

**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**

TABLE OF CONTENTS

	Page
I. QUALIFICATIONS AND BACKGROUND.....	1
A. EDUCATION AND EXPERIENCE	1
B. PRIOR TESTIMONY	5
C. BASIS FOR OPINIONS AND MATERIALS CONSIDERED	6
D. RETENTION AND COMPENSATION	6
II. LEGAL STANDARDS	7
III. PERSON OF ORDINARY SKILL IN THE ART	9
IV. BRIEF SUMMARY OF OPINIONS	11
V. THE '462 PATENT.....	12
A. THE SPECIFICATION AND CLAIMS OF THE '462 PATENT.....	12
B. THE PROSECUTION HISTORY OF THE '462 PATENT	14
VI. CLAIM CONSTRUCTION	17
VII. BACKGROUND	18
A. PHARMACOKINETICS AND PHARMACODYNAMICS.....	18
B. DRUG DEVELOPMENT – CLINICAL TRIAL DESIGN	21
C. PHARMACOKINETICS AND PHARMACODYNAMICS RELATED TO GLP-1 AND SEMAGLUTIDE	27
1. GLP-1	28
2. GLP-1 derivatives	29
D. SEMAGLUTIDE CLINICAL TRIALS.....	36
VIII. SCOPE AND CONTENT OF THE PRIOR ART.....	41
A. WO '421	42
B. LOVSHIN 2009.....	45
C. WO '537	47
D. SEMAGLUTIDE CLINICAL TRIALS.....	49
1. NCT00696657.....	49
2. NCT00851773.....	51

TABLE OF CONTENTS

(continued)

	Page
3. Public Availability of ClinicalTrials.gov.....	54
E. KNUDSEN 2004.....	60
F. LUND.....	61
G. SEINO	65
H. VICTOZA LABEL	67
I. SHARGEL	69
J. TAMIMI.....	70
K. FDA EXPOSURE RESPONSE 2003	72
L. ICH 1994	74
M. KNUDSEN 2010B	77
N. BHANSALI.....	77
O. MADSBAD 2011.....	82
P. '833 PATENT	84
Q. ADDITIONAL PRIOR ART AND REFERENCES	85
IX. INVALIDITY OF THE '462 PATENT	86
A. CLAIMS 1 AND 3 OF THE '462 PATENT ARE ANTICIPATED BY WO '421, LOVSHIN 2009, OR NCT00696657.....	86
1. WO '421 Anticipated Claims 1 and 3 of the '462 Patent.....	86
2. Lovshin 2009 Anticipated Claims 1 and 3 of the '462 Patent.....	92
3. NCT00696657 Anticipated Claims 1 and 3 of the '462 Patent.....	97
B. CLAIMS 1, 3-5, AND 7 OF THE '462 PATENT WOULD HAVE BEEN OBVIOUS	101
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	101

TABLE OF CONTENTS
(continued)

	Page
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.....	120
3. Claims 1, 3-5, and 7 of the '462 Patent Would Have Been Obvious Over WO '537 in View of Lovshin 2009.....	132
X. CONCLUSION.....	145

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.

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.