaglutide dose with a reasonable expectation that it would provide significantly more than a minimal level of efficacy in treating type 2 diabetes.

348. Moreover, as discussed above, a skilled artisan would have been aware that the purpose of a phase II study would be to evaluate a variety of doses, including suboptimal doses and maximum effective doses to provide a dose-response curve and determine the optimal doses. Further, a skilled artisan would also understand that prior to undergoing any phase I or phase II human studies, Novo Nordisk would have collected a substantial amount of pre-clinical data (i.e., *in vitro* and healthy and diseased animal models) related to the pharmacokinetics and pharmacodynamics of semaglutide. *See* Tamimi at c127; Knudsen 2010b at 4. Thus, a skilled artisan would have understood that the doses selected in Novo Nordisk's dose-ranging study were

supported by a breadth of internal preclinical studies and knowledge about semaglutide. *See supra* paragraphs 68-77.

349. In my opinion, a skilled artisan would have further understood that the lower doses, such as 0.1, 0.2, and 0.4 mg, would have been selected by Novo Nordisk to provide information about the suboptimal semaglutide doses on the dose-response curve. In my opinion, these doses on the lower end of the range would still provide some degree of efficacy but would be suboptimal doses (*see* Seino at 166 (“[a]ll doses of liraglutide tested showed a degree of efficacy)). A skilled artisan would have also understood that higher doses, such as the 0.8 mg and 1.6 mg doses, were chosen by Novo Nordisk to evaluate the maximum response of semaglutide on the dose-response curve. Moreover, a skilled artisan would have understood that the 1.6 mg dose was expected to be on the plateau of the dose-response curve, such that it would provide a maximum effect. *See* Shargel at 577-78, Figs. 19-1 and 19-2. Thus, a skilled artisan would have been motivated to optimize the weekly dose of semaglutide to between 0.8 mg and 1.6 mg and would have understood that the disclosed range included a discrete number of dosing steps, typically proceeding in 0.1 mg increments. A skilled artisan would have been motivated to try a 1.0 mg dose with a reasonable expectation that it would be effective in treating type-2 diabetes because it would have been one of seven 0.1 mg dose increments to test between 0.8 mg to 1.6 mg.

350. Moreover, a skilled artisan would be further motivated to optimize to a 1.0 mg dose within the 0.8 mg to 1.6 mg range because the 1.6 mg dose would likely result in unwanted side effects, such as gastrointestinal problems. That the 0.8 mg dose was tested in NCT00696657 with and without titration and the 1.6 mg dose was tested only with titration would have suggested to skilled artisans that Novo Nordisk had reservations about the tolerability of the 1.6 mg dose considering it was only being tested with titration, whereas, the 0.8 mg dose was being tested with and without titration, which suggests that this dose would have a better balance between efficacy and side effects. Indeed, other GLP-1-receptor agonists, such as the similarly structured liraglutide, produced gastrointestinal problems at higher doses. *See, e.g.,* Victoza label at 2668 (allowing for titration of liraglutide from 0.6 to 1.2 mg dose “to reduce gastrointestinal symptoms during initial titration.”). Thus, a skilled artisan would be motivated to look to optimize to a dose below the highest 1.6 mg dose tested in the phase II study, to provide effective treatment without unwanted side effects.

351. Indeed, the NCT00851773¹⁵ phase I study, assessing the safety and tolerability of semaglutide, further confirms that skilled artisans would have been

¹⁵ My ultimate opinions that claims 1 and 3 would have been obvious do not require the disclosure of the NCT00851773 study. This disclosure only confirms that claims 1 and 3 would have been obvious.

motivated to optimize to a weekly dose such as 1.0 mg semaglutide. Similar to the NCT00696657 phase II study, the 2009 NCT00851773 protocol indicated that the 0.8 mg dose was tested with and without titration and the 1.6 mg dose was tested only with titration. NCT00696657 at 7-8. As discussed above, that the 1.6 mg dose was only tested with titration would have suggested to a skilled artisan that Novo Nordisk had reservations about the tolerability of the 1.6 mg dose, which confirms skilled artisans would have been motivated to optimize using a dose lower than 1.6 mg.

352. Moreover, in the later version of NCT00851773 (2010 NCT00851773), the highest dose tested was 1.2 mg, not 1.6 mg semaglutide. By the earliest alleged priority date of July 1, 2012, a skilled artisan would have known that the NCT00696657 phase II study was completed in February 2009 (NCT00696657 at 15), which was the same month that the NCT00851773 phase I study was just starting. *See* NCT00851773 at 7 (disclosing a “Study Start Date” of “February 2009.”).

353. A skilled artisan would have known that the highest doses tested in the 2010 NCT00851773 phase I study differed from the highest doses tested in the NCT00696657 phase II study. In particular, instead of testing the same once weekly doses that were tested in the NCT00696657 phase II study, i.e., 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, and 1.6 mg semaglutide, the 2010 NCT00851773 phase I study instead

tested 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, and 1.2 mg semaglutide once weekly, effectively reducing the 1.6 mg semaglutide dose, the highest dose tested in the phase II study, to 1.2 mg semaglutide. *Compare* NCT00696657 at 15-16 with NCT00851773 at 7 (2010 NCT00851773). In my opinion, a skilled artisan would have understood that this change from using a 1.6 mg dose to using a 1.2 mg dose means that Novo Nordisk was fine tuning its clinical protocol, perhaps based on data collected from the earlier performed NCT00696657 phase II study.

354. In my opinion, this would further narrow the range of potential doses from between 0.8 mg to 1.2 mg semaglutide providing an even further reasonable expectation that the once weekly 1.0 mg semaglutide dose would be successful for treating type 2 diabetes.

355. Moreover, because liraglutide was shown to exhibit the classic, sigmoidal dose/response profile for lowering HbA_{1c}, (*see* Seino at 164, Fig. 1), and because semaglutide is also a GLP-1 agonist with a similar structure and mechanism of action, a skilled artisan would have a strong scientific basis to expect a similar dose response relationship with semaglutide for lowering HbA_{1c}. The animal and human studies with liraglutide, the basic understanding of the pharmacokinetics and pharmacodynamics of GLP-1 receptor agonists, and the appreciation that several other agents were in development for once weekly dosing (e.g., Lovshin 2009 at Table 1) would have led a skilled artisan to expect consistency in responses between

liraglutide and semaglutide on lowering glucose and HbA_{1c} in diabetic patients leading to progressive reductions of these biomarkers from lower to higher doses until reaching a plateau. In my opinion, these disclosures further supported the skilled artisan's reasonable expectation that a once weekly 1.0 mg semaglutide dose would be successful as "[a] method for treating type 2 diabetes."

356. Accordingly, claim 1 of the '462 patent would have been obvious to a skilled artisan over WO '537 in view of Lovshin 2009.

b. Claim 3 would have been obvious over WO '537 in view of Lovshin 2009

357. In my opinion, claim 3 of the '462 patent would have been obvious over WO '537 in view of Lovshin 2009. Claim 2 depends from claim 1 and recites, "[t]he method according to claim 1, wherein the semaglutide is administered by parenteral administration." Claim 3 depends from claim 2 and recites, "[t]he method according to claim 2, wherein the solution is administered by subcutaneous injection."

358. WO '537 disclosed, "[p]arenteral administration may be performed by subcutaneous, intramuscular, intraperitoneal or intravenous injection by means of a syringe, optionally a pen-like syringe." WO '537 at 34:15-16. In my opinion, skilled artisans would have known that subcutaneous injection is necessarily a solution.

359. Accordingly, claim 3 of the '462 patent would have been obvious to a skilled artisan over WO '537 in view of Lovshin 2009.

c. Claims 4, 5, and 7 would have been obvious over WO '537 in view of Lovshin 2009

360. As I described above, it is my opinion that claims 1 and 3 of the '462 patent would have been obvious over WO '537 in view of Lovshin 2009. It is my understanding that the defendants' formulation expert, Dr. Dalby, is submitting an expert report and providing an opinion that claims 4, 5, and 7 of the '462 patent would have been obvious over WO '537 in view of Lovshin 2009. It is therefore my opinion that claims 4, 5, and 7 of the '462 patent would have been obvious over WO '537 in view of Lovshin 2009 for the reasons discussed above and for the reasons discussed by Dr. Dalby.

X. CONCLUSION

361. I reserve the right to supplement and/or expand on the opinions I have set forth in this report based on the information I have reviewed and/or based on any additional information produced in discovery, modifications of the Court's claim construction, in response to any expert reports submitted on behalf of Novo Nordisk, or any other circumstances that may impact my opinions.

362. Moreover, at trial I may rely upon documents and/or other materials produced in this litigation, publicly available documents, and/or any documents the parties have exchanged, such as discovery responses. Additionally, I may rely on visual aids and/or demonstrative exhibits that I prepare or have been prepared on my behalf based upon my opinions.

Dated: 3/19/2024

By:



William J. Jusko, Ph.D.

EXHIBIT A

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Education:

Salamanca High School, NY	1956-1960 Secondary Education
State University of New York at Buffalo	1960-1965 B.S. Pharmacy
State University of New York at Buffalo	1966-1969 Ph.D. 1970

Appointments:

State University of New York at Buffalo, School of Pharmacy and Pharmaceutical Sciences, Department of Pharmaceutical Sciences	
SUNY Distinguished Professor	Nov 2008 - present
UB Distinguished Professor	April 2007 - Nov 2008
Professor	April 1977 - Apr 2007
Chair, Department of Pharmaceutical Sciences	Jan 2001 – May 2016
Director, Center of Excellence in Pharmacokinetics and Pharmacodynamics	Dec 2005 -present
Vice-Chairman, Department of Pharmacy	April 1984 - Oct. 1986
Director, Doctor of Pharmacy Program	Sept. 1981 - Aug. 1986
Associate Professor of Pharmaceutics	March 1974 - April 1977
Assistant Professor of Pharmaceutics	Aug.1972 - March 1974
Millard Fillmore Hospital, Buffalo, NY	Aug. 1972 - Sept. 1981
Director, Clinical Pharmacokinetics Laboratory	
Mario Negri Institute for Pharmacological Research, Milan, Italy, Visiting Scientist	Sept. 1978 - June 1979
Veterans Administration Hospital, Boston, MA	Sept. 1969 - July 1972
Clinical Pharmacology Section, Research Pharmacologist	
Boston University School of Medicine	June 1970 - July 1972
Department of Pharmacology, Assistant Professor of Pharmacology	
Boston Collaborative Drug Surveillance Program	Sept. 1969 - July 1972
Boston University Medical Center, Research Associate	
State University of New York at Buffalo	Sept. 1966 - Aug. 1969
Dept. of Pharmaceutics, Research Assistant	

Soby's Pharmacy, Buffalo, NY, Pharmacist

March 1966 - June 1968

Children's Hospital of Buffalo, NY, Hospital Pharmacist

Sept. 1962 - Feb. 1966

Consultant:

Council for International Exchange of Scholars (Fulbright Scholar Program)
Medical Sciences Award Committee, 1980-84

National Institutes of Health, Pharmacology Study Section, 1980-84, 1997-01; Others: at present
Food and Drug Administration, CDER, Clinical Pharmacology Advisory Committee, 1999-2007

Various pharmaceutical companies, 1978-present

Awards and Honors:

NIH Predoctoral Research Fellowship, 1966-1969.

Fulbright-Hays Award to Mario Negri Institute, Milan, Italy, 1978-1979.

Fellow, Academy of Pharmaceutical Sciences, 1980.

Rorer Award, Second Best paper in: Am. J. Gastroent., 1980, (Ref. 116).

Fellow, American Association for the Advancement of Science, 1985.

Fellow, American Association of Pharmaceutical Scientists, 1986.

Rawls-Palmer Award, Am. Soc. Clinical Pharmacology & Therapeutics, 1987.

Doctor Honoris Causae, Jagiellonian University, Krakow, Poland, 1987.

Russell R. Miller Award, Am. College of Clinical Pharmacy, 1988.

Citizen of the Year (Health/Medicine), Am-Pol Eagle, Buffalo, NY, 1987

Distinguished Service Award, Am. College Clinical Pharmacology, 1989.

Fellow, American College of Clinical Pharmacology, 1989.

Faculty Exchange Scholar, State University of New York, 1990

Kosciusko Award, General Pulaski Assn. of Niagara Frontier, 1996

Research Achievement Award in PPDM, AAPS, 1998

John G. Wagner Lectureship, University of Michigan, 1999

Sustained Achievement Award, University at Buffalo, 2002

Roland T Lakey Award Lecture, Wayne State University, 2003

Chancellor's Award, University at Buffalo, 2003

ISI Most Highly Cited List in Pharmacology, 2003

MERIT Award, National Institutes of Health, 2005-2015

Volwiler Research Achievement Award, Am Assn Colleges of Pharmacy, 2005

Swintosky Distinguished Lecturer, University of Kentucky, 2006

Paul Ehrlich Magic Bullet Lifetime Achievement Award, Germany, Oct 2008

AAPS Meritorious Manuscript Award, 2008 (Ref. #469)

Leadership Award, American Society of Pharmacometrics, 2011

Distinguished Investigator Award, Am College of Clinical Pharmacology, Sept 2012

ASCPT Sheiner-Beal Pharmacometrics Award, March 2013

Collegium of Eminent Scientists, Kosciuszko Foundation, 2015

Doctor Honoris Causae, University of Paris Descartes, Sept. 2015

Fellow, International Society of Pharmacometrics, Oct. 2016

ASCPT/FDA William Abrams Lecture Award, May 2017

ASCPT Oscar B. Hunter Career Award in Therapeutics, March 2018

Lewis B. Sheiner Pharmacometrics Award, ISoP, Oct. 2019

AAPS Distinguished Pharmaceutical Scientist Award, Oct. 2020

William J. Jusko Dedicated Issue of JPharmSci®, January 2024, "Giants of Pharmaceutical Sciences"

Memberships:

American Association of Pharmaceutical Scientists (1986-present)
American Association of Colleges of Pharmacy (1972-present)
American Association for the Advancement of Science (1970-present)
American Society for Clinical Pharmacology and Therapeutics (1976-present)
American Pharmaceutical Association (1962-2012)
American Society for Microbiology (1975-1994)
American Society for Pharmacology and Experimental Therapeutics (1974-present)
Kappa Psi Pharmaceutical Fraternity (1962-1965)
Rho Chi Pharmaceutical Honor Society (1968)
American College of Clinical Pharmacy (1980-2009)
Federation Internationale Pharmaceutique (1980-2009)
American College of Clinical Pharmacology (1989-present)
European Federation for Pharmaceutical Sciences (1999-2009)
American Society of Pharmacometrics (2011-present)

Listings:

American Men and Women of Science, Who's Who (various venues)

Editorial Boards:

Journal of Pharmaceutical Sciences, 1976-81, 1992-2001
Antimicrobial Agents and Chemotherapy, 1978-1989
Biopharmaceutics and Drug Disposition, 1980-present
Journal of Pharmacokinetics and Pharmacodynamics, 1982-2005
Developmental Pharmacology and Therapeutics, 1980-1982
Drug Intelligence and Clinical Pharmacy, 1982-1987
Clinical Pharmacology and Therapeutics, 1986-2014
Journal of Clinical Pharmacology, 1993-present
American Journal of Therapeutics, 1994-present
Pharmaceutical Research, 1995-1997; Board of Consulting Editors, 2006-2014
Pharmacotherapy, 1995-2002
Journal of Pharmacology and Experimental Therapeutics, 1999-2015
Drug Metabolism and Pharmacokinetics (Japan), 2002-present
Open Access Bioinformatics, March 2009- present
Editor-in-Chief: Journal of Pharmacokinetics and Pharmacodynamics, 2005-2019
CPT: Pharmacometrics & Systems Pharmacology, 2012-2017
Current Pharmacology Reports, 2014-present

Other:

Registered Pharmacist in New York State (License No. 25534, March 1, 1966).
Laboratory Director in Toxicology, Certificate of Qualification No. 588, New York State Department of Public Health (Issued August 13, 1973).

Patents:

1. Benincosa L and Jusko WJ, Novel Method of Treatment, Patent No. WO 00/27341 (May 2000).

Publications:

1. Levy G, and Jusko WJ, Effect of Viscosity on Drug Absorption, J. Pharm. Sci. 54: 219-225 (1965). PMID: 14293807
2. Levy G., and Jusko WJ, Factors Affecting the Absorption of Riboflavin in Man, J. Pharm. Sci. 54: 285-289 (1966). PMID: 5960174
3. Levy G and Jusko WJ, Apparent Renal Tubular Secretion of Riboflavin in Man, J. Pharm. Sci. 55: 1322 (1966). PMID: 5969798
4. Jusko WJ, and Levy G, Absorption, Metabolism, and Excretion of Riboflavin-5'-Phosphate in Man, J. Pharm. Sci. 56: 58-62 (1967). PMID: 6030496
5. Jusko WJ and Levy G, Effect of Probenecid on Riboflavin Absorption and Excretion in Man, J. Pharm. Sci. 56: 1145-1149 (1967). PMID: 6049701
6. Levy G and Jusko WJ, Case History of a Pharmaceutical Formulation Failure, Clin. Pharmacol. Ther. 8: 887-889 (1967). PMID: 6072698
7. Jusko WJ and Levy G, Plasma Protein Binding of Riboflavin and Riboflavin-5'-Phosphate in Man, J. Pharm. Sci. 58: 58-62 (1969). PMID: 5765837
8. Levy G, Gibaldi M, and Jusko WJ, Multicompartment Pharmacokinetic Models and Pharmacologic Effects, J. Pharm. Sci. 58: 422-424 (1969). PMID: 5787438
9. Jusko WJ, Ph.D. Thesis, The Absorption, Distribution, Metabolism, and Elimination of Riboflavin in Man. State University of New York at Buffalo (1970). Dissertation Abst. 31: 71-6083 (1971).
10. Jusko WJ, Levy G, Yaffe SJ, and Gorodischer R, Effect of Probenecid on Renal Clearance of Riboflavin in Man, J. Pharm. Sci. 59: 473-477 (1970). PMID: 5440673
11. Jusko WJ, Rennick B, and Levy G, Renal Excretion Kinetics of Riboflavin in the Dog, Am. J. Physiol. 218: 1046-1053 (1970). PMID: 5435402
12. Jusko WJ, Levy G, and Yaffe SJ, Effect of Age on Intestinal Absorption of Riboflavin in Humans, J. Pharm. Sci. 59: 487-490 (1970). PMID: 5440675
13. Jusko WJ, Leonards JA, and Levy G., Riboflavin Distribution and Elimination in Two Functionally Anephric Human Patients, J. Pharm. Sci. 59: 566-567 (1970). PMID: 5440692
14. Jusko WJ and Levy G, Pharmacokinetic Evidence for Saturable Renal Tubular Reabsorption of Riboflavin, J. Pharm. Sci. 59: 765-772 (1970). PMID: 5463652
15. Jusko WJ, Khanna N., Levy G, Stern L, and Yaffe SJ, Riboflavin Absorption and Excretion in the Neonate, Pediatrics 45: 945-949 (1970). PMID: 5422117
16. Jusko WJ, Levy G., Yaffe SJ, and Allen J, Riboflavin Absorption in Children with Biliary Obstruction, Am. J. Dis. Child. 121: 48-52 (1971). PMID: 5539814
17. Jusko WJ, Fluorometric Analysis of Ampicillin in Biological Fluids, J. Pharm. Sci. 60: 728-732 (1971). PMID: 5125772
18. Jusko WJ, Pharmacodynamics of Chemotherapeutic Effects: Dose-TimeResponse Relationships for Phase-Nonspecific Agents, J. Pharm. Sci. 60: 892-895 (1971). PMID: 5166939
19. Lewis GP, Jusko WJ, Burke CW, Graves L, and the Boston Collaborative Drug Surveillance Program, Prednisone Side-Effects and Serum-Protein Levels: A Collaborative Study, Lancet ii: 778-781 (1971). PMID: 4106604
20. Jusko WJ, Lewis GP, and Dittert LW, Integral Coefficients of Multicompartment Pharmacokinetic Models: Application to Chemotherapy, Chemotherapy 17: 109-120 (1972). PMID: 5046835
21. Jusko WJ, and Lewis GP, Precaution in Pharmacokinetic Evaluation of Ampicillin Precursors, Lancet i: 690-691 (1972). PMID: 4125194
22. Jusko, W.J., and Lewis, G.P., Effect of Hepatic Disease on Liver Flavin and Protein Levels, Am J Clin Nutr 25: 265-268 (1972). PMID: 5011906
23. Cohen JL, Jao JT, Jusko WJ, Pharmacokinetics of Cyclophosphamide in Man, Brit. J. Pharmacol. 43: 677-680 (1971). PMID: 5157730
24. Lewis GP, Jusko WJ, Coughlin L, and Hartz S., The Contribution of Cigarette Smoking to Cadmium

- Accumulation in Man, *Lancet* i: 291-292 (1972). PMID: 4109933
25. Wizwer P, Lewis GP, Jusko WJ, and Slone D, A New System For Drug Ordering, Dispensing and Administration in Hospitals, *Am. J. Hosp. Pharm.* 29: 28-29 (1972). PMID: 5021507
26. Jusko WJ and Gibaldi M, Effects of Change in Elimination on Various Parameters of the Two-Compartment Open Model, *J. Pharm. Sci.* 61: 1270-1273 (1972). PMID: 5050376
27. Wizwer P, Lewis GP, Jusko WJ, and Slone D, System Records Drug Orders, Drug Effects, *J. Am. Hosp. Assn.*, 16: 86-94 (1972). PMID: 5055143
28. Jusko WJ, Pharmacodynamic Principles in Chemical Teratology: Dose-Response Relationships, *J. Pharmacol. Exp. Ther.* 183: 469-480 (1972). PMID: 4636387
29. Jao JY, Jusko WJ, and Cohen JL, Phenobarbital Effects on Cyclophosphamide Pharmacokinetics in Man, *Cancer Res.* 32: 2761-2764 (1972). PMID: 4678592
30. Jusko WJ, and Lewis GP, Comparison of Ampicillin and Hetacillin Pharmacokinetics in Man, *J. Pharm. Sci.* 62: 69-76 (1973). PMID: 4630199
31. Jusko WJ, Lewis GP, and Schmitt G, Ampicillin and Hetacillin Pharmacokinetics in Normal and Anephric Subjects, *Clin. Pharmacol. Ther.* 14: 90-99 (1973). PMID: 4345622
32. Lewis GP, Jusko WJ, Coughlin LL, and Hartz S, Cadmium Accumulation in Man: Influence of Smoking, Occupation, Alcoholic Habit, and Disease, *J. Chron. Dis.* 26: 717-726 (1973). PMID: 4648516
33. Jusko WJ, Pharmacokinetic Principles of Pediatric Pharmacology, *Pediatr. Clin. North Am.* 19: 81-100 (1972). PMID: 5049220
34. Jusko WJ, Pharmacokinetic Principles in Chemical Teratology, *Proc. Europ. Soc. Study Drug Toxicity* 14: 9-19 (1973).
35. Jusko WJ, The Bioavailability of Drug Products: Ampicillin APhA Pilot Project on Bioavailability, *Am. Pharm. Assn.*, pp. 19-23 (1973).
36. Jusko WJ, A Pharmacodynamic Model for Cell Cycle-Specific Chemotherapeutic Agents, *J. Pharmacokin. Biopharm.* 1: 175-200 (1973).
37. Jusko WJ, Gretch M, and Gasset R, Precipitation of Diazepam from Intravenous Preparations, *JAMA* 225: 176 (1973). PMID: 4740282
38. Jusko WJ, The Clinical Status of Predictive Pharmacokinetics, in: "Regulation and Control in Physiological Systems", A.S. Iberall and A.C. Guyton, editors, 1973, Instr. Soc. of America, Pittsburgh, pp. 57-60.
39. Szefer SJ and Jusko WJ, Decreased Volume of Distribution of Digoxin in a Patient with Renal Failure, *Res. Comm. Chem. Path. Pharmacol.* 6: 1095-1098 (1973). PMID: 4760884
40. Jusko WJ, Rapporteur: in: "Pharmacology and Pharmacokinetics", T. Teorell, R.L. Dedrick, and P.G. Condliffe, editors, Plenum Press, New York (1974), pp. 312-313, 336-337, 348-349, 366-368.
41. Jusko WJ, Szefer SJ, and Goldfarb AL, Pharmacokinetic Design of: Digoxin Dosage Regimens in Relation to Renal Function, *J. Clin. Pharmacol.* 14: 525-635 (1974). PMID: 4430731
42. Jusko WJ and Weintraub M, Myocardial Distribution of Digoxin and Renal Function, *Clin. Pharmacol. Ther.* 16: 449-454 (1974). PMID: 4414761
43. Jusko WJ, Interpretation of Cell Proliferation Curves Using a Two-Compartment Cell Model, *Math. Biosci.* 21: 31-37 (1974).
44. Gretch M, Jusko WJ, Interpretation of Drug Binding Changes in Relation to Protein Concentration, *Br J Anesth* 46: 545 (1974). PMID: 4458779
45. Jusko WJ, Clinical Pharmacokinetics of Digoxin, in: "Clinical Pharmacokinetics - A Symposium", G Levy, editor, APhA., Academy of Pharmaceutical Sciences, Washington, 1974, pp. 31-43.
46. Jusko WJ, Pharmacokinetic Management of Antibiotic Therapy, in: "Clinical Pharmacokinetics - A Symposium", G.Levy, editor, A.Ph.A. Academy of Pharmaceutical Sciences, Washington, 1974, pp. 111-127.
47. Jusko WJ, Conti DR, Molson A, Kuritzky P, Giller J, and Schultz R, Digoxin Absorption from Tablets and Elixir: The Effect of Radiation-Induced Malabsorption, *JAMA* 230: 1554-1555 (1974). PMID: 4479663
48. Danish M, Schultz R, and Jusko WJ, Pharmacokinetics of Gentamicin and Kanamycin During Hemodialysis, *Antimicrob. Ag. Chemother.* 6: 841-847 (1974). PMID: 4451356

49. Jusko WJ, Slaunwhite WR, and Aceto T, Partial Pharmacodynamic Model for the Circadian-Episodic Secretion of Cortisol in Man, *J. Clin. Endocrinol. Metab.* 40: 278-289 (1975). PMID: 163972
50. Garrettson LK and Jusko WJ, Diphenylhydantoin Elimination Kinetics in Overdosed Children, *Clin. Pharmacol. Ther.* 17: 481-491 (1975). PMID: 1122689
51. Lalka D, Jusko WJ, and Bardos TJ, Reactions of 2,2-Dimethylaziridine-Type Alkylating Agents in Biological Systems. II. A Comparative Pharmacokinetic Study in Dogs, *J. Pharm. Sci.* 64: 230-235 (1975). PMID: 236372
52. Jusko WJ, Factors Affecting the Pharmacokinetics of Some Psychoactive Drugs, *Proc. of the Symposium: Clinical Pharmacology and Toxicology of Psychoactive Drugs*, E.M. Sellers, ed, Addict Research Found, Toronto, pp.55-72 (1975).
53. Jusko WJ and Levy G, Absorption, Protein Binding, and Elimination of Riboflavin, Chapter 4 in *Riboflavin*, Rivlin R.S., editor, Plenum Press, New York, 99-152 (1975).
54. Jusko WJ, Gerbracht LM, Golden LH, and Koup J., Digoxin Concentrations in Serum and Saliva, *Res. Comm. Chem. Path. Pharmacol.* 10: 189-192 (1975). PMID: 1124317
55. Jusko WJ, Mosovich LL, Gerbracht LM, Mattar ME, and Yaffe SJ, Enhanced Elimination of Dicloxacillin in Patients with Cystic Fibrosis, *Pediatrics* 56: 1038-1044 (1975). PMID: 1196754
56. Koup JR, Jusko WJ, Elwood CM, and Kohli RK, Digoxin Pharmacokinetics: Role of Renal Failure in Dosage Regimen Design, *Clin. Pharmacol. Ther.* 18: 9-21 (1975). PMID: 1149366
57. Koup JR, Jusko WJ, Goldfarb AL, pH-Dependent Secretion of Procainamide into Saliva, *J. Pharm. Sci.* 64: 2008-2010 (1975). PMID: 1514
58. Koup JR, Greenblatt DJ, Jusko WJ, Smith TW, and Koch-Weser J, Pharmacokinetics of Digoxin in Normal Subjects After Intravenous Bolus and Infusion Doses, *J. Pharmacokin. Biopharm.* 3: 181-192 (1975). PMID: 1159622
59. Lewis GP and Jusko WJ, Pharmacokinetics of Ampicillin in Cirrhosis, *Clin. Pharmacol. Ther.* 18: 475-484 (1975). PMID: 1164828
60. Jusko WJ, Drug Dosage Adjustments in Diseased Patients, *Rational Drug Therapy* 10: 1-8 (1976). PMID: 951505
61. Gorodischer R, Jusko WJ, and Yaffe SJ, Renal Clearance of Digoxin in Young Infants, *Res. Comm. Chem. Path. Pharmacol.* 16: 363-374 (1977). PMID: 847290
62. Gorodischer R, Jusko WJ, and Yaffe SJ, Tissue and Erythrocyte Distribution of Digoxin in Infants, *Clin. Pharmacol. Ther.* 19: 256-263 (1976). PMID: 1261163
63. Koup JR, DeLattre M, Jusko WJ, and Vance JW, Caution in the Use of Variable Heparin Strengths, *Drug Intell. Clin. Pharm.* 9: 387-388 (1975).
64. Jusko WJ, Bioavailability Monograph on "Ampicillin", *J. Am. Pharmaceut. Assn., NS* 15: 591-594 (1975). PMID: 1184921
65. Jusko WJ and Poliszczuk A, Analysis of Theophylline in Biological Fluids by HPLC, Dupont Liquid Chromatography Applications Report, DuPont Instruments, Wilmington, Del. (1975).
66. Yurchak AM and Jusko WJ, Theophylline Secretion into Breast Milk, *Pediatrics* 57: 518-520 (1976). PMID: 1264548
67. Jusko WJ, Baliah T, Kim KH, Gerbracht LM, and Yaffe SJ, Pharmacokinetics of Gentamicin During Peritoneal Dialysis in Children, *Kidney International* 9: 430-438 (1976). PMID: 940277
68. Jusko WJ and Gretch M., Plasma and Tissue Protein Binding of Drugs in Pharmacokinetics, *Drug Met. Rev.* 5: 43-140 (1976). PMID: 829788 & PMID: 780085
69. Hunt SN, Jusko WJ, Yurchak AM, Effect of Smoking on Theophylline Disposition, *Clin. Pharmacol. Ther.* 19: 546-551 (1976). PMID: 1277710
70. Thiessen JJ, Bernardo PD, Seitz J, and Jusko WJ, Prednisolone: Bioavailability Monograph, *J. Am. Pharm. Assn. NS* 16: 143-146 (1976).
71. Jusko WJ, Bioavailability and Disposition Kinetics of Phenytoin in Man, In: "Quantitative Analytic Studies in Epilepsy", Kellaway P and Peterson I., editors, Raven Press, New York, 115-136 (1976).
72. Jusko WJ, Koup JR, and Alvan G, Nonlinear Assessment of Phenytoin Bioavailability, *J. Pharmacokin.*

- Biopharm. 4: 327-336 (1976). PMID: 978395
73. Jusko WJ, Pharmacokinetics in Disease States Changing Protein Binding, Chapter 7, in: "The Effects of Disease States on Drug Pharmacokinetics," L Benet, editor, Acad. Pharmaceut. Sci., Washington, D.C., 99-123 (1976).
 74. Parsons RL, Jusko WJ, and Young JM, Pharmacokinetics of Antibiotic Absorption in Coeliac Disease, J. Antimicrob. Chemother. 2: 214-215 (1976). PMID: 956085
 75. Koup JR, Schentag JJ, Vance JW, Kuritzky PM, Pyszczyński DR, and Jusko WJ, System for Clinical Pharmacokinetic Monitoring of Theophylline Therapy, Am. J. Hosp. Pharm. 33: 949-956 (1976). PMID: 790952
 76. Jusko WJ and Poliszczuk A, High Pressure Liquid Chromatographic and Spectrophotometric Assays for Theophylline in Biological Fluids, Am. J. Hosp. Pharm. 33: 1193-1196 (1976). PMID: 998637
 77. Giacoia G, Jusko WJ, Menke J, and Koup JR, Theophylline Pharmacokinetics in Premature Infants with Apnea, J. Ped. 89: 829-32 (1976). PMID: 789845
 78. Yaffe SJ, Gerbracht LM, Mosovich LL, Mattar ME, and Jusko WJ, Methicillin Pharmacokinetics in Cystic Fibrosis, J. Inf. Dis. 135: 828-831 (1977). PMID: 404369
 79. Jusko WJ, Koup JR, Vance JW, Kuritzky PM, and Schentag JJ, Intravenous Theophylline Therapy: Nomogram Guidelines, Ann. Int. Med., 86: 400-404 (1977). PMID: 848801
 80. Schentag JJ and Jusko WJ, Gentamicin Persistence in the Body, The Lancet i: 486 (1977). PMID: 65590
 81. Rose JQ, Choi HK, Schentag JJ, Kinkel WR, and Jusko WJ, Intoxication Caused by Interaction of Chloramphenicol and Phenytoin, JAMA 237: 2630-2631 (1977). PMID: 576989
 82. Resman BH, Blumenthal HP, and Jusko WJ, Breast-Milk Distribution of Theobromine from Chocolate, J. Ped. 91: 477-480 (1977). PMID: 894424
 83. Schentag JJ, Jusko WJ, Plaut ME, Cumbo TJ, Vance JW, and Abrutyn E, Tissue Persistence of Gentamicin in Man, JAMA 238: 327-329 (1977). PMID: 406431
 84. Schentag JJ, and Jusko WJ, Renal Clearance and Tissue Accumulation of Gentamicin in Man, Clin. Pharmacol. Ther. 22: 364-370 (1977). PMID: 330081
 85. Schentag JJ, Jusko WJ, Vance JW, Cumbo TJ, Abrutyn E, DeLattre M, and Gerbracht LM, Gentamicin Disposition and Tissue Accumulation on Multiple Dosing, J. Pharmacokin. Biopharm. 5: 559-577 (1977). PMID: 599407
 86. Lima JJ, Kuritzky PM, Schentag JJ, and Jusko WJ, Fetal Uptake and Neonatal Disposition of Procainamide and NAPA: A Case Report, Pediatrics 61: 491-493 (1978). PMID: 643424
 87. Lima JJ and Jusko WJ, Determination of Procainamide Acetylase Status, Clin. Pharmacol. Ther. 23: 25-29 (1978). PMID: 618707
 88. Jusko WJ, Role of Tobacco Smoking in Pharmacokinetics, J. Pharmacokin. Biopharm. 6: 7-39 (1978). PMID: 349132
 89. Lima JJ and Jusko WJ, Micromethod for Procainamide and Its Acetylated Metabolite by HPLC, In: GL Hawk, editor; Biological/Biochemical Application of Liquid Chromatography, Marcel Dekker, New York, 10: 573-583 (1979).
 90. Gal P, Jusko WJ, Yurchak AM, and Franklin BA, Theophylline Disposition in Obesity, Clin Pharmacol. Ther. 23: 438-444 (1978). PMID: 630791
 91. Mangione A, Imhoff TE, Lee RV, Shum LY, and Jusko WJ, Pharmacokinetics of Theophylline in Hepatic Disease, Chest 73: 616-622 (1978). PMID: 648214
 92. Jusko WJ, Schentag JJ, Clark JH, Gardner M, and Yurchak AM, Enhanced Biotransformation of Theophylline in Marijuana and Tobacco Smokers, Clin. Pharmacol. Ther. 24: 406-410 (1978). PMID: 688731
 93. Schentag JJ, Lasezkay G, Plaut ME, Jusko WJ, and Cumbo TJ, Tissue Accumulation and Prolonged Washout of Gentamicin and Tobramycin in Humans, Current Chemotherapy 2: 957-959 (1978).
 94. Colburn WA, Schentag JJ, Jusko WJ, and Gibaldi M., A Model for the Prospective Identification of the Pre-Nephrotoxic State During Gentamicin Therapy, J. Pharmacokin. Biopharm. 6: 179-186 (1978). PMID: 671224

95. MacKichan JJ, Pyszczynski DR, and Jusko WJ, Analysis and Disposition of Low Dose Oral Propranolol, *Res. Commun. Chem. Pathol. Pharmacol.* 20: 531-538 (1978). PMID: 674830
96. Overbach J, Johnson NF, Bates TR, Pieniaszek HJ, and Jusko WJ, High Performance Liquid Chromatograph Assay of Sulfapyridine and Acetylsulfapyridine in Biological Fluids, *J. Pharm. Sci.* 67: 1250-53 (1978). PMID: 690830
97. Schentag JJ, Lasezkay G, Cumbo TJ, Plaut ME, and Jusko WJ, Accumulation Pharmacokinetics of Tobramycin, *Antimicrob. Agents Chemother.* 13: 649-656 (1978). PMID: 666293
98. Rose JQ, Barron SA, and Jusko WJ, Phenytoin Disposition in Smokers and Nonsmokers, *Int. J. Clin. Pharmacol. Biopharm.* 16: 547-550 (1978). PMID: 730422
99. Jusko WJ, Therapeutic Implications of Digoxin Kinetics in Impaired Renal Function, *Proc. Int. Symposium on Cardiac Glycosides*, G Bodem and HJ Dengler, Eds., Bonn-1977, pp. 265-272 (1978).
100. Rose JQ and Jusko WJ, Corticosteroid Analysis in Biological Fluids by High Performance Liquid Chromatography, *J. Chromatogr.* 162: 273-280 (1979). PMID: 528595
101. Schentag JJ, Lasezkay G, Plaut ME, Jusko WJ, and Cumbo TJ, Comparative Tissue Accumulation of Gentamicin and Tobramycin in Patients, *J. Antimicrob. Chemother.* 4 (Suppl. A): 23-30 (1978). PMID: 659346
102. Lima JJ, Conti DR, Goldfarb AL, Golden LH, and Jusko WJ, Pharmacokinetic Approach to Intravenous Procainamide Therapy, *Europ. J. Clin. Pharmacol.* 13: 303-308 (1978). PMID: 668789
103. Schentag JJ, Cumbo TJ, Jusko WJ, Plaut ME, Gentamicin Tissue Accumulation and Nephrotoxic Reactions, *JAMA* 240: 2067-9 (1978). PMID: 702701
104. Lima JJ, Conti DR, Goldfarb AL, Tilstone WJ, Golden LH, and Jusko WJ, Clinical Pharmacokinetics of Procainamide Infusions in Relation to Acetylator Phenotype, *J. Pharmacokin. Biopharm.* 7: 69-85 (1979). PMID: 458558
105. Schentag JJ, Jusko WJ, Vance J, Cumbo TJ, Abrutyn E., and Plaut ME, Aminoglycoside Nephrotoxicity in Relation to Tissue Accumulation, In: *Nephrotoxicity*, J-P Fillastre, Ed., Masson Publ. Inc., New York (1978), pp. 63-82.
106. Schentag JJ, Sutfin TA, Plaut ME, and Jusko WJ, Early Detection of Aminoglycoside Nephrotoxicity with Urinary Beta Microglobulin, *J. Med.* 9: 201-210 (1978). PMID: 84037
107. Lima JJ, Goldfarb AL, Conti DR, Golden LH, Bascomb BL, Benedetti GM, and Jusko WJ, Safety and Efficacy of Procainamide Infusions, *Am. J. Cardiol.* 43: 98-105 (1979). PMID: 758776
108. Sutfin TA and Jusko WJ, High Performance Liquid Chromatographic Assay for Imipramine, Desipramine, and Their 2-Hydroxylated Metabolites, *J. Pharm. Sci.* 68: 703-705 (1979). PMID: 458567
109. MacKichan JJ, Pyszczynski DR, and Jusko WJ, Dose-Dependent Disposition of Oral Propranolol in Normal Subjects, *Biopharm. Drug Disp.* 1: 159-166 (1980). PMID: 7448344
110. Jusko WJ, Influence of Cigarette Smoking on Drug Metabolism in Man, *Drug Metab. Rev.* 9: 221-236 (1979). PMID: 385272
111. MacKichan JJ and Jusko WJ, Stability of Hydrocortisone in Human Feces, *J. Pharm. Sci.* 68: 623-625 (1979). PMID: 430502
112. Hilligoss DM, Jusko WJ, Hart BA, Koup JR, and Giacoia G, Factors Affecting Theophylline Pharmacokinetics in Premature Infants with Apnea, *Dev. Pharmacol. Ther.* 1: 6-15 (1980). PMID: 7438966
113. Plaut ME, Schentag JJ, and Jusko WJ, Aminoglycoside Nephrotoxicity: Comparative Assessment in Critically Patients, *J. Med.* 10: 257-266 (1979). PMID: 294466
114. Potter WZ, Calil HM, Zavadil AP, Jusko WJ, Sutfin T, Rapoport JL, and Goodwin FK. Steady-State Concentrations of Hydroxylated Metabolites of Tricyclic Antidepressants in Patients: Relationship to Clinical Effect, *Psychopharmacol. Bull.* 16: 32-34 (1980).
115. Lima JJ, Giller J, MacKichan JJ, and Jusko WJ, Bioavailability of Hydrocortisone Retention Enemas in Normal Subjects, *Am. J. Gastroenterol.* 73: 232-237 (1980). PMID: 7405924
116. Jusko WJ, Concepts for Population Pharmacokinetics of Theophylline, In: *25 Jahre Pharmakokinetik (Symposium)*, E Gladke and G Hermin, Eds., Gustav Fisher Verlag, Stuttgart, pp. 181-189 (1980).
117. Jusko WJ, Gardner M, Mangione A, Schentag JJ, Koup JR, and Vance JW, Factors Affecting Theophylline

- Clearances: Age, Tobacco, Marihuana, Cirrhosis, Congestive Heart Failure, Obesity, Oral Contraceptives, Benzodiazepines, Barbiturates, and Ethanol, *J. Pharm. Sci.* 68: 1358-1366 (1979). PMID: 41932
118. Schentag JJ, Gengo FM, Plaut ME, Danner D, Mangione A, and Jusko WJ., Urinary Casts as an Indicator of Renal Tubular Damage in Patients, *Antimicrob. Ag. Chemother.* 16: 468-474 (1979). PMID: 518076
 119. MacKichan JJ, Jusko WJ, Duffner PK, and Cohen ME, Liquid Chromatographic Assay of Diazepam and Its Major Metabolites in Plasma, *Clin. Chem.* 25: 856-859 (1979). PMID: 448518
 120. Rose JQ, Yurchak AM, Jusko WJ, and Powell D, Bioavailability and Disposition of Prednisone and Prednisolone from Prednisone Tablets, *Biopharm. Drug Disp.* 1: 247-258 (1980).
 121. Rose JQ, Yurchak AM, Meikle AQ, and Jusko WJ, Effect of Smoking on Prednisone, Prednisolone, and Dexamethasone Pharmacokinetics, *J. Pharmacokin. Biopharm.* 9: 1-14 (1981). PMID: 7229914
 122. DeVane CL, Wolin RE, and Jusko WJ, Pharmacokinetic Basis for Predicting Steady-State Serum Drug Concentrations of Imipramine from Single Dose Data, *Res. Commun. Psychopharm.* 3: 353-357 (1979). PMID: 548214
 123. Lima JJ and Jusko WJ, The Bioavailability of Hydrocortisone Retention Enemas in Relation to Absorption Kinetics, *Clin. Pharmacol. Ther.* 28: 262-269 (1980). PMID: 7398193
 124. Janssen FW, Jusko WJ, Chiang ST, Kirkman SK, Southgate PJ, Coleman AJ, and Ruelius HW, Metabolism and Pharmacokinetics of Oxaprozin in Normal Subjects, *Clin. Pharmacol. Ther.* 27: 352-362 (1980). PMID: 7357792
 125. Rocci ML, Johnson NF, and Jusko WJ, Serum Protein Binding of Prednisolone in Four Species, *J. Pharm. Sci.* 69: 977-978 (1980). PMID: 7400951
 126. Jusko WJ, Therapeutic Drug Monitoring: Pharmacokinetic Aspects, In: Breimer, DD, Editor, *Towards Better Safety of Drugs and Pharmaceutical Products*, pp. 153-165, Elsevier/North-Holland Biomedical Press (1980).
 127. Assael BM, Cavanna G, Jusko WJ, Marini A, Parini R, Sereni F, and Vigano A., Multiexponential Elimination of Gentamicin. A Kinetic Study During Development, *Dev. Pharmacol. Ther.* 1: 171-181 (1980). PMID: 6927546
 128. Jusko WJ and Rose JQ, Monitoring Prednisone and Prednisolone, *Ther. Drug Monit.* 2: 169-176 (1980). PMID: 6762710
 129. Rose JQ, Nickelsen, JA, Middleton E, Yurchak AM, Park B, and Jusko WJ, Prednisolone Disposition in Steroid Dependent Asthmatics, *J. Allerg. Clin. Immunol.* 66: 366-373 (1980). PMID: 7440853
 130. Tognoni G., Latini R., and Jusko WJ, Editors, *Frontiers in Therapeutic Drug Monitoring*, Raven Press, NY (1980).
 131. Szeffler SJ, Rose JQ, Ellis EF, Spector SL, Green AW, and Jusko WJ, The Effect of Troleandomycin on Methylprednisolone Disposition, *J. Allerg. Clin. Immunol.* 66: 447-451 (1980). PMID: 6968763
 132. Jusko WJ, Guidelines for Collection and Pharmacokinetic Analysis of Drug Disposition Data, In: Evans, WE., Schentag J.J, and Jusko WJ, Eds., *Applied Pharmacokinetics*, Appl. Ther. Inc., San Francisco, pp. 639-680 (1980).
 133. Evans WE, Schentag JJ, and Jusko WJ, Eds, *Applied Pharmacokinetics*, Applied Therapeutics Inc., San Francisco (1980).
 134. Rocci ML, Szeffler SJ, Acara M, and Jusko WJ, Prednisolone Metabolism and Excretion in the Isolated Perfused Rat Kidney, *Drug Met. Disp.* 9: 177-182 (1981). PMID: 6113924
 135. DeVane CL, Wolin RE, Rovere RA, Panahon NC, Sutfin TA, and Jusko WJ, Excessive Plasma Concentrations of Tricyclic Antidepressants Resulting from Usual Doses: A Report of Six Cases, *J. Clin. Psych.* 42: 143-147 (1981). PMID: 7204359
 136. Rose JQ, Yurchak AM, and Jusko WJ, Dose-Dependent Pharmacokinetics of Prednisone and Prednisolone in Man, *J. Pharmacokin. Biopharm.* 9: 389-417 (1981). PMID: 7310640
 137. Rose JQ, Nickelsen JA, Ellis EF, Middleton E, Park B, and Jusko WJ, Prednisolone Disposition in Steroid Dependent Asthmatic Children, *J. Allerg. Clin. Immunol.* 67: 188-193 (1981). PMID: 7462536
 138. DeVane CL, Savett M, and Jusko WJ, Desipramine and 2-HydroxyDesipramine Pharmacokinetics in Normal Volunteers, *Eur. J. Clin. Pharmacol.* 19: 61-64 (1981). PMID: 7461025

139. DeVane CL and Jusko WJ, Pharmacokinetics of High Clearance Drugs and Their Metabolites, In: Usdin, E., Dahl SG., Gram L., Linghaerde O., Eds., Clinical Pharmacology in Psychiatry, MacMillan & Co., London, pp. 253-261 (1981).
140. DeVane CL and Jusko WJ, Plasma Concentration Monitoring of Hydroxylated Metabolites of Imipramine and Desipramine, Drug Intell. Clin. Pharm. 15: 263-266 (1981). PMID: 7274042
141. Janicke DM, Mangione A, Schultz R, and Jusko WJ, Mezlocillin Disposition in Chronic Hemodialysis Patients, Antimicrob. Agents Chemother. 20: 590-594 (1981). PMID: 6459760
142. Jusko WJ, Smoking and Drug Response, Pharmacy Int. 2: 10-13 (1981).
143. Rocci ML and Jusko WJ, Analysis of Prednisone, Prednisolone, and Their 20-Beta-Hydroxylated Metabolites by High Performance Liquid Chromatography, J. Chrom. Biomed. Appl. 224: 221-227 (1981).
144. Rocci ML and Jusko WJ, Blood Collection Technique: No Effect on In Vitro Protein Binding of Prednisolone, J. Pharm. Sci. 70: 1160-1161 (1981). PMID: 7299653
145. Rocci ML and Jusko WJ, Dose-Dependent Protein Binding and Disposition of Prednisolone in Rabbits, J. Pharm. Sci. 70: 1201-04 (1981). PMID: 7299663
146. Jusko WJ and Chiang ST, Distribution Volume Related to Body Weight and Protein Binding, J. Pharm. Sci. 71: 469-470 (1982). PMID: 7086663
147. DeVane CL and Jusko WJ, Dosage Regimen Design, Pharmacol. Ther. 17: 143-163 (1982). PMID: 6757976
148. Gardner MJ, Jusko WJ, Effect of Age and Sex on Theophylline Clearances in Young Subjects, Ped Pharmacol. 2: 157-69 (1982). PMID: 12760407
149. Mangione A, Janicke DM, Boudinot FD, Schultz RM, and Jusko WJ, Dose-Dependent Pharmacokinetics of Mezlocillin in Subjects with Normal and Impaired Renal Function, J. Antimicrob. Chemother. 9: Suppl. A, 81-85 (1982). PMID: 6210686
150. Potter WZ, Calil HM, Sutfin TA, Zavadil AP, Jusko WJ, Rapoport J and Goodwin FK, Active Metabolites of Imipramine and Desipramine in Man, Clin. Pharmacol. Ther. 31: 393-401 (1982). PMID: 7060321
151. Rocci ML, D'Ambrosio R, Johnson NF, and Jusko WJ, Prednisolone Binding to Albumin and Transcortin in the Presence of Cortisol, Biochem. Pharmacol. 31: 289-292 (1982). PMID: 7073761
152. Mangione A, Boudinot FD, Schultz RM, and Jusko WJ, Dose-Dependent Pharmacokinetics of Mezlocillin in Relation to Renal Impairment, Antimicrob. Ag. Chemother. 21: 428-435 (1982). PMID: 6213190
153. Meacham RH, Chiang ST, Kick CJ, Sisenwine SF, Jusko WJ, and Ruelius H, Pharmacokinetic Disposition of Guanabenz in the Rhesus Monkey, Drug Metab. Disp. 9: 509-514 (1982). PMID: 6120807
154. Pautler DB and Jusko WJ, Determination of Metoprolol and Alpha-Hydroxymetoprolol in Plasma by High Performance Liquid Chromatography, J. Chrom. Biomed. Appl. 228: 215-222 (1982). PMID: 7076745
155. Jusko WJ and Eaton ML, Factors Affecting Theophylline Disposition, In: Therapy Update, MacLeod SM. and Isles A eds., Astra Pharmaceuticals Canada Ltd., Mississauga, Ontario (1982) pp. 19-29.
156. Tornatore KM., Kanarkowski R, McCarthy TL, Gardner MJ, Yurchak AM, and Jusko WJ, Effect of Chronic Oral Contraceptive Steroids on Theophylline Disposition, Eur. J. Clin. Pharmacol., 23: 129-134 (1982). PMID: 7140802
157. Szeffler SJ, Ellis EF, Brenner M, Rose JQ, Spector SL, Yurchak AM, Andrew F, and Jusko WJ, Steroid-Specific and Anticonvulsant Interaction Aspects of Troleandomycin-Steroid Therapy, J. Allerg. Clin. Immunol., 69: 455-460 (1982). PMID: 6978898
158. Szeffler SJ, Spector SL, Jusko WJ, Brenner M, Fleisher KA, and Ellis EF, Dose and Time-Dependent Effect of Troleandomycin on Methylprednisolone Elimination, Clin. Pharmacol. Ther. 32: 166-171 (1982). PMID: 6980076
159. Christoff PB, Conti DR, Naylor C and Jusko WJ, Procainamide Disposition in Obesity, Drug Intell. Clin. Pharm., 17: 516-522 (1983). PMID: 6191939
160. DeVane CL and Jusko WJ, Drug and Metabolite Concentrations Combined in Prediction of Steady-State Concentrations from Test Doses, Biopharm. Drug Disp., 4: 19-29 (1983). PMID: 6839000
161. Jusko WJ, Smoking Effects in Pharmacokinetics, In: Benet LZ, Gambertoglio JG, Massoud M, Eds., The Pharmacokinetic Basis of Drug Treatment, Raven Press, 311-320 (1982).
162. Rocci ML, Assael BM, Appiani AC, Edefonti A, and Jusko WJ, Effect of Nephrotic Syndrome on

- Absorption and Disposition of Prednisolone in Children, *Int. J. Ped. Nephrol.*, 3: 159-166 (1982). PMID: 7141787
163. Assael BM, Banfi G, Appiani AC, Edefonti A, and Jusko WJ, Disposition of Pulse-Dose Methylprednisolone in Adult and Pediatric Patients with Nephrotic Syndrome, *Eur. J. Clin. Pharmacol.*, 23: 429-433 (1982). PMID: 7151847
 164. Milsap RL, George DE, Szeffler SJ, Murray KA, Lebenthal E, and Jusko WJ, The Effects of Inflammatory Bowel Disease on Absorption and Disposition of Prednisolone, *Dig. Dis. Sci.*, 28: 161-168 (1983). PMID: 6825536
 165. Clarke DF, George D, Milsap RL, Pogonowska-Wala E, Owerbach J, Lebenthal E, and Jusko WJ, Sulfasalazine Metabolite Pharmacokinetics in Pediatric Patients with Inflammatory Bowel Disease: Effects of Disease Activity, Acetylator Phenotype and Age. *Ped. Pharmacol.* 2: 323-333 (1982). PMID: 6152489
 166. Milsap RL and Jusko WJ, Binding of Prednisolone to α_1 -Acid Glycoprotein, *J. Steroid Biochem.*, 18: 191-194 (1983). PMID: 6843123
 167. Boekenooogen SJ, Szeffler SJ, and Jusko WJ, Prednisolone Disposition and Protein Binding in Oral Contraceptive Users, *J. Clin. Endocrin. Met.* 56: 702-709 (1983). PMID: 6833459
 168. Gardner MJ, Tornatore KM, Jusko WJ, and Kanarkowski R, Effects of Tobacco Smoking and Oral Contraceptive Use on Theophylline Disposition, *Brit. J. Clin. Pharmacol.* 16: 271-280 (1983). PMID: 6626419
 169. Rocci ML and Jusko WJ, LAGRAN Program for Area and Moments in Pharmacokinetic Analysis, *Comput. Progr. Biomed.*, 16: 203-216 (1983). PMID: 6688572
 170. Fava GA, Molnar G, Carson SW, Perini GI, Jusko WJ, The Metyrapone Test in Depression, *Neuroendocr Lett* 5: 259-63 (1983).
 171. Gengo FM, Schentag JJ, and Jusko WJ, Pharmacokinetics of Capacity-Limited Tissue Distribution of Methicillin in Rabbits, *J. Pharm. Sci.*, 73: 867-73 (1984). PMID: 6470946
 172. Cuddy Stotter ML, Jusko WJ, Mangione A, Yurchak AM, Gardner MJ, and Paigen B, Theophylline Disposition in Residents Living Near a Chemical Waste Site, *Biopharm. Drug Disp.* 5: 345-355 (1984). PMID: 6525442
 173. Khalafallah N and Jusko WJ, Tissue Distribution of Prednisolone in the Rabbit, *J. Pharmacol. Exp. Ther.* 229: 719-725 (1984). PMID: 6726655
 174. Khalafallah N and Jusko WJ, Determination and Prediction of Tissue Binding of Prednisolone in the Rabbit, *J. Pharm. Sci.*, 73: 362-366 (1984). PMID: 6716244
 175. Sutfin TA, DeVane CL, and Jusko WJ, The Analysis and Disposition of Imipramine and Its Active Metabolites in Man, *Psychopharmacol.*, 82: 310-317 (1984). PMID: 6427820
 176. Boudinot FD and Jusko WJ, Fluid Shifts and Other Factors Affecting Plasma Protein Binding of Prednisolone by Equilibrium Dialysis, *J. Pharm. Sci.*, 73: 774-780 (1984). PMID: 6204037
 177. Gardner MJ and Jusko WJ, Endogenous Factors Affecting Theophylline Clearance, In: JHG Jonkman, JW Jenne, and FER Simons, Eds., *Sustained Release Theophylline*, Excerpta Medica, Elsev. Sci. Publ., Amsterdam, pp. 52-66 (1984).
 178. Green AW, Ebling WF, Gardner MJ, and Jusko WJ, Case Study of Cimetidine - Methylprednisolone - Theophylline Interaction, *Am. J. Med.*, 77: 1115-18 (1984). PMID: 6507464
 179. Ebling WF, Szeffler SJ, and Jusko WJ, Analysis of Cortisol, Methylprednisolone, and Methylprednisolone Hemisuccinate: Absence on Effects of Troleandomycin on Ester Hydrolysis, *J. Chrom., Biomed. Appl.*, 305: 271-280 (1984). PMID: 6368578
 180. Fava GA, Carson SW, Perini GI, Morphy M, Molnar G, and Jusko WJ, The Metyrapone Test in Affective Disorders and Schizophrenia, *J. Affect. Disord.*, 6: 241-247 (1984). PMID: 6235255
 181. Fava GA, Morphy MA, Carson SW, Perini GI, Molnar G, and Jusko WJ, A Modified Metyrapone Test in Depressed Patients and Healthy Subjects, *Neuroendocrinol. Lett.* 6: 81-87 (1984).
 182. Shum L and Jusko WJ, Theophylline Disposition in Obese Rats, *J. Pharmacol. Exp. Ther.*, 228: 380-386 (1984). PMID: 6694116
 183. Carson SW and Jusko WJ, Simultaneous Analysis of Cortisol and Cortisone by High Performance Liquid

- Chromatography, *J. Chromatogr., Biomed. Appl.* 306: 345-350 (1984). PMID: 6715472
184. Gardner MJ, McCarthy TL, and Jusko WJ, Relationship of Serum Thiocyanate Concentrations to Smoking Characteristics, *J. Toxicol. Environ. Health*, 14: 393-406 (1984). PMID: 6502741
 185. Sutfin TA, D'Ambrosio R, and Jusko WJ, Liquid Chromatographic Determination of Eight Tri- and Tetracyclic Antidepressants and Their Active Metabolites, *Clin. Chem.*, 30: 471-474 (1984). PMID: 6697502
 186. Boudinot FD and Jusko WJ. Plasma Protein Binding Interaction of Prednisone and Prednisolone, *J. Steroid Biochem.*, 21: 337-9 (1984). PMID: 6492791
 187. Lui N, Almon RR, and Jusko WJ, Comparison of Filtration and Equilibrium Dialysis Methods for ³H-Imipramine Binding to Human Platelets, *Anal. Biochem.*, 139: 42-57 (1984). PMID: 6331229
 188. Janicke DM, Rubio TT, Wirth FH, Karotkin EH, and Jusko WJ, Developmental Pharmacokinetics of Mezlocillin in Newborn Infants, *J. Ped.* 104: 773-781 (1984). PMID: 6716226
 189. Milsap RL, Plaisance KL, Jusko WJ, Pharmacokinetics of Prednisolone in Obese Men, *Clin. Pharmacol. Ther.* 36: 824-31 (1984). PMID: 6499362
 190. Perini GI, Fava GA, Morphy MA, Carson SW, Molnar G, and Jusko WJ, The Metyrapone Test in Manic Patients and Healthy Subjects, *Pharmacopsychiat.* 17: 94-97 (1984). PMID: 6739539
 191. Janicke DM, Cafarelli RF, Parker SW, Apicella MA, and Jusko WJ, Pharmacokinetics of Aztreonam in Patients with Gram-Negative Infection, *Antimicrob. Ag. Chemother.*, 27: 16-20 (1985). PMID: 4039117
 192. Perini GI, Fava GA, Carson SW, Morphy MA, Molnar G, and Jusko WJ, The Metyrapone Test in Affective Disorders and Schizophrenia II: Changes Upon Treatment, *J. Affect. Disord.*, 7: 265-272 (1984). PMID: 6151957
 193. Ebling WF, Szeffler SJ, and Jusko WJ, Methylprednisolone Disposition in Rabbits: Analysis, Pro-drug Conversion, Reversible Metabolism, and Comparison with Man, *Drug Met. Disp.*, 13: 296-304 (1985). PMID: 2861987
 194. Boudinot FD, Homon CA, Jusko WJ, and Ruelius HW, Protein Binding of Oxazepam and its Glucuronide Conjugates to Human Albumin, *Biochem. Pharmacol.*, 34: 2115-2121 (1985). PMID: 4004929
 195. Morphy MA, Fava GA, Carson SW, Perini GI, Molnar G, and Jusko WJ, The Metyrapone Test in Schizophrenic Patients and Healthy Subjects, *Neuropsychobiol.*, 14: 35-38 (1985). PMID: 4069347
 196. Sutfin TA and Jusko WJ, Compendium of Active Drug Metabolites, In: *Drug Metabolism and Disposition*, MD Rawling and GR Wilkinson, Eds., MTP Press Ltd, Lancaster, UK, pp. 91-159, (1985).
 197. Morse GD, Janicke DM, Cafarell RF, Piontek K, Apicella M., Jusko WJ, and Walshe J, Moxalactam Epimer Disposition in Patients Undergoing Continuous Ambulatory Peritoneal Dialysis, *Clin. Pharmacol. Ther.*, 38: 150-156 (1985). PMID: 4017417
 198. Morse GD, Janicke DM, Cafarell RF, Apicella MA, Jusko WJ, Venuto RC, and Walshe JJ, IP Administration of Moxalactam During CAPD, *Frontiers in Peritoneal Dialysis*, Field, Rich, Assoc., NY, pp. 135-140 (1986).
 199. Ebling WF, Milsap RL, Szeffler SJ, and Jusko WJ, 6 α -Methylprednisolone and 6 α -Methylprednisone Plasma Protein Binding in Humans and Rabbits, *J. Pharm. Sci.*, 75: 760-763 (1986). PMID: 3772747
 200. Janicke DM, Morse GD, Apicella MA, Jusko WJ, and Walshe JJ, Pharmacokinetic Modeling of Bidirectional Transfer During Peritoneal Dialysis, *Clin. Pharmacol. Ther.*, 40: 209-218 (1986). PMID: 3731683
 201. Szeffler SJ, Ebling WF, Georgitis J, and Jusko WJ, Methylprednisolone versus Prednisolone Pharmacokinetics in Relation to Dose in Adults, *Eur. J. Clin. Pharmacol.* 30: 323-329 (1986). PMID: 3732369
 202. Jusko WJ, Guidelines for Collection and Analysis of Pharmacokinetic Data, In: *Applied Pharmacokinetics*, Sec. Ed., WE Evans, JJ Schentag, and WJ Jusko, Eds., Applied Therapeutics Inc., San Francisco, CA, pp. 9-54 (1986).
 203. Evans WE, Schentag JJ, and Jusko WJ, Eds, *Applied Pharmacokinetics*, Sec. Ed., Applied Ther. Inc., SF, CA (1986).
 204. Ebling W and Jusko WJ, The Determination of Essential Clearance, Volume, and Residence Time

- Parameters of Recirculating Metabolic Systems: The Reversible Metabolism of Methylprednisolone and Methylprednisone in Rabbits, *J. Pharmacokin. Biopharm.* 14: 557-599 (1986). PMID: 3820091
205. Gardner MJ and Jusko WJ, Effects of Oral Contraceptives and Tobacco Use on the Metabolic Pathways of Theophylline, *Int. J. Pharmaceut.*, 33 55-64 (1987).
 206. Glynn AM, Slaughter RL, Brass C, D'Ambrosio R, and Jusko WJ, Effects of Ketoconazole on Methylprednisolone Pharmacokinetics and Cortisol Secretion, *Clin. Pharmacol. Ther.* 39: 654-659 (1986). PMID: 3709030
 207. Shum L and Jusko WJ, Pharmacokinetics of Tritiated Water in Normal and Dietary-Induced Obese Rats, *J. Pharmacol. Methods*, 16: 83-89 (1986). PMID: 3747548
 208. Jusko WJ, The Role of the Pharmacist in Clinical Research, In: DD Breimer and P Speiser, eds, *Topics in Pharmaceutical Sciences*, Elsevier Sci. Publ., Amsterdam, pp. 417-430 (1985).
 209. Shum L and Jusko WJ, Reversed-Phase High-Performance Liquid Chromatographic Determination of Verophylline in Rat Serum, *J. Chromatogr. Biomed. Appl.* 382: 207-213 (1986). PMID: 3782387
 210. Jungbluth GL, Cooper DL, Doyle GD, Chudzik GM, and Jusko WJ, Pharmacokinetics of Ticarcillin and Clavulanic Acid (Timentin) in Relation to Renal Function, *Antimicrob. Ag. Chemother.*, 30:896-900 (1986). PMID: 3492959
 211. Boudinot FD and Jusko WJ, Dose-Dependent Pharmacokinetics of Prednisolone in Normal and Adrenalectomized Rats, *J. Pharmacokin. Biopharm.*, 14: 453-467 (1986). PMID: 3806371
 212. Boudinot FD, D'Ambrosio R, and Jusko WJ, Receptor-Mediated Pharmacodynamics of Prednisolone in the Rat, *J. Pharmacokin. Biopharm.*, 14: 469-493 (1986). PMID: 2879901
 213. Chow AT and Jusko WJ, Application of Moment Analysis to Nonlinear Drug Disposition Described by the Michaelis-Menten Equation, *Pharmaceut. Res.*, 4: 59-61 (1987). PMID: 3508531
 214. Shum L and Jusko WJ, Theophylline Tissue Partitioning and Volume of Distribution in Normal and Dietary-Induced Obese Rats, *Biopharm. Drug Disp.* 8: 353-364 (1987). PMID: 3620594
 215. Ebling WF, Rich SA, Szeffler SJ, and Jusko WJ, Troleandomycin Effects on Methylprednisolone and Methylprednisone Interconversion and Disposition in the Rabbit, *Eur. J. Drug Met. Pharmacokin.*, 12: 49-57 (1987). PMID: 3497038
 216. Gardner MJ, Schatz M, Cousins L, Zeigler R., Middleton E., and Jusko WJ, Longitudinal Effects of Pregnancy on the Pharmacokinetics of Theophylline, *Europ. J. Clin. Pharmacol.*, 32: 289-295 (1987). PMID: 3595701
 217. Kandrotas RJ, Slaughter RL, Brass C, and Jusko WJ, Ketoconazole Effects on Methylprednisolone Disposition and Their Joint Suppression of Endogenous Cortisol, *Clin. Pharmacol. Ther.*, 42: 465-470 (1987). PMID: 3311551
 218. Sutfin TA, Perini GI, Molnar G, and Jusko WJ, Multiple-Dose Pharmacokinetics of Imipramine and Its Major Active and Conjugated Metabolites in Depressed Patients, *J. Clin. Psychopharm.*, 8: 48-53 (1988). PMID: 3350999
 219. Haughey DB and Jusko WJ, Theophylline Disposition in Foundry Workers Exposed to Coke Oven Effluent, *Biopharm. Drug Disp.*, 9: 405-409 (1988). PMID: 3207860
 220. Kanarkowski R, Tornatore DM, D'Ambrosio R, Gardner MJ, and Jusko WJ, Pharmacokinetics of Single and Multiple Doses of Ethinylestradiol and Levonorgestrel in Relation to Smoking, *Clin. Pharmacol. Ther.*, 43: 23-31 (1988). PMID: 3121231
 221. Jungbluth GL, Wirth FH, Rubio TT, Janicke DM, and Jusko WJ, Developmental Pharmacokinetics of Mezlocillin in 4 Newborn Infants, *Dev. Pharmacol. Ther.* 11: 317-321 (1988). PMID: 3229277
 222. Cheng H and Jusko WJ, Mean Residence Time Concepts for Pharmacokinetic Systems with Nonlinear Drug Elimination Described by the Michaelis-Menten Equation, *Pharm. Res.* 5: 156-164 (1988). PMID: 3244627
 223. Kong A-N and Jusko WJ, Definitions and Applications of Mean Transit and Residence Times in Reference to the Two-Compartment Mammillary Plasma Clearance Model, *J. Pharm. Sci.* 77: 157-165 (1988). PMID: 3361431
 224. Matsumoto RM, Jusko WJ, and Corcoran GB, Cytochrome P450 and In Vitro Drug Metabolism in an Overfed Rat Model of Obesity, *Drug Nutr. Int.* 5: 237-247 (1988). PMID: 3149237

225. Green C, Kraus C, Lemonske R, Farrell P, and Jusko WJ, Rapid Methylprednisolone Clearance in a Patient with Cystic Fibrosis, *Drug Intell. Clin. Pharm.* 22: 876-878 (1988). PMID: 3234253
226. Janicke DM, Parker SW, Cafarell RF, Apicella MA, and Jusko WJ, Pharmacokinetics of Two Multiple-Dose Mezlocillin Regimens, *Antimicrob. Agents Chemother.* 32: 777-779 (1988). PMID: 3395106
227. Haughey DB and Jusko WJ, Analysis of Methylprednisolone, Methylprednisone and Corticosterone for Assessment of Methylprednisolone Disposition in the Rat, *J. Chromatogr. Biomed. Appl.* 430: 241-248 (1988). PMID: 3235500
228. Kong AN, Slaughter RL, and Jusko WJ, Simultaneous Analysis of Methylprednisolone Hemisuccinate, Cortisol, and Methylprednisolone by Normal-Phase High-Performance Liquid Chromatography in Human Plasma, *J. Chromatogr. Biomed. Appl.* 430: 308-314 (1988). PMID: 3065346
229. Cheng H and Jusko WJ, An Area Function Method for Calculating the Apparent Elimination Rate Constant of a Metabolite, *J. Pharmacokin. Bioph.* 17: 125-130 (1989). PMID: 2715930
230. Cheng H and Jusko WJ, The Area Function Method for Assessing the Drug Absorption Rate in Linear Systems with Zero-Order Input, *Pharm. Res.* 6: 133-139 (1989). PMID: 2762213
231. Cheng H and Jusko WJ, Application of Mean Residence Time Concepts to Pharmacokinetic Systems with Noninstantaneous Input and Nonlinear Elimination, *Pharm. Res.* 6: 4-12 (1989). PMID: 2717515
232. Cheng H and Jusko WJ, Mean Residence Time of Drugs Showing Simultaneous First-Order and Michaelis-Menten Kinetics, *Pharmaceu. Res.* 6: 258-261 (1989). PMID: 2726685
233. Jungbluth GL and Jusko WJ, Dose-Dependent Pharmacokinetics of Mezlocillin in Rats, *Antimicrob. Ag. Chemother.* 33: 839-843 (1989). PMID: 2764534
234. Jungbluth GL, Pasko MT, Beam TR, and Jusko WJ, Ceftriaxone Disposition in Open Heart Surgery Patients, *Antimicrob. Ag. Chemother.* 33: 850-856 (1989). PMID: 2764536
235. Jungbluth GL, Janicke DM, and Jusko WJ, Reversed-Phase High-Performance Liquid Chromatographic Assay for Determination of Mezlocillin in Human and Rat Biological Samples, *J. Chromatogr.* 494: 376-380 (1989). PMID: 2584336
236. Jungbluth GL and Jusko WJ, Ion-Paired Reversed-Phase High-Performance Liquid Chromatography Assay for Determination of Ceftriaxone in Human Plasma and Urine, *J. Pharm.Sci.* 78: 968-970 (1989). PMID: 2621584
237. Giacoia GP, Jungbluth GL, and Jusko WJ, Effect of Formula Feeding on Oral Absorption of Caffeine in Premature Infants, *Dev. Pharmacol. Ther.* 12: 205-210 (1989). PMID: 2766923
238. Shum L and Jusko WJ, Effects of Obesity and Ancillary Variables (Dialysis Time and Drug, Albumin, and Fatty Acid Concentrations) on Theophylline Serum Protein Binding, *Biopharm. Drug Disp.*, 10: 549-562 (1989). PMID: 2611356
239. Kong A-N, Ludwig EA, Slaughter RL, DiStefano PM, DeMasi J, Middleton E, and Jusko WJ, Pharmacokinetics and Pharmacodynamic Modeling of Direct Suppression Effects of Methylprednisolone on Serum Cortisol and Blood Histamine in Human Subjects. *Clin. Pharmacol. Ther.* 46: 616-628 (1989). PMID: 2689044
240. Jungbluth GL, Pasko MT, and Jusko WJ, Factors Affecting Ceftriaxone Plasma Protein Binding During Open Heart Surgery, *J. Pharm. Sci.* 78: 807-811 (1989). PMID: 2600784
241. Nichols AI, Boudinot FD, and Jusko WJ, Second Generation Model for Prednisolone Pharmacodynamics in the Rat, *J. Pharmacokin. Biopharm.*, 17: 209-227 (1989). PMID: 2571711
242. Nichols AI, D'Ambrosio R, Pyszczynski NA, and Jusko WJ, Pharmacokinetics and Pharmacodynamics of Prednisolone in Obese Rats, *J. Pharmacol. Exp. Ther.* 250: 963-970 (1989). PMID: 2778721
243. Cheng H and Jusko WJ, Relationships Between Steady-State and Single-Dose Plasma Drug Concentrations for Pharmacokinetic Systems with Nonlinear Elimination, *Biopharm. Drug Disp.* 10: 513-528 (1989). PMID: 2804255
244. Ludwig EA, Slaughter RL, Savliwala M, Brass C, and Jusko WJ, Steroid-Specific Effects of Ketoconazole on Corticosteroid Disposition: Unaltered Prednisolone Elimination, *DICP: The Annals of Pharmacotherapy*, 23: 858-861 (1989). PMID: 2596127
245. Jusko WJ, Pharmacokinetics of Capacity-Limited Pharmacokinetic Systems, *J. Clin. Pharmacol*, 29: 488-

- 493 (1989). PMID: 2666450
246. Tornatore KM, Morse GD, Jusko WJ, and Walshe JJ, Methylprednisolone Disposition in Renal Transplant Recipients Receiving Triple Drug Suppression, *Transplantation*, 48: 962-965 (1989). PMID: 2595785
247. Cheng H and Jusko WJ, Effects of Variation in Drug Elimination on Five Methods for Assessing Zero-Order Drug Absorption Rates, *Pharmaceut. Res.* 7: 76-79 (1990). PMID: 2300540
248. Cheng H and Jusko WJ, Mean Residence Times of Multi-Compartmental Drugs Undergoing Reversible Metabolism, *Pharmaceut. Res.*, 7: 103-107 (1990). PMID: 2300529
249. Kong A-N, Jungbluth GL, Pasko MT, Beam TR, and Jusko WJ, Pharmacokinetics of Methylprednisolone Sodium Succinate and Methylprednisolone in Patients Undergoing Cardiopulmonary Bypass. *Pharmacother.*, 10: 29-34 (1990). PMID: 2179900
250. Jusko WJ, Corticosteroid Pharmacodynamics: Models for a Broad Array of Receptor-Mediated Pharmacologic Effects, *J. Clin. Pharmacol.*, 30: 303-310 (1990). PMID: 1971281
251. Nichols AI and Jusko WJ, Receptor Mediated Prednisolone Pharmacodynamics in Rats: Model Verification Using a Dose-Sparing Regimen, *J. Pharmacokin. Bioph.*, 18: 189-208 (1990). PMID: 1974305
252. Murata R, Haughey DB, and Jusko WJ, Effects of Thyroid Dysfunction on Prednisolone and Prednisone Interconversion and Disposition in the Rat, *Drug. Met. Dispos.*, 18: 403-408 (1990). PMID: 1976060
253. Reiss WG, Slaughter RL, Ludwig EA, Middleton E, and Jusko WJ, Steroid Dose-Sparing: Pharmacodynamic Responses to Single Versus Divided Doses of Methylprednisolone in Man, *J. Allergy Clin. Immunol.*, 85: 1058-1066 (1990). PMID: 2191992
254. Cheng H and Jusko WJ, Constant-Rate Intravenous Infusion Methods for Estimating Steady-State Volumes of Distribution and Mean Residence Times in the Body for Drugs Undergoing Reversible Metabolism, *Pharm. Res.*, 7: 628-632 (1990). PMID: 2367330
255. Huang M-L and Jusko WJ, Nonlinear Pharmacokinetics and Interconversion of Prednisolone and Prednisone in Rats, *J. Pharmacokin. Biopharm.*, 18: 401-421 (1990). PMID: 2266496
256. Cheng H and Jusko WJ, Mean Interconversion Times and Distribution Rate Parameters for Drugs Undergoing Reversible Metabolism, *Pharm. Res.*, 7: 1003-1010 (1990). PMID: 2281028
257. Chow AT and Jusko WJ, Michaelis-Menten Metabolite Formation Kinetics: Equations Relating Area Under the Curve and Metabolite Recovery to the Administered Dose, *J. Pharm. Sci.*, 79: 902-906 (1990). PMID: 2280360
258. Cheng H and Jusko WJ, Drug Redistribution and Mean Transit Time Concepts For Nonlinear Pharmacokinetic Systems, *Biopharm. Drug Disp.* 12: 73-79 (1991). PMID: 2039813
259. Cheng H and Jusko WJ, Noncompartmental Determination of the Mean Residence Time and Steady-State Volume of Distribution During Multiple Dosing, *J. Pharm. Sci.*, 80: 202-204 (1991). PMID: 2051333
260. Cheng H and Jusko WJ, Mean Residence Times and Distribution Volumes for Drugs Undergoing Linear Reversible Metabolism and Tissue Distribution and Linear or Nonlinear Elimination from the Central Compartments, *Pharm. Res.*, 8:508-511 (1991). PMID: 1871048
261. Cheng H, Jusko WJ, and Gillespie WR, Relationships Between the Area Under the First Moment Curve After Single Bolus Injection and the Integral of Plasma Concentrations After Constant-Rate Intravenous Infusion, *J. Pharm. Sci.*, 80: 507-510 (1991). PMID: 1880736
262. Kong A-N and Jusko WJ, Disposition of Methylprednisolone and Its Sodium Succinate Prodrug In Vivo and In Perfused Liver of Rats: Nonlinear and Sequential First-Pass Elimination, *J. Pharm. Sci.*, 80: 409-415 (1991). PMID: 1880717
263. Veng-Pedersen P, Cheng H and Jusko WJ, Regarding Dose Independent Pharmacokinetic Parameters in Nonlinear Pharmacokinetics, *J. Pharm. Sci.*, 80: 608-612 (1991). PMID: 1941554
264. Yamashita SK, Ludwig EA, Middleton E Jr. E and Jusko WJ, Lack of Pharmacokinetic and Pharmacodynamic Interactions Between Ketoconazole and Prednisolone, *Clin. Pharmacol. Ther.* 49: 558-570 (1991). PMID: 1827622
265. Cheng H and Jusko WJ, Mean Residence Time of Drugs in Pharmacokinetic Systems with Linear Distribution, Linear or Nonlinear Elimination and Noninstantaneous Input, *J. Pharm. Sci.* 80:1005-1006 (1991). PMID: 1783996

266. Dunn TE, Ludwig EA, Slaughter RL, Camara DS, and Jusko WJ, Pharmacokinetics and Pharmacodynamics of Methylprednisolone in Obesity, *Clin. Pharmacol. Ther.* 50: 536-549 (1991). PMID: 1827621
267. Cheng H and Jusko WJ, Pharmacokinetics of Linear Reversible Metabolic Systems, In: *Advanced Methods of Pharmacokinetic and Pharmacodynamic Systems Analysis*, D.D'Argenio, Ed., Plenum Press, NY, p 13-20 (1991).
268. Jusko WJ, Pharmacokinetics/Dynamics of Corticosteroids, In: *Advanced Methods of Pharmacokinetic and Pharmacodynamic Systems Analysis*, D. D'Argenio, Ed., Plenum Press, New York, pp. 61-68 (1991).
269. Garg V and Jusko WJ, Simultaneous Analysis of Prednisone, Prednisolone, and Their Major Hydroxylated Metabolites in Urine by High-Performance Liquid Chromatography, *J. Chrom. Biomed. Appl.*, 567: 39-47 (1991). PMID: 1918259
270. Shum L and Jusko WJ, Verophylline Pharmacokinetics in Normal and Dietary-Induced Obese Rats: Role of Fat Mass and Protein Binding in Determining Volume of Distribution, *Xenobiotica*, 21: 1419-1430 (1991). PMID: 1763516
271. Haughey DB and Jusko WJ, Effect of Ketoconazole on Methylprednisolone Pharmacokinetics and Receptor/Gene-Mediated Pharmacodynamics, *J. Pharmacol. Exper. Ther.*, 259: 826-832 (1991). PMID: 1941630
272. Jusko WJ, D'Ambrosio R, Monitoring FK506 Concentrations in Plasma and Whole Blood, *Transplant Proc* 23:2732-2735 (1991). PMID: 1721260
273. Wald JA, Salazar DE, Cheng H and Jusko WJ, Two-Compartment Basophil Cell Trafficking Model for Methylprednisolone Pharmacodynamics, *J. Pharmacokin. Biopharm.* 19: 521-536 (1991). PMID: 1783990
274. Jusko WJ, Kung L-P, and Schmelter RD, Immunopharmacokinetics of ¹¹¹In-CYT-103 in Ovarian Cancer Patients, In: *Diagnosis of Colorectal and Ovarian Carcinoma: Application of Immunoscintigraphic Technology*, Eds. R.T. Maguire and D. Van Nostrand, Marcel Dekker Inc., New York, 177-190 (1992). Also: *Targeted Diagn. & Ther.* 6: 177-190 (1990). PMID: 1576345
275. Garg V, Blum R, Wilner KD, and Jusko WJ, Effect of the Anti-Inflammatory Agent Tenidap on the Pharmacokinetics and Pharmacodynamics of Prednisolone, *J. Clin. Pharmacol.* 32: 222-230 (1992). PMID: 1564126
276. Haughey DB and Jusko WJ, Bioavailability and Nonlinear Disposition of Methylprednisolone/Methylprednisone in the Rat, *J. Pharm. Sci.* 80: 117-121 (1992). PMID: 1545348
277. Wald JA and Jusko WJ, Corticosteroid Pharmacodynamic Modeling: Osteocalcin Suppression by Prednisolone, *Pharm. Res.*, 9: 1096-1098 (1992). PMID: 1409384
278. Jusko WJ and Ludwig EA, Corticosteroids, Chap. 27 in "Applied Pharmacokinetics: Principles of Therapeutic Drug Monitoring", Third Ed, WE Evans, JJ Schentag, WJ Jusko, Eds., Appl Ther. Inc., Vancouver, WA, pp. 27-1 to 34 (1992).
279. Evans WE, Schentag JJ, and Jusko WJ, Editors: *Applied Pharmacokinetics: Principles of Therapeutic Drug Monitoring*, Third Edition, Applied Therapeutics Inc., Vancouver WA (1992) & Jusko WJ, *Guidelines for Collection and Analysis of Pharmacokinetic Data*, Chapter 2, pp: 1-43 (1992).
280. Fisher LE, Ludwig EA, Wald JA, Sloan RR, Middleton E, and Jusko WJ, Pharmacokinetics and Pharmacodynamics of Methylprednisolone When Administered at 8 AM versus 4 PM, *Clin. Pharmacol. Ther.*, 51: 677-688 (1992). PMID: 1535301
281. Dove AM, Szeffler SJ, Hill MR, Jusko WJ, Larsen GL and Accurso FJ, Altered Prednisolone Pharmacokinetics in Patients with Cystic Fibrosis, *J. Pediatrics*, 120: 789-794 (1992). PMID: 1578318
282. Klammer KJ, Maloney K, Rudolph RL, Sisenwine SF, Jusko WJ, and Chiang ST, Introduction of a Composite Parameter to the Pharmacokinetics of Venlafaxine and Its Active O-Desmethyl Metabolite, *J. Clin. Pharmacol.*, 32: 716-724 (1992). PMID: 1487561
283. Haughey DB and Jusko WJ, Receptor-Mediated Methylprednisolone Pharmacodynamics in Rats: Steroid-Induced Receptor Down-Regulation, *J. Pharmacokin. Biopharm.* 20: 333-355 (1992). PMID: 1362219
284. Fisher LE, Ludwig EA, and Jusko WJ, Pharmacokinetics of Methylprednisolone: Trafficking of Helper T Lymphocytes, *J. Pharmacokin. Biopharm.* 20: 319-331 (1992). PMID: 1479558
285. Cheng H and Jusko WJ, Mean Residence Time of Oral Drugs Undergoing First-Pass and Linear Reversible

- Metabolism, *Pharmaceut. Res.*, 10: 8-13 (1993). PMID: 8430064
286. Jusko WJ, Conceptualization of Drug Distribution to a Hypothetical Pharmacodynamic Effect Compartment, *Clin. Pharmacol. Ther.* 54: 112-113 (1993). PMID: 8330459
287. Ludwig EA, Kong A-N, Camara DS, and Jusko WJ, Pharmacokinetics of Methylprednisolone Hemisuccinate and Methylprednisolone in Chronic Liver Disease, *J. Clin. Pharmacol.* 33: 805-810 (1993). PMID: 8227476
288. Piekoszewski W and Jusko WJ, Plasma Protein Binding of Tacrolimus (FK506) in Man, *J. Pharm. Sci.*, 82: 340-341 (1993). PMID: 7680714
289. Chow AT, Meek PD, and Jusko WJ, High-Pressure Liquid Chromatographic Assay of Theophylline in Dog Feces Following Oral Administration of Sustained-Release Products, *J. Pharm. Sci.*, 82: 956-958 (1993). PMID: 8229696
290. Wald JA, Law RM, Ludwig EA, Sloan RR, Middleton E Jr., Jusko WJ, Evaluation of Dose-Related Pharmacokinetics and Pharmacodynamics of Prednisolone in Man, *J. Pharmacokin. Biopharm.*, 20: 567-589 (1993). PMID: 1302763
291. Dubois DC, Almon RR, and Jusko WJ, Molar Quantification of Specific Messenger Ribonucleic Acid Expression in Northern Hybridization Using cRNA Standards, *Analyt. Biochem.* 210: 140-144 (1993). PMID: 7683846
292. Piekoszewski W, Chow FS, and Jusko WJ, Disposition of Tacrolimus (FK506) in Rabbits: Role of Red Cell Binding in Hepatic Clearance, *Drug Met. Dispos.*, 21: 690-698 (1993). PMID: 7690698
293. Jusko WJ and Milsap RL, Pharmacokinetic Principles of Drug Distribution in Saliva, *Ann NY Acad Sci*, 694: 36-47 (1993). PMID: 8215084
294. Mishina EV, Straubinger RM, Pyszczynski NA, and Jusko WJ, Enhancement of Tissue Delivery and Receptor Occupancy of Methylprednisolone in Rats by a Liposomal Formulation, *Pharm. Res.*, 10: 1402-1410 (1993). PMID: 8272400
295. Lew KH, Ludwig EA, Milad MA, Donovan K, Middleton E, Ferry JJ, and Jusko WJ, Gender-Based Effects on Methylprednisolone Pharmacokinetics and Pharmacodynamics, *Clin. Pharmacol. Ther.* 54: 402-414 (1993). PMID: 8222483
296. Pleyer U, Lutz S, Jusko WJ, Nguyen K, Narawane M, Rückert D, Mondino BJ, and Lee VHL, Ocular Absorption of Topically Applied FK506 from Liposomal and Oil Formulations in the Rabbit Eye, *Invest. Ophth Vis. Sci.*, 34: 2737-42 (1993). PMID: 7688360
297. Milad MA and Jusko WJ, Pharmacodynamic Interpretation of Adrenocorticotropin Stimulation Tests, *Annals Pharmacother.* 27: 1195-1197 (1993). PMID: 8251686
298. Cheng H and Jusko WJ, Pharmacokinetics of Reversible Metabolic Systems, *Biopharm. Drug Disp.*, 14: 721-766 (1993). PMID: 8298069
299. Dayneka N, Garg V, and Jusko WJ, Comparison of Four Basic Models of Indirect Pharmacodynamic Responses, *J. Pharmacokin. Biopharm.*, 21: 457-478 (1993). PMID: 8133465
300. D'Ambrosio R, Girzaitis N, and Jusko WJ, Validation and Quality Assurance Program for Monitoring Tacrolimus (FK 506) Concentrations in Plasma and Whole Blood, *Ther. Drug Monitor.*, 15: 414-426 (1993). PMID: 7504339
301. Lew KH and Jusko WJ, Pharmacodynamic Modeling of Cortisol Suppression from Fluocortolone, *Europ. J. Clin. Pharmacol.*, 45: 581-583 (1993). PMID: 8157047
302. D'Ambrosio R, Stabler T, Kobayashi M, and Jusko WJ, Improved Procedures for Enzyme Immunoassay of Tacrolimus (FK 506) in Whole Blood, *Clin. Chemistry*, 40: 159-160 (1994). PMID: 7507007
303. Garg V and Jusko WJ, Pharmacodynamic Modeling of NSAIDs: Antipyretic Effect of Ibuprofen, *Clin. Pharmacol. Ther.*, 55: 87-88 (1994). PMID: 8299322
304. Cheng H, Gong Y, and Jusko WJ, A Computer Program for Calculating Distribution Parameters for Drugs Behaving Nonlinearly Based on Disposition Decomposition Analysis, *J. Pharm. Sci.*, 83: 110-112 (1994). PMID: 8138898
305. Ermer JC, Hicks DR, Wheeler SC, Kraml M, and Jusko WJ, Concomitant Etodolac Affects Neither the Unbound Clearance Nor the Pharmacologic Effect of Warfarin, *Clin. Pharmacol. Ther.*, 55: 305-316 (1994).

PMID: 8143396

306. Garg V and Jusko WJ, Bioavailability and Reversible Metabolism of Prednisone and Prednisolone in Man, *Biopharm. Drug Dispos.*, 15: 163-172 (1994). PMID: 8011967
307. Garg V and Jusko WJ, Effect of Indomethacin on the Pharmacokinetics and Pharmacodynamics of Prednisolone in Rats, *J. Pharm. Sci.*, 83: 747-750 (1994). PMID: 7915309
308. Mishina EV and Jusko WJ, Inhibition of Rat Splenocyte Proliferation with Methylprednisolone: In Vivo Effect of Liposomal Formulation, *Pharm. Res.*, 11: 848-854 (1994). PMID: 7937524
309. Garg V, Hon YY, and Jusko WJ, Effects of Acute and Chronic Inflammation on the Pharmacokinetics of Prednisolone in Rats, *Pharm. Res.*, 11: 541-544 (1994). PMID: 8058612
310. Troy SM, Hicks DR, Parker VD, Jusko WJ, Rofsky HE, and Porter RJ, Differences in Pharmacokinetics and Comparative Bioavailability Between Premarin and Estratab in Healthy Postmenopausal Women, *Curr. Ther. Res.*, 55: 359-372 (1994).
311. Piekoszewski W, Chow FS, and Jusko WJ, Pharmacokinetic and Pharmacodynamic Effects of Coadministration of Methylprednisolone and Tacrolimus in Rabbits, *J. Pharmacol. Exper. Ther.*, 269: 103-109 (1994). PMID: 7513355
312. D'Ambrosio R, Girzaitis N, and Jusko WJ, Multicenter Comparison of Tacrolimus (FK 506) Whole Blood Concentrations as Measured by the Abbott IM_x Analyzer and Enzyme Immunoassay with Methylene Chloride Extraction, *Ther. Drug Monitor.*, 16: 287-292 (1994). PMID: 7521979
313. Milad MA, Ludwig EA, Lew KH, Kohli RK, and Jusko WJ, The Pharmacokinetics and Pharmacodynamics of Methylprednisolone in Chronic Renal Failure, *Am. J. Ther.*, 1:49-57 (1994). PMID: 11835067
314. Mishina EV and Jusko WJ, Selected Tissue Distribution of Liposomal Methylprednisolone in Rats, *Res. Commun. Chem. Path. Pharmacol.*, 84: 47-52 (1994). PMID: 8042008
315. Cheng H, Yu C, and Jusko WJ, An Algorithm and Computer Program for Calculating the Mean Transit Time and Distribution Rate Parameters of Generated Metabolites Undergoing Linear Tissue Distribution and Linear or Non-linear Central Elimination, *Biopharm. Drug Disp.* 15: 273-294 (1994). PMID: 8068866
316. Jusko WJ, Receptor-Mediated Pharmacodynamics of Corticosteroids, In: "Receptor-Mediated Biological Processes: Implications for Evaluating Carcinogenesis", HL Spitzer, TJ Slaga, WF Greenlee, M McClain, ed, Wiley-Liss, NY, pp. 261-270 (1994). PMID: 7972251
317. Jusko WJ and Ko HC, Physiologic Indirect Response Models Characterize Diverse Types of Pharmacodynamic Effects, *Clin. Pharmacol. Ther.*, 56: 406-419 (1994). PMID: 7955802
318. Wald JA and Jusko WJ, Prednisolone Pharmacodynamics: Leukocyte Trafficking in the Rat, *Life Sci.*, 55: PL371-378 (1994). PMID: 7968208
319. Jusko WJ, Pyszczynski NA, Bushway MS, D'Ambrosio R, and Mis SM, Fifteen Years of Operation of a High-Performance Liquid Chromatographic Assay for Prednisolone, Cortisol and Prednisone in Plasma, *J. Chrom. Biomed. Appl.*, 658: 47-54 (1994). PMID: 7952131
320. Piekoszewski W, Chow FS, and Jusko WJ, Inhibition of Phytohaemagglutinin-Induced Lymphocyte Proliferation by Immunosuppressive Drugs: Use of Whole Blood Culture, *Immunopharmacol. Immunotoxicol.*, 16: 389-401 (1994). PMID: 7798592
321. Binder J, Mishina EV, Jusko WJ, and Kupiec-Weglinski JW, Prolongation of Cardiac Allograft Survival in Rats by Liposome-Encapsulated Methylprednisolone, *Transplantation*, 58: 633-635 (1994). PMID: 8091492
322. The U.S. Multicenter FK506 Liver Study Group, Comparison of Tacrolimus (FK506) and Cyclosporine for Immunosuppression in Liver Transplantation, *New Engl. J. Med.*, 331: 1110-1115 (1994). PMID: 7523946
323. Cheng H, Gillespie WR, and Jusko WJ, Mean Residence Time Concepts for Nonlinear Pharmacokinetic Systems, *Biopharm. Drug Disp.*, 15: 627-641 (1994). PMID: 7888595
324. Mishina EV, Binder J, Kupiec-Weglinski JW, and Jusko WJ, Effect of Liposomal Methylprednisolone on Heart Allograft Survival and Immune Function in Rats, *J. Pharmacol. Exp. Ther.*, 271: 868-874 (1994). PMID: 7965807
325. Milsap RL and Jusko WJ, Pharmacokinetics in the Infant, *Environ. Health Persp.*, 102 [Suppl. 11]: 107-110 (1994). PMID: 7737034

326. Jusko WJ, Milad MA, Ludwig EA, Lew KH, and Kohli RK, Methylprednisolone Pharmacokinetics and Pharmacodynamics in Chronic Renal Failure, *Clinical Nephrol.*, 43: S16-S19 (1995). PMID: 7781199
327. Jusko WJ, Piekoszewski W, Klintmalm GB, Schaeffer M, Hebert MF, Piergies AA, Lee C, Schechter P, and Mekki QA, Pharmacokinetics of Tacrolimus (FK506) in Liver Transplant Patients, *Clin. Pharmacol. Ther.*, 57: 281-290 (1995). PMID: 7535213
328. Xu Z-X, Lee M-J, Blum RA, and Jusko WJ, Pharmacodynamic Modeling of Prednisolone Effects on Natural Killer Cell Trafficking, *Pharm. Res.*, 12: 459-463 (1995). PMID: 7617538
329. Fasanmade AA and Jusko WJ, An Improved Pharmacodynamic Model for Formation of Methemoglobin by Antimalarial Drugs, *Drug Met. Disp.*, 23: 573-576 (1995). PMID: 7587933
330. Abouljoud MS, Levy MF, Klintmalm GB, and The US Multicenter Study Group, Hyperlipidemia After Liver Transplantation: Long-Term Results of the FK506/Cyclosporine: A US Multicenter Trial, *Transplant. Proc.*, 27: 1121-1123 (1995). PMID: 7533360
331. Ko HC, Jusko WJ, Pharmacodynamic Modeling of Finasteride, a 5α -Reductase Inhibitor, *Pharmacother.*, 15: 509-511 (1995). PMID: 7479205
332. Lee MJ, Straubinger RM, and Jusko WJ, Physicochemical, Pharmacokinetic and Pharmacodynamic Evaluation of Liposomal Tacrolimus (FK 506) in Rats, *Pharm. Res.*, 12: 1055-1059 (1995). PMID: 7494802
333. Ko HC, Almon RR, and Jusko WJ, Effect of Corticosteroid Binding Globulin on the Pharmacokinetics of Prednisolone in Rats, *Pharm. Res.*, 12: 902-904 (1995). PMID: 7667198
334. Lee M-L, Pyszczynski N, and Jusko WJ, Combined Inhibition Effects of Tacrolimus and Methylprednisolone on In Vitro Human Lymphocyte Proliferation, *Immunopharmacol. Immunotoxicol.* 17: 335-345 (1995). PMID: 7544367
335. Fasanmade AA and Jusko WJ, Effect of Halofantrine and its Desbutyl Metabolite on Lymphocyte Proliferation Dynamics, *Life Sci. Pharmacol. Letters*, 57: 175-180 (1995). PMID: 7564875
336. Szeffler SJ, Bender BG, Jusko WJ, Lanier BQ, Lemanske RF, Skoner DP, and Stempel DA, Evolving Role of Theophylline in Treatment of Chronic Childhood Asthma, *J. Peds.* 127: 176-185 (1995). PMID: 7636640
337. Milad MA, Ludwig EA, Ane S, Middleton E, and Jusko WJ, Pharmacodynamic Model for Joint Exogenous and Endogenous Corticosteroid Suppression of Lymphocyte Trafficking, *J. Pharmacokin. Biopharm.*, 22: 469-480 (1994). PMID: 7473077
338. Fasanmade, AA, Jusko WJ, Optimizing Whole Blood Lymphocyte Proliferation in the Rat, *J. Immun. Meth.*, 184: 163-167 (1995). PMID: 7658020
339. DuBois DC, Xu Z-X, McKay L, Almon RR, Pyszczynski N, and Jusko WJ, Differential Dynamics of Receptor Down-Regulation and Tyrosine Aminotransferase Induction Following Glucocorticoid Treatment, *J. Steroid Biochem. Mol. Biol.*, 54: 237-243 (1995). PMID: 7577705
340. Jusko WJ, Ko HC, and Ebling WF, Convergence of Indirect and Direct Pharmacodynamic Response Models, *J. Pharmacokin. Biopharm.*, 23: 5-8 (1995). PMID: 8576844
341. Xu Z-X, Sun Y-N, Dubois DC, Almon RR, Jusko WJ, Third-Generation Model for Corticosteroid Pharmacodynamics: Roles of Glucocorticoid Receptor mRNA and Tyrosine Aminotransferase mRNA in Rat Liver, *J. Pharmacokin Biopharm* 23: 163-181 (1995). PMID: 8719235
342. Van Griensven, JMTh, Jusko WJ, Lemkes HHPJ, Kroon R, Chiang ST, and AF Cohen, Tolrestat Pharmacokinetic and Pharmacodynamic Effects on Red Blood Cell Sorbitol Levels in Normal Volunteers and in Patients with Insulin-Dependent Diabetes, *Clin. Pharmacol. Ther.*, 58: 631-640 (1995). PMID: 8529328
343. Nash RA, Etzioni R, Storb R, Furlong T, Gooley T, Anasetti C, Appelbaum FR, Doney K, Martin P, Slattery J, Sullivan K, van der Jagt R, Witherspoon R, Jusko WJ, Zager RA, and Deeg MJ, Tacrolimus (FK506) Alone or in Combination with Methotrexate or Methylprednisolone for the Prevention of Acute Graft-Versus-Host Disease After Marrow Transplantation from HLA-Matched Siblings: A Single-Center Study, *Blood*, 85: 3746-3753 (1995). PMID: 7540071
344. Jusko WJ, Analysis of Tacrolimus (FK506) in Relation to Therapeutic Drug Monitoring, *Ther Drug Monit*, 17: 596-601 (1995). PMID: 8588227
345. Jusko WJ, Thomson AW, Fung J, McMaster P, Wong SH, Zylber-Katz E, Christians U, Winkler M,

- Fitzsimmons WE, Lieberman R, McBride J, Kobayashi M, Warty V, and Soldin SJ, Consensus Document: Therapeutic Monitoring of Tacrolimus (FK-506), *Ther. Drug Monit.*, 17: 606-614 (1995). PMID: 8588229
346. Cheng H and Jusko WJ, Disposition Decomposition Analysis for Pharmacodynamic Modeling of the Link Compartment, *Biopharm. Drug Disp.*, 17: 117-124 (1996). PMID: 8907718
347. Mishina EV and Jusko WJ, Liposomal Methylprednisolone in Rats: Dose-Proportionality and Chronic-Dose Pharmacokinetics/Dynamics, *Pharm. Res.*, 13: 141-145 (1996). PMID: 8668664
348. Jusko WJ, Pharmacokinetics and Receptor-Mediated Pharmacodynamics of Corticosteroids, *Toxicol.* 102: 189-196 (1995). PMID: 7482553
349. Slayter KL, Ludwig EA, Lew KH, Middleton Jr, E, Ferry JJ, and Jusko WJ, Oral Contraceptive Effects on Methylprednisolone Pharmacokinetics and Pharmacodynamics, *Clin. Pharmacol. Ther.*, 59: 312-321 (1996). PMID: 8653994
350. Jusko WJ, Physiologically Based Models in Pharmacodynamics, Ch 2.7 in "Pharmacokinetic/Pharmacodynamic Analysis: Accelerating Drug Discovery and Development", J Schlegel, Ed., Int. Bus. Comm. Inc., Southborough MA, pp.1-20 (1996).
351. Ferron GM, Rochdi M, Jusko WJ, and Scherrmann J-M, Oral Absorption Characteristics and Pharmacokinetics of Colchicine in Healthy Volunteers after Single and Multiple Doses, *J. Clin. Pharmacol.*, 36: 874-883 (1996). PMID: 8930773
352. Meno-Tetang Guy ML, Hon YY, and Jusko WJ, Synergistic Interaction Between Dehydroepiandrosterone and Prednisolone in the Inhibition of Rat Lymphocyte Proliferation, *Immunopharm. Immunotoxicol* 18: 443-456 (1996). PMID: 8872495
353. Sharma A and Jusko WJ, Characterization of Four Basic Models of Indirect Pharmacodynamic Responses, *J. Pharmacokin. Biopharm.* 24: 611-635 (1996). PMID: 9300353
354. Jusko WJ, Ferron GM, Mis SM, Kahan BD, and Zimmerman JJ, Pharmacokinetics of Prednisolone During Administration of Sirolimus in Patients with Renal Transplants, *J. Clin. Pharmacol.*, 36: 1100-1106 (1996). PMID: 9013365
355. Ferron GM, Mishina EV, Zimmerman JJ, and Jusko WJ, Population Pharmacokinetics of Sirolimus in Kidney Transplant Patients, *Clin. Pharmacol. Ther.*, 61: 416-428 (1997). PMID: 9129559
356. Cheng H, Gong Y, and Jusko WJ, A Computer Program Using Disposition Decomposition Analysis in Pharmacodynamics, *Biopharm. Drug Dispos.*, 18: 9-15 (1997). PMID: 9008265
357. Chow FS, Piekoszewski W, and Jusko WJ, Effect of Hematocrit and Albumin Concentration on Hepatic Clearance of Tacrolimus (FK 506) During Rabbit Liver Perfusion, *Drug Met. Disp.*, 25: 610-616 (1997). PMID: 9152601
358. Sharma A and Jusko WJ, Indirect Pharmacodynamic Models for Tolerance and Rebound Phenomena, Chap. 3.2 In: *Pharmacokinetic/Pharmacodynamic Analysis II*, Int. Bus. Commun. Inc., Southborough, MA (1997).
359. Krzyzanski W and Jusko WJ, Application of Moment Analysis to the Sigmoid Effect Model for Drug Administered Intravenously, *Pharmaceut. Res.*, 14: 949-952 (1997). PMID: 9244156
360. Ko HC, Jusko WJ, and Ebling WF, Nonlinear Perpendicular Least Squares Regression in Pharmacodynamics, *Biopharm. Drug Disp.*, 18: 711-716 (1997). PMID: 9373727
361. Krzyzanski W and Jusko WJ, Mathematical Formalism for the Properties of Four Basic Models of Indirect Pharmacodynamic Responses, *J. Pharmacokin. Biopharm.* 25: 107-123 (1997). PMID: 9353696
362. McKay LI, DuBois DC, Sun Y-N, Almon RR, and Jusko WJ, Corticosteroid Effects in Skeletal Muscle: Gene Induction/Receptor Autoregulation, *Muscle & Nerve*, 20: 1318-1320 (1997). PMID: 9324091
363. Ferron GM, Conway WD, and Jusko WJ, Lipophilic Benzamide and Anilide Derivatives as High-Performance Liquid Chromatography Internal Standards: Application to Sirolimus (Rapamycin) Determination, *J ChromB.*, 703: 243-251 (1997). PMID: 9448082
364. Krzyzanski W and Jusko WJ, Integrated Functions for Four Basic Models of Indirect Pharmacodynamic Response, *J. Pharm. Sci.*, 87: 67-72 (1998). PMID: 9452970
365. Ferron GM and Jusko WJ, Species Differences in Sirolimus Stability in Humans, Rabbits and Rats, *Drug Metab. Disp.*, 26: 83-84 (1998). PMID: 9443858
366. Sharma A and Jusko WJ, Characteristics of Indirect Pharmacodynamic Models and Applications to Clinical

- Drug Responses, *Brit. J. Clin. Pharmacol.*, 45: 229-239 (1998). PMID: 9517366
367. Segal JL, Maltby BF, Langdorf MI, Jacobson R, Brunnemann SR, and Jusko WJ, Methylprednisolone Disposition Kinetics in Humans with Acute Spinal Cord Injury, *Pharmacotherapy*, 18: 16-22 (1998). PMID: 9469676
 368. Sun Y-N and Jusko WJ, Transit Compartments versus Gamma Distribution Function to Model Signal Transduction Processes in Pharmacodynamics, *J. Pharm. Sci.*, 87: 732-737 (1998). PMID: 9607951
 369. Ferron GM, Pyszczynski NA, and Jusko WJ, Gender-Related Assessment of Cyclosporine/Prednisolone/Sirolimus Interactions in Three Human Lymphocyte Proliferation Assays, *Transplantation*, 65: 1203-1209 (1998). PMID: 9603169
 370. Ferron GM and Jusko WJ, Species- and Gender-Related Differences in Cyclosporine/Prednisolone/Sirolimus Interactions in Whole Blood Lymphocyte Proliferation Assays, *J. Pharmacol. Exp. Ther.*, 286: 191-200 (1998). PMID: 9655860
 371. Sharma A, Ebling WF, and Jusko WJ, Precursor-Dependent Indirect Pharmacodynamic Response Model for Tolerance and Rebound Phenomena, *J. Pharm. Sci.*, 87: 1577-1584 (1998). PMID: 10189270
 372. Gobburu JVS and Jusko WJ, Role of Dosage Regimen in Controlling Indirect Pharmacodynamic Responses, *Adv. Drug Del. Rev.*, 33: 221-233 (1998). PMID: 10837662
 373. Gobburu JVS, TenHoor C, Rogge MC, Frazier DE, Thomas D, Benjamin C, Hess DM, and Jusko WJ, Pharmacokinetics/Dynamics of 5c8, a Monoclonal Antibody to CD154 (CD40 Ligand): Suppression of an Immune Response in Monkeys, *J. Pharmacol. Exp. Ther.*, 286: 925-930 (1998). PMID: 9694951
 374. Gumbhir-Shah K, Kellerman DJ, DeGraw S, Koch P, and Jusko WJ, Pharmacokinetic-Pharmacodynamic Characteristics and Safety of Inhaled Albuterol Enantiomers in Healthy Volunteers, *J. Clin. Pharmacol.*, 38: 1096-1106 (1998). PMID: 11301561
 375. Sharma A, Slugg PH, Hammett JL, and Jusko WJ, Estimation of Oral Bioavailability of a Long Half-Life Drug in Healthy Subjects, *Pharm. Res.*, 15: 1782-1786 (1998). PMID: 9834003
 376. Sun Y-N, DuBois DC, Almon RR, and Jusko WJ, Fourth-Generation Model for Corticosteroid Pharmacodynamics: A Model for Methylprednisolone Effects on Receptor/Gene-Mediated Glucocorticoid Receptor Down-Regulation and Tyrosine Aminotransferase Induction in Rat Liver, *J. Pharmacokin. Biopharm.*, 26: 289-316 (1998). PMID: 10098101
 377. Krzyzanski W and Jusko WJ, Characterization of Pharmacodynamic Recession Slopes for Direct and Indirect Response Models, *J. Pharmacokin. Biopharm.*, 26: 409-435 (1998). PMID: 10214560
 378. Radwanski E, Chakraborty A, Van Wart S, Huhn RD, Cutler DL, Affrime MB, and Jusko WJ, Pharmacokinetics and Leukocyte Responses of Recombinant Human Interleukin-10, *Pharm. Res.*, 15: 1895-1901 (1998). PMID: 9892475
 379. Krzyzanski W and Jusko WJ, Mathematical Formalism and Characteristics of Four Basic Models of Indirect Pharmacodynamic Responses for Drug Infusions, *J. Pharmacokin. Biopharm.*, 26: 385-408 (1998). PMID: 10214559
 380. Ferron GM and Jusko WJ, Pharmacokinetic and Pharmacodynamic Interactions between Prednisolone and Sirolimus in Rabbits, *Pharm. Res.*, 15: 1888-1894 (1998). PMID: 9892474
 381. Sharma A, Slugg PH, Hammett JL, and Jusko WJ, Clinical Pharmacokinetics and Pharmacodynamics of a New Squalene Synthase Inhibitor, BMS-188494, in Healthy Volunteers, *J. Clin. Pharmacol.*, 38: 1116-1121 (1998). PMID: 11301563
 382. Flores-Murrieta FJ, Ko HC, Flores-Acevedo DM, Lopez-Munoz FJ, Jusko WJ, Sale ME, and Castaneda-Hernandez G, Pharmacokinetic-Pharmacodynamic Modeling of Tolmetin Antinociceptive Effect in the Rat Using an Indirect Response Model: A Population Approach, *J. Pharmacokin. Biopharm.*, 26: 547-557 (1998). PMID: 10205770
 383. Sun Y-N, DuBois DC, Almon RR, Pyszczynski NA, and Jusko WJ, Dose-Dependence and Repeated-Dose Studies for Receptor/Gene Mediated Pharmacodynamics of Methylprednisolone on Glucocorticoid Receptor Down-Regulation and Tyrosine Aminotransferase Induction in Rat Liver, *J. Pharmacokin. Biopharm.*, 26: 619-648 (1998). PMID: 10485078
 384. Krzyzanski W and Jusko WJ, Caution in Use of Empirical Equations for Pharmacodynamic Indirect

- Response Models, *J. Pharmacokin. Biopharm.*, 26: 735-741 (1998). PMID: 10485083
385. Meno-Tetang GML, Gobburu JVS, and Jusko WJ, Influence of Gender on Prednisolone Effects on Whole Blood T-Cell Deactivation and Trafficking in Rats, *J. Pharm. Sci.*, 88: 46-51 (1999). PMID: 9874701
 386. Meno-Tetang, GML, Hon YY, VanWart S, and Jusko WJ, Pharmacokinetic and Pharmacodynamic Interactions Between Dehydroepiandrosterone and Prednisolone in the Rat, *Drug Met. Drug Interact.*, 15: 51-70 (1999). PMID: 10707113
 387. Sun Y-N, McKay LI, DuBois DC, Jusko WJ, and Almon RR, Pharmacokinetic-Pharmacodynamic Models for Corticosteroid Receptor Down-Regulation and Glutamine Synthetase Induction in Rat Skeletal Muscle by a Receptor/Gene-Mediated Mechanism, *J. Pharmacol. Exper. Ther.*, 288: 720-728 (1999). PMID: 9918581
 388. Chakraborty A, Blum RA, Cutler DL, and Jusko WJ, Pharmacodynamic Interactions of IL-10 and Prednisone in Healthy Volunteers, *Clin. Pharmacol. Ther.*, 65: 304-318 (1999). PMID: 10096263
 389. Sharma A, Jusko WJ, Fulmor IE, Norton J, Uderman HD, and Salazar DE, Clinical Pharmacokinetics and Pharmacodynamics of Avitriptan During Intravenous Administration in Healthy Subjects, *J. Clin. Pharmacol.*, 39: 685-694 (1999). PMID: 10392323
 390. Chakraborty A, Blum RA, Mis SM, Cutler DL, and Jusko WJ, Pharmacokinetic and Adrenal Interactions of IL-10 and Prednisone in Healthy Volunteers, *J. Clin. Pharmacol.*, 39: 624-635 (1999). PMID: 10354967
 391. Sun Y-N, Lee HJ, and Almon RJ, A Pharmacokinetic/Pharmacodynamic Model for Recombinant Human Growth Hormone (rhGH) Effects on Induction of Insulin-Like Growth Factor I (IGF-I) in Monkeys, *J. Pharmacol. Exp. Ther.*, 289: 1523-32 (1999). PMID: 10336548
 392. Ferron GM and Jusko WJ, Clinical Pharmacokinetics and Pharmacodynamics of Glucocorticoids in Transplant Patients, *Graft*, 2: 182-186 (1999).
 393. Ferron GM, Pyszczynski NA, and Jusko WJ, Pharmacokinetic and Pharmacodynamic Interactions Between Prednisolone and Sirolimus in Adrenalectomized Rats, *J. Pharmacokin. Biopharm.*, 27: 1-21 (1999). PMID: 10533695
 394. Krzyzanski W, Chakraborty A, and Jusko WJ, Algorithm for Application of Fourier Analysis for Biorhythmic Baselines of Pharmacodynamic Indirect Response Models, *Chronobiol. Internat.*, 17: 77-93 (2000). PMID: 10672436
 395. Chakraborty A, Krzyzanski W, and Jusko WJ, Mathematical Modeling of Circadian Cortisol Concentrations Using Indirect Response Models: Comparison of Several Methods, *J. Pharmacokin. Biopharm.*, 27: 23-43 (1999). PMID: 10533696
 396. Gumbhir-Shah K, Kellerman DJ, DeGraw S, Koch P, and Jusko WJ, Pharmacokinetics and Pharmacodynamics of Cumulative Single Doses of Inhaled Albuterol Enantiomers in Asthmatic Subjects, *Pulm. Pharmacol. Ther.*, 12: 353-362 (1999). PMID: 10587476
 397. Imani S, Jusko WJ, and Steiner R, Diltiazem Retards the Metabolism of Oral Prednisone with Effects on T-Cell Markers, *Pediatr. Transplant.*, 3: 126-130 (1999). PMID: 10389134
 398. Davis CB, Tobia LP, Kwok DC, Oishi CM, Kheterpal N, Hebburn TW, Benincosa LJ, Chow FS, and Jusko WJ, Accumulation of Antibody-Target Complexes and the Pharmacodynamics of Clotting after Single Intravenous Administration of Humanized Anti-Factor IX Monoclonal Antibody to Rats, *Drug Delivery*, 6: 171-179 (1999).
 399. Gobburu JVS, Agerso H, Jusko WJ, and Ynddal L, Pharmacokinetic-Pharmacodynamic Modeling of Ipamorelin, a Growth Hormone Releasing Peptide, in Human Volunteers, *Pharmaceut. Res.*, 16: 1412-1416 (1999). PMID: 10496658
 400. Sun Y-N and Jusko WJ, Role of Baseline Parameters in Determining Indirect Pharmacodynamic Responses, *J. Pharm. Sci.*, 88: 987-990 (1999). PMID: 10514344
 401. Fasanmade AA and Jusko WJ, Immunodynamics of Methylprednisolone Induced T-Cell Trafficking and Deactivation Using Whole Blood Lymphocyte Proliferation Techniques in the Rat, *Biopharm. Drug Disp.*, 20: 255-261 (1999). PMID: 10594870
 402. Benincosa LJ, Chow F-S, Tobia LP, Kwok DC, Davis CB, and Jusko WJ, Pharmacokinetics and Pharmacodynamics of a Humanized Monoclonal Antibody to Factor IX in Cynomolgus Monkeys, *J.*

- Pharmacol. Exp. Ther., 292: 810-816 (2000). PMID: 10640322
403. Krzyzanski W, Ramakrishnan R, and Jusko WJ, Basic Pharmacodynamic Models for Agents which Alter Production of Natural Cells, *J. Pharmacokin. Biopharm.*, 27: 467-489 (2000). PMID: 10948694
404. Chow F-S, Sharma A, and Jusko WJ, Modeling Interactions between Adrenal Suppression and T-Helper Lymphocyte Trafficking During Multiple-Dosing of Methylprednisolone, *J. Pharmacokin. Biopharm.*, 27: 559-575 (1999). PMID: 11153446
405. Gabrielsson J, Jusko WJ, and Alari L, Modeling of Dose-Response-Time Data: Four Examples of Generating Kinetic Functions from Response Profiles, *Biopharm. Drug Disp.*, 21: 41-52 (2000). PMID: 11100906
406. Levy G, Zamacona MK, and Jusko, WJ. Developing Compliance Instructions for Drug Labeling, *Clin. Pharmacol. Ther.*, 68: 586-591 (2000). PMID: 11180017
407. Wyska E and Jusko WJ, Approaches to Pharmacokinetic/Pharmacodynamic Modeling during Pregnancy, *Seminars in Perinatology*, 25: 124-132 (2001). PMID: 11453607
408. Puchalski TA, Krzyzanski W, Blum RA, and Jusko WJ. Pharmacodynamic Modeling of Lansoprazole Using an Indirect Irreversible Response Model, *J. Clin. Pharmacol.*, 41: 251-258 (2001). PMID: 11269565
409. Krzyzanski W and Jusko WJ, Indirect Pharmacodynamic Models for Responses with Multicompartmental Distribution or Polyexponential Disposition, *J. Pharmacokin. Pharmacodyn.*, 28: 57-78 (2001). PMID: 11253614
410. Mager DE and Jusko WJ, Pharmacodynamic Modeling of Time-Dependent Transduction Systems, *Clin. Pharmacol. Ther.*, 70: 210-216 (2001). PMID: 11557908
411. Jusko WJ, Relationship of Dose- and Time-Dependent Corticosteroid Responses to Receptor Turnover, Proceedings of a Workshop on "The Anti-Asthmatic Actions and Selectivity of Inhaled Steroids", Chap 5, pp. 95-112, Eds. RP Schleimer, P O'Bryne, SJ Szefer, and R Brattsand, Marcel Dekker Inc, New York (2001).
412. Magee MH, Blum RA, Lates CD, and Jusko WJ, Prednisolone Pharmacokinetics and Pharmacodynamics in Relation to Sex and Race, *J. Clin. Pharmacol.*, 41: 1180-1194 (2001). PMID: 11697751
413. Meno-Tetang G, Blum RA, Schwartz KE, Jusko WJ, Effects of Oral Prasterone (Dehydroepiandrosterone) on Single-Dose Pharmacokinetics of Oral Prednisone and Cortisol Suppression in Normal Women, *J. Clin. Pharmacol.*, 41: 1195-1205 (2001). PMID: 11697752
414. Ramakrishnan R and Jusko WJ, Interactions of Aspirin and Salicylic Acid with Prednisolone for Inhibition of Lymphocyte Proliferation, *Internat. Immunopharmacol.*, 1: 2035-2042 (2001). PMID: 11606034
415. Chakraborty A and Jusko WJ, Pharmacodynamic Interaction of Recombinant Interleukin-10 and Prednisolone Using In Vitro Whole Blood Lymphocyte Proliferation, *J. Pharm. Sci.*, 91: 1334-1342 (2002). PMID: 11977109
416. Chow F-S, Benincosa LJ, Sheth SB, Wilson D, Davis CB, Minthorn EA, Jusko WJ, Pharmacokinetic and Pharmacodynamic Modeling of Humanized Anti-Factor IX Antibody (SB 249417) in Humans, *Clin. Pharm. Ther.*, 71: 235-245 (2002). PMID: 11956506
417. Ramakrishnan R, Dubois D, Almon RA, Pyszczynski NA, and Jusko WJ, Pharmacodynamics and Pharmacogenomics of Methylprednisolone during 7-Day Infusion in Rats, *J. Pharmacol. Exper. Ther.*, 300: 245-256 (2002). PMID: 11752123
418. Magee MH, Blum RA, Lates CD, and Jusko WJ, Integrated Pharmacokinetic/Pharmacodynamic Model for Prednisolone Inhibition of Ex Vivo Whole Blood Lymphocyte Proliferation, *Brit. J. Clin. Pharmacol.*, 53: 474-484 (2002). PMID: 11994053
419. Mager DE and Jusko WJ, General Pharmacokinetic Model for Drugs Exhibiting Target-Mediated Drug Disposition, *J. Pharmacokin. Biopharm.*, 28: 507-532 (2001). PMID: 11999290
420. Ramakrishnan R, DuBois D, Almon RA, Pyszczynski NA, and Jusko WJ, Fifth-Generation Model for Corticosteroid Pharmacodynamics: Steady-State Receptor Down-Regulation and Enzyme Induction Patterns During Seven-Day Continuous Infusion of Methylprednisolone in Rats, *J. Pharmacokin. Pharmacodyn.*, 29: 1-24 (2002). PMID: 12194533
421. Bernstein SH, Jusko WJ, Krzyzanski, W., Nichols J, and Wetzler M, Pharmacodynamic Modeling of

- Thrombopoietin, Platelet and Megakaryocyte Dynamics in Patients with Acute Myeloid Leukemia Undergoing Dose Intensive Chemotherapy, *Cancer Res.*, *J. Clin. Pharmacol.*, 42: 501-511 (2002). PMID: 12017344
422. Zimmerman JJ, Harper D, Getsy J, Jusko WJ, Pharmacokinetic Interactions Between Sirolimus and Microemulsion Cyclosporine When Orally Administered Jointly and 4 Hours Apart in Healthy Volunteers, *J. Clin. Pharmacol.*, 43: 1168-76 (2003). PMID: 14517200
 423. Li H, Meno-Tetang GML, Chiba K, Arima N, Heining P, Jusko WJ, Pharmacokinetics and Cell Trafficking Dynamics of FTY720 in Cynomolgus Monkeys Following Single Oral and Intravenous Doses, *J. Pharmacol. Exp. Ther.*, 301: 519-526 (2002). PMID: 11961052
 424. Almon RA, Dubois DC, Brandenburg EH, Shi W, Zhang S, Straubinger RM, and Jusko WJ, Pharmacodynamics and Pharmacogenomics of Diverse Receptor-Mediated Effects of Methylprednisolone in Rats using Microarray Analysis, *J. Pharmacokin. Pharmacodyn.*, 29: 103-129 (2002). PMID: 12361239
 425. Mager DE and Jusko WJ, Quantitative Structure-Pharmacokinetic/Pharmacodynamic Relationships of Corticosteroids in Man, *J. Pharm. Sci.*, 91: 2441-2451 (2002). PMID: 12379930
 426. Booker BM, Magee M, Blum RA, Lates CD, and Jusko WJ, Pharmacokinetic and Pharmacodynamic Interactions between Diltiazem and Methylprednisolone in Healthy Volunteers, *Clin. Pharmacol. Ther.* 72: 370-382 (2002). PMID: 12386639
 427. Krzyzanski W and Jusko WJ, Multiple-Pool Cell Lifespan Model of Hematologic Effects of Anticancer Agents, *J. Pharmacokin. Pharmacodyn.*, 29: 311-337 (2002). PMID: 12518707
 428. Levy G, Mager DE, Cheung WK, and Jusko WJ, Comparative Pharmacokinetics of Coumarin Anticoagulants I: Physiologic Modeling of S-Warfarin in Rats and Pharmacologic Target-Mediated Disposition in Man, *J. Pharm. Sci.*, 92: 985-994 (2003). PMID: 12712418
 429. Mager DE, Pyszczynski N, and Jusko WJ, Integrated QSPR – Pharmacodynamic Model of Genomic Effects of Several Corticosteroids, *J. Pharm. Sci.*, 92: 881-889 (2003). PMID: 12661073
 430. Mager DE and Jusko WJ, Receptor-Mediated Pharmacokinetic/Pharmacodynamic Model of Interferon-Beta in Man, *Pharm. Res.*, 19: 1537-1543 (2002). PMID: 12425473
 431. Jeng S, Chanchairujira T, Jusko WJ, and Steiner R, Prednisone Metabolism in Recipients of Kidney or Liver Transplants and in Lung Recipients Receiving Ketoconazole, *Transplantation*, 75: 792-795 (2003). PMID: 12660503
 432. Petersen KB, Jusko WJ, Rasmussen M, and Schmiegelow K, Population Pharmacokinetics of Prednisolone in Children with Acute Lymphoblastic Leukemia, *Cancer Chemother. Pharmacol.*, 51: 465-473 (2003). PMID: 12698270
 433. Ramakrishnan R, Cheung WK, Farrell F, Jolliffe L, and Jusko WJ, Pharmacokinetic and Pharmacodynamic Modeling of Recombinant Human Erythropoietin after Intravenous and Subcutaneous Single Dose Administrations in Cynomolgous Monkeys, *J. Pharmacol. Exp. Ther.*, 306: 324-331 (2003). PMID: 12676891
 434. Mager DE, Moledina N, and Jusko WJ, Relative Immunosuppressive Potency of Therapeutic Corticosteroids Measured by Whole Blood Lymphocyte Proliferation, *J. Pharm. Sci.*, 92: 1521-1525 (2003). PMID: 12820156
 435. Mager DE, Wyska E, Jusko WJ, Diversity of Mechanism-Based Pharmacodynamic Models, *Drug Met. Disp.*, 31: 510-518 (2003). PMID: 12695336
 436. Almon RR, DuBois DC, Pearson KE, Stephan DA, and Jusko WJ, Gene Arrays and Temporal Patterns of Drug Response: Corticosteroid Effects on Rat Liver, *Functional & Integrative Genomics*, 3: 171-179 (2003). PMID: 12928814
 437. Mager DE, Neuteboom B, Efthymiopoulos C, Munafo A, and Jusko WJ, Receptor-Mediated Pharmacokinetics and Pharmacodynamics of Interferon- β 1a Following Intravenous and Subcutaneous Dosing in Monkeys, *J. Pharmacol. Exp. Ther.*, 306: 262-270 (2003). PMID: 12660309
 438. Jin JY, Almon RR, Dubois DC, and Jusko WJ, Modeling of Corticosteroid Pharmacogenomics in Rat Liver Using Gene Microarrays, *J. Pharmacol. Exp. Ther.*, 307: 93-109 (2003) [*featured on cover of November 2003 issue of journal*]. PMID: 12808002

439. Mager DE, Lin SX, Blum RA, Lates CD, and Jusko WJ, Dose Equivalency Evaluation of Major Corticosteroids I. Pharmacokinetics and Cell Trafficking and Cortisol Dynamics, *J. Clin. Pharmacol.*, 43: 1216-1227 (2003). PMID: 14551176
440. Jin JY, Dubois DC, Almon RR, and Jusko WJ, Receptor/Gene-Mediated Pharmacodynamic Effects of Methylprednisolone on Phosphoenolpyruvate Carboxylase Regulation in Rat Liver, *J. Pharmacol. Exper. Ther.*, 309: 328-339 (2004). PMID: 14722324
441. Samtani MN, Schwab M, Nathanielsz PW, and Jusko WJ, Stabilization and HPLC Analysis of Betamethasone Sodium Phosphate in Plasma, *J. Pharm. Sci.*, 93: 726-732 (2004). PMID: 14762910
442. Almon RR, Chen J, Snyder G, Dubois DC, Jusko WJ, and Hoffman EP. In Vivo Multi-Tissue Corticosteroid Microarray Time Series Available Online at Public Expression Profile Resource (PEPR). *Pharmacogenomics*, 4: 791-799 (2003). PMID: 14596642
443. Chen J, Zhao P, Massaro D, Clerch LB, Almon RR, Dubois DC, Jusko WJ, and Hoffman EP, The PEPR GeneChip Data Warehouse, and Implementation of a Dynamic Time Series Query Tool (SGQT) with Graphical Interface, *Nucleic Acids Research*, 32: D578-D581 (2004). PMID: 14681485
444. Jusko WJ, Jin JY, Dubois DC, and Almon RR. Pharmacodynamics and Pharmacogenomics of Corticosteroids: Microarray Studies, In: *Advanced Methods of Pharmacokinetic and Pharmacodynamics Systems Analysis*, Volume 3, D.Z. D'Argenio, Editor, Kluwer Academic Publishers, Boston, pp. 85-103 (2004).
445. Smith PF, Bullock JM, Booker BM, Haas CE, Berenson C, and Jusko WJ, Induction of Imatinib Metabolism by Hypericum Perforatum, *Blood*, 104: 1229-30 (2004). PMID: 15294859
446. Lima JJ, Matsushima N, Kissoon N, Wang J, Sylvester JE, Jusko WJ, Modeling the Metabolic Effects of Terbutaline in β_2 Adrenergic Receptor Diplotypes, *Clin. Pharmacol. Ther.*, 76: 27-37 (2004). PMID: 15229461
447. Almon RR, DuBois DC, Piel WH, Jusko, WJ. The Genomic Response of Skeletal Muscle to Methylprednisolone Using Microarrays: Tailoring Data Mining to the Structure of the Pharmacogenomic Time Series, *Pharmacogenomics*, 5: 525-552 (2004). PMID: 15212590
448. Lepist E-I, Jusko WJ. Modeling and Allometric Scaling of s(+)Ketoprofen Pharmacokinetics and Pharmacodynamics: A Retrospective Analysis. *J. Vet. Pharmacol. Ther.*, 27: 211-218 (2004). PMID: 15305849
449. Earp J, Krzyzanski W, Chakraborty A, Zamacona MK, and Jusko WJ, Assessment of Drug Interactions Relevant to Pharmacodynamic Indirect Response Models, *J. Pharmacokin. Pharmacodyn.*, 31: 345-380 (2004). PMID: 15669772
450. Kamal MA and Jusko WJ, Interactions of Prednisolone and Other Immunosuppressants Used in Dual Treatment of Systemic Lupus Erythematosus in Lymphocyte Proliferation Assays, *J. Clin. Pharmacol.*, 44: 1034-1045 (2004). PMID: 15317831
451. Ramakrishnan R, Cheung WK, Wacholtz MC, Minton N, and Jusko WJ, Pharmacokinetic and Pharmacodynamic Modeling of Recombinant Human Erythropoietin after Single and Multiple Doses in Healthy Volunteers, *J. Clin. Pharmacol.*, 44: 991-1002 (2004). PMID: 15317827
452. Smith PF, Bullock JM, Booker BM, Haas CE, Berenson CS, Jusko WJ, The Influence of St. John's Wort on the Pharmacokinetics and Protein Binding of Imatinib Mesylate, *Pharmacotherapy*, 24: 1508-1514 (2004). PMID: 15537555
453. Samtani MN, Nathanielsz PW, Schwab M, and Jusko WJ, Area/Moment and Compartmental Modeling of Pharmacokinetics during Pregnancy: Applications to Maternal/Fetal Exposures to Corticosteroids in Sheep and Rats, *Pharm. Res.*, 21: 2279-2292 (2004). PMID: 15648260
454. Chakraborty A, Yeung S, Pyszczynski NA, and Jusko WJ, Pharmacodynamic Interactions between Recombinant Mouse Interleukin-10 and Prednisolone Using a Mouse Endotoxemia Model, *J. Pharm. Sci.*, 94: 590-603 (2005). PMID: 15666292
455. Almon RR, DuBois DC, Jin JY, Jusko WJ, Pharmacogenomic Responses of Rat Liver to Methylprednisolone: An Approach to Mining a Rich Microarray Time Series, *The AAPS Journal*, 7: E156-E194 (2005). PMID: 16146338

456. Mager DE, Neuteboom B, Jusko WJ, Pharmacokinetics and Pharmacodynamics of Pegylated IFN- β 1a Following Subcutaneous Administration in Monkeys, *Pharm. Res.*, 22: 58-61 (2005). PMID: 15771230
457. Chow F-S and Jusko WJ, Immunosuppressive Interactions among Calcium Channel Antagonists and Selected Corticosteroids and Macrolides Using Human Whole Blood Lymphocytes, *Drug Metab. & Pharmacokin.*, 19: 413-421 (2004). PMID: 15681895
458. Samtani M and Jusko WJ, Comparison of Dexamethasone Pharmacokinetics in Female Rats after Intravenous and Intramuscular Administration, *Biopharm. & Drug Dispos.*, 26: 85-91 (2005). PMID: 15654687
459. Almon RR, DuBois DC, Jin JY, Jusko WJ, Temporal Profiling of the Transcriptional Basis for the Development of Corticosteroid-Induced Insulin Resistance in Rat Muscle, *J. Endocrinol.*, 184: 219-232 (2005). PMID: 15642798
460. Jusko WJ, Guidelines for Collection and Analysis of Pharmacokinetic Data, Burton ME, Shaw LM, Schentag JJ, Evans WE, Editors, *Applied Pharmacokinetics & Pharmacodynamics*, 4th Edition, Lippincott Williams & Wilkins, Philadelphia, pp 9-29 (2005).
461. Samtani M, Lohle M, Grant A, Nathanielsz PW, and Jusko WJ, Betamethasone Pharmacokinetics after Two Prodrug Formulations in Sheep: Implications for Antenatal Corticosteroid Use, *Drug Metab. Dispos.*, 33: 1124-1130 (2005). PMID: 15860658
462. Krzyzanski W, Jusko WJ, Wacholtz, Minton N, Cheung WK, Pharmacokinetic and Pharmacodynamic Modeling of Recombinant Human Erythropoietin after Multiple Subcutaneous Doses in Healthy Subjects, *Eur. J. Pharm. Sci.*, 26: 295-306 (2005). PMID: 16102948
463. Almon RR, Lai W, DuBois DC, Jusko WJ, Corticosteroid Regulated Genes in Rat Kidney: Mining Time Series Array Data, *Am. J. Physiol., Endocrinology and Metabolism*, 289: E870-E882 (2005). PMID: 15985454
464. Ruixo JJP, Kimko HC, Chow AT, Piotrovsky V, Krzyzanski W, and Jusko WJ, Population Cell Lifespan Models for Effects of Drugs Following Indirect Mechanisms of Action, *J. Pharmacokin. Pharmacodyn.*, 32: 767-793 (2005). PMID: 16328102
465. Gordi T, Xie R, and Jusko WJ, Semi-Mechanistic Pharmacokinetic/Pharmacodynamic Modelling of the Antimalarial Effect of Artemisinin, *Brit. J. Clin. Pharmacol.*, 60: 594-604 (2005). PMID: 16305583
466. Krzyzanski W, Woo S, and Jusko WJ, Pharmacodynamic Models for Agents that Alter Production of Natural Cells with Various Distributions of Lifespans, *J. Pharmacokin. Pharmacodyn.*, J. Pharmacokin. Pharmacodyn., 33: 125-166 (2006). PMID: 16565883
467. Samtani M and Jusko WJ, Stability of Dexamethasone Sodium Phosphate in Rat Plasma, *Int. J. Pharmaceutics*, 301: 262-266 (2005). PMID: 16054309
468. Yao Z, Krzyzanski W, and Jusko WJ, Assessment of Basic Indirect Response Models with Physiological Limits, *J. Pharmacokin. Pharmacodyn.*, 33: 167-193 (2006). PMID: 16547797
469. Yao Z, DuBois DC, Almon RA, and Jusko WJ, Modeling Circadian Rhythms of Glucocorticoid Receptor and Glutamine Synthetase Expression in Rat Skeletal Muscle, *Pharm. Res.*, 23: 670-679 (2006). PMID: 16673181
470. Samtani M, Pyszczynski NA, DuBois D, Almon RR, and Jusko WJ, Modeling Glucocorticoid-Mediated Fetal Lung Maturation I. Temporal Patterns of Corticosteroids in Rat Pregnancy, *J. Pharmacol. Exp. Ther.*, 317: 117-126 (2006). PMID: 16371449
471. Samtani M, Pyszczynski NA, DuBois D, Almon RR, and Jusko WJ, Modeling Glucocorticoid-Mediated Fetal Lung Maturation II. Temporal Patterns of Gene Expression in Fetal Rat Lung, *J. Pharmacol. Exp. Ther.*, 317: 127-138 (2006). PMID: 16371448
472. Qu J, Jusko WJ, and Straubinger RM, Utility of Cleavable Isotope-Coded Affinity-Tagged Reagents for Quantification of Low-Copy Proteins Induced by Methylprednisolone Using Liquid Chromatography/Tandem Mass Spectrometry, *Anal. Chem.*, 78: 4543-4552 (2006). PMID: 16808464
473. Hon YY, Jusko WJ, Zhou HH, Chen GL, Guo D, Zhou G, Spratlin VE, Jann MW, Endogenous Histamine and Cortisol Levels in Subjects with Different Histamine N-Methyltransferase C314T Genotypes, *Mol. Diag. Ther.*, 10: 109-114 (2006). PMID: 16669609

474. Hon YY, Jusko WJ, Spratlin VE, and Jann MW, Altered Methylprednisolone Pharmacodynamics in Healthy Subjects with Histamine N-Methyltransferase C314T Genetic Polymorphism, *J. Clin. Pharmacol.*, 46: 408-417 (2006). PMID: 16554448
475. Lee SJ, Jusko WJ, Salaita CG, Calis KA, Jann MW, Spratlin VE, Goldstein JA, and Hon YY, Reduced Methylprednisolone Clearance Causing Prolonged Pharmacodynamics in a Healthy Subject Was Not Associated with CYP3A5*3 Allele or a Change in Diet Composition, *J. Clin. Pharmacol.*, 46: 515-526 (2006). PMID: 16638735
476. Schwab M, Coksaygan T, Samtani MN, Jusko WJ, and Nathanielsz PW, Kinetics of Betamethasone and Fetal Cardiovascular Adverse Effects in Pregnant Sheep after Different Doses, *Obstetrics & Gynecology* 108: 617-625 (2006). PMID: 16946223
477. Almon RR, DuBois DC, Jin JY, Yao Z, Hazra A, Samtani M, Snyder G, Piel W, Jusko WJ, Development, Analysis, and Use of Pharmacogenomic Time Series for Pharmacokinetic/Pharmacodynamic Modeling of Multi-Tissue Polygenic Responses to Corticosteroids, In: *New Research on Pharmacogenetics*, ISBN 1-60021-056-2, Chapter 2, Nova Publishers (2006).
478. Krzyzanski W, Dmochowski J, Matsushima N, Jusko WJ, Assessment of Dosing Impact on Intra-Individual Variability in Estimation of Parameters for Basic Indirect Response Models, *J. Pharmacokin. Pharmacodyn.* 33: 635-655 (2006). PMID: 16941234
479. Meno-Tetang GML, Li H, Mis S, Pyszczynski N, Heining P, Lowe P, and Jusko WJ, Physiologically-Based Pharmacokinetic Modeling of FTY720 (2-Amino-2[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride) in Rats Following Oral and Intravenous Doses, *Drug Met. Disp.*, 34: 1480-1487 (2006). PMID: 16751263
480. Hazra A, Krzyzanski W, and Jusko WJ, Mathematical Assessment of Properties of Precursor-Dependent Indirect Pharmacodynamic Response Models, *J. Pharmacokin. Pharmacodyn.*, 33: 683-717 (2006). PMID: 17053985
481. Woo S, Krzyzanski W, and Jusko WJ, Pharmacokinetic and Pharmacodynamic Modeling of Recombinant Human Erythropoietin after Intravenous and Subcutaneous Administration in Rats, *J. Pharmacol. Exper. Ther.* 319: 1297-1306 (2006). PMID: 16973883
482. Hazra A, Pyszczynski N, DuBois DC, Almon RR, and Jusko WJ, Pharmacokinetics of Methylprednisolone after Intravenous and Intramuscular Administration in Rats, *Biopharm. & Drug Disp.* 28: 263-273 (2007). PMID: 17569107
483. Samtani MN and Jusko WJ, Quantification of Dexamethasone and Corticosterone in Rat Biofluids and Fetal Tissue Using Highly Sensitive Analytical Methods: Assay Validation and Application to a Pharmacokinetic Study, *Biomed. Chromatog.* 21: 585-597 (2007). PMID: 17385808
484. Wetzler M, Earp JC, Brady MT, Keng MK, and Jusko WJ, Synergism Between Arsenic Trioxide and Heat Shock Protein 90 Inhibitors on Signal Transducer and Activator of Transcription Protein 3 Activity – Pharmacodynamic Drug-Drug Interaction Modeling, *Clin. Cancer Res.* 13: 2261-2270 (2007). PMID: 17404111
485. Hazra A, DuBois DC, Almon RR, and Jusko WJ, Assessing the Dynamics of Nuclear Glucocorticoid-Receptor Complex; Adding Flexibility to Gene Expression Modeling, *J. Pharmacokin. Pharmacodyn.*, 34: 333-354 (2007). PMID: 17285360
486. Woo S and Jusko WJ, Interspecies Comparisons of Pharmacokinetics and Pharmacodynamics of Recombinant Human Erythropoietin, *Drug Met. Disp.* 35: 1672-1678 (2007). PMID: 17576810
487. Mager DE and Jusko WJ, Mechanistic Pharmacokinetic/Pharmacodynamic Models II, In: *Pharmacometrics, The Science of Quantative Pharmacology*, Ette EI & Williams PJ, Editors, Wiley & Sons, Inc, Chapter 23, pp. 607-631 (2007).
488. Jin JY and Jusko WJ, Pharmacogenomics and Pharmacokinetic/Pharmacodynamic Modeling, In: *Pharmacometrics, The Science of Quantative Pharmacology*, Ette EI & Williams PJ, Editors, Wiley & Sons, Inc, Chapter 19, pp. 509-528 (2007).
489. Yao Z, Zhao B, Hoffman EP, Ghimbovski S, DuBois DB, Almon RR, and Jusko WJ, Application of a Scaling Factor in Simultaneous Modeling of Microarray Data from Diverse Chips, *Pharmaceut. Res.* 24:

- 643-649 (2007). PMID: 17318415
490. Hong Y, Mager DE, Blum RA, and Jusko WJ, Population Pharmacokinetic/Pharmacodynamic Modeling of Systemic Corticosteroid Inhibition of Whole Blood Lymphocytes: Modeling Interoccasion Pharmacodynamic Variability, *Pharm. Res.* 24: 1088-1097 (2007). PMID: 17385022
 491. Almon RR, DuBois DC, and Jusko WJ, Microarray Analysis of the Temporal Response of Liver to Methylprednisolone: Comparative Analysis of Two Dosing Regimens, *Endocrinology*, 148: 2209-2225 (2007). PMID: 17303664
 492. Yang E, Simcha D, Almon RR, DuBois DC, Jusko WJ, and Androulakis IP, Context Specific Transcription Factor Prediction, *Ann. Biomed. Eng.*, 35: 1053-1067 (2007). PMID: 17377845
 493. Hazra A, Pyszczynski NA, DuBois DC, Almon RR, and Jusko WJ, Modeling of Corticosteroid Effects on Hepatic Low-Density Lipoprotein Receptors and Plasma Lipid Dynamics in Rats, *Pharm. Res.*, 25: 769-780 (2008). PMID: 17674160
 494. Woo S, Krzyzanski W, and Jusko WJ, Target-mediated Pharmacokinetics and Pharmacodynamics of Recombinant Human Erythropoietin (rHuEPO), *J. Pharmacokin. Pharmacodyn.*, 34: 849-868 (2007). PMID: 17943422
 495. Yao Z, DuBois DC, Almon RR, and Jusko WJ, Pharmacokinetic/Pharmacodynamic Modeling of Corticosterone Suppression and Lymphocytopenia by Methylprednisolone in Rats, *J. Pharm. Sci.*, 97: 2820-2832 (2008). PMID: 17828751
 496. Almon RR, DuBois DC, Yao Z, Hoffman EP, Ghimbovski S, and Jusko WJ, Microarray Analysis of the Temporal Response of Skeletal Muscle to Methylprednisolone: Comparative Analysis of Two Dosing Regimens, *Physiol. Genomics* 30: 282-299 (2007). PMID: 17473217
 497. Hazra A, Pyszczynski NA, DuBois DC, Almon RR, and Jusko WJ, Modeling Receptor/Gene-Mediated Effects of Corticosteroids on Hepatic Tyrosine Aminotransferase Dynamics in Rats: Dual Regulation by Endogenous and Exogenous Corticosteroids, *J. Pharmacokin. Pharmacodyn.*, 34: 643-667 (2007). PMID: 17593325
 498. Woo S, Krzyzanski W, Duliege A-M, Stead RR, and Jusko WJ, Population Pharmacokinetics and Pharmacodynamics of Peptidic Erythropoiesis Receptor Agonist (ERA) in Healthy Volunteers, *J. Clin. Pharmacol.* 48: 43-52 (2008). PMID: 18025524
 499. Hazra A, DuBois DC, Almon RR, Snyder GH, and Jusko WJ, Pharmacodynamic Modeling of Acute and Chronic Effects of Methylprednisolone on Hepatic Urea Cycle Genes in Rats, *Gene Reg. Sys. Biol.* 2: 1-19 (2008). PMID: 19787073
 500. Woo S, Krzyzanski W, and Jusko WJ, Pharmacodynamic Model for Chemotherapy-Induced Anemia in Rats, *Cancer Chem. Pharmacol.*, 62: 123-133 (2008). PMID: 17891399
 501. Landersdorfer CB and Jusko WJ, Pharmacokinetic/Pharmacodynamic Modelling in Diabetes, *Clin. Pharmacokin.*, 47:417-448 (2008). PMID: 18563953
 502. Yang E, Almon RR, DuBois DC, Jusko WJ, and Androulakis IP, Extracting Global System Dynamics of Corticosteroid Genomic Effects in Rat Liver, *J. Pharmacol. Exp. Ther.* 324: 1243-1254 (2008). PMID: 18086872
 503. Yao Z, Hoffman EP, Ghimbovski S, DuBois DC, Almon RR, and Jusko WJ, Mathematical Modeling of Corticosteroid Pharmacogenomics in Rat Muscle Following Acute and Chronic Methylprednisolone Dosing, *Mol. Pharm.*, 5: 328-339 (2008). PMID: 18271548
 504. Mager DE and Jusko WJ, Development of Translational Pharmacokinetic-Pharmacodynamic Models, *Clin. Pharmacol. Ther.* 83: 909-912 (2008). PMID: 18388873
 505. Earp JC, Pyszczynski NA, Molano DS and Jusko WJ, Pharmacokinetics of Dexamethasone in a Rat Model of Rheumatoid Arthritis, *Biopharm. Drug Disp.*, 29: 366-372 (2008). PMID: 18613033
 506. Earp JC, DuBois DC, Almon RR, and Jusko WJ, Quantitative Dynamic Models of Arthritis Progression in the Rat, *Pharm. Res.* 26: 196-203 (2009). PMID: 18758921
 507. Yao Z, Hoffman EP, Ghimbovski S, DuBois DC, Almon RA, and Jusko WJ, Pharmacodynamic/Pharmacogenomic Modeling of Insulin Resistant Genes in Rat Muscle after Methylprednisolone Treatment: Exploring Regulatory Signaling Cascades, *Gene Reg. Sys. Biol.*, 2: 141-

- 161 (2008). PMID: 19787081
508. Earp JC, DuBois DC, Molano DS, Pyszczynski NA, Keller CE, Almon RR, and Jusko WJ, Modeling Corticosteroid Effects in a Rat Model of Rheumatoid Arthritis I: Mechanistic Disease Progression Model for the Time Course of Collagen-Induced Arthritis in Lewis Rats, *J. Pharmacol. Exp. Ther.*, 326: 532-545 (2008). PMID: 18448865
 509. Earp JC, DuBois DC, Molano DS, Pyszczynski NA, Almon RR, and Jusko WJ, Modeling Corticosteroid Effects in a Rat Model of Rheumatoid Arthritis II: Mechanistic Pharmacodynamic Model for Dexamethasone Effects in Lewis Rats with Collagen-Induced Arthritis, *J. Pharmacol. Exp. Ther.*, 326: 546-554 (2008). PMID: 18448864
 510. Rohatagi S, Carrothers TJ, Jin JY, Jusko WJ, Khariton T, Walker J, Truitt K, and Salazar DE, Model-Based Development of a PPAR γ Agonist, Rivoglitazone, to Aid Dose Selection and Optimize Clinical Trial Designs, *J. Clin. Pharmacol.* 48: 1420-1429 (2008). PMID: 18936283
 511. Almon RR, Yang E, Lai W, Androulakis IP, DuBois DC, Jusko WJ, Circadian Variations in Rat Liver Gene Expression: Relationships to Drug Actions, *J. Pharmacol. Exp. Ther.* 326: 700-716 (2008). PMID: 18562560
 512. Almon RR, Yang E, Lai W, Androulakis IP, Ghimbovski S, Hoffman EP, Jusko WJ, and DuBois DC, Relationships Between Circadian Rhythms and Modulation of Gene Expression by Glucocorticoids in Skeletal Muscle, *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 295: R1031-R1047 (2008). PMID: 18667713
 513. Bulitta JB, Ly NS, Yang JC, Forrest A, Jusko WJ, Tsuji BT, Development and Qualification of a Pharmacodynamic Model for the Pronounced Inoculum Effect of Ceftazidime against *Pseudomonas aeruginosa*, *Antimicrob. Ag. Chemother.* 53: 46-56 (2009). PMID: 18852268
 514. Bulitta JB, Zhao P, Arnold RD, Kessler DR, Daifuku R, Pratt J, Luciano G, Hanauske A-R, Gelderblom H, Awada A, Jusko WJ: Mechanistic Population Pharmacokinetics of Total and Unbound Paclitaxel for a New Nanodroplet Formulation vs. Taxol in Cancer Patients, *Cancer Chemother. Pharmacol.*, 63: 1049-1063 (2009). PMID: 18791718
 515. Bulitta JB, Zhao P, Arnold RD, Kessler DR, Daifuku R, Pratt J, Luciano G, Hanauske A-R, Gelderblom H, Awada A, Jusko WJ: Multiple-Pool Lifespan Models for Neutropenia to Assess the Population Pharmacodynamics of Unbound Paclitaxel from Two Formulations in Cancer Patients, *Cancer Chemother. Pharmacol.*, 63: 1035-1048 (2009). PMID: 18791717
 516. Landersdorfer CB, DuBois DC, Almon RR and Jusko WJ, Mechanism-Based Modeling of Nutritional and Leptin Influences on Growth in Normal and Type 2 Diabetic Rats, *J. Pharmacol. Exp. Ther.*, 328: 644-651 (2009). PMID: 18971370
 517. Mager DE, Woo S, and Jusko WJ, Scaling Pharmacodynamics from In Vitro and Preclinical Animal Studies to Humans, *Drug Metab. Pharmacokin.* 24: 16-24 (2009). PMID: 19252333
 518. Jin JY and Jusko WJ, Pharmacodynamics of Glucose Regulation by Methylprednisolone. I. Adrenalectomized Rats, *Biopharm. Drug Disp.*, 30: 21-34 (2009). PMID: 19156931
 519. Jin JY and Jusko WJ, Pharmacodynamics of Glucose Regulation by Methylprednisolone. II. Normal Rats, *Biopharm. Drug Disp.*, 30: 35-48 (2009). PMID: 19156669
 520. Almon RR, DuBois DC, Lai W, Xue B, Nie J and Jusko WJ, Gene Expression Analysis of Hepatic Roles in Cause and Development of Diabetes in Goto-Kakizaki Rats, *J. Endocrin.*, 200: 331-346 (2009). PMID: 19074471
 521. Cho H-Y, Blum RA, Sunderland T, Cooper GJS, and Jusko WJ, Pharmacokinetic and Pharmacodynamic Modeling of a Copper-Selective Chelator (TETA) in Healthy Adults, *J. Clin. Pharmacol.*, 49: 916-928 (2009). PMID: 19602718
 522. Yang EH, Almon RR, Dubois DC, Jusko WJ, and Androulakis IP, Identification of Global Transcriptional Dynamics, *PLoS One*, 4:e5992 (2009). PMID: 19593450
 523. Khinkis LA, Krzyzanski W, Jusko WJ, and Greco WR, D-Optimal Designs for Parameter Estimation for Indirect Pharmacodynamic Response Models, *J. Pharmacokin. Pharmacodyn.* 36: 523-539 (2009). PMID:

19904585

524. Woo S, Pawaskar D, and Jusko WJ, Methods of Utilizing Baseline Values for Indirect Response Models, *J. Pharmacokin. Pharmacodyn.* 36: 381-405 (2009). PMID: 19697107
525. Freishtat RJ, Nagaraju K, Jusko WJ, and Hoffman EP, Glucocorticoid Efficacy in Asthma: Is Improved Tissue Remodeling Upstream of Anti-Inflammation, *J. Invest. Med.* 58: 19-22 (2010).
526. Wiczling P, Rosenzweig M, Vaickus L, and Jusko WJ, Pharmacokinetics and Pharmacodynamics of a Chimeric/Humanized Anti-CD3 Monoclonal Antibody, Otelixizumab (TRX4), in Subjects with Psoriasis and with Type 1 Diabetes Mellitus, *J. Clin. Pharmacol.* 50: 494-506 (2010). PMID: 19934031
527. Bulitta JB, Yang JC, Yohonn L, Ly NS, Brown SV, D'Hondt RE, Jusko WJ, Forrest A, Tsuji BT, Attenuation of Colistin Bactericidal Activity by High Inoculum of *Pseudomonas Aeruginosa* Characterized by a New Mechanism-Based Population Pharmacodynamic Model, *Antimicrob Agents Chemother.* 54: 2051-2062 (2010). PMID: 20211900
528. Scheff JD, Almon RR, DuBois DC, Jusko WJ, and Androulakis IP, A New Symbolic Representation for the Identification of Informative Genes in Replicated Microarray Experiments, *OMICS J. Integrative Bio.*, 14: 239-248 (2010). PMID: 20455749
529. Nguyen TT, Almon RR, DuBois DC, Jusko WJ, and Androulakis IP, Importance of Replication in Analyzing Time-Series Gene Expression Data: Corticosteroid Dynamics and Circadian Patterns in Rat Liver, *BMC Bioinformatics*, 11:279 (2010). PMID: 20500897
530. Hale G, Rebello P, al Bakir I, Bolam E, Wiczling P, Jusko WJ, Vandemeulebrouck E, Keymeulen B, Mathieu C, Ziegler A, Chatenoud L, Pipeleers D, and Waldmann H, Pharmacokinetics and Antibody Responses to a CD3 Antibody Otelixizumab Used in the Treatment of Type 1 Diabetes, *J. Clin. Pharmacol.* 50:1238-1248 (2010). PMID: 20147616
531. Ghoshal (Gutpa) S, Rao I, Earp JC, Jusko WJ, and Wetzler M, Down-Regulation of Heat Shock Protein 70 Improves Arsenic Trioxide and 17-DMAG Effects on Constitutive Signal Transducer and Activator of Transcription 3 Activity, *Cancer Chemother. Pharmacol.* 66: 681-689 (2010). PMID: 20035426
532. Findling RL, Landersdorfer CB, Kafantaris V, Pavuluri M, McNamara NK, McClellan J, Frazier JA, Sikich L, Kowatch R, Lingler J, Faber J, Taylor-Zapata P, and Jusko WJ, First-Dose Pharmacokinetics of Lithium Carbonate in Children and Adolescents, *J. Clin. Psychopharm.* 30: 404-410 (2010). PMID: 20531219
533. Landersdorfer CB and Jusko WJ, Pharmacokinetic/Pharmacodynamic Modeling of Glucose Clamp Effects of Inhaled and Subcutaneous Insulin in Healthy Volunteers and Diabetic Patients, *Drug Met. Pharmacokin.* 25:418-429 (2010). PMID: 20924141
534. Sukumaran S, Almon RR, DuBois DC, and Jusko WJ, Circadian Rhythms in Gene Expression: Relationship to Physiology, Disease, Drug Disposition and Drug Action, *Adv. Drug Delivery Rev.*, 62: 904-917 (2010). PMID: 20542067
535. Sukumaran S, Xue B, Jusko WJ, DuBois DC, and Almon RR, Circadian Variations in Gene Expression in Rat Abdominal Adipose Tissue and Relationship to Physiology, *Physiol. Genomics*, 42A:141-152 (2010). PMID: 20682845
536. Ovacik MA, Sukumaran S, Almon RR, DuBois DC, Jusko WJ, and Androulakis IP, Circadian Signatures in Rat Liver: From Gene Expression to Pathways, *BMC Bioinformatics*, 11:540 (2010). PMID: 21040584
537. Nguyen TT, Almon RR, DuBois DC, Jusko WJ, and Androulakis IP, Comparative Analysis of Acute and Chronic Corticosteroid Pharmacogenomic Effects in Rat Liver: Transcriptional Dynamics and Regulatory Structures, *BMC Bioinformatics*, 11:515 (2010). PMID: 20946642
538. Gao W, Bihorel S, DuBois DC, Almon RR, and Jusko WJ, Mechanism-Based Disease Progression Modeling of Type 2 Diabetes in Goto-Kakizaki Rats, *J. Pharmacokin. Pharmacodyn.*, 38:143-162 (2011). PMID: 21127951
539. Gao W and Jusko WJ, Pharmacokinetic and Pharmacodynamic Modeling of Exendin-4 in Type 2 Diabetic Goto-Kakizaki Rats, *J. Pharmacol Exper. Ther.* 336: 881-890 (2011). PMID: 21156817
540. Nie J, DuBois DC, Jusko WJ, and Almon RR, Mechanistic Population Modeling of Diabetes Disease Progression in Goto-Kakizaki Rat Muscle, *Biopharm. Drug Disp.*, 32: 50-63 (2011). PMID: 21162119

541. Nie J, Xue B, Sukumaran S, Jusko WJ, DuBois DC, and Almon RR, Differential Muscle Gene Expression as a Function of Disease Progression in Goto-Kakizaki Diabetic Rats, *Mol. Cell. Endocrin.*, 338: 10-17 (2011). PMID: 21356272
542. Bai JPF, Bell R, Burckart GJ, Buckman S, Eichler HG, Goodsaid FM, Fang KC, Jusko WJ, Lesko LL, Meibohm B, Patterson SD, Puig O, Smerage JB, Wagner JA, Wang J, Walton M, and Weiner R, Translational Biomarkers: From Preclinical to Clinical, A Report of 2009 AAPS/ACCP Biomarker Workshop, *AAPS J*, 13: 274-283 (2011). PMID: 21448748
543. Xue B, Sukumaran S, Nie J, Jusko WJ, DuBois DC, and Almon RR, Adipose Tissue Deficiency and Chronic Inflammation in Diabetic Goto-Kakizaki Rats, *PLoS One*, 6:e17386 (2011). PMID: 21364767
544. Scheff JD, Almon RR, DuBois DC, Jusko WJ, and Androulakis IP, Assessment of Pharmacologic Area Under the Curve when Baselines are Variable, *Pharm. Res.*, 28: 1081-1089 (2011). PMID: 21234658
545. Lon H-K, Liu D, Zhang Q, DuBois DC, Almon RR, and Jusko WJ, Pharmacokinetic-Pharmacodynamic-Disease Progression Model for Effect of Etanercept in Lewis Rats with Collagen-Induced Arthritis, *Pharm. Res.* 28: 1622-1630 (2011). PMID: 21360252
546. Landersdorfer CB, He YL, Jusko WJ, Mechanism-Based Population Pharmacokinetic Modelling in Diabetes: Vildagliptin as a Tight Binding Inhibitor and Substrate of Dipeptidyl Peptidase IV, *Brit. J. Clin. Pharmacol.* 73: 391-401 (2012). PMID: 22442826
547. Landersdorfer CB, He YL, Jusko WJ, Mechanism-Based Population Modelling of the Effects of Vildagliptin on GLP-1, Glucose and Insulin in Patients with Type 2 Diabetes, *Brit. J. Clin. Pharmacol.* 73: 373-390 (2012). PMID: 22442825
548. Fang J, DuBois DC, He Y, Almon RR, and Jusko WJ, Dynamic Modeling of Methylprednisolone Effects on Body Weight and Glucose Regulation in Rats, *J. Pharmacokin. Pharmacodyn.* 38: 293-316 (2011). PMID: 21394487
549. Moller JB, Jusko WJ, Gao W, Hansen T, Pedersen O, Holst JJ, Overgaard RV, Madsen H, and Ingwersen SH, Mechanism-Based Population Modelling for Assessment of L-Cell Function Based on Total GLP-1 Response Following an Oral Glucose Tolerance Test, *J. Pharmacokin. Pharmacodyn.*, 38: 713-725 (2011). PMID: 21922329
550. Sukumaran S, Jusko WJ, DuBois DC, and Almon RR, Light/Dark Oscillations in the Lung Transcriptome: Implications for Lung Homeostasis, Repair, Metabolism, Disease and Drug Action, *J. Appl. Physiol.* 110:1732-1747 (2011). PMID: 21436464
551. Sukumaran S, Jusko WJ, DuBois DC, and Almon RR, Mechanistic Modeling of the Effects of Glucocorticoids and Circadian Rhythms on Adipokine Expression, *J. Pharmacol. Exp. Ther.* 337: 734-746 (2011). PMID: 21398515
552. Cao Y, DuBois DC, Sun H, Almon RR, and Jusko WJ, Modeling Diabetes Disease Progression and Salsalate Intervention in Goto-Kakizaki Rats, *J. Pharmacol. Exp. Ther.* 339: 896-904 (2011). PMID: 21903749
553. Cao Y, Gao W, and Jusko WJ, Pharmacokinetic/Pharmacodynamic Modeling of GLP-1 in Healthy Rats, *Pharm. Res.* 29: 1078-1086 (2012). PMID: 22179928
554. Liu D, Lon H-K, DuBois DC, Almon RR, and Jusko WJ, Population Pharmacokinetic - Pharmacodynamic - Disease Progression Model for Effects of Anakinra in Lewis Rats with Collagen-Induced Arthritis, *J. Pharmacokin. Pharmacodyn.* 38: 769-786 (2011). PMID: 22002845
555. Gao W and Jusko WJ, Target-Mediated Pharmacokinetic and Pharmacodynamic Model of Exendin-4 in Rats, Monkeys and Man, *Drug Met. Disp.* 40: 990-997 (2012). PMID: 22338110
556. Gao W and Jusko WJ, Modeling Disease Progression and Rosiglitazone Intervention in Type 2 Diabetic Goto-Kakizaki Rats, *J. Pharmacol. Exp. Ther.* 341: 617-625 (2012). PMID: 22378938
557. Sukumaran S, DuBois DC, Jusko WJ, and Almon RR, Glucocorticoid Effects on Adiponectin Expression in Adiponectin, *Vitamins & Hormones Series*, ISBN: 978-0-12-398313-8, Vol. 90, Chpt 7, pp. 163-186, Elsevier Inc., Editor: G. Litwack (2012). PMID: 23017716
558. Sukumaran S, Lepist E-I, DuBois DC, Almon RR, and Jusko WJ, Pharmacokinetic/Pharmacodynamic Modeling of Methylprednisolone Effects on iNOS mRNA Expression and Nitric Oxide During LPS-

- Induced Inflammation in Rats, *Pharm. Res.* 29: 2060-2069 (2012). PMID: 22422321
559. Cao Y, DuBois DC, Almon RR, and Jusko WJ, Pharmacokinetics of Salsalate and Salicylic Acid in Normal and Diabetic Rats, *Biopharm. Drug Disp.*, 33: 285-291 (2012). PMID: 22782506
 560. Jusko WJ, Use of Pharmacokinetic Data Below Lower Limit of Quantitation Values, *Pharm. Res.* 29: 2628-2631 (2012). PMID: 22729370
 561. Lon H-K, Liu D, and Jusko WJ, Pharmacokinetic/Pharmacodynamic Modeling in Inflammation, *Crit. Rev. Biomed Eng.* 40: 295-312 (2012). PMID: 23140121
 562. Almon RR, DuBois DC, Sukumaran S, Wang X, Xue B, Nie J and Jusko WJ, Effects of High Fat Feeding on Liver Gene Expression in Diabetic Goto-Kakizaki Rats, *Gene Regulation and Systems Biology* 6: 151-168 (2012). PMID: 23236253
 563. Cao Y and Jusko WJ, Applications of Minimal Physiologically-Based Pharmacokinetic Models, *J. Pharmacokin. Pharmacodyn.* 39: 711-723 (2012). PMID: 23179857
 564. Fang J, Landersdorfer CB, Cirincione B, and Jusko WJ, Study Reanalysis Using a Mechanism-Based Pharmacokinetic/Pharmacodynamic Model of Pramlintide in Subjects with Type 1 Diabetes, *AAPSJ* 15: 15-29 (2013). PMID: 23054970
 565. Pawaskar DK, Straubinger RM, Fetterly GJ, Ma WW, and Jusko WJ, Interactions of Everolimus and Sorafenib in Pancreatic Cancer Cells, *AAPSJ* 15: 78-84 (2013). PMID: 23054975
 566. DuBois DC, Sukumaran S, Jusko WJ, and Almon RR, Evidence for a Glucocorticoid Receptor Beta Splice Variant in the Rat and Its Physiological Regulation in Liver, *Steroids* 78: 312-320 (2013). PMID: 23257260
 567. Pawaskar DK, Straubinger RM, Fetterly GJ, Ma WW, and Jusko WJ, Interactions of Everolimus and Sorafenib in Whole Blood Lymphocyte Proliferation, *Pharm. Res.* 30: 707-713 (2013). PMID: 23151723
 568. Pawaskar DK, Straubinger RM, Fetterly GJ, Hylander BH, Repasky EA, Ma WW, and Jusko WJ, Synergistic Interactions Between Sorafenib and Everolimus in Pancreatic Cancer Xenografts in Mice, *Cancer Chemother. Pharmacol.* 71: 1231-1240 (2013). PMID: 23455452
 569. Pawaskar DK, Straubinger RM, Fetterly GJ, Hylander BH, Repasky EA, Ma WW, and Jusko WJ, Physiologically-Based Pharmacokinetic Models for Everolimus and Sorafenib in Mice, *Cancer Chemother. Pharmacol.* 71: 1219-1229 (2013). PMID: 23455451
 570. Sorger PK, Allerheiligen SRB, Abernethy DR, Altman RB, Brouwer KLR, Califano A, D'Argenio DZ, Iyenger R, Jusko WJ, Lalonde R, Lauffenburger DA, Shoichet B, Stevens JL, Subramaniam S, Van der Graaf P, and Vicini P, Quantitative and Systems Pharmacology in the Postgenomic Era: New Approaches to Discovering and Understanding Therapeutic Drugs and Mechanisms, An NIH White Paper from the QSP Workshop Group – July, 2011, <http://www.nigms.nih.gov/News/Reports/201110-syspharma.htm>.
 571. Liu D-Y, Lon H-K, Wang Y-L, DuBois DC, Almon RR, and Jusko WJ, Pharmacokinetics, Pharmacodynamics, and Toxicities of Methotrexate in Healthy and Collagen-induced Arthritic Rats, *Biopharm. Drug Disp.* 34: 203-214 (2013). PMID: 23456770
 572. Jusko WJ, Moving from Basic toward Systems Pharmacodynamic Models, *J. Pharm. Sci.* 102: 2930-2940 (2013). PMID: 23681608
 573. Cao Y, Balthasar JP, and Jusko WJ, Second-Generation Minimal Physiologically-Based Pharmacokinetic Model for Monoclonal Antibodies, *J. Pharmacokin. Pharmacodyn.* 40: 597-607 (2013). PMID: 23996115
 574. Hamed SS, Straubinger RM, and Jusko WJ, Pharmacodynamic Modeling of Cell Cycle and Apoptotic Effects of Gemcitabine on Pancreatic Adenocarcinoma Cells, *Cancer Chemother. Pharmacol.* 72: 553-563 (2013). PMID: 23835677
 575. Lon H-K, Liu D-Y, DuBois DC, Almon RR, and Jusko WJ, Modeling Pharmacokinetics/Pharmacodynamics of Abatacept and Disease Progression in Collagen-Induced Arthritic Rats: A Population Approach, *J. Pharmacokin. Pharmacodyn.* 40: 701-712 (2013). PMID: 24233383
 576. Fang J, Sukumaran S, DuBois DC, Almon RR, and Jusko WJ, Meta-Modeling of Methylprednisolone Effects on Glucose Regulation in Rats, *PLoS One* 8: e81679 (2013). PMID: 24312573
 577. Nguyen T, Almon RR, DuBois DC, Sukumaran S, Jusko WJ, and Androulakis IP, Tissue-specific Gene

- Expression and Regulation in Liver and Muscle following Chronic Corticosteroid Administration, *Gene Reg. Sys. Biol.* 8:75-87 (2014). PMID: 24653645
578. He Y, Brunstrom-Hernandez JE, Thio LL, Lackey S, Gaebler-Spira G, Kuroda MM, Stashinko E, Hoon Jr AH, Vargus-Adams J, Stevenson RD, Lowenhaupt S, McLaughlin JF, Christensen A, Dosa NP, Butler M, Schwabe A, Lopez C, Roge D, Kennedy D, Tilton A, Krach LE, Lewandowski A, Dai H, Gaedigk A, Leeder JS, and Jusko WJ, Population Pharmacokinetics of Oral Baclofen in Pediatric Patients with Cerebral Palsy, *J. Peds.* 164: 1181-1188 (2014). PMID: 24607242
 579. Cao Y and Jusko WJ, Survey of Monoclonal Antibody Disposition in Man Utilizing a Minimal Physiologically-Based Pharmacokinetic Model, *J. Pharmacokin. Pharmacodyn.* 41: 571-580 (2014). PMID: 25146360
 580. Grimsrud KN, Ait-Oudhia S, Durbin-Johnson BP, Rocke DM, Mama KR, Rezende ML, Stanley SD, and Jusko WJ, Pharmacokinetic and Pharmacodynamic Analysis Comparing Diverse Effects of Detomidine, Medetomidine and Dexmedetomidine in the Horse: A Population Analysis, *J. Vet. Pharmacol. Ther.* 38: 24-34 (2014). PMID: 25073816
 581. Nouri-Nigjeh E, Sukumaran S, Tu C, Li J, Yu H, Duan X, DuBois DC, Almon RR, Jusko WJ and Qu J, Highly Multiplexed and Reproducible Ion Current-Based Strategy for Large-Scale Quantitative Proteomics with Application to Protein Expression Dynamics Induced by Methylprednisolone in 60 Animals, *Analytical Chem.* 86: 8149-8157 (2014). PMID: 25072516
 582. Wang X, DuBois DC, Sukumaran S, Ayyar V, Jusko WJ, and Almon RR, Diabetes disease progression in Goto-Kakizaki rats: effects of salsalate treatment, *Diabetes Metab. Syndr. Obes.: Targets and Therapy* 7: 381-389 (2014). PMID: 25120374
 583. Cao Y and Jusko WJ, Incorporating Target-Mediated Drug Disposition in a Minimal Physiologically-Based Pharmacokinetic Model for Monoclonal Antibodies, *J. Pharmacokin. Pharmacodyn.* 41: 375-387 (2014). PMID: 25077917
 584. Wang X, DuBois DC, Sukumaran S, Ayyar V, Jusko WJ, and Almon RR, Variability in Zucker Diabetic Fatty Rats: Differences in Disease Progression in Hyperglycemic and Normoglycemic Animals, *Diabetes Metab. Syndr. Obes.: Targets and Therapy* 7: 531-541 (2014). PMID: 25419150
 585. Kamisoglu K, Sukumaran S, Nouri-Nigjeh E, Tu C, Li J, Shen X, Duan X, Qu J, Almon RR, DuBois DC, Jusko WJ, and Androulakis IP, Tandem Analysis of Transcriptome and Proteome Changes after a Single Dose of Corticosteroid: A System Approach to Liver Function in Pharmacogenomics, *OMICS J. Integrative Bio.* 19: 80-91 (2015). PMID: 25611119
 586. Ayyar V, Almon RR, Jusko WJ, and DuBois DC, Quantitative Tissue-Specific Dynamics of In Vivo GILZ mRNA Expression and Regulation by Endogenous and Exogenous Glucocorticoids, *Physiol Rep.* 3(6):e12382 (2015). PMID: 26056061
 587. Chen X, DuBois DC, Almon RR, and Jusko WJ, Biodistribution of Etanercept to Tissues and Sites of Inflammation in Arthritic Rats, *Drug Met. Disp.* 43:898-907 (2015). PMID: 25834031
 588. Zhao J, Cao Y, and Jusko WJ, Across-Species Scaling of Monoclonal Antibody Pharmacokinetics Using a Minimal PBPK Model, *Pharm. Res.* 32: 3269-3281 (2015). PMID: 25939552
 589. Xue B, Nie J, Wang X, DuBois DC, Jusko WJ and Almon RR, Effects of High Fat Feeding on Adipose Tissue Gene Expression in Diabetic Goto-Kakizaki Rats, *Gene Reg. Sys. Bio.* 9: 15-26 (2015). PMID: 26309393
 590. Lon HK, DuBois DC, Earp JC, Almon RR and Jusko WJ, Modeling Effects of Dexamethasone on Disease Progression of Bone Mineral Density in Collagen-Induced Arthritic Rats, *Pharmacol. Res. Perspect.*, 3(5):e00169 (2015). PMID: 26516581
 591. Yoo H, Iirola T, Vilo S, Manner T, Aantaa R, Lahtinen M, Scheinin M, Jusko WJ, and Olkkola KT, Mechanism-Based Population Pharmacokinetic and Pharmacodynamic Modeling of Intravenous and Intranasal Dexmedetomidine in Healthy Subjects, *Eur. J. Clin. Pharmacol.* 71: 1197-1207, (2015). PMID: 26233335
 592. Estep JH, Melloni C, Thornburg CD, Wiczling P, Rogers Z, Rothman JA, Green NS, Liem R, Brandow AM, Crary SE, Howard TH, Morris MH, Lewandowski A, Garg U, Jusko WJ, and Neville KA, on behalf

- of the Best Pharmaceuticals for Children Act – Pediatric Trials Network Administrative Core Committee, Pharmacokinetics and Bioequivalence of a Liquid Formulation of Hydroxyurea in Children with Sickle Cell Anemia, *Blood*, J. Clin. Pharmacol. 56: 298-306 (2016). PMID: 26201504
593. Zhu X, Straubinger RM, and Jusko WJ, Mechanism-Based Mathematical Modeling of Combined Gemcitabine and Birinapant in Pancreatic Cancer Cells, *J. Pharmacokin. Pharmacodyn.* 42: 477-496 (2015). PMID: 26252969
 594. Miao X, Koch G, Straubinger RM, and Jusko WJ, Pharmacodynamic Modeling of Combined Chemotherapeutic Effects Predicts Synergistic Activity of Gemcitabine and Trabectedin in Pancreatic Cancer Cells, *Cancer Chemother. Pharmacol.* 77: 181-193 (2016). PMID: 26604207
 595. Fung H-L and Jusko WJ, Perspectives on the History and Scientific Contributions of Gerhard Levy, *J. Pharmacokin. Pharmacodyn.* 42:429–446 (2015). PMID: 26403702
 596. Cao Y and Jusko WJ, Mechanistic Physiologically Based Pharmacokinetic Models in Development of Therapeutic Monoclonal Antibodies in: ADME and Translational PK/PD of Therapeutic Proteins, ISBN: 978-1-118-89864-2, Chpt 12, pp. 159-174, John Wiley & Sons, Inc., New Jersey, Editors: H. Zhou & F.P. Theil (2015).
 597. Rao R, DuBois DC, Almon RR, Jusko WJ, and Androulakis I, Mathematical Modeling of the Circadian Dynamics of the Neuroendocrine-Immune Network in Experimentally Induced Arthritis, *Am. J. Physiol. Endocrinol. Metab.* 311:E310-24 (2016). PMID: 27221115
 598. Chen X, Jiang X, Jusko WJ, Zhou H, and Wang W, Minimal Physiologically-Based Pharmacokinetic (mPBPK) Model for a Monoclonal Antibody against Interleukin-6 in Mice with Collagen-Induced Arthritis, *J. Pharmacokin. Pharmacodyn.* 43:291-304 (2016). PMID: 27119518
 599. Koch G, Schropp J, and Jusko WJ, Assessment of Non-linear Combination Effect Terms for Drug-Drug Interactions, *J. Pharmacokin. Pharmacodyn.* 43: 461-479 (2016). PMID: 27638639
 600. Jusko WJ, Perspectives on Variability in Pharmacokinetics of an Oral Contraceptive Product, *Contraception*, 95: 5-9 (2017). PMID: 27475034
 601. Jusko WJ, Clarification of Contraceptive Drug Pharmacokinetics in Obesity, *Contraception*, 95: 10-16 (2017). PMID: 27542520
 602. Miao X, Koch G, Ait-Oudhia S, Straubinger RM, and Jusko WJ, Pharmacodynamic Modeling of Cell Cycle Effects of Drug Combinations in Pancreatic Cancer Cells: Analysis of Gemcitabine and Trabectedin Interactions, *Front. Pharmacol.* <http://dx.doi.org/10.3389/fphar.2016.00421> 7: Article 421: 1-16 (2016). PMID: 27895579
 603. Jusko WJ, Foundations of Pharmacodynamic Systems Analysis, In: *Systems Pharmacology and Pharmacodynamics*, AAPS Advances in the Pharmaceutical Sciences Series 23, ISBN: 978-3-319-44534-2, Chap. 8, pp. 161-175, Springer, NY, Editors: DM Mager and H Kimko (2016).
 604. Koch G, Jusko WJ, and Schropp J, Target-Mediated Drug Disposition with Drug-Drug Interaction, Part I: Single Drug Case in Alternative Formulations, *J. Pharmacokin. Pharmacodyn.*, 44:17-26 (2017). PMID: 28074395
 605. Koch G, Jusko WJ, and Schropp J, Target-Mediated Drug Disposition with Drug-Drug Interaction, Part II: Competitive and Uncompetitive Cases, *J. Pharmacokin. Pharmacodyn.*, 44:27-42 (2017). PMID: 28074396
 606. Vali P, Chandrasekharan P, Rawat M, Gugino S, Koenigsknecht C, Helman J, Jusko WJ, Wyckoff MH, Mathew B, Berkelhamer S, Nair J, and Lakshminrusimha S, Evaluation of Timing and Route of Epinephrine in a Neonatal Model of Asphyxial Arrest, *J. Amer. Heart Assoc.*, Feb 18;6(2) (2017). PMID: 28214793
 607. Kamisoglu K, Acevedo A, Almon RR, Coyle S, Corbett S, DuBois DC, Nguyen TT, Jusko WJ, and Androulakis IP, Understanding Physiology in the Continuum: Integration of Information from Multiple -omics Levels, *Front. Pharmacol.* <https://doi.org/10.3389/fphar.2017.00091> 8: Article 91: 1-19 (2017). PMID: 28289389
 608. Ayyar VS, Almon RR, DuBois DC, Sukumaran S, Qu J, and Jusko WJ, Functional Proteomic Analysis of

- Corticosteroid Pharmacodynamics in Rat Liver: Relationship to Hepatic Stress, Signaling, Energy Regulation, and Drug Metabolism, *J. Proteomics* <http://dx.doi.org/10.1016/j.jprot.2017.03.007> 160:84-105 (2017). PMID: 28315483
609. Li X, DuBois DC, Almon RR, and Jusko WJ, Effect of Disease-Related Changes in Plasma Albumin on the Pharmacokinetics of Naproxen in Male and Female Arthritic Rats, *Drug Metab. Disp.* 45: 476-483 (2017). PMID: 28246126
 610. Li X, DuBois DC, Almon RR, and Jusko WJ, Modeling Sex Differences in Pharmacokinetics, Pharmacodynamics, and Disease Progression Effects of Naproxen in Rats with Collagen-Induced Arthritis, *Drug Metab. Disp.* 45:484-491 (2017). PMID: 28246127
 611. Chen X, DuBois DC, Almon RR, and Jusko WJ, Characterization and Interspecies Scaling of rhTNF- α Pharmacokinetics with Minimal Physiologically-Based Pharmacokinetic (mPBPK) Models, *Drug Metab. Disp.* 45:798-806 (2017). PMID: 28411279
 612. Chen X, DuBois DC, Almon RR, and Jusko WJ, Interrelationships between Infliximab and rhTNF- α in Plasma using Minimal Physiologically-Based Pharmacokinetic (mPBPK) Models, *Drug Metab. Disp.* 45:790-797 (2017). PMID: 28411280
 613. Li X, DuBois DC, Song D, Almon RR, Jusko WJ and Chen X, Modeling Combined Immunosuppressive and Anti-inflammatory Effects of Dexamethasone and Naproxen in Rats Predicts the Steroid-Sparing Potential of Naproxen, *Drug Metab. Disp.* 45:834-845 (2017). PMID: 28416614
 614. Nie J, DuBois DC, Xue B, Jusko WJ and Almon RR, Effects of High Fat Feeding on Skeletal Muscle Gene Expression in Diabetic Goto-Kakizaki Rats, *Gene Reg. Syst. Biol.* 11: 1-11 (2017). PMID: 28607540
 615. Ayyar VS, DuBois DC, Almon RR, and Jusko WJ, Mechanistic Multi-Tissue Modeling of Glucocorticoid-Induced Leucine Zipper Regulation: Integrating Circadian Gene Expression with Receptor-Mediated Corticosteroid Pharmacodynamics, *J. Pharmacol. Exp. Ther.* 363:45-57 (2017). PMID: 28729456
 616. McLaughlin MJ, He Y, Brunstrom-Hernandez J, Thio LL, Carleton BC, Ross CJD, Gaedigk A, Lewandowski A, Dai H, Jusko WJ, and Leeder JS, Pharmacogenomic Variability of Oral Baclofen Clearance and Clinical Response in Children with Cerebral Palsy, *PM&R* 10: 235-244 (2018). PMID: 28867665
 617. Zhu X, Shen X, Qu J, Straubinger RM, and Jusko WJ, Proteomic Analysis of Combined Gemcitabine and Birinapant in Pancreatic Cancer, *Front. Pharmacol.* <https://doi.org/10.3389/fphar.2018.00084> 9: Article 84: 1-14 (2018). PMID: 29520231
 618. Chen X, Jiang X, Doddareddy R, Geist B, McIntosh T, Jusko WJ, Zhou H, and Wang W, Development and Translational Application of a Minimal Physiologically-Based Pharmacokinetic (mPBPK) Model for a Monoclonal Antibody (mAb) Against Interleukin 23 (IL-23) in IL-23-Induced Psoriasis-Like (PsL) Mice, *J. Pharmacol. Exp Ther.* 365:140-155 (2018). PMID: 29420255
 619. Ayyar V, Sukumaran S, DuBois DC, Almon RR, Qu J, and Jusko WJ, Receptor/Gene/Protein-Mediated Signaling Connects Methylprednisolone Exposure to Metabolic and Immune-Related Pharmacodynamic Actions in Liver, *J. Pharmacokin. Pharmacodyn.* doi: 10.1007/s10928-018-9585-x, 45: 557-575 (2018). PMID: 29704219
 620. Mavroudis PD, DuBois DC, Almon RR and Jusko WJ, Daily Variation of Gene Expression in Diverse Rat Tissues, *PLoS One*, 13: e0197258 (2018). PMID: 29746605
 621. Mavroudis PD, DuBois DC, Almon RR and Jusko WJ, Modeling Circadian Variability of Core-Clock and Clock-Controlled Genes in Four Tissues of the Rat, *PLoS One*, 13: e0197534 (2018). PMID: 29894471
 622. Molins EAG and Jusko WJ, Assessment of Three-Drug Combination Pharmacodynamic Interactions in Pancreatic Cancer Cells, *AAPS J* 20:80 doi: 10.1208/s12248-018-0235-4 (2018). PMID: 29951754
 623. Zhu X, Shen X, Qu J, Straubinger RM, and Jusko WJ, Multi-Scale Network Model Supported by Proteomics Data for Combined Gemcitabine and Birinapant Effects in Pancreatic Cancer Cells, *CPT:PSP* 7: 549-561 (2018). PMID: 30084546
 624. Li X, Jusko WJ and Cao Y, Role of Interstitial Fluid Turnover on Target Suppression by Therapeutic Biologics Using a Minimal Physiologically-based Pharmacokinetic (mPBPK) Model, *J. Pharmacol. Exp.*

- Ther. 367: 1-8 (2018). PMID: 30002096
625. Zhu X, Trueman S, Straubinger RM, and Jusko WJ, Physiologically-Based Pharmacokinetic and Pharmacodynamic Models for Gemcitabine and Birinapant in Pancreatic Cancer Xenografts, *J. Pharmacokin. Pharmacodyn.* 45: 733-746 (2018). PMID: 30069744
 626. Ayyar V, Sukumaran S, DuBois DC, Almon RR, and Jusko WJ, Modeling Corticosteroid Pharmacogenomics and Proteomics in Rat Liver, *J. Pharmacol. Exp. Ther.* 367: 168-183 (2018). PMID: 30087156
 627. Conklin LS, Damsker JM, Hoffman EP, Jusko WJ, Mavriodis P, Schwartz BD, Mengle-Gaw LJ, Smith EC, Mah JK, Guglieri M, Nevo Y, Kuntz N, McDonald CM, Tulinius M, Ryan M, Webster R, Castro D, Finkel RS, Smith AL, Morgenroth LP, Arrieta A, Shimony M, Jaros M, Shale P, McCall JM, Hathout Y, Nagaraju K, van den Anker J, Ward LM, Ahmet A, Cornish MR, and Clemens PR, Phase IIa Trial in Duchenne Muscular Dystrophy Shows Vamorolone is a First-in-class Dissociative Steroidal Anti-inflammatory Drug, *Pharmacol. Res.* 136: 140-150 (2018). PMID: 30219580
 628. Song D, DuBois DC, Almon RR, and Jusko WJ, Modeling Sex Differences in Anti-inflammatory Effects of Dexamethasone in CIA Rats, *Pharm. Res.* 35: 203 (2018). PMID: 30191329
 629. Mavroudis PD, van den Anker J, Conklin LS, Damsker JM, Hoffman EP, Nagaraju K, Clemens PR, and Jusko WJ, Population Pharmacokinetics of Vamorolone (VBP15) in Healthy Men and Boys with Duchenne Muscular Dystrophy, *J Clin. Pharmacol.*, On Line First (2019). PMID: 30742306
 630. Ayyar VS, Krzyzanski W, and Jusko WJ, Indirect Pharmacodynamic Models for Responses with Circadian Removal, *J. Pharmacokin. Pharmacodyn.*, 46: 89-101 (2019). PMID: 30694437
 631. Luo D, Westhoff CL, Edelman AB, Natavio M, Stanczyk FZ, and Jusko WJ, Altered Pharmacokinetics of Combined Oral Contraceptives in Obesity – Multi-Study Assessment, *Contraception*, 99: 256-263 (2019). PMID: 30684471
 632. Luo D, Carter K, He, X, Jusko, W, and Lovell, J, Pharmacokinetics and Pharmacodynamics of Liposomal Chemophototherapy with Short Drug-Light Intervals, *J. Control. Rel.*, 297: 39-47 (2019). PMID: 30684512
 633. Natavio M, Stanczyk FZ, Molins EA, Nelson AL, and Jusko WJ, Pharmacokinetics of the 1.5 mg Levonorgestrel Emergency Contraceptive in Women with Normal, Obese and Extremely Obese Body Mass Index, *Contraception*, 99: 306-311 (2019). PMID: 30703352
 634. Acevedo A, Berthel A, DuBois D, Almon RR, Jusko WJ, and Androulakis IP, Pathway-Based Analysis of the Liver Response to Intravenous Methylprednisolone Administration in Rats: Acute Versus Chronic Dosing. *Gene Regul. Syst. Bio.*, 13: 1–20 (2019). PMID: 31019365
 635. Ayyar VS, Song D, DuBois DC, Almon RR, Jusko WJ, Modeling Corticosteroid Pharmacokinetics and Pharmacodynamics – I: Determination and Prediction of Dexamethasone and Methylprednisolone Tissue Binding in the Rat, *J. Pharmacol. Exp. Ther.*, 370: 318-326 (2019). PMID: 31197020
 636. Ayyar VS, DuBois DC, Nakamura T, Almon RR, and Jusko WJ, Modeling Corticosteroid Pharmacokinetics and Pharmacodynamics – II: Sex Differences in Methylprednisolone Pharmacokinetics and Corticosterone Suppression, *J. Pharmacol. Exp. Ther.*, 370:327-336 (2019). PMID: 31197019
 637. Ayyar VS, DuBois DC, Almon RR, and Jusko WJ, Modeling Corticosteroid Pharmacokinetics & Pharmacodynamics – III: Estrous Cycle- and Estrogen Receptor-Dependent Antagonism of GILZ Enhancement by Corticosteroids, *J. Pharmacol. Exp. Ther.*, 370: 337-349 (2019). PMID: 31197018
 638. Barcellos T, Natavio M, Stanczyk FZ, Luo D, Jusko WJ, and Bender NM, Effects of Ritonavir-Boosted Protease Inhibitors on Combined Oral Contraceptive Pharmacokinetics and Pharmacodynamics in HIV-Positive Women, *Contraception*, 100:2 83-287 (2019). PMID: 31194965
 639. Mavroudis PD, Ayyar VS, and Jusko WJ, ATLAS mPBPK: a MATLAB-based Tool for Modeling and Simulation of Minimal Physiologically Based Pharmacokinetic Models, *CPT:PSP*, 8: 557-566 (2019). PMID: 31154668
 640. Yu R, Song D, DuBois DC, Almon RR, and Jusko WJ, Modeling Combined Anti-Inflammatory Effects of Dexamethasone and Tofacitinib in Arthritic Rats, *AAPS J* 21: 93 (pp. 1-9) (2019). PMID: 31342216
 641. Jusko WJ, Journal Editor's Final Report, *J. Pharmacokin. Pharmacodyn.*, 46: 511-512 (2019). PMID:

31720983

642. Jobe AH, Milad MA, Peppard T, and Jusko WJ, Pharmacokinetics and Pharmacodynamics of Intramuscular and Oral Betamethasone and Dexamethasone in Reproductive Age Women in India, *Clin Transl Sci.* 13: 391-399 (2020). PMID: 31808984
643. Ayyar VS and Jusko WJ, Transitioning from Basic Towards Systems Pharmacodynamic Models: Lessons from Corticosteroids, *Pharmacol. Rev.*, 72: 414-438 (2020). PMID: 32123034
644. Yu R, Li X, DuBois DC, Almon RR, Cao Y, and Jusko WJ, Interactions of Tofacitinib and Dexamethasone on Lymphocyte Proliferation, *Pharm. Res.*, 37: 105 (2020). PMID: 32458079
645. Li X, Conklin LS, van den Anker J, Hoffman EP, Clemens PR, and Jusko WJ, Exposure-Response Analysis of Vamorolone (VBP15) in Boys with Duchenne Muscular Dystrophy, *J Clin. Pharm.* 60: 1385-1396 (2020). PMID: 32434278
646. Acevedo A, Dubois D, Almon RR, Jusko WJ, and Androulakis IP, Modeling Pathway Dynamics of the Skeletal Muscle Response to Intravenous Methylprednisolone (MPL) Administration in Rats: Dosing and Tissue Effects, *Frontiers in Bioengineering and Biotechnology, Special Issue on Biol. Control Systems and Disease Modeling* 8: Article 759: 1-18, DOI=10.3389/fbioe.2020.00759; <https://www.frontiersin.org/article/10.3389/fbioe.2020.00759> (2020). PMID: 32760706
647. Chen X, Song D, Nakada S, Qiu J, Iwamoto K, Chen RH, Lim YP, Jusko WJ, and Stonestreet BS, Pharmacokinetics of Inter-Alpha Inhibitor Proteins and Effects on Hemostasis after Hypoxic-Ischemic Brain Injury in Neonatal Rats., *Curr. Pharm. Des.* 26: 1-10 (2020). PMID: 32316887
648. Ramanadhan S, Jusko WJ, and Edelman A, Pharmacokinetics of Hormonal Contraception in Individuals with Obesity: a Review, *Curr. Obstet. Gynecol. Rep.*, 9: 72-78 (2020). PMID: 33117601
649. Song D, Sun L, DuBois DC, Almon RR, Meng S, and Jusko WJ, Physiologically-Based Pharmacokinetics of Dexamethasone in Rats, *Drug Metab. Disp.*, 48: 811-818 (2020). PMID: 32601175
650. Elmeliegy M, Den Haese J, Talati C, Wetzler M, and Jusko WJ, Towards Better Combination Regimens of Cytarabine and FLT3 Inhibitors in Acute Myeloid Leukemia, *Cancer Chemother. Pharmacol.* 86: 325-337 (2020). PMID: 32748108
651. Li X, DuBois DC, Almon RR, and Jusko WJ, Physiologically-Based Pharmacokinetic Modeling Involving Nonlinear Plasma and Tissue Binding: Application to Prednisolone and Prednisone in Rats, *J. Pharmacol. Exp. Ther.*, 375: 385-396 (2020). PMID: 32883831
652. Jusko WJ, Molins EAG, and Ayyar VS, Seeking Nonspecific Binding: Assessing the Reliability of Tissue Dilutions for Calculating Fraction Unbound, *Drug Metab. Disp.*, 48: 894-902 (2020). PMID: 32759367
653. Liu X and Jusko WJ, Physiologically-Based Pharmacokinetics of Lysosomotropic Chloroquine in Rat and Man, *J. Pharmacol. Exp. Ther.*, 376: 261- 272 (2020). PMID: 33277347
654. Krzyzanski W, Milad MA, Jobe AH, Peppard T, Bies RR, and Jusko WJ, Population Pharmacokinetic Modeling of Intramuscular and Oral Dexamethasone and Betamethasone in Indian Women, *J. Pharmacokin. Pharmacodyn.*, 48: 261-272 (2021). PMID: 33389521
655. Song D and Jusko WJ, Across-Species Meta-Analysis of Dexamethasone Pharmacokinetics Utilizing Three Allometric Modeling Approaches, *Biopharm. Drug Disp.*, 42: 191-203 (2021). PMID: 33638217
656. Krzyzanski W, Milad MA, Jobe AH, Peppard T, Bies RR, and Jusko WJ, Population Pharmacodynamic Modeling of Intramuscular and Oral Dexamethasone and Betamethasone Effects on Six Biomarkers with Circadian Complexities in Indian Women, *J. Pharmacokin. Pharmacodyn.*, 48: 411-438 (2021). PMID: 33954911
657. Mavroudis P and Jusko WJ, Mathematical Modeling of Mammalian Circadian Clocks Affecting Drug and Disease Responses, *J. Pharmacokin. Pharmacodyn.*, 48: 375-386 (2021). PMID: 33725238
658. Acevedo A, Mavroudis P, Dubois D, Almon RR, Jusko WJ, and Androulakis IP, Pathway-Level Analysis of Genome-wide Circadian Dynamics in Diverse Tissues in Rat and Mouse, *J. Pharmacokin. Pharmacodyn.*, 48: 361-374 (2021). PMID: 33768484
659. Lin Q, Qian Z, Mager D, Jusko WJ, Ma WW, and Straubinger RM, Synergistic Pharmacodynamic Effects of Gemcitabine and Fibroblast Growth Factor Receptor Inhibitors on Pancreatic Cancer Cell Cycle Kinetics and Proliferation, *J. Pharmacol. Exp. Ther.*, 377: 370-384 (2021). PMID: 33753538

660. Jeong YS and Jusko WJ, Meta-Assessment of Metformin Absorption and Disposition Pharmacokinetics in Nine Species, *Pharmaceuticals*, 14(6): Article 545; <https://doi.org/10.3390/ph14060545> (2021). PMID: 34200427
661. Pawaskar D, Chen X, Glassman F, May F, Roberts A, Biondo M, McKenzie A, Nolte MW, Jusko WJ, and Tortorici M, Pharmacokinetic/Pharmacodynamic Modeling for Dose Selection in a First-in-Human Trial of Activated Factor XII Inhibitor Garadacimab (CSL312), *Clin. Transl. Sci.*, 15:709–720. (2022). PMID: 34811931
662. Jusko WJ and Li X, Assessment of the Kochak-Benet Equation for Hepatic Clearance for the Parallel-Tube Model: Relevance of Classic Clearance Concepts in PK and PBPK. *AAPS J* 24: 5 <https://doi.org/10.1208/s12248-021-00656-z> (2022). PMID: 34853928
663. Swierczek A, Pomierny B, Wyska E, and Jusko WJ, Pharmacokinetic/Pharmacodynamic Assessment of Selective Phosphodiesterase Inhibitors in a Mouse Model of Autoimmune Hepatitis, *J. Pharmacol. Exp. Ther.*, 381:151–163 (2022). PMID: 35221290
664. Jeong Y-S and Jusko WJ, Consideration of Fractional Distribution Parameter f_d in the Chen and Gross Method for Tissue-to-Plasma Partition Coefficients: Comparison of Several Methods, *Pharm. Res.*, 39:463-479 (2022). PMID: 35288804
665. Ren T, Zhu X, Jusko NM, Krzyzanski W, and Jusko WJ, Pharmacodynamic Model of Slow Reversible Binding and Its Applications in Pharmacokinetic/Pharmacodynamic Modeling: Review and Tutorial, *J. Pharmacokin. Pharmacodyn.*, 49: 493-510 (2022). PMID: 36040645
666. Jeong Y-S and Jusko WJ, Determinants of Biological Half-Lives and Terminal Slopes in Physiologically-Based Pharmacokinetic Systems: Assessment of Limiting Conditions, *AAPS J.* 24:96 (2022). PMID: 36042121
667. Li X and Jusko WJ, Assessing Liver-to-Plasma Partition Coefficients and In Silico Calculation Methods: When Does the Hepatic Model Matter in PBPK?, *Drug Metab. Disp.* 50:1501-1512, doi: 10.1124/dmd.122.000994 (2022). PMID: 36195337
668. Lin Q, Shen S, Qian Z, Rasam SS, Jusko WJ, Kandel ES, Qu J, and Straubinger RM, Comparative Proteomic Analysis Identifies Key Metabolic Regulators of Gemcitabine Resistance in Pancreatic Cancer, *Mol. Cell Proteomics* 21(10):100409. doi: 10.1016/j.mcpro.2022.100409 (2022). PMID: 36084875
669. Swierczek A and Jusko WJ, Pharmacokinetic/Pharmacodynamic Modeling of Dexamethasone Anti-Inflammatory and Immunomodulatory Effects in LPS-Challenged Rats: A Model for Cytokine Release Syndrome, *J. Pharmacol. Exp. Ther.*, 384:455–472, doi: 10.1124/jpet.122.001477 (2023). PMID: 36631280
670. Krzyzanski W, Milad MA, Jobe AH, and Jusko WJ, Minimal Physiologically-Based Hybrid Model of Pharmacokinetics in Pregnant Women: Application to Antenatal Corticosteroids, *CPT Pharmacometrics Syst. Pharmacol.* 12:668–680 (2023). PMID: 36917704
671. Li X and Jusko WJ, Exploring the Pharmacokinetic Mysteries of the Liver: Application of Series-Compartment Models of Hepatic Elimination, *Drug Metab. Disp.*, 51:618–628 (2023). PMID: 36732075
672. Jeong Y-S and Jusko WJ, Theoretical Examination Seeking a Tangible Physical Meaning of Slopes and Intercepts of the Plasma Concentration-Time Relationships in Minimal Physiologically Based Pharmacokinetic Models, *AAPS J.* 25(1):19. doi: 10.1208/s12248-022-00779-x (2023). PMID: 36702940
673. Swierczek A and Jusko WJ, Anti-Inflammatory Effects of Dexamethasone in COVID-19 Patients: Translational Population PK/PD Modeling and Simulation, *Clin. Translat. Sci.*, 16:1667-1679 (2023). PMID: 37386717
674. Jeong Y-S and Jusko WJ, A Complete Extension of Classical Clearance Models Using Fractional Distribution Parameter f_d in Physiologically Based Pharmacokinetics, *J. Pharm. Sci.*, 113: 95–117 (2024). PMID: 37279835
675. Li X and Jusko WJ, Utility of Minimal Physiologically-Based Pharmacokinetic (mPBPK) Models for Assessing Fractional Distribution, Oral Absorption and Series-Compartment Models of Hepatic Clearance, *Drug Metab. Disp.*, 1(10):1403-1418 (2023). PMID: 37460222
676. Miao X, Shen S, Koch G, Wang X, Li J, Shen X, Qu J, Straubinger RM and Jusko WJ, Systems

- Pharmacodynamic Model of Combined Gemcitabine and Trabectedin in Pancreatic Cancer Cells. Part I: Effects on Signal Transduction Pathways Related to Tumor Growth, *J. Pharm. Sci.*, 113: 214-227 (2024). PMID: XXXXX
677. Miao X, Koch G, Shen S, Wang X, Li J, Shen X, Qu J, Straubinger RM and Jusko WJ, Systems Pharmacodynamic Model of Combination Gemcitabine and Trabectedin in Pancreatic Cancer Cells. Part II: Cell Cycle, DNA Damage Response, and Apoptosis Pathways, *J Pharm Sci.*, 113: 235-245 (2024). PMID: 37918792
678. Sadan O, Jeong YS, Cohen-Sadan S, Sathialingam E, Buckley EM, Kandiah PA, Grossberg JA, Asbury W, Jusko WJ, Samuels OB, Cerebrospinal Fluid Pharmacokinetics of Nicardipine Following Intrathecal Administration in Subarachnoid Hemorrhage Patients, *medRxiv* Oct 18:2023.10.17.23297116. doi: 10.1101/2023.10.17.23297116. Preprint: *On-Line-First* (2023). PMID: 37905152
679. Li X, Sabbatini D, Pegoraro E, Bello L, Clemens P, Guglieri M, van den Anker J, Damsker J, McCall J, Dang UJ, Hoffman EP, and Jusko WJ, Assessing Pharmacogenomic *loci* Associated with the Pharmacokinetics of Vamorolone in Boys with Duchenne Muscular Dystrophy, *J. Clin. Pharmacol.*, Submitted (2024).

EXHIBIT B

DOCUMENTS CONSIDERED BY DR. WILLIAM J. JUSKO

I understand that there may be multiple versions of the materials reviewed and cited herein that have been produced, or may be produced, during the course of this litigation. To the extent that I have cited to or reviewed the documents listed herein, I reserve the right to cite to or consider otherwise identical documents that have been or will be produced during the course of the litigation that bear alternative document numbers or exhibit labels.

To the extent not listed below, documents considered also include all documents cited in my report in this case.

PATENTS/APPLICATIONS

1. U.S. Patent No. 10,335,462 and prosecution history
2. U.S. Patent No. 8,114,833
3. U.S. Patent No. 5,512,549
4. U.S. Patent Pub. No. 2011/0166321
5. U.S. Patent Pub. No. 2004/0102486
6. WO 91/11457
7. WO 2006/097537
8. WO 2011/058193
9. WO 2011/073328
10. WO 2011/138421

ARTICLES/PUBLICATIONS

1. Bell, *Hamster Preproglucagon Contains the Sequence of Glucagon and Two Related Peptides*, 302 NATURE 716 (1983)
2. Bhansali, *Historical Overview of Incretin Based Therapies*, 58 J. ASSOC. OF PHYSICIANS OF INDIA 10 (2010)

3. Blonde, *Comparison of Liraglutide Versus Other Incretin-Related Anti-Hyperglycaemic Agents*, 14 (suppl. 2) DIABETES, OBESITY & METABOLISM 20 (2012)
4. Drab, *Incretin-Based Therapies for Type 2 Diabetes Mellitus: Current Status and Future Prospects*, 30 PHARMACOTHERAPY 609 (2010)
5. EMA, *ICH Topic S 7 A Safety Pharmacology Studies for Human Pharmaceuticals* (June 2001)
6. FDA Guidance for Industry, *Exposure-Response Relationships - Study Design, Data, Analysis, and Regulatory Applications* (Apr. 2003)
7. Garber, *Efficacy of Metformin in Type II Diabetes: Results of a Double-Blind, Placebo-Controlled, Dose-Response Trial*, 102 AM. J. MED. 491 (1997)
8. Holst, *Truncated Glucagon-like Peptide I, an Insulin-Releasing Hormone from the Distal Gut*, 211 (2) FEBS LETTERS 169 (1987)
9. *International Conference on Harmonisation; Dose-Response Information to Support Drug Registration; Guideline; Availability*, 59 Fed. Reg. 55972 (Nov. 9, 1994)
10. Kirillova, *Results and Outcome Reporting in ClinicalTrials.gov, What Makes it Happen?*, 7(6) PLOS ONE 1 (2012)
11. Knudsen, *Glucagon-like Peptide-1: The Basis of a New Class of Treatment for Type 2 Diabetes*, 47 J. MED. CHEMISTRY 4128 (2004)
12. Knudsen, *Liraglutide: The Therapeutic Promise from Animal Models*, 64(suppl 167) INT J CLIN PRACT 4 (2010)
13. Landersdorfer, *Pharmacokinetic/Pharmacodynamic Modelling in Diabetes Mellitus*, 47(7) CLIN PHARMACOKINET 417 (2008)
14. Landersdorfer, *Mechanism-Based Population Pharmacokinetic Modelling in Diabetes: Vildagliptin as a Tight Binding Inhibitor and Substrate of Dipeptidyl Peptidase IV*, 73 Br J Clin Pharmacol 391 (2011)
15. Landersdorfer, *Mechanism-Based Population Modelling of the Effects of Vildagliptin on GLP-1, Glucose and Insulin in Patients with Type 2 Diabetes*, 73 BR J CLIN PHARMACOL 373 (2011)

16. Lovshin, *Incretin-Based Therapies for Type 2 Diabetes Mellitus*, 5 NATURE REV. ENDOCRINOLOGY 262 (2009)
17. Lund, *Emerging GLP-1 Receptor Agonists*, 16 EXPERT OP. ON EMERGING DRUGS 607 (2011)
18. Madsbad, *An Overview of Once-Weekly Glucagon-Like Peptide-1 Receptor Agonists - Available Efficacy and Safety Data and Perspectives for the Future*, 13 DIABETES, OBESITY & METABOLISM 394 (2011)
19. Mojsov, *Insulintropin: Glucagon-like Peptide I (7-37) Co-encoded in the Glucagon Gene is a Potent Simulator of Insulin Release in the Perfused Rat Pancreas*, 79 J. CLIN. INVEST. 616 (1987)
20. Møller, *Mechanism-Based Population Modelling for Assessment of L-Cell Function Based on Total GLP-1 Response Following an Oral Glucose Tolerance Test*, 38 J. PHARMACOKINET PHARMACODYN 713 (2011)
21. Monami, *Effects of Glucagon-Like Peptide-1 Receptor Agonists on Body Weight: A Meta-Analysis*, 2012 EXPERIMENTAL DIABETES RSCH. 1 (2012)
22. Murphy, *Review of the Safety and Efficacy of Exenatide Once Weekly for the Treatment of Type 2 Diabetes Mellitus*, 46 ANN PHARMACOTHER 812 (2012)
23. Rohatagi, *Model-Based Development of a PPAR γ Agonist, Rivoglitazone, to Aid Dose Selection and Optimize Clinical Trial Designs*, 48 J. CLIN. PHARM. 1420 (2008)
24. Seino, *Dose-Dependent Improvement in Glycemia with Once-Daily Liraglutide without Hypoglycemia or Weight Gain: A Double-Blind, Randomized, Controlled Trial in Japanese Patients with Type 2 Diabetes*, 81 DIABETES RSCH. & CLINICAL PRACTICE 161 (2008)
25. Shargel, APPLIED BIOPHARMACEUTICS & PHARMACOKINETICS (5th ed. 2005)
26. Tamimi, *Drug Development: From Concept to Marketing!*, 113 NEPHRON CLIN PRACT C125 (2009)
27. Tasneem, *The Database for Aggregate Analysis of ClinicalTrials.gov (AACT) and Subsequent Regrouping by Clinical Specialty*, 7(3) PLoS ONE 1 (2012)

28. Yun, *Pharmacokinetic and Pharmacodynamic Modelling of the Effects of Glimepiride on Insulin Secretion and Glucose Lowering in Healthy Humans*, 31 J. CLIN. PHARM. & THER. 469 (2006)

29. Zarin, *The ClinicalTrials.gov Results Database—Update and Key Issues*, 364 NEW ENGL. J. MED. 852 (2011)

WEBSITE

1. Clinical Trial No. NCT00696657 (Internet Archive)
2. Clinical Trial No. NCT00851773 (Internet Archive)
3. *Award: ClinicalTrials.gov*, <https://ash.harvard.edu/news/clinicaltrials.gov> (last visited Mar. 15, 2024)
4. *ClinicalTrials.gov Background*, CLINICALTRIALS.GOV, <https://clinicaltrials.gov/ct2/about-site/background> (last visited Mar. 15, 2024)

LABELS

1. *Victoza*, PHYSICIANS' DESK REFERENCE (65th ed. 2011)

CASE DOCUMENTS

1. Claim Construction Order (July 25, 2023), D.I. 148