

Filed: March 16, 2023

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,

Petitioner,

v.

NOVO NORDISK A/S,

Patent Owner.

Case No. IPR2023-00723

Patent No. 8,129,343

**PETITION FOR *INTER PARTES* REVIEW OF
U.S. PATENT NO. 8,129,343**

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CASES

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<i>Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH</i> , IPR2019-01469, Paper 6 (PTAB Feb. 13, 2020) (precedential)	64
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<i>Aquestive Therapeutics, Inc. v. Neurelis, Inc.</i> , IPR2019-00451, Paper 8 (PTAB Aug. 13, 2019).....	68
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<i>Donner Tech., LLC v. Pro Stage Gear, LLC</i> , 979 F.3d 1353 (Fed. Cir. 2020)	54
<i>E.I. DuPont de Nemours & Co. v. Synvina C.V.</i> , 904 F.3d 996 (Fed. Cir. 2018)	25
<i>Eisai Co. v. Dr. Reddy's Labs., Ltd.</i> , 533 F.3d 1353 (Fed. Cir. 2008)	25
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<i>In re Applied Materials, Inc.</i> , 692 F.3d 1289 (Fed. Cir. 2012)	25, 42, 50, 56
<i>In re Boesch</i> , 617 F.2d 272 (CCPA 1980)	25, 55, 57, 59
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<i>In re Kao</i> , 639 F.3d 1057 (Fed. Cir. 2011)	60
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<i>Pentec, Inc. v. Graphic Controls Corp.</i> , 776 F.2d 309 (Fed. Cir. 1985)	62
<i>Pfizer, Inc. v. Apotex, Inc.</i> , 480 F.3d 1348 (Fed. Cir. 2007)	59

<i>Sand Revolution II, LLC v. Cont’l Intermodal Grp.,</i> IPR2019-01393, Paper 24 (PTAB June 16, 2020)	70
<i>Standard Oil Co. v. Am. Cyanamid Co.,</i> 774 F.2d 448 (Fed. Cir. 1985)	52
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<i>UCB, Inc. v. Accord Healthcare, Inc.,</i> 890 F.3d 1313, 1329 (Fed. Cir. 2018)	53
<i>Weatherford U.S., L.P. v. Enventure Glob. Tech., Inc.,</i> IPR2020-01684, Paper 16 (PTAB Apr. 14, 2021)	68
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<i>ZUP, LLC v. Nash Mfg., Inc.,</i> 896 F.3d 1365 (Fed. Cir. 2018)	60
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OTHER AUTHORITIES

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TABLE OF EXHIBITS

EXHIBIT	DESCRIPTION
1001	U.S. Patent No. 8,536,122
1002	U.S. Patent No. 8,129,343
1003	Prosecution history excerpts for U.S. Patent No. 8,536,122
1004	Prosecution history excerpts for U.S. Patent No. 8,129,343
1005	Adelhorst, <i>Structure-Activity Studies of Glucagon-like Peptide-1*</i> , 269(9) J. BIO. CHEM. 6275 (1994)
1006	Albericio, <i>Orthogonal Protecting Groups for N(alpha)-amino and C-terminal carboxyl functions in Solid-Phase Peptide Synthesis</i> , 55(2) BIOPOLYMERS 123 (2000)
1007	Baggio, <i>A Recombinant Human Glucagon-Like Peptide (GLP)-1–Albumin Protein (Albugon) Mimics Peptidergic Activation of GLP-1 Receptor–Dependent Pathways Coupled with Satiety, Gastrointestinal Motility, and Glucose Homeostasis</i> , 53(9) DIABETES 2492 (2004) (“Baggio 2004a”)
1008	Cistola, <i>Carbon 13 NMR Studies of Saturated Fatty Acids Bound to Bovine Serum Albumin. I. The filling of Individual Fatty Acid Binding Sites</i> , 262(23) J BIOL CHEM. 10971 (1987) (“Cistola I”)
1009	Cistola, <i>Carbon 13 NMR Studies of Saturated Fatty Acids Bound to Bovine Serum Albumin. II. Electrostatic Interactions in Individual Fatty Acid Binding Sites</i> , 262(23) J BIOL CHEM. 10980 (1987) (“Cistola II”)
1010	Knudsen, <i>Glucagon-Like Peptide-1: The Basis of a New Class of Treatment for Type 2 Diabetes</i> , 47(17) J MED CHEM. 4128 (2004)
1011	Knudsen, <i>GLP-1 Derivatives as Novel Compounds for the Treatment of Type 2 Diabetes: Selection of NN2211 for Clinical Development</i> , 26(7) DRUGS OF THE FUTURE (2001)
1012	U.S. Patent No. 6,268,343 (“Knudsen Patent”)

EXHIBIT	DESCRIPTION
1013	Dong, <i>Glucagon-Like Peptide-1 Analogs with Significantly Improved in vivo Activity</i> , in PEPTIDES: THE WAVE OF THE FUTURE (Michal Lebl et al. eds., 2001)
1014	U.S. Patent No. 6,514,500 (“Bridon”)
1015	Clodfelter, <i>Effects of Non-Covalent Self-Association on the Subcutaneous Absorption of a Therapeutic Peptide</i> , 15(2) PHARM. RSCH. 254 (1998)
1016	Nulf, <i>DNA Assembly using Bis-Peptide Nucleic Acids (bisPNAs)</i> , 30(13) NUCLEIC ACIDS RES.2782 (2002)
1017	Drucker, <i>Development of Glucagon-Like Peptide-1-Based Pharmaceuticals as Therapeutic Agents for the Treatment of Diabetes</i> , 7 CURRENT PHARM. DESIGN 1399 (2001)
1018	Drucker, <i>Discovery, Characterization, and Clinical Development of the Glucagon-Like Peptides</i> , 127(12) J. CLIN. INVEST. 4217 (2017)
1019	U.S. Patent No. 5,359,030
1020	Declaration of Peter Flatt, Ph.D.
1021	CV of Peter Flatt, Ph.D.
1022	Declaration of Christopher Soares, Ph.D.
1023	CV of Christopher Soares, Ph.D.
1024	Declaration of Paul Dalby, Ph.D.
1025	CV of Paul Dalby, Ph.D.
1026	Declaration of John Bantle, MD
1027	CV of John Bantle, MD
1028	U.S. Patent No. 7,576,050

EXHIBIT	DESCRIPTION
1029	Veronese, <i>Introduction and Overview of Peptide and Protein Pegylation</i> , 54 ADVANCED DRUG DELIVERY REVIEWS 453 (2002)
1030	Holst, <i>The Incretin Approach for Diabetes Treatment Modulation of Islet Hormone Release by GLP-1 Agonism</i> , 53 (suppl. 3) DIABETES S197 (2004)
1031	Holz, <i>Glucagon-Like Peptide-1 Synthetic Analogs: New Therapeutic Agents for Use in Treatment of Diabetes Mellitus</i> , 10 CURRENT MED. CHEM. 2471 (2003)
1032	Kenyon, <i>¹³C NMR Studies of the Binding of Medium-Chain Fatty Acids to Human Serum Albumin</i> , 35(3) J LIPID RES. 458 (1994)
1033	Kim, <i>Development and Characterization of a Glucagon-Like Peptide 1-Albumin Conjugate: The Ability to Activate the Glucagon-Like Peptide 1 Receptor In Vivo</i> , 52(3) DIABETES 751 (2003)
1034	Knudsen, <i>Potent Derivatives of Glucagon-Like Peptide-1 with Pharmacokinetic Properties Suitable for Once Daily Administration</i> , 43(9) J MED CHEM. 1664 (2000)
1035	Kurtzhals, <i>Albumin Binding of Insulins Acylated with Fatty Acids: Characterization of the Ligand-Protein Interaction and Correlation between Binding Affinity and Timing of the Insulin Effect in vivo</i> , 312 BIOCHEM J. 725 (1995)
1036	LEHNINGER PRINCIPLES OF BIOCHEMISTRY (David L. Nelson et al. eds., 4th ed. 2005)
1037	Luu, <i>Automated Multiple Peptide Synthesis: Improvements in Obtaining Quality Peptides</i> , 47 INT'L J. PEPTIDE PROTEIN RSCH 91 (1996)
1038	Markussen, <i>Soluble, Fatty Acid Acylated Insulins Bind to Albumin and Show Protracted Action in Pigs</i> , 39(3) DIABETOLOGIA 281 (1996)

EXHIBIT	DESCRIPTION
1039	Meinenhofer, <i>Peptide Synthesis: A Review of the Solid-Phase Method</i> , in HORMONAL PROTEINS AND PEPTIDES (Choh Hao Li ed., 1973)
1040	Tonsgard, <i>Binding of Straight-Chain Saturated Dicarboxylic Acids to Albumin</i> , 82 J. CLIN. INVEST. 1567 (1988)
1041	Pasut, <i>Protein, Peptide and Non-Peptide Drug PEGylation for Therapeutic Application</i> , 14 EXPERT OPINION ON THERAPEUTIC PATENTS 859 (2004)
1042	Peters, ALL ABOUT ALBUMIN BIOCHEMISTRY, GENETICS, AND MEDICAL APPLICATIONS (1996)
1043	Rando, <i>Functional Incorporation of Synthetic Glycolipids into Cells</i> , 77(5) PROC. NATL. ACAD. SCI. USA 2510 (1980)
1044	Roberts, <i>Chemistry for Peptide and Protein PEGylation</i> , 54(4) ADV DRUG DELIV. REV. 459 (2002)
1045	WO 03/074005 (“Sato”)
1046	U.S. Patent No. 5,512,549
1047	WO 91/11457 (“Buckley”)
1048	Banting, <i>The Internal Secretion of the Pancreas</i> , 7(5) J. LAB. & CLIN. MED. 251 (1922)
1049	Bell, <i>Hamster Preproglucagon Contains the Sequence of Glucagon and Two Related Peptides</i> , 302 NATURE 716 (1983)
1050	Holst, <i>Truncated Glucagon-like Peptide I, an Insulin-Releasing Hormone from the Distal Gut</i> , 211 (2) FEBS LETTERS 169 (1987)
1051	Mojsov, <i>Insulintropin: Glucagon-Like Peptide I (7-37) Co-Encoded in the Glucagon Gene is a Potent Stimulator of Insulin Release in the Perfused Rat Pancreas</i> , 79 J. CLIN. INVEST. 616 (1987)

EXHIBIT	DESCRIPTION
1052	Ørskov, <i>Biological Effects and Metabolic Rates of Glucagonlike Peptide-1 7-36 Amide and Glucagonlike Peptide-1 7-37 in Healthy Subjects are Indistinguishable</i> , 42 DIABETES 658 (1993)
1053	U.S. Patent No. 6,284,727
1054	Gutniak, <i>Antidiabetogenic Effect of Glucagon-Like Peptide-1 (7-36) Amide in Normal Subjects and Patients with Diabetes Mellitus</i> , 326 N. ENGL. J. MED. 1316 (1992)
1055	Madsbad, <i>Improved Glycemic Control with No Weight Increase in Patients with Type 2 Diabetes after Once-Daily Treatment with the Long-Acting Glucagon-Like Peptide 1 Analog Liraglutide (NN2211)</i> , 27 DIABETES CARE 1335 (2004)
1056	Nauck, <i>Normalization of Fasting Hyperglycaemia by Exogenous Glucagon-Like Peptide 1 (7-36 Amide) in Type 2 (Non-Insulin-Dependent) Diabetic Patients</i> , 36 DIABETOLOGIA 741 (1993)
1057	WO 87/06941
1058	Amblard, <i>Fundamentals of Modern Peptide Synthesis</i> , in PEPTIDE SYNTHESIS AND APPLICATIONS 3 (John Howl ed., 2005)
1059	Kiso, <i>Amide Formation, Deprotection, and Disulfide Formation in Peptide Synthesis</i> , in PEPTIDES: SYNTHESIS, STRUCTURES, AND APPLICATIONS 39 (Bernd Gutte ed., 1995)
1060	Bhattacharya, <i>Crystallographic Analysis Reveals Common Modes of Binding of Medium and Long-Chain Fatty Acids to Human Serum Albumin</i> , 303 J. MOL. BIOL. 721 (2000)
1061	EP 0 946 750
1062	Schmidt, <i>Fatty Acylation of Proteins</i> , 988 BIOCHIMICA ET BIOPHYSICA ACTA 411 (1989)
1063	Ozempic prescribing information (Oct. 2022)
1064	U.S. Patent No. 6,110,676

EXHIBIT	DESCRIPTION
1065	U.S. Patent No. 6,528,486
1066	U.S. Patent Application Publication No. 2007/0117743
1067	Sewald, PEPTIDES: CHEMISTRY AND BIOLOGY (2002)
1068	Drucker, <i>Enhancing Incretin Action for the Treatment of Type 2 Diabetes</i> , 26 DIABETES CARE 2929 (2003)
1069	Baggio, <i>Glucagon-like Peptide 1 and Glucagon-like Peptide 2</i> , 18 BEST PRAC. & RSCH. CLINICAL ENDOCRINOLOGY & METABOLISM 531 (2004) (“Baggio 2004b”)
1070	Luna, <i>Oral Agents in the Management of Type 2 Diabetes Mellitus</i> , 63 AM. FAM PHYSICIAN 1747 (2001)
1071	Cooper, <i>Peptides as a Platform for Targeted Therapeutics for Cancer: Peptide – Drug Conjugates (PDCs)</i> , 50 CHEM. SOC. REV. 1480 (2021)
1072	Deacon, <i>Dipeptidyl Peptidase IV Resistant Analogues of Glucagon-Like Peptide-1 which have Extended Metabolic Stability and Improved Biological Activity</i> , 41 DIABETOLOGIA 271 (1998)
1073	Joy, <i>Incretin Mimetics as Emerging Treatments for Type 2 Diabetes</i> , 39 ANN. PHARMACOTHER. 1108 (2005)
1074	Korc, <i>Update on Diabetes Mellitus</i> , 20 DISEASE MARKERS 161 (2004)
1075	Mentlein, <i>Dipeptidyl-Peptidase IV Hydrolyses Gastric Inhibitory Polypeptide, Glucagon-Like Peptide-1(7-36)Amide, Peptide Histidine Methionine and is Responsible for their Degradation in Human Serum</i> , 214 EUR. J. BIOCHEM. 829 (1993)
1076	Pyne, <i>Cyclic Nucleotide Phosphodiesterases in Pancreatic Islets</i> , 46 DIABETOLOGIA 1179 (2003)
1077	Takiya, <i>Therapeutic Options for the Management of Type 2 Diabetes Mellitus</i> , 8(11) AM. J. MANAG. CARE 1009 (2002)

EXHIBIT	DESCRIPTION
1078	Bayliss, <i>The Mechanism of Pancreatic Secretion</i> , 28(5) J. PHYSIOLOGY 325 (1902)
1079	Buse, <i>Effects of Exenatide (Exendin-4) on Glycemic Control Over 30 Weeks in Sulfonylurea-Treated Patients with Type 2 Diabetes</i> , 27 DIABETES CARE 2628 (2004)
1080	Chang, <i>The GLP-1 Derivative NN2211 Restores β-Cell Sensitivity to Glucose in Type 2 Diabetic Patients After a Single Dose</i> , 52 DIABETES 1786 (2003)
1081	Degn, <i>One Week's Treatment with the Long-Acting Glucagon-Like Peptide 1 Derivative Liraglutide (NN2211) Markedly Improves 24-h Glycemia and α- and β-Cell Function and Reduces Endogenous Glucose Release in Patients with Type 2 Diabetes</i> , 53 DIABETES 1187 (2004)
1082	Edwards, <i>GLP-1: Target for a New Class of Antidiabetic Agents?</i> , 97 J. R. SOC. MED. 270 (2004)
1083	Elbrond, <i>Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of a Single-Dose of NN2211, a Long-Acting Glucagon-Like Peptide 1 Derivative, in Healthy Male Subjects</i> , 25 DIABETES CARE 1398 (2002)
1084	Gault, <i>Glucose-Dependent Insulinotropic Polypeptide Analogues and Their Therapeutic Potential for the Treatment of Obesity-Diabetes</i> , 308 BIOCHEM. & BIOPHYSICAL RSCH. COMM'NS 207 (2003)
1085	Harder, <i>The Effect of Liraglutide, a Long-Acting Glucagon-Like Peptide 1 Derivative, on Glycemic Control, Body Composition, and 24-h Energy Expenditure in Patients with Type 2 Diabetes</i> , 27 DIABETES CARE 1915 (2004)
1086	Larsen, <i>Systemic Administration of the Long-Acting GLP-1 Derivative NN2211 Induces Lasting and Reversible Weight Loss in Both Normal and Obese Rats</i> , 50 DIABETES 2530 (2001)

EXHIBIT	DESCRIPTION
1087	Ribel, <i>NN2211: A Long-Acting Glucagon-Like Peptide-1 Derivative with Anti-Diabetic Effects in Glucose-Intolerant Pigs</i> , 451 EUR. J. PHARMACOLOGY 217 (2002)
1088	REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY (Alfonso R. Gennaro ed., 20th ed. 2000)
1089	Boylan, <i>Parenteral Products</i> , in MODERN PHARMACEUTICS (Gilbert S. Banker et al. eds., 3d ed. 1996)
1090	MacDonald, <i>The Multiple Actions of GLP-1 on the Process of Glucose-Stimulated Insulin Secretion</i> , 51 (suppl. 3) DIABETES S434 (2002)
1091	U.S. Patent No. 7,022,674
1092	WO 00/37098
1093	WO 03/002136
1094	Accardo, <i>Physicochemical Properties of Mixed Micellar Aggregates Containing CCK Peptides and Gd Complexes Designed as Tumor Specific Contrast Agents in MRI</i> , 126 J. AM. CHEM. SOC. 3097 (2004)
1095	Autio, <i>Mini-PEG Spacering of VAP-1-Targeting ⁶⁸Ga-DOTAVAP-P1 Peptide Improves PET Imaging of Inflammation</i> , 1 EJNMMI RSCH. 1 (2011)
1096	U.S. Patent No. 7,615,532
1097	Göke, <i>Glycosylation of the GLP-1 Receptor is a Prerequisite for Regular Receptor Function</i> , 15(4) PEPTIDES 675 (1994)
1098	Nicholson, <i>The Role of Albumin in Critical Illness</i> , 85(4) BR. J. ANAESTHESIA 599 (2000)
1099	PDR MEDICAL DICTIONARY 472-73 (1st ed. 1995)

EXHIBIT	DESCRIPTION
1100	Holst, <i>Implementation of GLP-1 Based Therapy of Type 2 Diabetes Mellitus Using DPP-IV Inhibitors</i> , in DIPEPTIDYL AMINOPEPTIDASES IN HEALTH AND DISEASE (Martin Hildebrandt et al. eds., 2003)
1101	https://www.caranddriver.com/ford/f-150
1102	https://modernairliners.com/boeing-737/boeing-737-specifications/
1103	https://pubchem.ncbi.nlm.nih.gov/compound/Glucagon-like-peptide-1-_1-37
1104	https://pubchem.ncbi.nlm.nih.gov/compound/16133830
1105	Scheduling Order, <i>Novo Nordisk Inc. v. Rio Biopharmaceuticals Inc.</i> , No. 22-294 (CFC) (D. Del. June 30, 2022), ECF No. 22
1106	Transfer Order, <i>In re: Ozempic (Semaglutide) Patent Litigation</i> , No. 3038 (MDL Aug. 5, 2022)
1107	Victoza prescribing information (June 2022)
1108	Holst, <i>Glucagon-Like Peptide 1 and Inhibitors of Dipeptidyl Peptidase IV in the Treatment of Type 2 Diabetes Mellitus</i> , 4 CURRENT OP. IN PHARM. 589 (2004) (“Holst 2004b”)
1109	HARRISON’S PRINCIPLES OF INTERNAL MEDICINE Ch. 333 (Eugene Braunwald et al. eds., 15th ed. 2001)
1110	Giannoukakis, <i>CJC-1131 ConjuChem</i> , 4(10) CURRENT OP. IN INVESTIGATIONAL DRUGS 1245 (2003)
1111	Polonsky, <i>What’s so Tough About Taking Insulin? Addressing the Problem of Psychological Insulin Resistance in Type 2 Diabetes</i> , 22(3) CLINICAL DIABETES 147 (2004)
1112	ACS Publications, https://pubs.acs.org/toc/jmcmar/47/17 ; https://pubs.acs.org/doi/10.1021/jm030630m

I. INTRODUCTION

Mylan Pharmaceuticals Inc. (“Petitioner”) petitions for *inter partes* review of claims 1-6 (“the challenged claims”) of U.S. Patent No. 8,129,343 (“the ’343 patent”) (Ex. 1001), which is assigned to Novo Nordisk A/S (“Patent Owner”), under 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42. Petitioner seeks a determination that those claims be canceled as unpatentable.

The ’343 patent claims glucagon-like peptide 1 (“GLP-1”) analogue compounds that may be useful in treating type-2 diabetes, among other conditions. GLP-1 is a peptide hormone produced in the human body that promotes insulin secretion. Because native GLP-1 breaks down within minutes, researchers have long investigated chemically modified GLP-1 peptides (i.e., analogues) with extended durations of action (e.g., longer half-lives) to make a suitable drug product. Through these studies, scientists have discerned which parts of GLP-1 are important to its activity and which are amenable to changes, and what sort of changes should be made to extend the compound’s half-life. Patent Owner itself has produced prior art GLP-1 analogues, some with good pharmacological activity. The prior art was therefore replete with information concerning GLP-1 and its analogues, serving as a catalog of known variables and solutions from which scientists could choose to make new analogues.

Patent Owner made and characterized its first-generation GLP-1 analogue, called liraglutide, well before the priority date of the '343 patent. Using the catalog of well-known variables and solutions, Patent Owner made a few trivial changes to liraglutide to make its second-generation compound—semaglutide—which is encompassed by the challenged claims. But these trivial changes do not warrant patent protection; they fall squarely in the realm of obviousness. The Board should cancel these claims.

II. MANDATORY NOTICES

This Petition is filed in accordance with 37 C.F.R. § 42.106(a). Filed herewith is a power of attorney and exhibit list per § 42.10(b) and § 42.63(e). Under 37 C.F.R. § 42.103, the fee set forth in § 42.15(e) accompanies this Petition.

A. Real Parties-In-Interest

In accordance with 37 C.F.R. § 42.8(b)(1), the real parties-in-interest for Petitioner are Mylan Pharmaceuticals Inc., Mylan Inc., and Viatris Inc.

B. Related Matters

In accordance with 37 C.F.R. § 42.8(b)(2), Petitioner is not aware of any reexamination certificates or pending prosecution concerning the '343 patent. Petitioner is a defendant in the following litigation involving the '343 patent:

- *Novo Nordisk Inc. v. Mylan Pharmaceuticals Inc.*,
No. 22-cv-01040-CFC (D. Del.);

- *Novo Nordisk Inc. v. Viatris Inc.*,
No. 1:23-cv-00013-TSK (N.D. W. Va.);
- *Novo Nordisk Inc. v. Viatris Inc.*,
No. 1:23-cv-00101-CFC (D. Del.);
- *In re: Ozempic (Semaglutide) Patent Litig.*,
No. 22-md-3038-CFC (D. Del.).

In addition, the following litigations also involve the '343 patent:

- *Novo Nordisk Inc. v. Aurobindo Pharma USA, Inc.*,
No. 1:22-cv-00295 (D. Del.) (dismissed on March 28, 2022).
- *Novo Nordisk Inc. v. Rio Biopharmaceuticals, Inc.*,
No. 1:22-cv-00294 (D. Del.)
- *Novo Nordisk A/S v. Sun Pharm. Indus. Ltd.*,
No. 1:22-cv-00296 (D. Del.)
- *Novo Nordisk Inc. v. Zydus Worldwide DMCC*,
No. 1:22-cv-00297 (D. Del.)
- *Novo Nordisk Inc. v. Dr. Reddy's Labs. Ltd.*,
No. 1:22-cv-00298 (D. Del.)
- *Novo Nordisk Inc. v. Alvogen, Inc.*,
No. 1:22-cv-00299 (D. Del.)

Petitioner is concurrently filing a petition for one other patent in the same family as the '343 patent: U.S. Patent No. 8,536,122.

Petitioner is not aware of any other pending litigation, or any pending proceedings before the Patent Trial and Appeal Board.

C. Identification of Counsel (37 C.F.R. § 42.8(b)(3))

Lead Counsel	Back-Up Counsel
Brandon M. White Reg No. 52,354 Perkins Coie LLP 700 13th Street NW, Ste 800 Washington, DC 20005 Phone: (202) 654-6200	Emily J. Greb Reg No. 68,244 Perkins Coie LLP 33 East Main Street, Ste 1 Madison, WI 53703 Phone: (608) 663-7460
Back-Up Counsel	Back-Up Counsel
Courtney Prochnow, Ph.D. Reg. No. 67,639 Perkins Coie LLP 633 W. 5th St., Ste 5850 Los Angeles, CA 90071 Phone: (310) 788-9900	Christopher D. Jones Reg No. 76,472 Perkins Coie LLP 700 13th Street, NW, Ste 800 Washington, DC 20005 Phone: (202) 654-6200
Back-Up Counsel	Back-Up Counsel
Jonathan I. Tietz, Ph.D. Reg No. 76,753 Perkins Coie LLP 700 13th Street NW, Ste 800 Washington, DC 20005 Phone: (202) 654-6200	Matthew A. Lembo Reg No. 75,633 Perkins Coie LLP 1155 Avenue of the Americas, Floor 22 New York, NY 10036 Phone: (212) 262-6900

D. Service Information (37 C.F.R. § 42.8(b)(4))

Petitioner respectfully requests that all correspondence be directed to lead counsel and back-up counsel at the contact information provided above. Petitioner consents to electronic service by e-mail at the following email addresses:

White-ptab@perkinscoie.com;

Greb-ptab@perkinscoie.com;

Prochnow-ptab@perkinscoie.com;

Tietz-ptab@perkinscoie.com;

Jones-ptab@perkinscoie.com;
Lembo-ptab@perkinscoie.com; and
Semaglutide-Ozempic@perkinscoie.com.

III. REQUIREMENTS FOR *INTER PARTES* REVIEW

A. Grounds for Standing

Under 37 C.F.R. § 42.104(a), Petitioner certifies that the '343 patent is available for IPR and that Petitioner is not barred or estopped from requesting review on these grounds.

B. Identification of Challenge and Statement of Precise Relief Requested

Under 37 C.F.R. § 42.22(a) and 37 C.F.R. § 42.104(b), Petitioner requests IPR and cancellation of claims 1-6 on the following grounds:

Ground 1: Obviousness over Knudsen 2004 in view of the Knudsen Patent, Dong, and Bridon (lead-compound framework).

Ground 2: Obviousness over Knudsen 2001 in view of the Knudsen Patent, Dong, and Bridon (lead-compound framework).

Ground 3: Obviousness over the prior art and common drug development principles (under *KSR*).

Petitioner's statement of the reasons for the relief is set forth below. For support, Petitioner submits the Declarations of Peter Flatt, Ph.D. (Ex. 1020), Christopher Soares, Ph.D. (Ex. 1022), Paul Dalby, Ph.D. (Ex. 1024), and John Bantle, M.D. (Ex. 1026), and the Exhibits identified in the Listing of Exhibits.

Statement of No Redundancy: This is the first petition for review of the '343 patent by Petitioner. Grounds 1-3 in this Petition have not been before the Board.

IV. THRESHOLD REQUIREMENT FOR *INTER PARTES* REVIEW

An IPR petition must demonstrate a “reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” 35 U.S.C. § 314(a). This Petition clears that threshold.

V. STATEMENT OF REASONS FOR THE RELIEF REQUESTED

A. Summary of the Argument

GLP-1 is a well-known, naturally occurring peptide hormone made up of 37 amino acids, each occupying a “position” in the peptide chain. While naturally occurring GLP-1 degrades rapidly (within minutes), the prior art taught a synthetic, first-generation GLP-1 analogue—liraglutide—that tweaked GLP-1’s structure at certain positions so that it would remain active for hours. The claims challenged here encompass a second-generation GLP-1 analogue similar to liraglutide: semaglutide.

There are only three minor differences between liraglutide and semaglutide: (1) a different amino-acid residue at position 8; (2) a different fatty acid at position 26; and (3) a different spacer between the peptide and fatty acid. Each of these structural features were well-known, obvious-to-optimize variables, and it was understood that each of these modifications would increase the overall duration of action.

As set forth in Grounds 1 and 2, these changes to liraglutide would have been obvious under the lead-compound doctrine. Knudsen 2004 (Ground 1) or Knudsen 2001 (Ground 2) provided ample motivation to select liraglutide as a lead compound. Other prior art (the Knudsen Patent, Dong, Bridon) taught each of the three differences between liraglutide and semaglutide and motivated POSAs to make those changes.

The lead-compound doctrine is not the only applicable framework, and the claims would have also been obvious under the broader principles of *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007). Liraglutide was an obvious lead compound, and a handful of positions were known to be ripe for tweaking. The options at each position were also finite and well-known, with predictable effects. As a result, those skilled in the art would have naturally been led to synthesize and test semaglutide.

B. Level of Ordinary Skill in the Art

The claimed subject matter falls within the medicinal chemical and pharmacological arts and encompasses the skills, education, and expertise of a team of individuals working together to develop and formulate GLP-1 analogues to treat patients having type-2 diabetes or related conditions. Such a team would have

included persons of ordinary skill in the art (“POSA”)¹ with an M.D., Pharm.D., or doctoral degree(s) in chemistry, biochemistry, pharmaceuticals, pharmaceutical sciences, chemical engineering, biochemical engineering or related fields, with at least two years of experience in developing therapeutic peptides or proteins, and experience with the development, design, manufacture, formulation, or administration of therapeutic peptides or proteins, and the literature concerning protein or peptide formulation and design or diabetes treatments. Ex. 1020 ¶26; Ex. 1022 ¶26; Ex. 1024 ¶20; Ex. 1026 ¶24.

Alternatively, the POSA (1) would be a highly skilled scientist lacking an M.D., Pharm.D., or doctoral degree, but (2)(a) would have more than five years of experience in the area of developing therapeutic proteins or peptides and/or (b) would have 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. In either case, a higher educational level could substitute for some amount of the requisite experience. Such a team also would have included persons with an appropriate level of skill in medicinal synthetic chemistry, including the synthesis and chemical

¹ All references to a POSA’s knowledge and understanding are as of the earliest possible priority date (March 18, 2005), unless stated otherwise.

modification of peptides or proteins. Ex. 1020 ¶27; Ex. 1022 ¶27; Ex. 1024 ¶21; Ex. 1026 ¶¶25-26.

With respect to claims 2 and 5, the team would have included an individual with a Ph.D. in chemistry, biochemistry, pharmaceuticals, pharmaceutical sciences, chemical engineering, biochemical engineering, or related fields, with at least two years of experience in the formulation of therapeutic peptides or proteins. Ex. 1020 ¶29; Ex. 1022 ¶29; Ex. 1024 ¶23; Ex. 1026 ¶28.

With respect to claims 3 and 6, the team would have included an individual with an M.D. and experience treating patients having type-2 diabetes or related conditions. Ex. 1020 ¶30; Ex. 1022 ¶30; Ex. 1024 ¶24 Ex. 1026 ¶27.

In view of the relatively high level of skill and the clear teachings in the prior art, the level of skill of the POSA is not dispositive of any issue in this Petition.

C. The '343 Patent

1. Disclosure

The '343 patent is titled “Acylated GLP-1 Compounds.” Ex. 1002, Title; *id.*, 1:18-25. “A range of different approaches have been used for modifying the structure of [GLP-1] compounds in order to provide a longer duration of action,” and thereby reduce frequency of administration to patients. *Id.*, 1:21-23. The specification describes yet another “GLP-1 analog” having a handful of modifications. *Id.*, 1:57-63. They are (1) “at least one non-proteogenic amino acid

residue in positions 7 and/or 8”; (2) acylation at “the lysine residue in position 26”; and (3) at least two acidic groups, one attached terminally, at that acylation site. *Id.* The specification lists 22 example compounds with minor variations that meet these three conditions. One, Example 4, was ultimately marketed as “semaglutide.” Ex. 1020 ¶100.

2. Priority Date

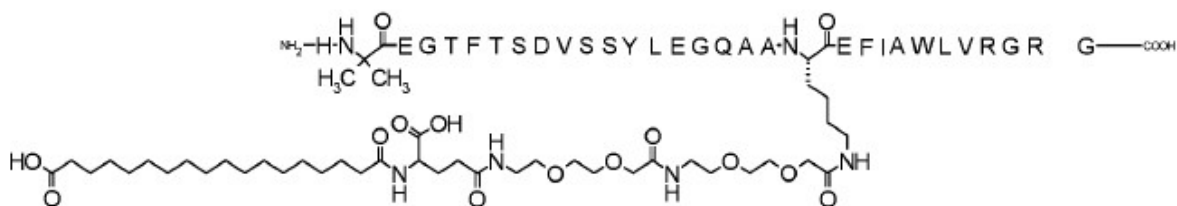
The ’343 patent issued on March 6, 2012, from application No. 11/908,834, filed on March 20, 2006. Ex. 1002 ¶¶(21)-(22). It names Jesper Lau, Paw Bloch, and Thomas Kruse Hansen as inventors and Novo Nordisk A/S as assignee. *Id.* ¶¶(75), (73). It claims priority from U.S. provisional application No. 60/664,497, filed March 23, 2005, and EP05102171, filed March 18, 2005. Under pre-AIA 35 U.S.C. § 102(b), the earliest possible priority date is March 18, 2005.

3. Claims

The challenged claims are directed to semaglutide, compositions containing semaglutide, and methods of treating type-2 diabetes using semaglutide. All challenged claims encompass semaglutide. *Infra* Sections V.H.1.c, V.H.2.

a. Claims 1 and 4

Claim 1 recites a compound of the structure:



where the amino acid sequence is that of SEQ ID No: 7.

Claim 4 recites the same compound as claim 1, defined by its chemical name instead: N- ϵ^{26} -[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. The only apparent difference between claims 1 and 4 is that claim 4 specifies that the compound is an (S)-isomer, whereas claim 1 may encompass both isomers.

b. Claims 2 and 5

Claims 2 and 5 are directed to a “pharmaceutical composition comprising” a compound and “a pharmaceutically acceptable excipient.” Claim 2 depicts the same compound as claim 1 and claim 5 recites the same compound as claim 4.

c. Claims 3 and 6

Claims 3 and 6 are directed to a “method for treating type 2 diabetes in a subject” comprising administering “an effective amount” of a compound. Claim 3 depicts the same compound as claim 1 and claim 6 recites the same compound as claim 4.

4. Prosecution History

Before any substantive examination had occurred, the claims of the '343 patent application underwent several revisions. The original claims (after light amendments upon national entry) were broadly directed to any GLP-1 analogue modified at “position 7 and/or 8” and acylated with “at least two acidic groups,” one attached at position 26, as well as pharmaceutical compositions and methods of treatment. Ex. 1004, 135-48. After an initial Examiner interview, *id.*, 101-102, several claims were cancelled and those remaining were directed to a different set of GLP-1 analogues, *id.*, 78-96. The Examiner still considered the claims too broad to form “a single general inventive concept” and required the applicant to elect a particular species. *Id.*, 72. In response, the applicant elected a specific compound—semaglutide—but maintained its broader genus claims that encompassed semaglutide. *Id.*, 68 (keeping, e.g., claim 7 as “read[ing] on the elected species”).

The Examiner then issued a non-final rejection in view of the prior art, *id.*, 54, which was later withdrawn and replaced, *id.*, 41. In the replacement office action, the Examiner rejected the then-pending claims in view of U.S. Patent No. 6,268,343 (“the Knudsen Patent”) because the Knudsen Patent taught “a genus of GLP-1 analog[s],” including “analogs encompassing the instantly claimed *generic* sequence.” *Id.*, 42. The Examiner also relied upon the Knudsen Patent for disclosing a series of modifications, including lipophilic substituents and spacers to extend

GLP-1's duration of action. *Id.*, 44. For several dependent claims, the Examiner relied on U.S. Patent No. 6,528,486 ("Larsen") for its teachings of modifying position 8 of GLP-1 with an aminoisobutyric acid ("Aib") residue. *Id.*, 45.

In response, applicant cancelled all pending claims and provided a new set of claims directed specifically to semaglutide (Example 4). *Id.*, 32-35. After an Examiner's Amendment correcting which Sequence ID Number in the specification the claims referenced, the Examiner allowed the claims. *Id.*, 26-27. The Examiner did not explain any basis for the allowance. *See id.*

D. Claim Construction (37 C.F.R. §§ 42.100(b), 42.104(b)(3))

Patent claims are construed in IPR the same as in district court, "including construing the claim in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent." 37 C.F.R. § 42.100(b). For this Petition, no claim terms currently require construction, and all terms have their plain meaning.²

² Petitioner may advance claim constructions and challenge the claims under 35 U.S.C. § 112 in district court litigation. Petitioner does not relinquish its claim construction or indefiniteness positions in those proceedings.

E. Scientific Background

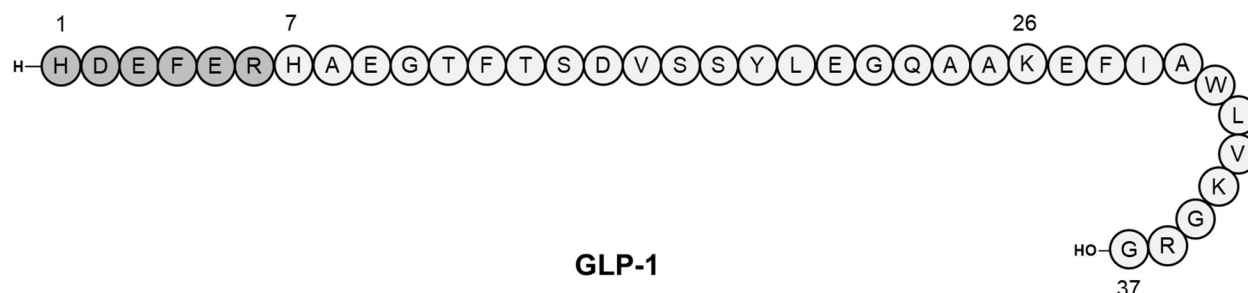
1. Diabetes

Diabetes is a collection of disorders that affect the production, processing, or secretion of insulin, a peptide hormone that regulates blood-glucose levels. Ex. 1020 ¶53; Ex. 1026 ¶41-43. Individuals with diabetes may suffer from high blood glucose levels (i.e., hyperglycemia), which can lead to additional complications if insufficiently managed. Ex. 1020 ¶53; Ex. 1026 ¶41-43.

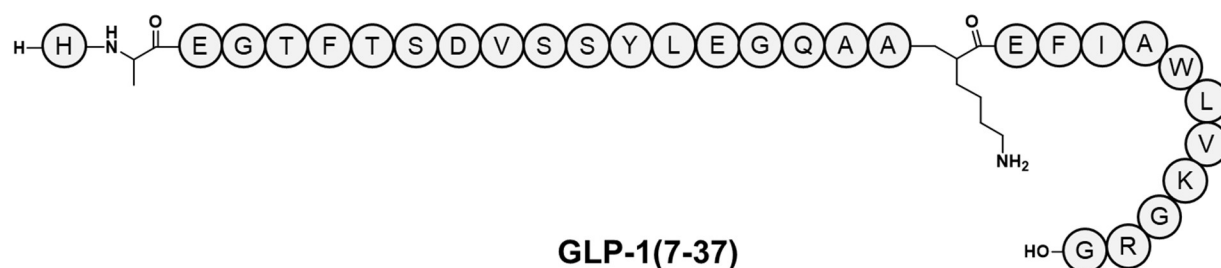
Because diabetes is widespread, treatment options have been developed over the past century that work through different pathways. Ex. 1020 ¶¶54-69. One of the most prevalent is injecting insulin. Ex. 1020 ¶¶55-56. Other treatments include biguanides (which inhibit glucose production and alleviate insulin resistance), sulfonylureas (which stimulate insulin production), and dipeptidyl peptidase-4 (“DPP-IV”) inhibitors (which prevent DPP-IV enzymes from degrading incretins, a class of peptides that stimulate insulin production). *Id.* ¶¶57-62.

2. GLP-1

In the 1990s, companies began investigating incretins as drugs. *See* Ex. 1020 ¶¶65–68. One that garnered substantial attention was GLP-1, a peptide released in the gut that induces insulin release, which had been discovered over a decade earlier. *Id.* ¶66; Ex. 1026 ¶46. Unprocessed GLP-1 has the following chemical structure (each circle identifying an amino acid residue at numbered positions):



Id. ¶77. GLP-1 is naturally converted into two truncated forms, one of which is referred to as GLP-1(7-37) because amino acids 1-6 are cleaved off the parent GLP-1 peptide. *Id.*



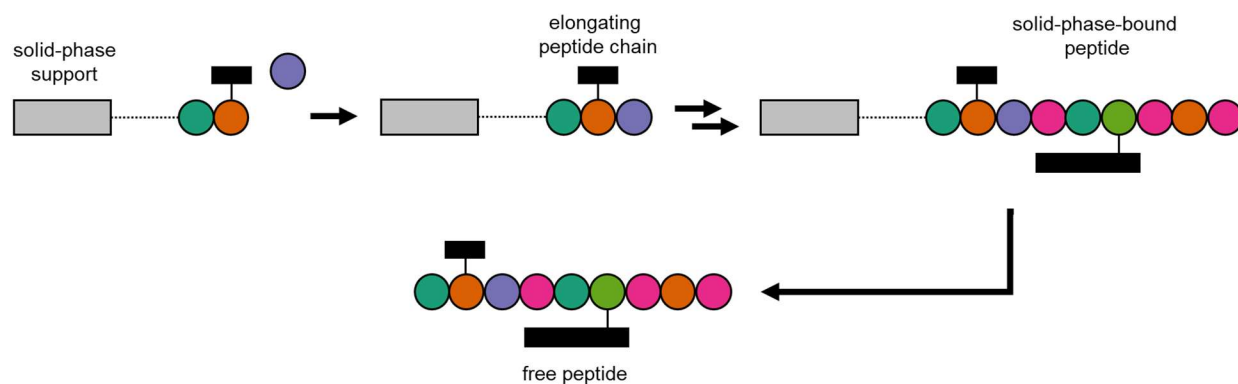
The truncated forms of GLP-1 are more potent than native GLP-1, so researchers focused on making analogues of the truncated forms. *Id.* ¶¶78-79. “GLP-1” in this Petition generally refers to the truncated forms.

One drawback of GLP-1 peptides as potential treatments was their extremely short half-lives, lasting just a few minutes before being degraded. *Id.* Accordingly, development of GLP-1 analogues focused on increasing the half-life while maintaining or improving pharmacological properties. *Id.* ¶79. As part of the drug-development process, researchers discovered how modifying different parts of

GLP-1's structure would affect its function. *Id.* ¶¶79-81; Ex. 1022 ¶¶63-64. This allowed researchers to modify GLP-1's structure with reasonably predictable results.

3. Peptide Synthesis and Structure Screening

In the 1960s—long before the intensive study of GLP-1—peptide-based drug development experienced a major advance with the invention of automated peptide-synthesizers. Ex. 1022 ¶¶57-62. These machines allowed scientists to synthesize peptides as if they were Lego blocks snapped together one after another. *Id.* Using machines or not, peptide synthesis was trivial, involving iterative chaining of amino acids on a solid support, then release of the peptide without significant handling or purification steps:



Id. ¶¶60-62. Unsurprisingly, scientists used these automated machines and methods to synthesize GLP-1 analogues. *Id.* ¶¶69-72. The Flatt and Soares declarations include tutorials on peptides generally. Ex. 1020 ¶¶71-75, Appendix B; Ex. 1022 ¶¶58-62.

F. Scope and Content of the Prior Art

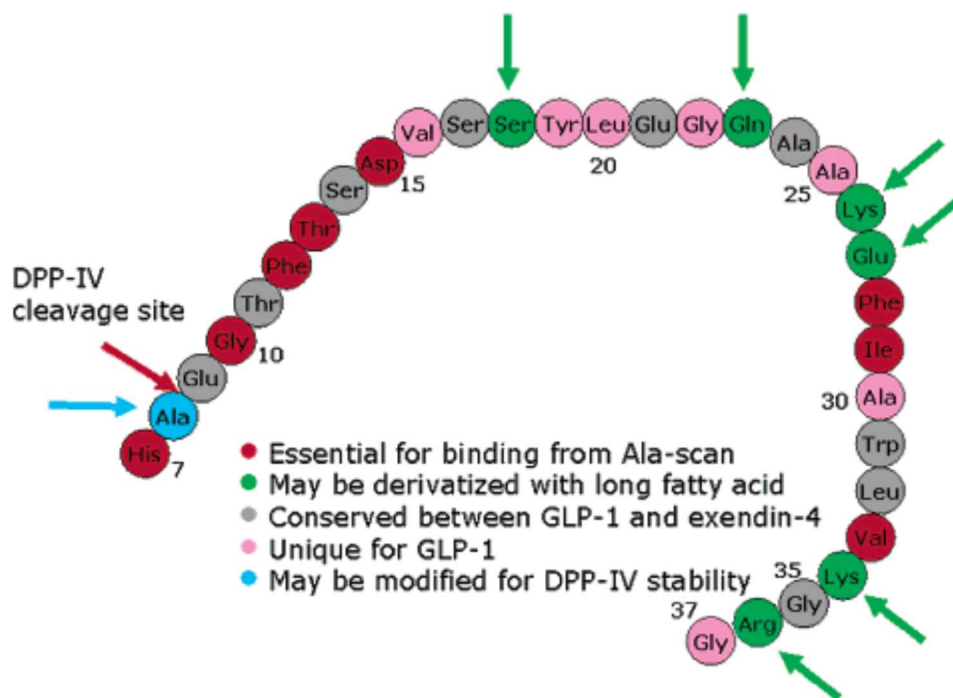
In addition to the prior art relied upon for Grounds 1-3, Petitioner relies on a POSA's knowledge and experience, and prior art contributing thereto. *See, e.g., infra* Section **Error! Reference source not found..** The Flatt, Soares, Dalby, and Bantle Declarations identify and address additional prior art showing a POSA's knowledge as of the priority date. Ex. 1020 ¶¶128-152; Ex. 1022 ¶¶88-97; Ex. 1024 ¶¶64-71; Ex. 1026 ¶¶104-123.

1. Knudsen 2004 (Ex. 1010)

On July 20, 2004, Lotte Bjerre Knudsen—an inventor of liraglutide—published a review article titled “Glucagon-like Peptide-1: The Basis of a New Class of Treatment for Type 2 Diabetes” (Ex. 1010, “Knudsen 2004”); *see also* Ex. 1112 (confirming publication date). The article reviewed the discovery of GLP-1 and the “current belief” that GLP-1 may be useful in treating *not only* type-2 diabetes, but also a host of other maladies (e.g., weight loss and cardiovascular benefits). Ex. 1010, 1. It reiterated the common view that GLP-1 had drawbacks as a treatment option because it was “degraded rapidly” by DPP-IV and eliminated less than 2 minutes after administration. *Id.*

According to Knudsen 2004, “it [wa]s clear that therapeutics for the GLP-1 receptor will be peptides, and thus, the drug discovery challenge is to make a stable compound with a long half-life.” *Id.*, 3. One such GLP-1 analogue identified by

Knudsen 2004 was liraglutide, which had an eight-hour half-life and with which “Novo Nordisk ha[d] completed phase 2 clinical trials.” *Id.* Liraglutide was “part of a series of acylated derivatives of GLP-1 that are aimed at being long-acting,” and Knudsen 2004 explained the long action arose from binding to plasma albumin. *Id.* Knudsen 2004 stated that “GLP-1 can be acylated at multiple sites [(as shown in the figure below)] with a hexadecanoyl fatty acid” and using a variety of spacers. *Id.* Indeed, Knudsen 2004 noted that “for acylated derivatives of GLP-1 the [structure-activity relationship (“SAR”)] is well understood,” and provided a figure that set forth possible modifications to GLP-1. *Id.*



Knudsen 2004 constitutes prior art under at least 35 U.S.C. § 102(a).

2. The Knudsen Patent (Ex. 1012)

On July 31, 2001, the Knudsen Patent issued to the very same Knudsen (and Patent Owner). It was directed to “Derivatives of GLP-1 Analogues” with “a protracted profile of action.” Ex. 1012, Title, Abstract. Like most efforts to optimize naturally occurring peptide-compounds, the Knudsen Patent recommended minimizing the number of modifications. *Id.*, 8:61-9:14. The Knudsen Patent further disclosed that its analogues could be formulated into pharmaceutical compositions to treat various disorders, including diabetes. *Id.*, 4:36-38, 167:63-168:8, 169:54-57, 170:5-10, 216:17-222:18.

The Knudsen Patent taught that several possible amino-acid substitutions could be made to improve GLP-1. *Id.*, 10:48-11:33. For instance, it taught that one of two lysines (positions 26/34) could be “substituted with a lipophilic substituent,” *id.*, 12:24-26, to produce a “satisfactory protracted profile of action,” *id.*, 16:57-59. The Knudsen Patent noted the lipophilic substituent could be an “acyl group of the formula $\text{HOOC}(\text{CH}_2)_m\text{CO—}$, wherein m is an integer from 4 to 38,” including “ $\text{HOOC}(\text{CH}_2)_{16}\text{CO—}$ ” (C_{18} diacid). *Id.*, 19:17-22. And it explained that “[i]n a most preferred embodiment, the lipophilic substituent is attached—optionally via a spacer—to the ϵ -amino group of a [lysine] residue contained in the parent peptide.” *Id.*, 17:55-57. “[S]uitable spacers” included “succinic acid, Lys, Glu or Asp, or a dipeptide such as Gly-Lys.” *Id.*, 17:59-60.

The Knudsen Patent highlighted a few specific analogues, including liraglutide, *see id.* claims 1, 14; *id.*, 187:41-188:4, whose half-life made it a potential once- or twice-daily treatment option. *Id.*, 192:30-60 (Table 1, Example 37). It further reported that liraglutide had antidiabetic efficacy comparable to truncated GLP-1(7-37). *Id.*, 193:35-45; *see also* Ex. 1020 ¶125. Liraglutide was also formulated into pharmaceutical compositions. Ex. 1012, 216:27-28, 27:23-55, 219:26-45, 220:62-221:20.

The Knudsen Patent also disclosed another analogue of interest. This analogue acylated the lysine at position 26 (“Lys²⁶”) with a C₁₈ fatty diacid, unlike liraglutide’s C₁₆ monoacid. *Id.*, 177:33-57, claim 10. According to the Knudsen Patent, this analogue had an even longer half-life than liraglutide. *Id.*, 192:30-60, Table 1 (compare Example 11 to Example 37).

The Knudsen Patent is prior art at least under 35 U.S.C. § 102(b) (pre-AIA).

3. Dong (Ex. 1013)

In 2001, Jesse Z. Dong et al. published an article titled “Glucagon-Like Peptide-1 Analogs with Significantly Improved *in vivo* Activity” (Ex. 1013, “Dong”). Like much of the GLP-1 art, Dong recognized that GLP-1’s “effectiveness in type 2 diabetes patients has been demonstrated in clinical evaluations,” but its use “as a therapeutic agent [wa]s greatly hampered by its short plasma half-life.” Ex. 1013, 6. Dong, like Knudsen 2004, noted that the bond between Ala⁸ and Glu⁹

(between positions 8 and 9) was vulnerable to DPP-IV cleavage. *Id.* To address this, Dong tested three GLP-1 analogues that replaced Ala⁸ with “some unnatural amino acids,” including “aminoisobutyric acid (Aib).” *Id.* The three “sterically hindered amino acids [tested] ma[d]e the peptide bond between positions 8 and 9 less accessible to the [DPP-IV] enzyme, yielding analogs with greater DPP-IV resistance” and thus longer half-lives than GLP-1. *Id.* As discussed below, the Aib analogues (e.g., Aib⁸) exhibited the best properties. *Infra* Sections V.H.1.b.i, V.I.1.b.i.

Dong is prior art at least under 35 U.S.C. § 102(b) (pre-AIA).

4. Bridon (Ex. 1014)

On February 4, 2003, U.S. Patent No. 6,514,500 (Ex. 1014, “Bridon”) issued, titled “Long Lasting Synthetic Glucagon Like Peptide [GLP-1],” and described “modified peptides [to be] administered to treat humans with diabetes,” Ex. 1014, Title, Abstract.

Bridon, like others, was principally concerned with creating GLP-1 analogues “with long duration of action for the treatment of diabetes.” *Id.*, 1:10-15. Bridon disclosed that “[l]inking groups”—also called spacers—could “link or connect reactive groups” to GLP-1. *Id.*, 3:10-20. Bridon disclosed that among the known linking groups was [2-(2-amino)ethoxy]ethoxy acetic acid (“AEEA”), *id.*, 3:19-20, and provided numerous examples of GLP-1 analogues that used two AEEA groups

(i.e., a di-AEEA spacer) attached to lysine residues. *See, e.g., id.*, 2:4-13, 28:56-30:67 (Example 5), 31:45-32:22 (Example 7).

Bridon further noted that the use of “automatic polypeptide synthesizer[s]” to make GLP-1 analogues, including those with di-AEEA spacers, was “well known in the art.” *Id.*, 14:10-13; *see also id.*, 24:5-37.

Bridon is prior art at least under 35 U.S.C. § 102(b) (pre-AIA).

5. Knudsen 2001 (Ex. 1011)

In 2001, the same Knudsen et al. also published an article titled “GLP-1 Derivatives as Novel Compounds for the Treatment of Type 2 Diabetes: Selection of NN2211 for Clinical Development.” Ex. 1011 (“Knudsen 2001”), 1.

Knudsen 2001 disclosed “a series of GLP-1 derivatives designed for once-daily administration,” *id.*, 1, achieved by “[d]erivatizing GLP-1 with long fatty acids[, which] has been shown to result in half-lives exceeding 10 h in healthy humans as well as type 2 diabetic patients after [subcutaneous] administration.” *Id.*, 3.

Knudsen 2001 described using “[f]atty acids or fatty diacids, optionally extended with a ‘spacer’ between the epsilon-amino group of the lysine side chain and the carboxyl group of the fatty acid.” *Id.* According to Knudsen 2001, “simple fatty acids” improved the half-life of GLP-1 because they “increase[d] the net negative charge of the resulting molecule,” and particularly “peptides acylated ...

with diacids provide[d] a further increase of the negative charge. The addition of a negative charge to the acylated molecule [wa]s expected to improve solubility at physiological pH.” *Id.* Knudsen 2001 disclosed that “[m]any different positions in the C-terminal part of GLP-1 could be derivatized with quite long fatty acids ... without affecting the potency.” *Id.*, 4.

Knudsen 2001—like Dong—recognized that “[a]mino acid substitutions in position 8 can give better metabolic stability against DPP-IV.” *Id.*, 5.

Knudsen 2001 further explained that a specific GLP-1 analogue—liraglutide (called “Compound 5” and “NN2211”)—“was selected as the best compound for several reasons.” *Id.* Among those reasons were liraglutide’s γ -L-Glu spacer, which “gave the most potent compound,” and the naturally occurring lysine residues at positions 26 and 34, which “were the most preferred amino acids to derivatize because they were natural lysines and could thus be derivatized easily and without introducing any potential immunogenic changes in the amino acid sequence.” *Id.* Indeed, Knudsen 2001 noted that derivatizing Lys²⁶ gave the most potent and metabolically stable compound. *Id.*

Knudsen 2001 further explained that liraglutide was selected for clinical development and provided clinical data that showed liraglutide was a promising drug candidate. *Id.*, 5-6. For instance, Knudsen 2001 noted that one study “showed a more pronounced glucose lowering effect of [liraglutide] than exendin-4,” another GLP-1

agonist. *Id.*, 6. While Knudsen 2001 reported on several potent GLP-1 analogues with fatty-acid lipophilic groups and spacers, liraglutide was singled out “as a promising new treatment for type 2 diabetes.” *Id.*

Knudsen 2001 is prior art at least under 35 U.S.C. § 102(b) (pre-AIA).

G. Legal Standard

All Grounds allege that the challenged claims would have been obvious in view of the prior art. Grounds 1 and 2 follow a lead-compound analysis because this is the Federal Circuit’s dominant approach. Ground 3, however, sets aside the arguably too-rigid lead-compound doctrine in favor of the more flexible principles established by the Supreme Court in *KSR*. Under either framework, the challenged claims would have been obvious.

The lead-compound analysis has two steps. The first step asks whether a “skilled artisan would have had a reason to select from the panoply of known compounds in the prior art” a lead compound for further development. *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1292 (Fed. Cir. 2012). The selection of a lead “is guided by evidence of the compound’s pertinent properties” such as “activity and potency,” “adverse effects such as toxicity,” and “other relevant characteristics.” *Id.* The word “lead” is a misnomer: the analysis “must, in keeping with *KSR*, not rigidly focus on the selection of a single, best lead compound,” but can encompass multiple possible leads. *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346,

1354 (Fed. Cir. 2010); *see also Mylan Pharms. Inc. v. Bausch Health Ir. Ltd.*, IPR2022-00722, Paper 16, 22 (PTAB Sept. 14, 2022).

Once a lead has been identified, the second step is to identify a reason or motivation to modify that lead to arrive at the claimed compound with a reasonable expectation of success. *Otsuka*, 678 F.3d at 1292. “[T]he requisite motivation can come from any number of sources and need not necessarily be explicit in the art.” *Eisai Co. v. Dr. Reddy’s Labs., Ltd.*, 533 F.3d 1353, 1357 (Fed. Cir. 2008). “[I]t is sufficient to show that the claimed and prior art compounds possess a sufficiently close relationship to create an expectation, in light of the totality of the prior art, that the new compound will have similar properties to the old.” *Id.* (cleaned up).

Even absent an affirmative motivation to make a particular modification, the claims may still be obvious. For instance, if a variable in the prior art is determined to be “result-effective”—that is, “if the prior art ... recognize[s] that the variable affects the relevant property or result,” *E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1009 (Fed. Cir. 2018)—then “discovery of an optimum value of a result effective variable” among known options with predictable results “is ordinarily within the skill of the art” and therefore unpatentable. *In re Boesch*, 617 F.2d 272, 276 (CCPA 1980); *see also In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012) (summarizing standard).

H. Ground 1: Knudsen 2004 in view of the Knudsen Patent, Dong, and Bridon (lead-compound framework)

All challenged claims would have been obvious under the lead-compound analysis. For the compounds recited in claims 1 and 4, a structurally similar compound—liraglutide—was well-known, had established properties and a well-understood structure, and a POSA would have identified it as a lead. Further, a POSA would have been motivated to modify liraglutide to make an analogue having a longer half-life through modifications that would yield semaglutide. Finally, it would have been obvious to formulate semaglutide into a pharmaceutical composition with an excipient (claims 2 and 4) to use semaglutide to treat type-2 diabetes (claims 3 and 6).

1. Claims 1 and 4

As explained above, claims 1 and 4 of the '343 patent recite the same specific GLP-1 analogue, claim 1 by chemical structure and claim 4 by chemical name.³ *Supra* Section V.C.3.a. That GLP-1 analogue is now known as semaglutide, and for the reasons discussed below, semaglutide would have been obvious.

³ As explained above, claim 4 specifies that the compound is an (S)-isomer, whereas claim 1 may encompass both isomers. *Supra* Section V.C.3.a.; *see also* Ex. 1020 ¶48.

Before the priority date, Patent Owner published not only about liraglutide's success but also about how and why it worked. *See* Exs. 1010-1012, 1034, 1055. It was clear that GLP-1 analogues were potential treatment options for diabetes and weight loss, and that they tolerated structural modifications at specific sites. Ex. 1020 ¶¶80-97; Ex. 1022 ¶¶145-149; *see also* Exs. 1005, 1007, 1010-1014, 1017, 1030-1031, 1033-1034, 1046-1047, 1050-1052, 1054-1056, 1068-1069, 1072-1073, 1075, 1080-1083, 1085-1087, 1090, 1100, 1108. For example, combining modifications at position 8 that improved DPP-IV resistance with other modifications that enabled albumin binding was known to result in efficacious analogues with longer half-lives. Ex. 1020 ¶¶80-97; Ex. 1022 ¶¶145-149; *see also* Exs. 1010-1014, 1017, 1030-1031, 1033-1034, 1046-1047, 1068, 1072-1073, 1108. The result: a template for GLP-1 analogues that survived longer in the blood but kept their antidiabetic properties. Semaglutide was at most an old chassis with bolted-on, aftermarket parts.

a. Liraglutide would have been pertinent prior art and a logical “lead” compound

For a POSA looking to develop a long-lasting GLP-1 analogue, liraglutide would have been a natural starting point. Ex. 1020 ¶¶154-168. Liraglutide did not *need* to be the *best* choice, but it would have been an excellent one nonetheless. *Supra* Section V.G.

As of the priority date, other diabetes treatments faced waning interest from the scientific community—too many side effects, too little efficacy. Ex. 1020 ¶¶63-68, 156-157. But GLP-1 analogues had sparked serious interest. Ex. 1020 ¶¶69-70, 157; Ex. 1026 ¶51. After all, they were similar to native, naturally produced GLP-1, *id.* ¶¶76-79, and because they were peptide-based, they were easy to synthesize and screen, *see* Ex. 1020 ¶75; Ex. 1022 ¶¶58-62. And whereas GLP-1's short half-life made it impractical as a medication, POSAs understood that the half-life could be easily improved using straightforward chemical modifications. Ex. 1020 ¶¶79-97; Ex. 1022 ¶¶145-149.

First, GLP-1 degrades quickly in the body due to a peptidase called DPP-IV. Ex. 1020 ¶79. But it was well known that minor modifications to GLP-1's N-terminal region (i.e., near the lower-numbered positions) could slow that degradation without hampering its antidiabetic properties. Ex. 1020 ¶¶83-84, 163; *see also* Exs. 1010-1013, 1017, 1031, 1033-1034, 1072.

Second, it was well understood that enabling GLP-1 analogues to bind to albumin (ubiquitous in blood serum) would improve its half-life. Ex. 1020 ¶¶87-95; *see also* Exs. 1010-1012, 1017, 1031, 1033-1034, 1046. That was a common strategy for all kinds of peptide-based drugs. Ex. 1020 ¶90; *see also* Exs. 1035, 1038. Patent Owner itself applied this technique to GLP-1(7-37) to make liraglutide, its first-generation GLP-1 analogue. Ex. 1020 ¶¶98-99.

Accordingly, GLP-1 analogues that included the above modifications were generally a good starting point for POSAs motivated to make long-lasting GLP-1 analogues. Many would have worked, but liraglutide particularly so. *Id.* ¶¶156-169. Knudsen 2004 disclosed liraglutide's structure, explained that it was equipotent to native GLP-1, and noted that its 11-15 hour half-life made it suitable for once-daily administration. Ex. 1010, 2-4; Ex. 1020 ¶158. A diagram depicting the differences between GLP-1(7-37) and liraglutide is provided below:

Knudsen 2004 also explained that liraglutide had completed phase 2 clinical trials. Ex. 1010, 2-4; Ex. 1020 ¶158; *see also* Ex. 1055. The Knudsen Patent likewise disclosed that liraglutide was suitable for once- or twice-daily dosing and retained acceptable efficacy. Ex. 1012, 192:30-60 (Table 1, Example 37), 193:35-45; Ex. 1020 ¶166.

¶¶167-168; *see also* Exs. 1031, 1034, 1055, 1068, 1073, 1080-1081, 1083, 1085-1087. Adverse effects were mild. Ex. 1010, 5; Ex. 1055, 1; *see also* Ex. 1020 ¶167. And Knudsen 2004 explained that liraglutide appeared to be a better option than other promising GLP-1-based clinical candidates, like CJC-1131 and exendin. Ex. 1010, 3-4; *see also* Ex. 1020 ¶¶162-163. Various articles disclosed liraglutide's additional beneficial properties, including weight loss and possible cardiovascular benefits. Ex. 1010, 1, 5; Ex. 1020 ¶¶159, 277; *see also* Exs. 1055, 1080-1083, 1086-1087. Accordingly, a POSA would have understood liraglutide not only to be a good choice because it was GLP-1-based, but also a better choice than other GLP-1 analogues.

Another advantage of liraglutide, relative to other prior-art GLP-1 analogues, was that its chemical structure and mechanism of protraction were well-published, as discussed above, Ex. 1020 ¶164, unlike other GLP-1 analogues in clinical testing that had non-public chemical structures and/or mechanisms, Ex. 1010, 2, Table 1; Ex. 1020 ¶164.

The literature also showed that there was room for improvement. After all, liraglutide's half-life allowed for at best once-daily administration, but that was inconvenient and risked patient noncompliance. *See* Ex. 1020 ¶¶169, 171; Ex. 1026 ¶¶52, 126-129. POSAs therefore would have endeavored to develop longer-lasting (e.g., two-day, three-day, or weekly administration cycles) analogues by increasing

the half-life. Ex. 1020 ¶169; Ex. 1026 ¶126-129. Longer administration cycles would have benefited manufacturers too—fewer doses would need to be made, fewer ingredients would be needed, and less could be spent on packaging. Ex. 1020 ¶172; Ex. 1022 ¶¶118, 121.

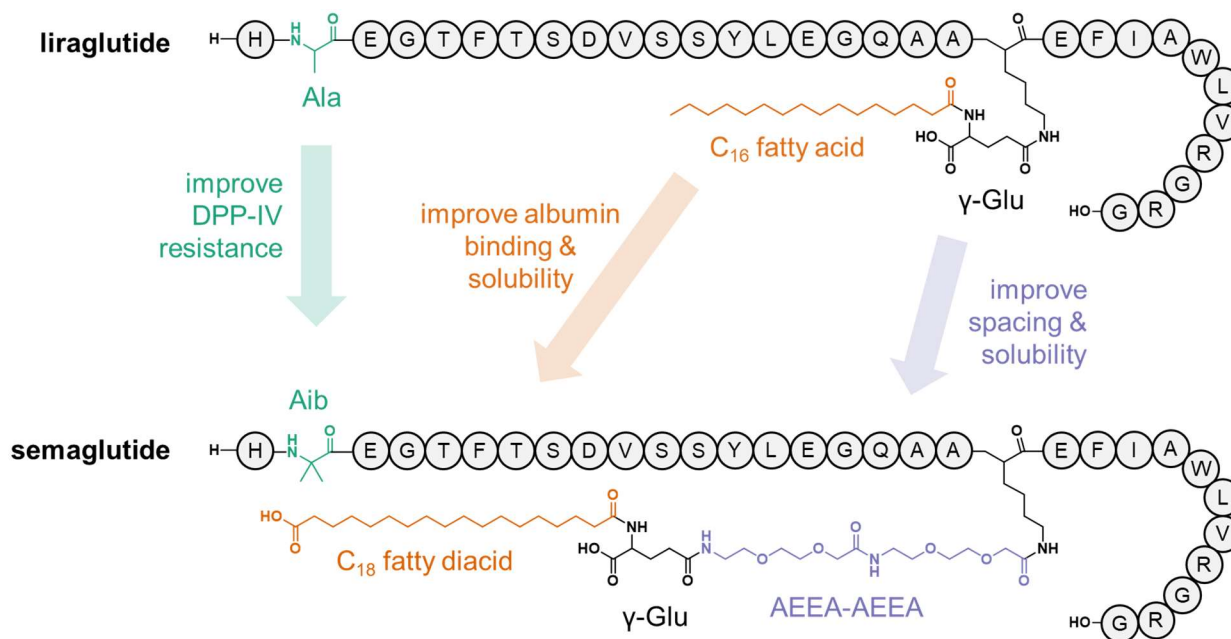
Further, GLP-1 and its analogues had flaws that frustrated formulators (e.g., solubility limitations), and so a more-soluble analogue was desirable. Ex. 1093, 3:21-24; Ex. 1024 ¶79; Ex. 1034, 1. Improved dissolution would make manufacturing and formulation easier, and it would make drug administration safer. Ex. 1020 ¶173; Ex. 1022 ¶¶118, 121; Ex. 1024 ¶79.

Accordingly, liraglutide would have been a natural choice for further development—and for selection as a “lead.” A POSA would have been motivated to harness liraglutide’s already increased half-life and make additional modifications to extend it further, with a reasonable expectation of success.

b. The path from liraglutide to semaglutide would have been obvious

Reaching semaglutide from liraglutide would not have been an exercise in creativity but in inevitability. The “differences between the prior art and the claims at issue” were predictable variations. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). Only three small modifications to liraglutide were required to make semaglutide: an Aib⁸ substitution, using a C₁₈ diacid at Lys²⁶ instead of a C₁₆

monoacid, and using a di-AEEA spacer. *Supra* Section V.A. The striking similarities between liraglutide and semaglutide can be visualized as follows:



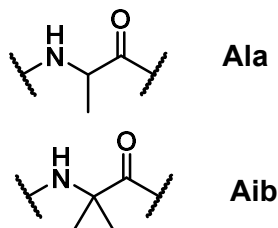
Because the prior art suggested that each modification was desirable and would work, both individually and cumulatively, it is no surprise that they did.

Accordingly, because a POSA would have been motivated to improve certain properties, *supra* Section V.H.1.a, the changes to liraglutide would have been obvious—either as obvious improvements, as predictable uses of known prior-art elements, or as mere optimizations of result-effective variables.

(i) *Using an Aib residue at position 8 would have been obvious*

Liraglutide has an alanine (Ala) residue at position 8, but a POSA would have expected an Aib substitution to protect the peptide from DPP-IV degradation.

Ex. 1020 ¶¶176-177; Ex. 1013, 6.



Making Aib⁸ substitutions in GLP-1 analogues—an extremely conservative change with highly favorable results—was old news to POSAs by the priority date. Ex. 1020 ¶¶183-184; Ex. 1022 ¶146; *see also* Exs. 1010-1013, 1017, 1031, 1033, 1047, 1072. The prior art makes the point explicit.

Dong disclosed that a chief culprit in GLP-1 degradation is DPP-IV, which cleaves the bond between Ala⁸ and Glu⁹ at GLP-1's N-terminus. Ex. 1013, 6; Ex. 1020 ¶177. Aib is more “sterically hindered” (bulkier) than Ala, making that bond less accessible to DPP-IV and effectively shielded from it. Ex. 1013, 6; Ex. 1020 ¶177. Dong reported that Aib⁸-modified GLP-1 analogues had significantly longer half-lives than unmodified ones and maintained their antidiabetic efficacy in vivo. Ex. 1013, 6-7; Ex. 1020 ¶¶177-178, 181-182. Further, a POSA would have viewed the analogue modified with only an Aib⁸ substitution as more promising than other analogues reported in Dong that had additional modifications. Ex. 1020 ¶¶178-180.

Knudsen 2004 also identified position 8 as one that “[m]ay be modified for DPP-IV stability.” Ex. 1010, 3 (Figure 3); Ex. 1020 ¶182. And the Knudsen Patent encouraged the use of amino-acid substitutions, including non-natural ones.

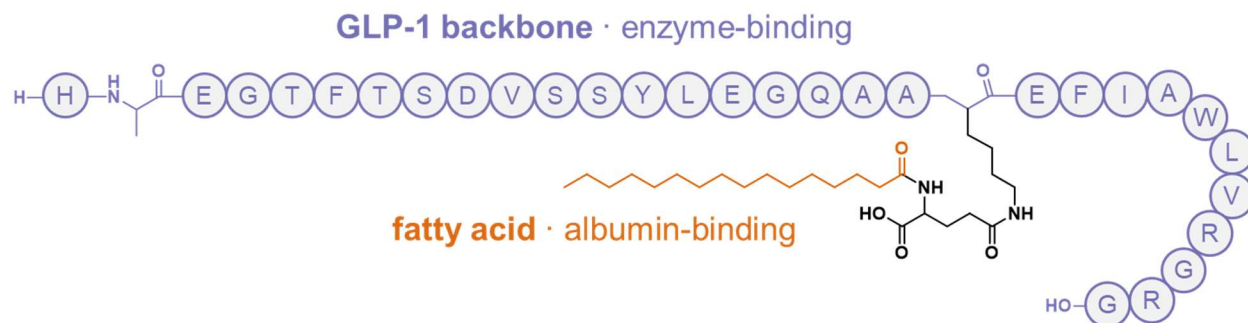
Ex. 1012, 8:61-9:14, 10:48-11:33; Ex. 1020 ¶182. That is no surprise: an Aib⁸ substitution was a well-accepted means to protract the half-life of GLP-1 analogues. Ex. 1020 ¶¶183-184; *see also* Exs. 1017, 1031, 1047, 1072.

Moreover, the chemical synthesis would have been trivial. Using Aib in therapeutic peptides was well known. Ex. 1020 ¶¶108, 136, 152, 177-186; *see also* Ex. 1067. And Aib-modified peptides could be easily synthesized using commercially available equipment that enabled protein synthesis with the push of a button. Ex. 1022 ¶71; *see also* Exs. 1065, 1066.

A POSA would have been motivated to substitute liraglutide's Ala⁸ with Aib⁸ and would have reasonably expected the resulting analogue to have a longer half-life than liraglutide. At the very least, a POSA would have considered an Aib⁸ substitution to be a “predictable use of [a] prior art element[] according to [its] established function[].” *KSR*, 550 U.S. at 417.

**(ii) *Using a di-AEEA spacer
would have been obvious***

Liraglutide's structure has two parts: a fatty-acid albumin-binding part (orange, below) and a receptor-binding part (purple, below). Ex. 1020 ¶98. The SAR of the GLP-1 backbone was well known. Ex. 1020 ¶80; *see also* Exs. 1005, 1010-1011, 1017, 1031, 1034, 1100. The fatty acid extended the half-life by binding to albumin. Ex. 1020 ¶¶92, 190, 214; *see also* Exs. 1010-1012, 1031, 1034.

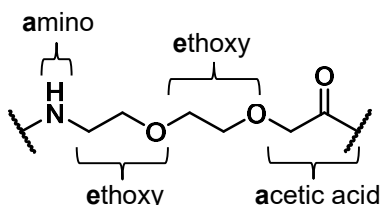


Specifically, liraglutide used a glutamyl spacer attached to Lys²⁶ to link the fatty acid to the GLP-1 backbone while providing distance between them. Ex. 1020 ¶¶98; Ex. 1022 ¶¶65-66. But Knudsen 2004 explained that “[s]pacers other than” glutamyl “can be used,” Ex. 1010, 3, and the Knudsen Patent explained that using a “spacer” to attach a lipophilic group to GLP-1 analogues at a lysine residue was “most preferred,” Ex. 1012, 17:55-57. The Knudsen Patent described several “suitable spacers,” indicating that GLP-1 analogues would tolerate other spacers, including multi-component spacers (e.g., “dipeptide[s]”). Ex. 1012, 17:59-60; Ex. 1020 ¶¶124, 193; Ex. 1022 ¶125. That is no surprise: POSAs knew that spacers were common in peptide synthesis and design. Ex. 1020 ¶¶96-97, 195, 200; Ex. 1022 ¶¶102-106. Indeed, others had suggested tweaking liraglutide’s spacer length to improve activity. Ex. 1030 at 5 (calling liraglutide’s spacer length “suboptimal”); *see also* Ex. 1020 ¶201; Ex. 1022 ¶107.

The spacer increases the distance between the peptide chain and the albumin-binding fatty acid. Ex. 1020 ¶203; Ex. 1022 ¶104. Albumin and the GLP-1 receptor each are around ~60-70 kDa in size; liraglutide, at about 3.7 kDa, is about 18 times

smaller. Ex. 1020 ¶203. That is like towing two Boeing 737s (albumin and the GLP-1 receptor) with a Ford F-150 (liraglutide). *Id.* Predictably, the bulkiness of both albumin and the GLP-1 receptor means the two interfere with each other at short distances. Ex. 1020 ¶203; Ex. 1022 ¶105. Lengthening the spacer attenuates this problem. Ex. 1020 ¶203; Ex. 1022 ¶105.

In particular, a POSA would have known that adding a longer, inert group like di-AEEA would be ideal. Ex. 1020 ¶203; Ex. 1022 ¶¶106, 108-111. “AEEA” is pictured below.⁴ Ex. 1020 ¶¶97, 100. It is a short form of the common moiety “PEG.” Ex. 1022 ¶108.



The AEEA spacer has been around since at least the 1980s and had been used abundantly in peptides by the priority date. Ex. 1020 ¶201; Ex. 1022 ¶111; *see also* Ex. 1043. Knudsen 2004 acknowledged that one GLP-1 analogue, CJC-1131, was “modified at site 8 to protect against DPP-IV degradation” and included an AEEA spacer-albumin binding substituent (maleimide, a small compound that forms a

⁴ AEEA also goes by “JJ,” “AdOO,” “mini-PEG,” di-8-amino-3,6-dioxaoctanoic acid, or other names. Ex. 1020 ¶¶97, 100; Ex. 1022 ¶67 & n.4.

covalent bond with albumin). Ex. 1010, 2, 4, Table 1. And Knudsen 2004 acknowledged that CJC-1131 had a very long half-life. Ex. 1010, 4; Ex. 1020 ¶192. Because of the GLP-1 backbone, the albumin binding substituent, and the position-8 modification, a POSA would have thought CJC-1131 and related peptides to be especially pertinent art—and Bridon disclosed CJC-1131 and similar peptides in detail. Ex. 1020 ¶192; Ex. 1022 ¶¶115-116; Ex. 1014, 2:4-13, 28:56-30:67, 31:45-32:22.

The strategy of using and optimizing a spacer was tried and true—both with therapeutic peptides in general and GLP-1 analogues specifically. Ex. 1020 ¶¶96-97, 189; Ex. 1022 ¶¶103-104, 116; *see also* Exs. 1010-1012, 1014, 1017, 1030, 1033, 1034, 1045, 1067. Bridon explained that spacers could easily be used in peptide drug design, including with GLP-1. Ex. 1014, 3:10-20; Ex. 1020 ¶189-192; Ex. 1022 ¶115. A “preferred linking group” was AEEA. Ex. 1014, 3:19-20. The pertinent literature contained many AEEA-modified GLP-1 analogues, which showed the use of an AEEA spacer does not negatively impact albumin binding. Ex. 1020 ¶¶195-199; Ex. 1022 ¶¶115-117. And it was reported that di-AEEA was generally “helpful in enhancing binding to target molecule[s]” and “should routinely be tested” for inclusion in new peptides. Ex. 1045, 125:4-8, 130:30-34; Ex. 1020 ¶¶197-199; Ex. 1022 ¶¶103-104.

Bridon linked an albumin-binding group to GLP-1 at a lysine sidechain to improve half-life—the same strategy Patent Owner used to make liraglutide. Ex. 1014, 4:35-63, 28:56-30:67, 31:45-32:22; Ex. 1020 ¶¶190-192. Bridon used a maleimide moiety, rather than a fatty acid, to bind albumin. But both are aimed at the same general task and AEEA's usefulness with one would extend to the other. Ex. 1020 ¶¶190-192; Ex. 1022 ¶¶117-118.

Di-AEEA would have had other obvious benefits too. First, inserting di-AEEA, which is hydrophilic, would make the analogue more water-soluble and therefore easier to manufacture and formulate. Ex. 1020 ¶204; Ex. 1022 ¶¶111-112; Ex. 1024 ¶¶79, 85-86. GLP-1 analogues had solubility problems that interfered with formulation, and a POSA would have been motivated to avoid them. Ex. 1093, 3:21-24; Ex. 1034, 1; Ex. 1020 ¶204; Ex. 1022 ¶¶111-112; Ex. 1024 ¶¶79, 85-86. Additionally, the modified analogue would retain the benefits of the negative charge of the glutamyl linker already present in liraglutide, further helping with solubility and improving albumin binding too. Ex. 1020 ¶¶204-205; Ex. 1022 ¶118; Ex. 1024 ¶85.

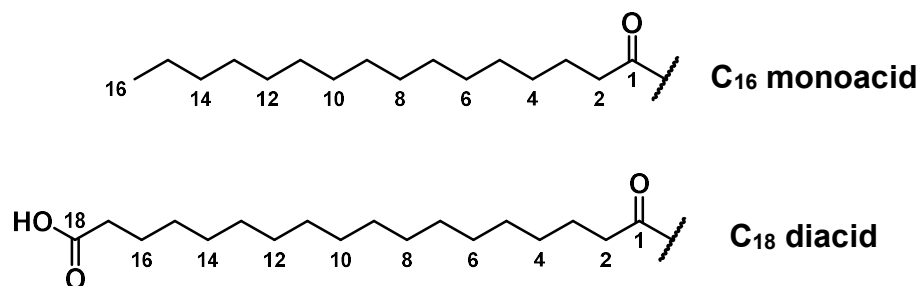
Chemical synthesis also would have been simple. Bridon taught that adding di-AEEA spacers used the same basic, automated synthetic technologies that peptide chemists already used. Ex. 1014, 14:10-13, 24:5-37, 28:56-30:67, 31:45-32:22; Ex. 1020 ¶¶189-191; Ex. 1022 ¶115. Indeed, the basic plug-and-play building blocks to

incorporate AEEA spacers were readily available well before the priority date. Ex. 1022 ¶¶58-62, 72. Plus, liraglutide only has one lysine—the amino acid in native GLP-1 with a side chain most suitable for this type of modification—and so there was no need to decide between multiple potential modification sites. Ex. 1020 ¶¶91-92, 191; Ex. 1022 ¶¶58-62, 72. As for whether di-AEEA would be inserted before or after the glutamyl linker, a POSA would have been more inclined to retain the glutamyl-fatty acid linkage that worked in liraglutide and was described as important to liraglutide’s properties. Ex. 1020 ¶¶204-205; Ex. 1022 ¶¶105-107, 118; *see also* Exs. 1010-1012, 1034.

A POSA would have been motivated to modify liraglutide by adding a di-AEEA spacer between Lys²⁶ and the glutamyl spacer and had a reasonable expectation of success in doing so. At the very least, a POSA would have considered using a di-AEEA spacer to be a “predictable use of [a] prior art element[] according to [its] established function[.]” *KSR*, 550 U.S. at 417.

(iii) *Using a C₁₈ fatty diacid would have been obvious*

As explained above, liraglutide used a “lipophilic” group—specifically, a fatty acid—to bind albumin and increase GLP-1’s half-life. A POSA would have realized not only that a C₁₈ diacid would have worked (motivation enough) but also that it would have worked *better* than liraglutide’s C₁₆ monoacid:



As explained above, POSAs understood how the lipophilic moiety (i.e., fatty acid) improved the half-life of GLP-1 analogues by binding to albumin. *Supra* Section V.H.1.b.ii; Ex. 1020 ¶¶87-95, 117, 131-134, 137-138, 143-147; Ex. 1022 ¶127. The Knudsen Patent confirmed that the lipophilic substituent was meant to extend the half-life, and that it was ideal to use only one such group in an analogue. Ex. 1012, 12:23-29, 16:56-67; Ex. 1020 ¶¶211, 214; Ex. 1022 ¶¶124-127. Knudsen 2004 reiterated that the lipophilic moiety worked by “binding to plasma albumin fatty acid binding sites.” Ex. 1010, 3; Ex. 1020 ¶214. Albumin’s fatty acid binding sites bind to more than just a C₁₆ monoacid, and so a POSA would expect that other fatty acids should work for that purpose. *See* Ex. 1020 ¶¶215-218; Ex. 1022 ¶¶129-133. And a POSA would expect that a fatty acid that bound albumin more tightly would work better. Ex. 1020 ¶¶215-224; Ex. 1022 ¶¶135-140.

As of the priority date, it was known that C₁₈ fatty acids bound albumin better than C₁₆ fatty acids. Ex. 1020 ¶¶215-218; Ex. 1022 ¶¶129-134; *see also* Exs. 1008, 1009, 1032, 1040, 1042, 1060. It was also known that albumin bound the carboxylic acid group of fatty acids (like diacids) even better than the lipophilic tail—owing to

the many positively charged amino acids in albumin—and using a C₁₈ diacid instead of a C₁₆ monoacid would ensure a GLP-1 analogue could take advantage of that stronger albumin-binding, while separately imparting improved solubility to the peptide. Ex. 1020 ¶¶216-218; Ex. 1022 ¶¶129-139; Ex. 1024 ¶¶80-85. And a POSA would have been motivated to keep the glutamyl spacer: Knudsen 2000 disclosed an “enhanced effect on binding to albumin” when the glutamyl spacer was used. Ex. 1034, 2; Ex. 1020 ¶224.

To that end, the Knudsen Patent disclosed a genus of lipophilic moieties that would work well, of which the C₁₈ diacid was a preferred species: an “acyl group of the formula $\text{HOOC}(\text{CH}_2)_m\text{CO—}$ ” ($m = 4\text{-}38$), including “ $\text{HOOC}(\text{CH}_2)_{16}\text{CO—}$ ” (C₁₈ diacid). Ex. 1012, 19:17-22; Ex. 1020 ¶212. The Knudsen Patent even included the C₁₈ diacid in an example that exhibited a longer half-life than liraglutide. Ex. 1012, 177:33-57, Claim 10; *id.*, 192:30-60, Table 1 (compare Example 11, Arg³⁴Lys²⁶ (N^ε-(ω-carboxyheptadecanoyl))-GLP-1(7-37)-OH, with Example 37, liraglutide). Ex. 1020 ¶213. A POSA would have been motivated by reading either Knudsen 2004 or the Knudsen Patent, or both, to use a C₁₈ diacid. Ex. 1020 ¶¶214-215; Ex. 1022 ¶¶134-135.

Chemical synthesis would have again been simple. Ex. 1022 ¶141. The C₁₈ diacid was a readily available building block that could have been substituted into the same synthetic pathway that liraglutide used. *Id.* Indeed, the ease of

synthesis and availability of materials would have been another motivation to select a C₁₈ diacid. *Id.*

A POSA would have been motivated to use a C₁₈ diacid in place of liraglutide's C₁₆ monoacid, and would have had a reasonable expectation of success. At the very least, a POSA would have considered using a C₁₈ diacid to be a “predictable use of [a] prior art element[] according to [its] established function[.]” *KSR*, 550 U.S. at 417. Further, the choice of a particular lipophilic fatty acid would have been a matter of “optimization” of a known “result-effective” variable. *Applied Materials*, 692 F.3d at 1295.

c. Semaglutide would have been obvious

As discussed above, a POSA would have been motivated to modify liraglutide with each of the three modifications required to reach semaglutide because they would have reasonably expected those modifications to extend the half-life of the peptide while retaining its therapeutic properties. Further, a POSA would have reasonably expected the changes to work together, synergistically, to improve the same properties. Ex. 1020 ¶226; Ex. 1022 ¶151; Ex. 1024 ¶86. Accordingly, claims 1 and 4 would have been obvious.

2. Claims 2 and 5

Claims 2 and 5 recite a “pharmaceutical composition” comprising semaglutide and a “pharmaceutically acceptable excipient.”

As explained, semaglutide would have been obvious, *see supra* Section V.H.1, and it would have further been obvious to formulate it as part of a pharmaceutical composition. The Knudsen Patent disclosed that GLP-1 analogues could be readily formulated into pharmaceutical compositions containing pharmaceutically acceptable excipients. Ex. 1012, 4:36-38, 167:63-168:8, 169:54-57, 170:5-10, 216:17-222:18. Ex. 1020 ¶228; Ex. 1024 ¶¶45, 91-96. Compounds *must* be formulated into pharmaceutical compositions, necessarily containing pharmaceutically acceptable excipients, to be useful. Ex. 1024 ¶¶37-39. That is how drugs work, and excipients are well known. *Id.* Additionally, a POSA looking to test a compound in humans or animals would need to formulate it, and would have to use excipients. *Id.* ¶97. A POSA would also believe semaglutide to be more appropriate than liraglutide for formulation, owing to its increased hydrophilicity and charge, thereby improving solubility. Ex. 1020 ¶228; Ex. 1022 ¶118; Ex. 1024 ¶98.

Accordingly, claims 2 and 5 would have been obvious because a POSA would have been motivated to formulate semaglutide into a pharmaceutical composition with pharmaceutically acceptable excipients and would have had a reasonable expectation of success.

3. Claims 3 and 6

Claims 3 and 6 recite a method for treating type-2 diabetes by administering to a subject in need of such treatment an effective amount of a “pharmaceutical composition” comprising semaglutide and a “pharmaceutically acceptable excipient.”

Semaglutide, and pharmaceutical compositions containing semaglutide and excipients, would have been obvious, *see supra* Sections V.H.1-2, and it would have further been obvious that semaglutide would be administered to treat type-2 diabetes. Such treatment would have been the motivation to develop semaglutide and compositions containing semaglutide at all. *Supra* Section V.E.1-2. The Knudsen Patent and Knudsen 2004 both explained that GLP-1 analogues could be used to treat type-2 diabetes in humans when administered in effective amounts. *See* Ex. 1010, 3, 5; Ex. 1012, 170:5-15, claim 39; Ex. 1034, 2, 4; Ex. 1020 ¶¶229-230; Ex. 1026 ¶¶130-144. It would have been obvious to give a treatment to a subject in need of that treatment. Ex. 1026 ¶¶130-144 .

Accordingly, a POSA would have been motivated to treat type-2 diabetes as claimed, and would have had a reasonable expectation of success.

I. Ground 2: Knudsen 2001 in view of the Knudsen Patent, Dong, and Bridon (Lead-Compound Framework)

As in Ground 1, under the lead-compound analysis, all challenged claims would have been obvious in view of the prior art combination of Ground 2.

1. Claims 1 and 4

The scope of claims 1 and 4 was described above. *Supra* Section V.H.1.

a. **Liraglutide would have been pertinent prior art and a logical “lead” compound**

As explained above, a POSA would have been motivated to make a GLP-1 analogue with a long half-life as a diabetes therapy. Ex. 1020 ¶¶231-235. A POSA would have identified liraglutide as a lead considering Knudsen 2001 instead of Knudsen 2004. Ex. 1020 ¶¶233-239.

As explained above, there was room for improvement to liraglutide’s half-life to reduce the frequency of dosing. *Supra* Section V.H.1.a; Ex. 1020 ¶240. Additionally, there was room to improve liraglutide’s properties with respect to manufacturing and formulation. *Supra* Section V.H.1.a; Ex. 1020 ¶240. A POSA would have been motivated by the reasons explained in Ground 1 (setting aside Knudsen 2004). *Supra* Section V.H.1.a.

Further, Knudsen 2001 disclosed a series of GLP-1 analogues, said that liraglutide was “selected as the best compound” among them, and disclosed promising clinical data. Ex. 1011, 5-6; Ex. 1020 ¶¶236-239. It explained that liraglutide was “designed” for “once-daily administration.” Ex. 1011, 1; Ex. 1020 ¶¶236-239. This also suggested that there was room for improvement, as the “most optimal pharmacokinetic profile” would be “a long half-life.” Ex. 1011, 3; Ex. 1020

¶¶236-239. For example, POSAs would be motivated to achieve twice-a-week or once-a-week dosing. Ex. 1020 ¶¶236-239; *see supra* Section V.H.1.a.

Knudsen 2001 explained why liraglutide would serve as a good lead. Its γ -L-Glu spacer and fatty acid-modified Lys²⁶ imparted a long half-life via albumin binding and gave particularly good activity. Ex. 1011, 3; Ex. 1020 ¶¶236-237. Knudsen 2001 also disclosed clinical data suggesting liraglutide was an effective treatment. Ex. 1011, 5-6; Ex. 1020 ¶238. For instance, liraglutide had a “more pronounced glucose lowering effect” than other GLP-1 analogues and was a “promising new treatment for type 2 diabetes.” Ex. 1011, 6; Ex. 1020 ¶¶236-238. Accordingly, in view of Knudsen 2001 and other prior art like the Knudsen Patent, a POSA would have selected liraglutide as a lead compound. Ex. 1020 ¶239. Namely, a POSA would have been motivated to take advantage of liraglutide’s already increased half-life (i.e., 11-15 hours) and to make additional modifications to produce an even longer-lasting GLP-1 analogue, and would have had a reasonable expectation of success in doing so. *Id.* ¶¶239-240.

b. Semaglutide would have been obvious over liraglutide

As in Ground 1, the art cited in Ground 2 would have motivated a POSA to modify liraglutide to make semaglutide. The prior art taught that the three modifications would work, individually and synergistically, to improve the properties of GLP-1 analogues, including liraglutide. The three minor changes to

liraglutide would have been obvious—either as obvious improvements, as predictable uses of known prior-art elements, or as mere optimizations of result-effective variables. *See supra* Section V.H.1.b.

**(i) *Using an Aib residue at position 8
would have been obvious***

As explained, Aib⁸ substitutions in GLP-1 analogues were known to result in extended half-lives by shielding the peptide from DPP-IV degradation while retaining suitable efficacy. *Supra* Section V.H.1.b.(i); Ex. 1020 ¶¶242-245. Dong made this point, even showing that Aib specifically was superior to certain other amino acids, and the Knudsen Patent reinforced the idea. Ex. 1013, 6-7; *see also supra* Section V.H.1.b.(i).

Knudsen 2001 provided POSAs further evidence of the promise of using Aib⁸. Knudsen 2001 recognized that DPP-IV metabolizes GLP-1 at position 8. Ex. 1011, 3; Ex. 1020 ¶244. Knudsen 2001 also explained that a large number of amino acid substitutions to GLP-1 would risk immunogenicity problems. Ex. 1011, 4; Ex. 1020 ¶244. A conservative Aib⁸ substitution would therefore be a solution to this problem. Ex. 1020 ¶244; Ex. 1022 ¶156.

A POSA would have been motivated to replace liraglutide's Ala⁸ with Aib⁸, and would have had a reasonable expectation of success in doing so. Ex. 1020 ¶¶242, 245. At the very least, a POSA would have considered using Aib⁸ to be a “predictable

use of [a] prior art element[] according to [its] established function[.]” *KSR*, 550 U.S. at 417.

**(ii) *Using a di-AEEA spacer
would have been obvious***

As explained, semaglutide contains a di-AEEA spacer that separates the albumin-binding fatty acid and the enzyme-binding GLP-1 backbone. *Supra* Section V.H.1.b.(ii). A POSA considering Knudsen 2001 instead of Knudsen 2004 would have still been motivated to use a di-AEEA spacer to separate the albumin-binding fatty acid and the enzyme-binding GLP-1 backbone. Indeed, the same reasons apply in view of Knudsen 2001, Bridon, and the Knudsen Patent. Ex. 1020 ¶246; *see also supra* Section V.H.1.b.(ii).

Knudsen 2001 explained that spacers were useful generally, various spacers could be used, and that the additional negative charges from the combination of a glutamyl spacer and fatty acid (relative to analogues not modified at Lys²⁶) would be favorable and “improve solubility at physiological pH.” Ex. 1011, 3; Ex. 1020 ¶¶248-249. Inserting a di-AEEA spacer (rather than simply replacing the glutamyl spacer) would enhance this favorable property. *Supra* Section V.H.1.b.(ii); Ex. 1020 ¶¶249-250. For the reasons already explained, a POSA would understand that the hydrophilic nature of di-AEEA (a known peptide spacer) would contribute favorably to liraglutide’s already desirable properties and result in an analogue that would be

easier to manufacture and formulate. *Supra* Section V.H.1.b.(ii); Ex. 1020 ¶¶198-199, 248.

A POSA would have been motivated to modify liraglutide by adding a di-AEEA spacer between Lys²⁶ and the glutamyl spacer with a reasonable expectation of success. At the very least, a POSA would have considered using di-AEEA to be a “predictable use of [a] prior art element[] according to [its] established function[.]” *KSR*, 550 U.S. at 417.

**(iii) *Using a C₁₈ fatty diacid
would have been obvious***

Using a C₁₈ fatty diacid instead of liraglutide’s C₁₆ fatty monoacid would also have been obvious. Ex. 1020 ¶251.

A POSA would have drawn the same motivations from the Knudsen Patent as explained previously. *Supra* Section V.I.1.b.(iii); Ex. 1020 ¶¶251-252. And a POSA would have understood from the Knudsen Patent that using a C₁₈ diacid resulted in an analogue with a longer half-life than liraglutide. Ex. 1012, 192:30-60; Ex. 1020 ¶¶253-255; Ex. 1022 ¶¶123-128. Knudsen 2001 also disclosed that “increas[ing] the net negative charge” by using a fatty *diacid* would “improve solubility.” Ex. 1011, 3; Ex. 1020 ¶254; Ex. 1024 ¶¶80-85; *see also* Ex. 1022 ¶¶129-139. Further, a C₁₈ diacid would have been one of a limited number of albumin-binding fatty acids, and one of the most similar to the C₁₆ acid—and so a natural choice to try in combination

with di-AEEA and γ -glutamyl spacer groups. *Supra* Section V.I.1.b.(iii); Ex. 1020 ¶255; Ex. 1022 ¶¶134-139; Ex. 1024 ¶134.

A POSA would have been motivated to use a C₁₈ diacid in place of liraglutide's C₁₆ monoacid, and would have reasonably expected the resulting analogue to have a longer half-life and improved solubility. At the very least, a POSA would have considered using a C₁₈ diacid to be a “predictable use of [a] prior art element[] according to [its] established function[.]” *KSR*, 550 U.S. at 417. Further, the choice of particular lipophilic fatty acid would have been a matter of “optimization” of a known “result-effective” variable. *Applied Materials*, 692 F.3d at 1295.

2. Claims 2 and 5

Claims 2 and 5 would have been obvious over this combination of prior art for the same reasons that they would have been obvious over Knudsen 2001 in view of the Knudsen Patent, Dong, and Bridon. *See supra* Section **Error! Reference source not found.**2; Ex. 1020 ¶¶258-259; Ex. 1024 ¶¶ 88-99.

3. Claims 3 and 6

Claims 3 and 6 would have been obvious over this combination of prior art for the same reasons that they would have been obvious over Knudsen 2001 in view of the Knudsen Patent, Dong, and Bridon. *See supra* Section **Error! Reference source not found.**; Ex. 1020 ¶¶260-261; Ex. 1026 ¶¶145-148.

J. Ground 3: Obviousness over the prior art and common drug development principles (under *KSR*)

While the Federal Circuit has repeatedly endorsed the usefulness of the lead-compound analysis, “[a] lead compound analysis is not the only way to demonstrate obviousness of a claimed compound or genus of compounds, ... and any rigid application of the lead compound doctrine risks running afoul of the broad, flexible obviousness test set forth by the Supreme Court in *KSR*.” *NOF Corp. v. Nektar Therapeutics*, IPR2019-01394, Paper 68, 32-33 (PTAB July 30, 2021) (first citing *Otsuka*, 678 F.3d at 1291; and then citing *Altana Pharma AG v. Teva Pharms. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009)). Here, the challenged claims are also obvious under the principles set forth in at least *KSR*, 550 U.S. at 415.

1. If applied as a rigid subject-matter-specific obviousness analysis, the lead-compound doctrine is inconsistent with *KSR*

The lead-compound doctrine began with *Yamanouchi Pharmaceutical Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339 (Fed. Cir. 2000). Prior cases evaluating the obviousness of chemical compounds had looked only to the structural similarity between the prior-art and claimed compounds, *see, e.g., In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc), but *Yamanouchi* imposed a heightened requirement: that, before identifying obvious modifications, patent challengers must first “show the required motivation for selecting [a prior-art compound] as a lead compound,” in the pharmaceutical drug-development sense. 231 F.3d at 1345. The Federal

Circuit has since reiterated this requirement for an initial motivation to select particular prior art. *Otsuka*, 678 F.3d at 1292; *Daiichi Sankyo*, 619 F.3d at 1354.

This requirement to prove an initial motivation to select the closest prior art appears unique to chemical cases. Such a requirement appears nowhere in § 102, which ascribes conditions of patentability over all existing prior art—full stop. *See* 35 U.S.C. § 102 (pre-AIA) (“A person shall be entitled to a patent unless ... the invention was known or used by others ... [or] patented or described in a printed publication....”). Nor does it appear in § 103, which says that “[a] patent for a claimed invention may not be obtained ... if the *differences* between the claimed invention and the prior art are such that claimed invention as a whole would have been obvious” (emphasis added). Neither section suggests that there must be a motivation to start at any one point *within* the prior art, presumably because a POSA “is presumed to be aware of *all* the pertinent prior art.” *Standard Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985) (emphasis added). In contrast, *Graham* instructs that “the scope and content of the prior art are to be determined,” then the “differences between the prior art and the claims at issue are to be ascertained,” before determining obviousness to a POSA. 383 U.S. at 17. And *KSR* rejected the need for a specific “teaching, suggestion, or motivation to combine” in the art. 550 U.S. at 418-19. Rather, patentability does not extend to “predictable variation[s],” to the “predictable use of prior art elements according to their

established functions,” or to the “simple substitution of one known element for another.” *Id.*, 417.

True, a chemical reference might describe only an impossibly broad genus, *see Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357, 1360 (Fed. Cir. 2007), but that does not justify the strictures imposed by the lead-compound framework in *all* chemical cases. *Cf. UCB, Inc. v. Accord Healthcare, Inc.*, 890 F.3d 1313, 1329 (Fed. Cir. 2018) (“[A]n obviousness rejection by an examiner, or a challenge in court, may be based on the closest prior art, which may not have been a lead compound that the inventor had in mind.”).

Where the prior art discloses only a broad genus, requiring a motivation to select a single one may make sense because the “prior art” fails to describe *any* pertinent species with sufficient specificity, and it might not make sense whether a structural variation would be inoperable. *Cf. Otsuka*, 678 at 1292 (“Absent a reason or motivation based on such prior art evidence, mere structural similarity ... does not inform the lead compound selection.”). But where a specific compound has been synthesized and described—regardless of whether it is accompanied by data often considered in the lead-compound analysis—that compound is indisputably “prior art” under § 102, and nothing in the statute requires a specific reason to select it as a starting point.

Indeed, hindsight is a concern in obviousness for every field of endeavor. Yet no requirement has been imposed in the mechanical or electrical arts for those of ordinary skill to justify their starting point among what already exists. *See, e.g., Intel Corp. v. PACT XPP Schweiz AG*, No. 2022-1037, slip op. at 11 (Fed. Cir. Mar. 13, 2023) (“Additionally, universal motivations known in a particular field to improve technology provide a motivation to combine prior art references *even absent any hint of suggestion* in the references themselves.” (cleaned up) (emphasis in original)). Such a requirement would make most patent examination, and subsequent patent challenges, untenable. The analogous-art doctrine is sufficient in other fields. *Donner Tech., LLC v. Pro Stage Gear, LLC*, 979 F.3d 1353, 1359 (Fed. Cir. 2020). “Two separate tests define the scope of analogous prior art: (1) whether the art is from the same field of endeavor, regardless of the problem addressed and, (2) if the reference is not within the field of the inventor’s endeavor, whether the reference still is reasonably pertinent to the particular problem with which the inventor is involved.” *Id.* (citation omitted). Patent Owner cannot seriously challenge the GLP-1 prior art here—which concerns the same peptide, same target, and same disease—as non-analogous, because it is independently “from the same field of endeavor” and “reasonably pertinent” to the problem.

Here, liraglutide’s specific chemical structure was described in detail (with experimental data) in numerous publications. Ex. 1020 ¶263; *see also, e.g.*, Ex. 1012,

187:41-188:4; Ex. 1010, 3; Ex. 1011, 5. The compound itself, therefore, should be treated as prior art under § 102 regardless of whether a pharmaceutical company would have had a reason to select it as a lead compound.

But the lead-compound analysis’s doctrinal inflexibility does not end there. Even after showing a compound to be a lead, challengers must also show “that the prior art would have suggested making the *specific* molecular modifications necessary to achieve the claimed invention.” *Takeda*, 492 F.3d at 1356 (citation omitted; emphasis added). This is a particularly high hurdle, and one that fails to account for the realities of modern drug development, and specifically drug-optimization of well-characterized classes of drugs having a known target (e.g., GLP-1 agonists).

Structure fine-tuning—where an effective compound has been identified and researchers are evaluating minor tweaks to improve its known properties—generally proceeds through targeted, iterative screening. Ex. 1022 ¶¶54-56. If the compound’s SAR is already understood (e.g., certain portions must be preserved to maintain efficacy; others can be modified with options known to extend duration-of-action), optimization proceeds on a routine track. *Id.* ¶¶55-56; *see also* Ex. 1020 ¶265. This is no more than tuning known results-effective variables. *See Boesch*, 617 F.2d at 276 (noting the general “rule that discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art”). Thousands of

compounds can be synthesized with various modifications—often using automated push-button processes that assemble large libraries automatically—and the properties of each quickly screened. Ex. 1022 ¶¶56-57. While drug developers may be motivated to try specific *classes* of substituents (e.g., testing a variety of long-chain fatty acids), it is typically trial and error that reveals the most effective variant. *Id.* ¶¶55-57. Where this results in only a difference in degree of effect, not kind, it is not inventive. *Applied Materials*, 692 F.3d at 1297.

“The motivation-to-combine analysis is a flexible one” which “need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.” *Intel*, No. 2022-1037, slip op. at 11 (quoting *KSR*, 550 U.S. at 418). Thus, the lead-compound framework’s particular-modification requirement places a too-high burden on patent challengers and violates the flexible approach to obviousness of *Graham* and *KSR*.

2. **Under *Graham* and *KSR*, semaglutide would have been obvious because the differences between it and the closest prior art, liraglutide, involve predictable elements and tweaking result-effective variables**

The obviousness analysis must be more flexible than the lead-compound analysis demands. Where a general motivation to test a certain *class* of modifications exists, and the number of options within that class are not prohibitive, ultimately

finding one *specific* modification within the class through routine trial-and-error should not result in a patentable invention. That is simply testing “a finite number of identified, predictable solutions.” *KSR*, 550 U.S. at 241.

That is the case here. As discussed, liraglutide’s structure was well understood such that modifying specific peptide positions—such as positions 8 and 26—had known predictable effects. Ex. 1020 ¶¶263-267; Ex. 1022 ¶¶143-145. It was known that the position 8 residue affected half-life, that spacing between GLP-1 and the albumin binding moiety affected solubility and antidiabetic activity, and that the length and charge of the fatty acid affected half-life. Ex. 1020 ¶¶266-267; Ex. 1022 ¶¶145-147; Ex. 1024 ¶¶79-83. These were known results-effective variables, each with a limited range of options. *See* Ex. 1020 ¶¶265-267; Ex. 1022 ¶¶145-147; Ex. 1024 ¶¶79-83; *Boesch*, 617 F.2d at 276.

A POSA, for instance, would have been motivated to replace Ala⁸ to “give better metabolic stability against DPP-IV.” Ex. 1011, 5; Ex. 1020 ¶¶176-85, 266; Ex. 1022 ¶146. There were a finite number of conservative (i.e., small) amino-acid substitutions that were known to have this effect. Ex. 1022 ¶146.

Furthermore, a POSA would have been motivated to attach a long-chain fatty acid using spacers at one of a limited number of positions to increase the duration of action of the GLP-1 analogue—and in liraglutide, specifically position 26. Ex. 1012, 191:32-192:67; Ex. 1010, 3 (noting fatty-acid addition to native GLP-1

limited to positions 18, 23, 26, 27, 34, and 36); Ex. 1012, 16:57-59, 17:55-57 (noting preferred fatty-acid addition to Lys at positions 26 or 34); Ex. 1011 (same, and specifically the Lys at position 26 for liraglutide); Ex.1020 ¶¶188-209, 267; Ex. 1022 ¶¶145, 147; Ex. 1024 ¶¶79-87. The binding of fatty acids to albumin was well understood, and there are a limited number of candidates that would have been expected to work. Ex. 1022 ¶147; Ex. 1024 ¶¶82-87. The exact length of a fatty acid and whether a carboxylic acid were present would have been known result-effective variables because these two factors were known to impact fatty acid/albumin interactions. Ex. 1022 ¶147.

Even further, the use of spacers to connect such fatty acids to a peptide was well known. *See* Ex. 1010, 3; Ex. 1012, 17:55-60; Ex. 1014, 3:10-20; Ex. 1011, 3; Ex. 1020 ¶188-202; Ex. 1022 ¶148; Ex. 1024 ¶¶82-85. The length of such a spacer, which would have separated the portion of the analogue binding GLP-1's receptor and the portion binding albumin, would have been a result-effective variable. Ex. 1020 ¶224; Ex. 1022 ¶148. A POSA would have also expected that any hydrophilic, chemically unreactive linker (e.g., PEG-like AEEA) would have worked, with the exact identity left to convenience or cost considerations. Ex. 1020 ¶224; Ex. 1022 ¶148; Ex. 1024 ¶¶83-87. At the very least, the choice of AEEA was the use of a predictable element of the prior art according to its known purpose. *Id.*

For each of these modifications, there were a relatively limited number of options from which to choose, and most options were structurally similar to each other and therefore would be expected to yield similar properties. Ex. 1020 ¶¶265-267; Ex. 1022 ¶¶145-149; Ex. 1024 ¶¶82-85. A POSA would have been motivated to simulate and/or synthesize compounds that had various combinations of modifications within these identifiable classes and test which collectively performed best. Ex. 1022 ¶150; *Boesch*, 617 F.2d at 276. Among those would have obviously been semaglutide, with its Aib⁸ substitution and C₁₈ di-acid moiety acylated using a di-AEEA spacer and γ -Glu linker at Lys²⁶. *Id.*; Ex. 1020 ¶¶262-268. Thus, applying the broader principles of obviousness endorsed by the Supreme Court in *Graham* and *KSR*, the challenged claims were obvious.

If semaglutide were obvious, the formulation and method of treatment claims would also be obvious for the reasons discussed in Grounds 1 and 2, respectively. *Supra* Sections **Error! Reference source not found., Error! Reference source not found.**, V.I.2, V.I.3; *see also* Ex. 1024 ¶¶91-99; Ex. 1026 ¶¶149-152.

K. Any Secondary Considerations Fail to Overcome Prima Facie Obviousness

Should Patent Owner invoke secondary considerations of non-obviousness, any such evidence would be “insufficient” to “overcome the strong [case] of obviousness” here. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007).

Patent Owner bears the burden of showing that any “evidence of secondary considerations [has] a ‘nexus’ to the claims.” *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019). For a nexus to exist, “[e]vidence of secondary considerations must be reasonably commensurate with the scope of the claims.” *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011).

Because Patent Owner bears the burden of production, Petitioner reserves the right to respond to any such arguments. *See ZUP, LLC v. Nash Mfg., Inc.*, 896 F.3d 1365, 1373 (Fed. Cir. 2018).

1. There were no unexpected or surprising results

The ’343 patent and its file history do not assert that the claimed subject matter, namely semaglutide, produces any unexpected results. Ex. 1026 ¶154. The types of modifications POSAs already contemplated—replacing the residue at position 8 and adding a fatty-acid group via a spacer to one of a handful of positions—had known and expected results: to extend half-life. Sections V.I, V.J.; Ex. 1020 ¶¶272-277; *see also* Ex. 1024 ¶¶100-102. *How much* a particular modification would have extended the compound’s half-life is a difference of degree, not kind, which is not a cognizable basis to find unexpected results. *See Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013).

2. The prior art did not teach away from semaglutide

The prior art did not teach away from modifying liraglutide to make semaglutide, particularly in view of the prior art discussed above and the knowledge and skill of a POSA. Ex. 1020 ¶¶278-279.

3. There was no long-felt but unmet need

Any long-felt but unmet need Patent Owner may allege was satisfied by other diabetes treatment options disclosed in the prior art. Ex. 1020 ¶280; Ex. 0024 ¶¶103-104; Ex. 1026 ¶155.

4. Commercial sales do not save the '343 patent

Patent Owner may claim commercial success of the claimed subject matter, but such evidence would be insufficient to show non-obviousness because it would lack a nexus to the claims. While a presumption of a nexus can attach when a commercial embodiment is coextensive with a patent's claims, no presumption applies where (as here) a commercial product is covered by multiple patents. *Therasense, Inc. v. Becton, Dickinson & Co.*, 593 F.3d 1289, 1299 (Fed. Cir. 2010), *reinstated in relevant part*, 649 F.3d 1276 (Fed. Cir. 2011) (en banc). Patent Owner has listed in the Orange Book twenty-two patents covering Ozempic, eight covering Rybelsus, and five covering Wegovy (all semaglutide drugs). To establish that any commercial success is attributable to the '343 patent, Patent Owner must show that the success is not attributable to subject matter claimed in any of these other patents.

Therasense, 593 F.3d at 1299 (commercial success not probative when an earlier patent issued before the drug came to market); *see also J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997).

Moreover, not only has Patent Owner marketed its semaglutide products extensively (evident by its non-stop TV commercials), but also for a reason entirely unattributable to the claims: it became a viral social media trend. Commercial success should be discounted where massive marketing and advertising are involved. *McNeil-PPC, Inc. v. L. Perrigo Co.*, 337 F.3d 1362, 1370 (Fed. Cir. 2003); *see also Pentec, Inc. v. Graphic Controls Corp.*, 776 F.2d 309, 316 (Fed. Cir. 1985).

5. There was no industry skepticism

The '343 patent presents no evidence of any skepticism in the art, and a POSA would have had no reason to doubt that semaglutide could work as a long-acting treatment option for at least type 2 diabetes. Ex. 1020 ¶281; Ex. 1024 ¶107; Ex. 1026 ¶156.

6. Copying by generic drug makers is irrelevant

Patent Owner may argue that Petitioner and other generic drug companies seek to copy the invention. But “evidence of copying in the [generic drug] context is not probative of nonobviousness.” *Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013).

VI. THIS PETITION SHOULD NOT BE DENIED INSTITUTION UNDER 35 U.S.C. § 325(d)

While the Board has discretion to deny institution under 35 U.S.C. § 325(d), the Board should not do so. The relevant non-exhaustive set of factors include

- (a) the similarities and material differences between the asserted art and the prior art involved during examination;
- (b) the cumulative nature of the asserted art and the prior art evaluated during examination; (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;
- (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art; (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and (f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments.

Becton, Dickinson & Co. v. B. Braun Melsungen AG, IPR2017-01586, Paper 8, 17-18 (PTAB Dec. 15, 2017) (precedential). The Board has noted that these factors fall into two groups. Factors (a), (b), and (d) ask whether “the same or substantially the same art or arguments previously were presented to the Office,” while “factors (c), (e), and (f) relate to whether the petitioner has demonstrated a material error by the

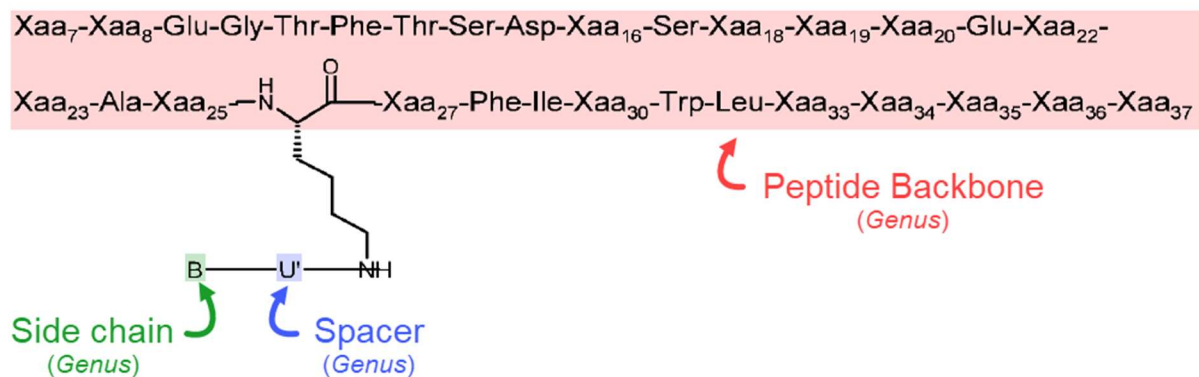
Office.” *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6, 9-11 (PTAB Feb. 13, 2020) (precedential).

The Board should not invoke its discretion because: (1) the Petition presents art and arguments that were not before the Examiner; and (2) the Examiner’s failure to consider such art and arguments was a material error.

A. This Petition Presents Different Art And Arguments than Were Before The Examiner

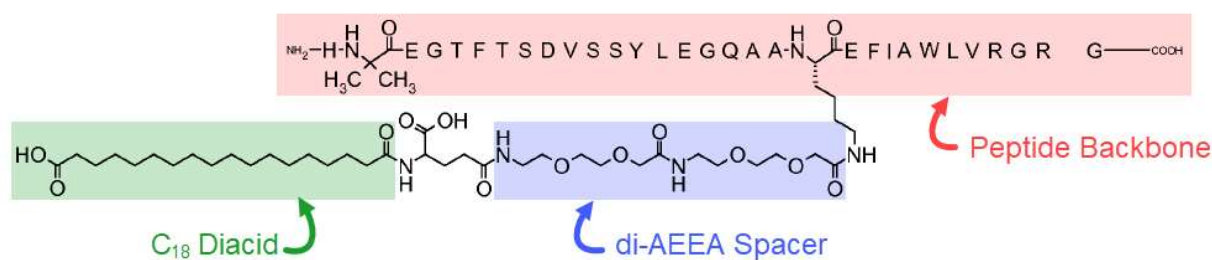
The Board should decline to invoke its discretion under § 325(d) because this Petition presents new prior art and arguments that were not before the Examiner during prosecution.

Only the Knudsen Patent—which is cited herein as a secondary reference—was relied upon by the Examiner during prosecution. But even so, the Examiner applied the Knudsen Patent differently. Specifically, the claims being examined at the time were directed to a broad genus of GLP-1 analogues comprising a peptide backbone, an acylated side chain B (also a genus), and a spacer U’ (also a genus). Ex. 1004, 78:



In a (replacement) Non-Final Rejection, the Examiner explained that the Knudsen Patent disclosed a variety of GLP-1 analogues (the backbone), spacers (U'), and lipophilic substituents (or “side chains,” B) that could be selected to arrive at analogues that fell within the scope of the broad claims, rendering them obvious and unpatentable. Ex. 1004, 41-45. The Examiner also identified a *specific* spacer disclosed by Knudsen as part of the rejection: NH-CH(COOH)(CH₂)₂CO. *Id.*, 44-45. For several dependent claims directed to a narrower set of analogues—those with an Aib residue at position 8 and a subset of side chains—the Examiner relied on Larsen and found the combination of Knudsen and Larsen rendered those claims obvious as well. *Id.*, 45-46.

In the face of the Examiner’s rejection over Knudsen and Larsen, the applicant canceled all pending claims and drafted new ones that not only specified the backbone and a C₁₈ diacid as the side chain (still consistent with the Knudsen Patent), but also *required* an di-AEEA spacer, which the Knudsen Patent did not disclose. Compare *id.*, 78, with *id.*, 32:



After an Examiner's Amendment correcting the claimed Sequence ID number provided in the specification (correcting SEQ ID. No. 6 to 7), the Examiner allowed the claims without discussion. *Id.*, 26-27.

While numerous prior-art references disclosed analogues of GLP-1 compounds because they were well known, and numerous prior-art references (like Larsen) also disclosed modifying position 8 to inhibit DPP-IV cleaving because that too was well known, *no* art was ever identified as teaching the newly claimed di-AEEA spacer, let alone in combination with the narrowed backbone and C₁₈ diacid. This Petition, however, provides new prior art (and testimony) never considered by the Examiner that shows that nothing about the di-AEEA spacer—or its use in a GLP-1 analogue—is novel.

The Examiner also applied a mode of analysis under § 103 different from the one in this Petition. Specifically, the Examiner only ever took a top-down approach to obviousness: whether the newly claimed, more specific GLP-1 analogue (a species) was obvious in view of a broader genus of GLP-1 analogues and high-level modifications taught primarily by the Knudsen Patent (and Larson for other

modifications). *See* MPEP 2131.02(III). In other words, the Examiner appears to have considered only whether the particular GLP-1 analogue claimed would have been evident with just a bucket of possible options in hand.

This Petition, however, proposes two distinct modes of analysis that were not advanced, let alone considered. This Petition first advances a lead-compound analysis (as set forth by the Federal Circuit) that it would have been obvious to modify a specific, existing compound (liraglutide) to arrive at the similar compound encompassed by the claim (semaglutide). *See* MPEP 2131.02(I). This is a distinct bottom-up approach to obviousness the Examiner never applied.

This Petition then contends that the synthesis of semaglutide would have been obvious under broader obviousness principles set forth in *KSR*, as opposed to the lead-compound analysis. Specifically, the prior art provided ample reason to start with liraglutide and modify it according to known principles, using known modifications, that had known effect on the desired properties.

Accordingly, in response to this Petition, Patent Owner cannot simply reassert its prosecution arguments that the claims are directed to a species of GLP-1 analogues patentably distinct from the broader genus in the Knudsen Patent, because this Petition shows the obviousness of that specific species. And when a patent owner is unable to make the same arguments in IPR that it made during prosecution, that suggests that the arguments being presented are different, and invoking

discretion under § 325(d) is unwarranted. *See Aquestive Therapeutics, Inc. v. Neurelis, Inc.*, IPR2019-00451, Paper 8, 37-39 (PTAB Aug. 13, 2019).

B. The Examiner Materially Erred

Institution is also warranted because the Examiner materially erred by citing references specifically directed to liraglutide (e.g., the Knudsen Patent and Knudsen 2004), yet failing to perform any sort of lead-compound analysis (or any other analysis) apart from the genus-centric assessment in the lone rejection. *See* MPEP 2143(I.B) (providing exemplary lead-compound analysis).

The Board has found that when a petition points out additional disclosures in the prior art that the Examiner overlooked—and the Examiner failed to consider additional references that fill a perceived gap in the prior art—that constitutes a sufficient identification of Examiner error. *See Weatherford U.S., L.P. v. Enventure Glob. Tech., Inc.*, IPR2020-01684, Paper 16, 18-19 (PTAB Apr. 14, 2021) (“Because Petitioner’s arguments and evidence persuade us that there was an oversight regarding amended claimed features made to distinguish over [the primary references cited by the Examiner] and the disclosures of [additional prior art], Petitioner demonstrates material error, and we decline to exercise discretion to deny institution under 35 U.S.C. § 325(d).”); *see also 10X Genomics, Inc. v. Bio-Rad Labs., Inc.*, IPR2021-00133, Paper 11, 15-19 (PTAB May 14, 2021) (finding factor weighed in petitioner’s favor when “the Examiner overlooked [a prior art’s]

disclosure related to [certain figures not clearly considered by the Examiner] and its relevance to the claims[.]”). Here, the Examiner should have recognized that both the Knudsen Patent and Knudsen 2004 taught a structurally similar compound (liraglutide) to the one presented in the amended claims. With such a disclosure, the Examiner could have considered specifically whether the claimed compound was patentably distinct from liraglutide, rather than fall back on the Knudsen Patent’s broader disclosure of various options for different GLP-1 analogues. And the Examiner should have been able to identify prior art describing the routine use of di-AEEA spacers to modify liraglutide. The Examiner’s failure to do so warrants further review.

* * *

Accordingly, there is no reasonable basis to discretionarily deny institution under § 325(d).

VII. THIS PETITION SHOULD NOT BE DENIED INSTITUTION UNDER 35 U.S.C. § 314

Under 35 U.S.C. § 314(a), as set forth in *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 (PTAB Mar. 20, 2020) (precedential), the Board considers several factors to determine whether to institute where there is parallel district court litigation, but none support a discretionary denial here. Applying the Director’s June 21, 2022 Interim Guidance, compelling, meritorious challenges will be allowed to proceed even where district court litigation is proceeding in parallel. This Petition

presents multiple grounds not considered during prosecution—based on new evidence—that render the asserted claims unpatentable. This weighs in favor of institution. Additionally, trial is not set in the Delaware litigation until September 30, 2024, likely after a final written decision would be due. In addition, Petitioner stipulates that if the Board institutes, Petitioner will not pursue in the district court any instituted grounds against the originally issued claims unless a change in law otherwise permits. *See Sand Revolution II, LLC v. Cont’l Intermodal Grp.*, IPR2019-01393, Paper 24, 11-12 (PTAB June 16, 2020) (informative). This further weighs in favor of institution.

VIII. CONCLUSION

Petitioner respectfully requests that the Board institute trial and find all claims of the ’343 patent unpatentable.

Respectfully submitted,
PERKINS COIE LLP

Dated: March 16, 2023

By: /Brandon M. White/
Brandon M. White
Reg No. 52,354
Perkins Coie LLP
700 13th Street NW, Ste 800
Washington, DC 20005
Phone: (202) 654-6200

Counsel for Petitioner
Mylan Pharmaceuticals Inc.

CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATION

This Petition complies with the type-volume limitation of 37 C.F.R. § 42.24(a)(1) because this Petition contains 13,892 words, as determined by the word-count function of Microsoft Word, excluding the parts of the Petition exempted by Rule (i.e., a table of contents, a table of authorities, mandatory notices under 37 C.F.R. § 42.8, a certificate of service or word count, or appendix of exhibits or claim listing).

Dated: March 16, 2023

/Brandon M. White/
Reg No. 52,354

Counsel for Petitioner
Mylan Pharmaceuticals Inc.

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105, I certify that I caused to be served a true and correct copy of the foregoing: Petition for *Inter Partes* Review of U.S. Patent No. 8,129,343 including Exhibits 1001-1112 and Petitioner's power of attorney, by Federal Express Next Business Day Delivery on this day on the Patent Owner's correspondence address of record for the subject patent as follows:

Novo Nordisk Inc.
Intellectual Property Department
800 Scudders Mill Road
Plainsboro, NJ 08536

Courtesy copies of the Petition for Inter Partes Review of U.S. Patent No. 8,129,343, including Exhibits 1001-1112, have been sent by Federal Express Next Business Day Delivery on this day to Patent Owner's counsel of record in the matter identified in Section II.B of the Petition as follows:

Jeff Oelke
Fenwick & West LLP
902 Broadway
Suite 14
New York, NY 10010-6035

Dated: March 16, 2023

/Brandon M. White/
Reg No. 52,354

Counsel for Petitioner
Mylan Pharmaceuticals Inc.