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Paper 9
Entered: October 2, 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.

IPR2023-00723
Patent 8,129,343 B2

Before JOHN G. NEW, SUSAN L. C. MITCHELL, and ROBERT A. POLLOCK, *Administrative Patent Judges*.

POLLOCK, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Petitioner, Mylan Pharmaceuticals Inc., filed a Petition for *inter partes* review of claims 1–6 of U.S. Patent No. 8,129,343 B2 (Ex. 1002, "the '343 patent"). Paper 1 ("Pet."). Patent Owner, Novo Nordisk A/S, timely filed a Preliminary Response. Paper 6 ("Prelim. Resp."). Petitioner further filed an authorized Reply to the Preliminary Response (Paper 7, "Reply"); Patent Owner filed a responsive Sur-Reply (Paper 8, "Sur-reply").

For the reasons provided below, we determine Petitioner has not satisfied the threshold requirement set forth in 35 U.S.C. § 314(a). Because Petitioner has not demonstrated a reasonable likelihood that at least one claim of the '343 patent is unpatentable, we do not institute an *inter partes* review on the Grounds raised in the Petition. *See SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1359–60 (2018); *PGS Geophysical AS v. Iancu*, 891 F.3d 1354, 1360 (Fed. Cir. 2018) (interpreting the statute to require "a simple yes-or-no institution choice respecting a petition, embracing all challenges included in the petition"); *see also* Guidance on the Impact of SAS on AIA Trial Proceedings (April 26, 2018).[1]

A. Real Parties in Interest

Petitioner identifies Mylan Pharmaceuticals Inc., Mylan Inc., and Viatris Inc. as the real parties-in-interest. Pet. 2. Patent Owner identifies Novo Nordisk A/S and Novo Nordisk Inc. as real parties-in-interest. Paper 4, 1.

[1] Available at https://www.uspto.gov/patents-application-process/patent-trial-and-appeal-board/trials/guidance-impact-sas-aia-trial ("Guidance").

B. Related Matters

In addition to the current matter, Petitioner challenges claims 1, 2, 4–11, 13 and 15 of U.S. Patent No. 8,536,122 B2 (Ex. 1001, "the '122 patent") in IPR2023-00722. The '122 patent is a continuation of application No. 11/908,834 that issued as the '343 patent.

According to the parties, the '343 patent is at issue in the following actions involving the parties, among other litigations:

> *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); and
>
> *In re: Ozempic (Semaglutide) Patent Litig.*, No. 22-md-3038-CFC (D. Del.).

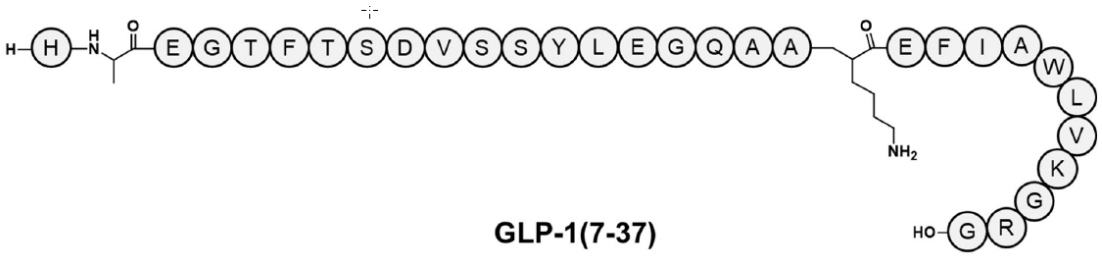
Pet. 2–3; Paper 4, 1–2.

C. The '343 Patent and Relevant Background

The '343 patent, titled "Acylated GLP-1 Compounds," is directed to modified analogs of glucagon-like peptide 1 (GLP-1). Ex. 1002, code (54), 1:55–2:5. GLP-1[2] is a naturally-occurring insulinotropic peptide hormone derived from a 37-amino acid precursor by the enzymatic removal of amino

[2] Although the unprocessed peptide is sometimes referred to as GLP-1 (*see* Pet. 17–18), we generally understand the term to refer to a processed form. *See, e.g.,* Ex. 1002, 3:25–28. For additional specificity, GLP-1 peptides may be identified with reference to its amino acid sequence as compared to the 37 amino acid precursor form. For example, GLP-1(1–37) may refer to the full-length parent molecule, and GLP-1(7–37) to a post-cleavage form in which amino acids 1–6 have been removed. *See* Prelim. Resp. 6, n.3.

acids 1–6 and modification of amino acids 8 and 26. *See, e.g., id.* at 3:25–33, Ex. 1011, 677.[3, 4] The structure of a naturally-occurring mature form is shown below.



GLP-1(7-37)

Pet. 18; Prelim. Resp. 7.[5] The above figure illustrates the structure of GLP-1(7–37) including the modifications to the alanine 7 and lysine 26.

In the body, GLP-1 is rapidly degraded by dipeptidyl aminopeptidase IV (DPP-IV), such that "the natural hormone is not very useful as a drug." Ex. 1011, 677. According to the '343 patent, the prior art discloses various "approaches . . . for modifying the structure of glucagon-like peptide 1 (GLP-1) compounds in order to provide a longer duration of action in vivo," but indicates that, because of the short half-lives, prior art GLP-1 compounds must be administered at least once daily. *See* Ex. 1002, 1:20–53.

The '343 patent discloses improved GLP-1 analogs intended to allow for reduced dosing frequency when treating type 2 diabetes. *Id.* at 1:50–2:5. In particular, the '343 patent describes GLP-1 analogs with modifications "of at least one non-proteogenic amino acid residue in positions 7 and/or 8

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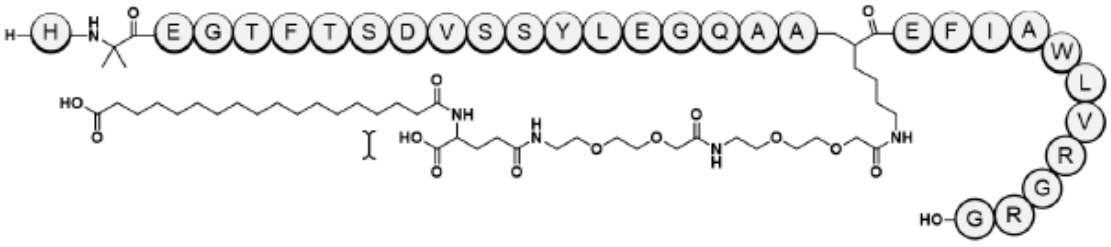
[3] L. B. Knudsen et al., *GLP-1 derivatives as novel compounds for the treatment of type 2 diabetes: selection of NN2211 for clinical development*, 26(7) DRUGS OF THE FUTURE 677–685 (2001). ("Knudsen 2001").

[4] We generally refer to the original page numbers of cited art rather than to the numbering assigned by the parties.

[5] Naturally occurring GLP-1 also occurs as an amide, GLP-1(7-36) amide. *See* Ex. 1011, 677.

relative to the sequence GLP-1(7-37) (SEQ ID No. 1), which is acylated with a moiety to the lysine residue in position 26," and wherein the moiety includes at least two acidic groups. *Id.* at 1:57–63. *See* Ex. 1002, 4:4–16, Ex. 1011, 677. The non-proteogenic amino acid residue in positions 7 and/or 8 protects the modified compounds from DPP-IV degradation as compared to native GLP-1. *See* Ex. 1002, 4:4–19; 6:18–22. The acylated GLP-1 analog binds to albumin and the GLP-1 receptor simultaneously. *Id.* at 5:4–6. Specifically, the acylated GLP-1 analog is acylated "with a lipophilic albumin binding moiety containing at least two free acidic chemical groups attached via a non-natural amino acid linker to the lysine residue in position 26." *Id.* at 6:11–14.

The '343 patent discloses a number of specific compounds, including semaglutide, 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). *Id.* at 61:1–62:37 (Example 4); Ex. 1020 ¶ 100. The structure of this peptide may also be illustrated as:



Ex. 1020 ¶ 100.

D. Relevant Prosecution History

Applicants conducted an initial Examiner interview discussing then-pending claims 7, 27, and 28 (Ex. 1004, 100–103), and thereafter submitted a preliminary amendment addressing those claims, among others (*id.* at 77–

97). The Examiner then issued a restriction requirement for the election of a "specific GLP-1 analog with all substitutes fully assigned." *Id.* at 72. In response, Applicants elected semaglutide for examination—but argued that most of the then-pending claims "read on the elected species." *Id.* at 68.[6]

In a first (and only) Office Action on the merits, the Examiner rejected certain claims in view the Knudsen Patent[7] and Larsen.[8] Ex. 1004, 41–45. The Examiner found that the Knudsen Patent discloses a genus of GLP-1 analogs that encompassed the claimed genus. *Id.* at 41–42. The Examiner further found that the Knudsen Patent teaches attaching lipophilic substituents to the GLP-1 moiety to "obtain a satisfactory protracted profile of action." *Id.* at 43. The lipophilic substituents may be attached by means of a hydrophilic spacer. *See id.* The Examiner also found that Larsen teaches modifying GLP-1 with alpha-amino-isobutyric acid (Aib) at position 8 and a lipophilic substituent. *Id.* at 45. The Examiner determined that one of ordinary skill in the art would have been motivated to select GLP-1 analogs, spacers and lipophilic substituents taught by the Knudsen Patent, further modified with Larsen's Aib amino acid at position 8. *Id.* at 44–45. According to the Examiner, a person of ordinary skill in the art would have been motivated to make the modifications to produce analogs with increased stability and a satisfactory protracted profile of action. *See id.*

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[6] The sole outlier, claim 18, was withdrawn as directed to a non-elected species. *See id.* at 41.

[7] L.B. Knudsen et al., US 6,268,343 B1, issued July 31, 2001. ("Knudsen Patent") (Ex. 1012).

[8] P.J. Larsen et al., *Systemic Administration of the Long-Acting GLP-1 Derivative NN2211 Induces Lasting and Reversible Weight Loss in Both Normal and Obese Rats*, 50 DIABETES 2530 (2001) ("Larsen") (Ex. 1086).

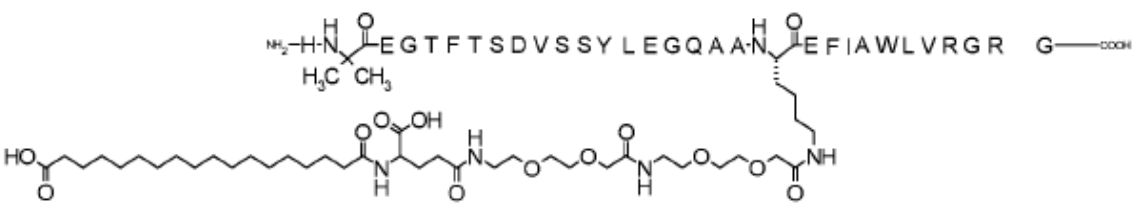
In response, the Applicant cancelled all claims and entered new claims that are substantially identical to those of the '343 patent. Ex. 1004, 31–33. The Applicant noted "that the new claims are directed to the compound disclosed in Example 4." *Id.* at 35. Following an Examiner's amendment to correct the sequence of the claimed formula, the Examiner issued a Notice of Allowance. *See id.* at 20–27.

E. Illustrative Claims

Petitioner challenges claims 1–6 of the '343 patent. Pet. 1. Each of claims 1–6 is independent. *See* Ex. 1002, 129:1–132:36, Certificate of Correction 1–2. Claims 1–3 recite the structure of the claimed compound and the amino acid sequence of SEQ ID NO: 7. *Id.* Claims 4–6 recite the chemical name of the claimed compound. *See id.* at 131:30–132:36. Claims 1 and 4 are drawn to the compound itself; claims 2 and 5 recite a pharmaceutical composition comprising the compound; and claims 3 and 6 are directed to methods of treating type 2 diabetes by administering the pharmaceutical composition. *Id.* at 129:1–132:36. There is no dispute that the recited compound is semaglutide, the active ingredient in Patent Owner's Ozempic, Rybelsus, and Wegovy products. *See* Prelim. Resp. 1, 7; Pet. 10, 61.

Challenged claim 1, reproduced below, is illustrative of the subject matter challenged.

1. A compound of the structure



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

Ex. 1002, Certificate of Correction 1.

F. Asserted Grounds of Unpatentability

Petitioner asserts that claims 1–6 would have been unpatentable on the following grounds (Pet. 5):

Ground	Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1	1–6	103	Knudsen 2004,[9] Knudsen Patent, Dong,[10] Bridon[11]
2	1–6	103	Knudsen 2001, Knudsen Patent, Dong, Bridon
3[12]	1–6	103	Knudsen 2004, Knudsen 2001, Knudsen Patent, Dong, Bridon

[9] L. B. Knudsen, *Glucagon-like Peptide-1: The Basis of a New Class of Treatment for Type 2 Diabetes*, 47 J. MED. CHEM. 4128–4134 (2004). ("Knudsen 2004") (Ex. 1010).

[10] J. Z. Dong et al., *Glucagon-Like Peptide-I Analogs with Significantly Improved in vivo Activity*, *in* PEPTIDES: THE WAVE OF THE FUTURE, PROCEEDINGS OF THE SECOND INTERNATIONAL AND THE SEVENTEENTH AMERICAN PEPTIDE SYMPOSIUM 670–671 (2001) ("Dong). (Ex. 1013).

[11] D.P. Bridon et al., US 6,514,500 B1, issued Feb. 4, 2003 ("Bridon") (Ex. 1014).

[12] Petitioner casts Ground 3 as directed to "[o]bviousness over the prior art and common drug development principles." Pet. 5. Insofar as Petitioner's review of the "Scope and Content of the Prior Art," addresses only Knudsen 2004, Knudsen 2001, Knudsen Patent, Dong, and Bridon, we infer that Ground 3 is also limited to these five references. *See id.* at 17–24; *see also* Reply, 1 (Petitioner's statement that "Ground 3 relies on the same prior art as Grounds 1 and 2.").

Petitioner further relies, *inter alia*, on the Declarations of Peter Flatt, Ph.D. (Ex. 1020), Christopher J. Soares, Ph.D. (Ex. 1022), Paul Dalby, Ph.D. (Ex. 1024), and John Bantle, M.D. (Ex. 1026). Patent Owner's Preliminary Response does not identify the testimony of subject matter declarant(s).

II. ANALYSIS

A. Legal Standards

"In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (2012) (requiring *inter partes* review petitions to identify "with particularity . . . the evidence that supports the grounds for the challenge to each claim")). This burden of persuasion never shifts to Patent Owner. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015) (discussing the burden of proof in *inter partes* review).

A claim is unpatentable under 35 U.S.C. § 103 if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence

of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

In analyzing the obviousness of a combination of prior art elements, it can be important to identify a reason that would have prompted one of skill in the art "to combine . . . known elements in the fashion claimed by the patent at issue." *KSR*, 550 U.S. at 418. A precise teaching directed to the specific subject matter of a challenged claim is not necessary to establish obviousness. *Id.* Rather, "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420. Accordingly, a party that petitions the Board for a determination of unpatentability based on obviousness must show that "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016) (internal quotations omitted).

The Federal Circuit provides a two-prong analysis to determine whether a new chemical compound is prima facie obvious over particular prior art. The fact finder first determines whether a chemist of ordinary skill would have selected one or more prior art compounds as lead compounds, or starting points, for further development efforts. (*Otsuka Pharm. Co. v. Sandoz Inc.*, 678 F.3d 1280, 1291 (Fed. Cir. 2012). The Court defines a lead compound as "a compound in the prior art that would be most promising to modify in order to improve upon its ... activity and obtain a compound with better activity," (*Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007), or "a natural choice for further

development efforts." *Altana Pharma AG v. Teva Pharm. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009). The second step involves determining "whether the prior art would have supplied one of ordinary skill in the art with a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success." *Otsuka*, 678 F.3d at 1292 (citing *Takeda*, 492 F.3d at 1357).

We address Petitioner's challenges with these standards in mind, and in view of the definition of the skilled artisan and the claim constructions discussed below.

B. Level of Ordinary Skill in the Art

In determining the level of skill in the art, we consider the type of problems encountered in the art, the prior art solutions to those problems, the rapidity with which innovations are made, the sophistication of the technology, and the educational level of active workers in the field. *See Custom Accessories, Inc. v. Jeffrey-Allan Industries, Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986); *see also Orthopedic Equip. Co. v. United States*, 702 F.2d 1005, 1011 (Fed. Cir. 1983).

In addressing the level of ordinary skill in the art, Petitioner contends that "[t]he 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 analogs to treat patients having type-2 diabetes or related conditions." Pet. 7. The persons of ordinary skill in the art ("POSA") making up the team would have

> an M.D., Pharm.D., or doctoral degree(s) in chemistry, biochemistry, pharmaceutics, 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.

Id. at 7–8 (citing Ex. 1020 ¶ 27; Ex. 1022 ¶ 27; Ex. 1024 ¶ 21; Ex. 1026 ¶¶ 25–26). [13] Patent Owner does not offer a different level of ordinary skill in the art. *See generally* Prelim. Resp.

On the current record, and for the purposes of this decision, we accept Petitioner's proposed definition, as it appears consistent with the level of skill in the art reflected in the prior art of record and the disclosure of the '343 Patent. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) ("the prior art itself [may] reflect[] an appropriate level" as evidence of the ordinary level of skill in the art) (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)).

C. Claim Construction

We interpret a claim "using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. 282(b)." 37 C.F.R. § 42.100(b) (2020). Under this standard, we construe 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." *Id.* Moreover, "the specification 'is always highly relevant to the claim construction analysis. Usually it is dispositive; it is the single best guide to the meaning of a disputed term.'" *In re Abbott*

[13] We need not consider Petitioner's similar alternative definitions. *See id.* at 8–9.

Diabetes Care Inc., 696 F.3d 1142, 1149 (Fed. Cir. 2012) (quoting *Phillips v. AWH Corp.,* 415 F.3d 1303, 1315 (Fed. Cir. 2005) (en banc)).

The parties contend that no claim term requires construction. Pet. 13. Prelim. Resp. 15. Having considered the record, we determine that no express claim construction of any claim term is necessary to reach our decision. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Ltd. v. Matal*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) ("[W]e need only construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy.'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))).

D. Overview of Asserted References

Petitioner's Grounds are based on a combinations of Knudsen 2004 and/or Knudsen 2001 with Knudsen Patent, Dong, and Bridon, which we briefly address below.

1. Knudsen 2004 (Ex. 1010)

Knudsen 2004 provides an overview of GLP-1 based compounds in development. Ex. 1010. By way of background, Knudsen 2004 discloses that "GLP-1 was discovered in 1984 and found to be an important incretin. It is a product of the preproglucagon gene and is released from the L-cells in the intestine upon food intake and potently releases insulin from the β-cells in the pancreas." *Id.* at 4128. "GLP-1 exists in two equipotent naturally occurring forms, GLP-1(7-37) and GLP-1(7-36)amide, the former corresponding to proglucagon(78-108)." *Id.* Knudsen 2004 explains that "[t]he numbering of GLP-1 starts with 7 because it was originally believed that GLP-1(1-37) was the active hormone." The current numbering system began when it was discovered that the active hormone is formed upon

removal of the first 6 N-terminal amino acids. *Id.* The naturally-occurring "hormone is degraded rapidly by the enzyme dipeptidyl peptidase IV (DDP-IV) and cleared by the kidneys resulting in a half-life of less than 2 min after iv administration and a clearance higher than that of the normal cardiac output." *Id.*

Knudsen 2004 explains that because natural GLP-1 "has a very short half-life because of cleavage by DPP-IV and rapid clearance," the challenge in making GLP-1 receptor peptide-therapeutics "is to make a stable compound with a long half-life." *Id.* at 1429, 4130. In this respect, Knudsen 2004 discloses that there are two subclasses of GLP-1 analogs in clinical development as treatments for Type 2 Diabetes: one based on natural GLP-1 and the other based on exendin-4, a peptide agonist isolated from the venom of the lizard Heloderma Suspectum, which shows a 53% structural homology to GLP-1. *Id.* at 4129.[14] Knudsen 2004 notes that exendin-4 is more resistant to proteolytic degradation than GLP-1, but that certain modifications designed to further increase its stability "may . . . be at the expense of an immune reaction to the peptide." *Id.* at 4130.

With respect to GLP-1, Knudsen 2004 illustrates the structure-activity relationships of GLP-1(7–37) in Figure 3, reproduced below.

[14] We presume without deciding that exendin-4 derivatives, such as exenatide, are GLP-1 analogs within the meaning of the '343 patent.

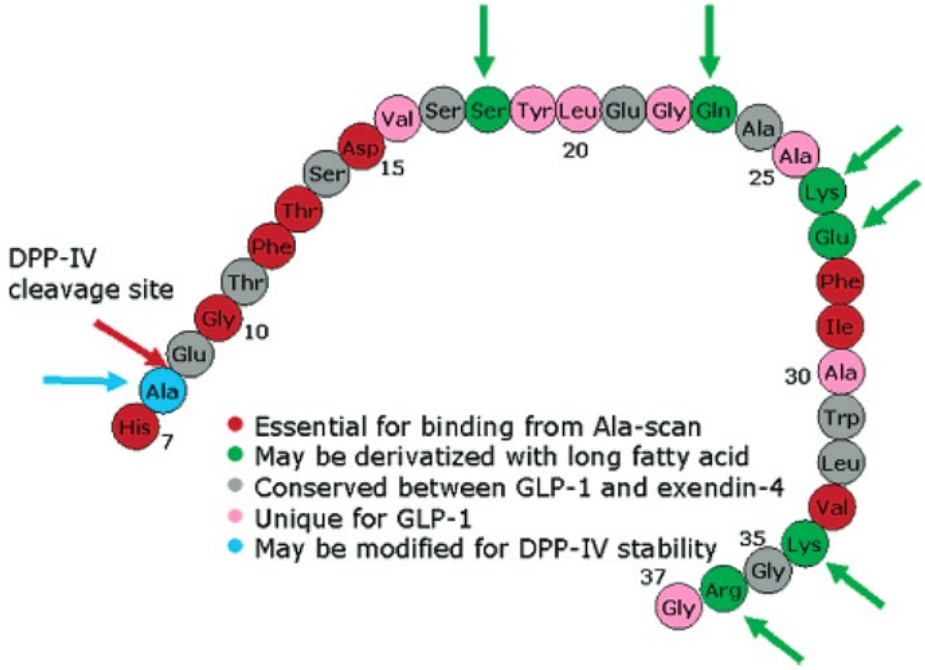


Figure 3 is a color-coded representation of GLP-1 amino acids 7–37. Ex. 1010, 4130. According to Knudsen 2004, "it has been proposed that the N-terminal part of the peptide is responsible for the high-affinity binding to the core of the receptor, whereas the C-terminal is more responsible for the selectivity by interacting with the large N-terminal of the receptor." *Id.* With respect to the individual amino acids shown in Figure 3, Knudson 2004 discloses that Ala^{8}, colored blue, may be modified for DPP-IV stability, whereas amino acids Ser^{18}, Gln^{23}, Lys^{26}, Glu^{27}, Lys^{34}, and Arg^{36}, colored green, may be derivatized with a long fatty acid. *Id.*

Knudsen 2004 lists seven known GLP-1 analogs, but states that most of these compounds "are in the discovery phase or in small-scale 1/2 phase clinical development" and "very little is published in peer-reviewed journals." *See* Ex. 1010, 4129, 4131. In contrast, Knudsen 2004 discloses that Novo Nordisk completed phase 2 clinical trials with liraglutide, (γ-L-glutamyl(*N*-α-hexadecanoyl))-Lys^{26},Arg^{34}-GLP-1(7–37) (NN2211). *Id.* at

4130.[15] Referencing "[s]everal preclinical and clinical studies," Knudsen 2004 states that "Liraglutide is equipotent to GLP-1 and has a half-life that is more than 10-fold larger that of exendin-4, 8 h vs 26 min after iv administration,[] respectively." *Id.* "Liraglutide is part of a series of acylated derivatives of GLP-1 that are aimed at being long-acting via two independent mechanisms, self-association and noncovalent binding to plasma albumin fatty acid binding sites, resulting in a pharmacokinetic profile with slow absorption and a long half-life." *Id.* Liraglutide in particular is acylated at Lysine 26 with ((γ-L-glutamoyl(N-ε-hexadecanoyl)). *Id.* Knudsen explains that acylation at different sites on GLP-1 may improve half-life while retaining potency or, alternatively, destroy potency. *See id.* With respect to the latter, Knudsen 2004 cautions that "[a] potency-destroying SAR[16] has . . . been generated in which acylation in the N-terminus position 8 leads to a compound about 20 times less potent than GLP-1," whereas, "[a]cylation with two fatty acids on both naturally present lysines in positions 26 and 34 destroys potency." *Id.*

2. Knudsen 2001 (Ex. 1011)

Knudsen 2001 explains that GLP-1's mode of action suggests it would provide "the ideal treatment of type 2 diabetes." Ex. 1011, 679. However, GLP-1 is "metabolized rapidly by DPP-IV" and "cleared very rapidly from the kidneys." *Id.* To address the short physiological half-life, Knudsen 2001 discloses GLP-1 derivatives for treating type 2 diabetes, specifically

[15] By way of context, liraglutide is now the active ingredient in Saxenda and Victoza commercial products. *See* Exs. 3002, 3003.

[16] "SAR" refers to Structure-Activity-Relationship. *See* Ex. 1020 ¶ 80.

NN2211, later named liraglutide. *See id.* at 677, 680 (Table 1, compound 5).

According to Knudsen 2001,

> [f]atty acid derivatization has been used successfully to protract the action of insulin by facilitating binding to plasma albumin. The same principle has been used to design derivatives of GLP-1 with half-lives longer than 10 h, thereby being optimal for once-daily administration. Fatty 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, were used. Acylation with simple fatty acids increases the net negative charge of the resulting molecule with one (by blocking the epsilon-amino group of the lysine), whereas peptides acylated with a L-glutamoyl-spacer or with diacids provides a further increase of the negative charge. The addition of a negative charge to the acylated molecule is expected to improve solubility at physiological pH.

Id. at 679 (internal citations omitted).

Knudsen 2001 provides twenty-two examples of GLP-1 "derivatized on position 8, 18, 23, 26, 27, 34, 36 or 38 with fatty acids and optionally a spacer." *See, e.g., id.* at 677, 680 (Table 1). "All compounds acylated with a fatty acid equal to or longer than 12 carbon atoms were considerabl[y] protracted compared to native GLP-1, which had a half-life after s.c. administration of only 1.2 h." *Id.* Focusing on a set of examples derivatized with a γ-glu-C16 monoacid, Knudsen 2001 notes that "[m]any different positions in the C-terminal part of GLP-1 could be derivatized with quite long fatty acids, visualized with compounds **3-9** (EC_{50} 30-121 pM) without affecting the potency." *Id.* at 680 (referencing compound numbers and potency data from Table 1). Focusing on a series of compounds derivatized on lysine 26, however, Knudsen further notes that, "[w]ithin the γ-Glu spacer monoacid series (**5**, 16-18), derivatization with a C18 acid (16, 194 pM) led to a significant loss of activity compared to C16 (**5**, 68 pM), C14

(**17**, 22 pm) and C12 (**18**, 27 pm). *Id.* Moreover, "[w]ithin the diacid series (**14, 15**), the diacid could be no longer than a C14 **(15,** 72 pM) before a loss in potency (**14,** 154 pM), compared to the y-Glu spacer monoacid series (**17, 18,** 22-27 pM) was seen." *Id*

Of the twenty-two compounds listed in Table 1, Knudsen 2001 identifies compounds 4, 5, 7, 8, 18, 20 and 21 as "very potent," with compounds 5, 7, and 8, showing "dramatic differences in plasma half-lives" as compared to naturally-occurring GLP-1. *Id.* at 679–680 (Table II). Knudsen 2001 explains that, although "[a] number of compounds were both very potent and had plasma half-lives above 10 h, making them suitable as drugs for the treatment of type 2 diabetes using once-daily administration," only liraglutide (compound 5) was selected for clinical development. *Id*. at 681–682. According to Knudsen 2001, liraglutide showed "equal potency to GLP-1" in in vitro testing, and its "mechanism of protraction involves binding to albumin, metabolic stability towards DPP-IV and slow release from the injection site." *Id.* Knudsen 2001 further describes the specific attributes of liraglutide and the reasons for choosing it as the best compound for clinical development. *Id.* Knudsen 2001 reports, for example, that acylation of lysine 26 with a γ-L-Glu spacer "gave the most potent" and "metabolically stable compound" with a half-life of 20 hours. *Id.* Although "[a]mino acid substitutions in position 8 can give better metabolic stability against DPP-IV," that was not needed for liraglutide because "quite a substantial protection against DPP-IV was obtained by acylation alone, and since any amino acid substitution poses a risk of immunogenicity." *Id.*

Knudsen 2001, concludes:

> [liraglutide] is a metabolically stable compound with potency equal to GLP-1. It has been characterized to act as a GLP-1

> compound in several animal models, including the ability to lower body weight. [liraglutide] is currently the only GLP-1 compound in clinical development that has been shown to possess pharmacokinetic properties applicable to once-daily administration. The only study carried out thus far in type 2 diabetic patients has confirmed its efficacy. Ongoing phase 2 clinical trials will reveal the potential of [liraglutide] as a promising new treatment for type 2 diabetes.

Id. at 682.

3. Knudsen Patent (Ex. 1012)

Knudsen Patent is a U.S. Patent for "Derivatives of GLP-1 Analogs." Ex. 1012, code (54). Knudsen Patent describes GLP-1 derivatives having a lipophilic substituent resulting in a protracted profile of action. *Id.* at code (57).

Knudsen Patent describes various modifications to naturally occurring GLP-1. *See* Ex. 1012, 8:13–23. Knudsen Patent states, For example, "[t]he GLP-1 derivatives of the present invention preferably have only one or two Lys wherein the ε-amino group of one or both Lys is substituted with a lipophilic substituent." *Id.* at 12:24–26. The lipophilic substituent may be attached via a spacer, wherein suitable spacers are α, ω-amino acids, such as "succinic acid, Lys, Glu or Asp, or a dipeptide such as Gly-Lys." *Id.* at 17:55–60. "Other preferred spacers are N^{ε}-(γ-L-glutamyl[)], N^{ε}-(β-L-asparagyl), N^{ε}-glycyl, and N-(α-(γ-aminobutanoyl)[)]." *Id.* at 18:11–13. "The lipophilic substituents preferably comprises 4–40 carbon atoms . . . The lipophilic substituent may be attached to an amino group of the GLP-1 moiety by means of a carboxyl group." *Id.* at 16:55–67. "In a further preferred embodiment, the lipophilic substituent is an acyl group of the formula $HOOC(CH_2)_mCO$-, wherein m is an integer from 4 to 38." *Id.* at 19:17–19.

Knudsen Patent lists 100 different examples of GLP-1 analogs, including liraglutide (Example 37). Ex. 1012, 187:40–188:4. Liraglutide, among other examples, had a protracted profile of action relative to GLP-1 and was much more persistent in plasma than GLP-1. *Id.* at 192:30–67 (Table 1).

4. Dong (Ex. 1013)

Dong discloses a series of novel human GLP-1 (hGLP-1) analogs with greatly improved plasma half-life and significantly enhanced *in vivo* activity. Ex. 1013, 670. In particular, Dong focuses on preventing enzymatic cleavage of GLP-1 by DPP-IV. *Id.* Dong describes "replac[ing] Ala8 with some unnatural amino acids, including N-methyl-D-alanine (N-Me-D-Ala), l-aminocyclopentane-1-carboxylic acid (A5c), and aminoisobutyric acid (Aib)," in peptides 1–3. *Id.* One of these compounds, peptide 3, includes [Aib8]hGLP-1(7–36)NH_2 with a half-life of 4.52 h. *Id.*

"Knowing that the amide bond between Lys34 and Gly35 of hGLP-1(1-36)NH_2 may also be cleaved *in vivo*," Dong also describes bi-substituted compounds 4–8, further substituting "the C-terminal Gly35 residue with Aib or β-alanine (β-Ala) with the goal of protecting the peptide bond" between Lys34 and Gly35. *Id.* As compared to the unmodified human GLP-1, all eight of Dong's mono- and bi-substituted compounds show "substantially enhanced plasma half-life, while retaining full receptor potency of the native hormone." *Id.* at 670 (Table 1), 671. Moreover, the "analogs bearing modifications at both positions 8 and 35 . . . have much longer plasma half-life than mono-substituted compounds," "[while retaining] receptor potency of the native hGLP-1." *Id.* at 670–671 (Table 1). Dong further notes that one of these bi-substituted analogs, "compound **4,** is significantly more

efficacious than hGLP-1 *in vivo,* and is effective in lowering blood glucose in the *db/db* mouse model of type 2 diabetes." *Id.* at 671.

5. Bridon (Ex. 1014)

Bridon is a U.S. Patent for "Long Lasting Synthetic Glucagon Like Peptide {GLP-1}." Ex. 1014, code (54), (57). Bridon describes "a need to modify GLP-1, exendin 3, exendin-4 and other insulinotropic peptides to provide longer duration of action in vivo, while maintaining their low toxicity and therapeutic advantages." *Id.* at 1:36–40. The modified peptides include a reactive group that reacts with blood compounds, e.g., albumin, to form stable covalent bonds. *Id.* at 1:57–60; 3:35–37.

The reactive groups may be linked to the peptide by a linking group. Ex. 1014, 3:10–12. A preferred linking group includes "AEEA ([2-(2-amino)ethoxy)]ethoxy acetic acid)." *Id.* at 3:17–20. Bridon discloses various examples of compounds with linking groups, including two GLP-1 analogs that include AEEA. *See id.*, 2:4–14; 28:55–64 (Example 5, GLP-1 (1–36)-Lys^{37}(ε-AEEA-AEEA-MPA)-NH_2.5TFA); 31:45–51 (Example 7, GLP-1 (7–36)-Lys^{37}(ε-AEEA-AEEA-MPA)-NH_2.4TFA).

E. Merits Analysis

Petitioner asserts three grounds involving the five asserted references described above. Pet. 5. Patent Owner does not challenge the prior art status of any asserted reference in its Preliminary Response. *See* Prelim. Resp. 3.

1. Ground 1: Obviousness over Knudsen 2004, Knudsen Patent, Dong and Bridon

As Ground 1, Petitioner challenges claims 1–6 as obvious in view of Knudsen 2004, Knudsen Patent, Dong and Bridon. Pet. 5, 26–44. For the purpose of this Decision, we focus our analysis on semaglutide, the

compound described in claims 1 and 4. In short, Petitioner argues that, motivated to make a GLP-1 analog having a longer half-life, one of ordinary skill in the art would have selected liraglutide as a lead compound for further development. *See e.g.*, Pet. 6–7, 26. Petitioner argues that from this starting point, "[r]eaching semaglutide . . . would not have been an exercise in creativity but in inevitability." *Id.* at 26, 31. Petitioner argues that, having arrived at the semaglutide compound of claims 1 and 4, it would also have been obvious to incorporate semaglutide into the pharmaceutical compositions of claims 2 and 5, and further use this compound to treat type-2 diabetes as recited in claims 3 and 6. *Id.* at 26, 42–44. Patent Owner opposes. Prelim. Resp. 18–48.

The lead compound analysis employed in Petitioner's Ground 1 arguments is defined by two steps. The fact finder first determines whether one of ordinary skill in the relevant art would have selected an asserted prior art compound as a lead compound, or starting point, for further development efforts. *Otsuka*, 678 F.3d at 1291). The Federal Circuit defines a lead compound as "a compound in the prior art that would be most promising to modify in order to improve upon its . . . activity and obtain a compound with better activity," (*Takeda*, 492 at 1357), or "a natural choice for further development efforts" (*Altana*, 566 at 1008). The second step involves determining "whether the prior art would have supplied one of ordinary skill in the art with a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success." *Otsuka*, 678 F.3d at 1292.

We address the specifics of the parties' positions below.

a) Selection of Liraglutide as a Lead Compound

Petitioner contends that, although the short half-life of naturally-occurring GLP-1 makes it impractical as a medication, those of ordinary skill in the art were aware of various approaches to designing more stable GLP-1 analogs "using straightforward chemical modifications." *See* Pet. 27–28. According to Petitioner, existing GLP-1 analogs having such modifications would have been "a good starting point for POSAs motivated to make long-lasting GLP-1 analogs." *Id.* at 28. Although Petitioner admits that many such analogs would have worked, it contends that "liraglutide would have been a natural starting point" for further development. *Id.* at 27, 29 (citations omitted). In this respect, Petitioner points to Knudsen 2004 as teaching that liraglutide was equipotent to native GLP-1, with an 11–15 hour half-life suitable for once-daily administration. *See generally*, Pet. 29–31 (citing Ex. 1010, 4129–4131); Ex. 1020 ¶¶ 157–166. Petitioner similarly points to the Knudsen Patent as disclosing that liraglutide retained acceptable efficacy and was suitable for once- or twice-daily dosing. *Id.* at 29 (citing Ex. 1012, 192:30–60 (Table 1, Example 37), 193:35–45; Ex. 1020 ¶ 166).

In asserting that liraglutide was "particularly" suited as a lead compound, Petitioner further contends that "skilled artisans considered liraglutide one of the most promising type-2 diabetes drugs under investigation," and that "[v]arious articles disclosed liraglutide's additional beneficial properties, including weight loss and possible cardiovascular benefits." Pet. at 29–30 (citing, *inter alia*, Ex. 1020 ¶¶ 167–168). Petitioner further points to Knudsen 2004's disclosure that liraglutide had completed phase 2 clinical trials, and that unlike other GLP-1 analogs in clinical

testing, "its chemical structure and mechanism of protraction were well-published." *Id.* at 30 (citing Ex. 1010, 2, Table 1; Ex. 1020 ¶ 164).

According to Patent Owner, Petitioner's lead compound analysis fails because it fails to establish that one of ordinary skill in the art would have focused on liraglutide over other GLP-1 candidates known in the prior art. Prelim. Resp. 19–20 (citing e.g., *Daiichi Sankyo Co. v. Matrix Lab'ys, Ltd.*, 619 F.3d 1346, 1353–54 (Fed. Cir. 2010)). Patent Owner further argues that in focusing on half-life and potency, Petitioner's analysis ignores numerous other "pertinent properties" of potential lead compounds (e.g., solubility, PK profile, metabolic stability, ability to formulate, immunogenicity). *Id.* at 20–21 n.9 (citing, e.g., *Otsuka*, 678 F.3d at 1292). Patent Owner further argues that, even considering only those two properties, Petitioner ignores prior art compounds that showed better potency and/or stability than liraglutide in preclinical tests. *Id.* at 21–23 (citing Ex. 1010, 4129; Ex. 1011, 680–681; Ex. 1012, 192:30–60 (Table 1), 193:35–46; Ex. 1013, 670; *Daiichi*, 619 F.3d at 1353–54; *Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000)).

On the record before us, Petitioner has the better argument. We agree with Petitioner it need not demonstrate that liraglutide would have been the *single* best choice for further development. *See* Pet. 24–25, 27; *Altana,* 566 F.3d at 1008 (disregarding the "suggest[ion] that the prior art must point to only a single lead compound," and finding no error in district court's finding that those of skill in the art would have pursued as many as 18 exemplary compounds from approximately 90 candidates). On the current record, Petitioner has sufficiently established that liraglutide would have been, at a minimum, one of the best candidates for further development.

We find particularly relevant the status of clinical investigations for

GLP-1 analogs as of the filing date of the '343 patent. In this respect, Knudsen 2004 provides an overview of the seven GLP-1 analogs then known to be under development. Ex. 1010, 4129 (Table 1). Of these, five were in a preclinical "discovery phase or in small-scale phase 1/2 clinical development." *Id.* at 4131. Of the remaining two, once-daily liraglutide had completed phase 2 trials, whereas exenatide had entered phase 3 trials—but with its 4 to 5-hour *in vivo* half-life, was subject to a less-desirable, twice-daily dosing regimen. *See id.* at 4129 (Table 1). We also find persuasive Knudsen 2004's disclosure that, but for liraglutide and exenatide, "very little is published in peer-reviewed journals." *See* Ex. 1010, 4129, 4131. We note also Knudsen 2004's discussion of the pharmacokinetics and structure-function relationships for liraglutide (*id.* at 4130, 4132; *see also* Ex. 1020 ¶ 164), and Dr. Flatt's review of clinical and preclinical effects of liraglutide for the treatment of diabetes and potentially other beneficial uses (Ex. 1020 ¶¶ 167–168 (citing, e.g., Ex. 1055[17])).

With respect to Patent Owner's arguments that Petitioner has ignored preclinical results on compounds with greater potency and/or substantially longer half-lives, it may be that some of these compounds may also have been suitable for further development. *See Altana*, 566 F.3d at 999. Nevertheless, the relative wealth of information on liraglutide, including Madsbad's report that, in a 12-week clinical trial, it showed improved glycemic control with no weight increase in patients with Type 2 Diabetes (Ex. 1055), strongly suggests that one of ordinary skill in the art would have

[17] S.M. Madsbad et al., *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)*, 27 DIABETES CARE 1335 (2004) ("Madsbad").

considered liraglutide among those suitable for further development, which satisfies the first prong of the lead compound test. Likewise, the preparation, execution, and results of that trial, indicate that the additional properties raised by Patent Owner (e.g., solubility, PK profile, metabolic stability, ability to formulate, immunogenicity,[18] side effects, and routes of administration), had been previously vetted for liraglutide and found at least acceptable. *See* Prelim. Resp. 21 n.9.

In sum, Petitioner has adequately established that one of ordinary skill in the art would have had reason to select liraglutide as a lead compound for further development. Accordingly, we proceed to step two of the analysis.

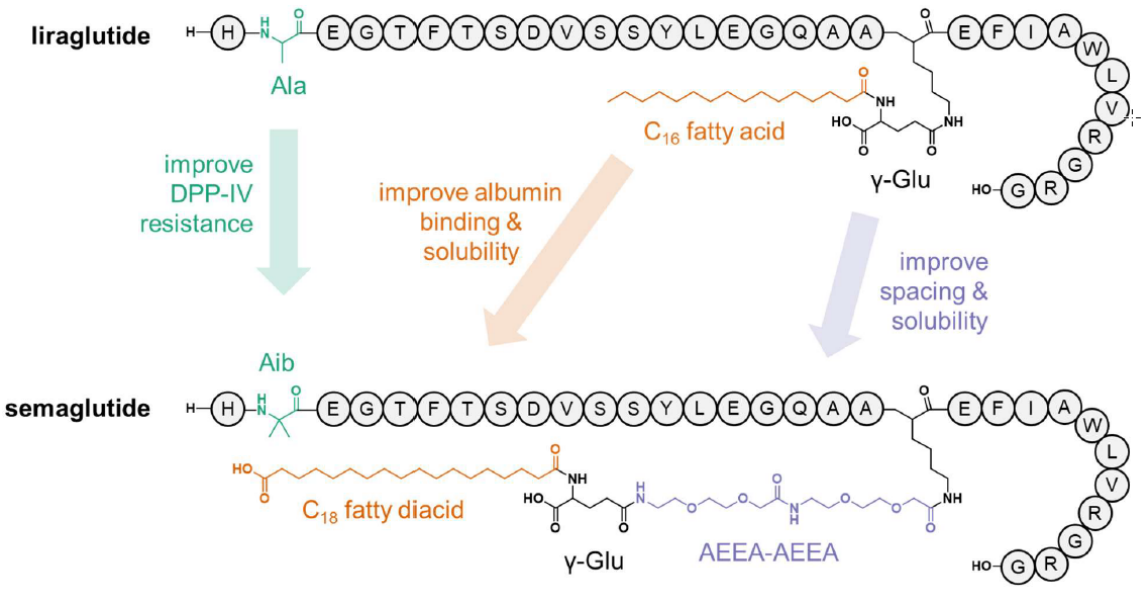
b) Reasons to Modify Liraglutide to Arrive at the Claimed Invention

In the second stage of our analysis, we analyze whether there was a reason to modify a lead compound to make the claimed compound with a reasonable expectation of success. *Otsuka*, 678 F.3d at 1292; *see also Eisai Co. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1357 (Fed. Cir. 2008) ("Obviousness based on structural similarity [] can be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (i.e. a lead compound) in a particular way to achieve the claimed compound.").

By Petitioner's count, one of ordinary skill in the art would have been motivated to make "[o]nly three small modifications to liraglutide" to arrive

[18] We note that, in contrast to liraglutide, Knudsen 2004 reports that "[a]ntibody formation against exenatide has been reported," and that "[t]he challenge for [the CJC-1131] approach is perhaps slightly greater than for the others because of the in vivo covalent attachment to albumin." *See* Ex. 1010, 4130–4131.

at semaglutide as claimed. Pet. 31–42. For reference, we reproduce below, Petitioner's illustration of the required modifications.



Id. at 32.

The above figure illustrates the differences between liraglutide and semaglutide, defined by Petitioner as (1) substituting the alanine at position 8 with Aib (aminoisobutyric acid); (2) introducing an additional di-AEEA (AEEA-AEEA) spacer at Lys^{26} and, (3) substituting the C_{16} mono acid at Lys^{26} with a C_{18} diacid. *See id.* at 31–32. Noting that the last of these differences involves two distinct substitutions (extending the length of the albumin-binding fatty acid carbon chain and exchanging a mono-acid for a di-acid), Patent Owner reasonably characterizes the same set of modifications as four steps, and further argues that Ground 1 is unsupported by sufficient motivation and reasonable expectation of success. Prelim. Resp. 23–53. We address the parties' arguments below and determine that Patent Owner has the better position.

(1) Aib[8]

According to Petitioner, one of ordinary skill in the art would have been motivated to substitute the non-naturally occurring amino acid, Aib, for alanine at position 8 because Knudsen 2004 identified Ala[8] as a position that "[m]ay be modified for DPP-IV stability," whereas the Knudsen Patent "encouraged the use of amino-acid substitutions, including non-natural ones." Pet. 33–34 (citing, e.g., Ex. 1010, 4130 (Fig. 3); Ex. 1012, 8:61–9:14, 10:48–11:33; Ex. 1020 ¶¶ 178–180, 182). According to Petitioner, the use of Aib in therapeutic peptides was well known, including in the field of GLP-1 analogs. *Id.* (citing, e.g., Ex. 1020 ¶¶ 183–184). Petitioner relies, in particular, on Dong's attempts to limit enzymatic cleavage of GLP-1. *Id.* at 33. According to Petitioner:

> Dong disclosed that a chief culprit in GLP-1 degradation is DPP-IV, which cleaves the bond between Ala[8] and Glu[9] 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 Aib[8]-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.

Id.

As noted in section II.D.4, above, in addition to Aib[8], Dong also investigated substitutions, and combinations of substitutions, at Arg[26], Phe[31], Arg[34], and Ala[35]. *See* Ex. 1013, 670 (Table 1). Among these are bi-substituted compounds 4–8, further substituting "the C-terminal Gly35 residue with Aib or β-alanine (β-Ala) with the goal of protecting the peptide bond [between Lys34 and Gly35]." *Id.* According to Dong, both the mono- and bi-substituted compounds show "substantially enhanced plasma half-

life, while retaining full receptor potency of the native hormone." *Id.* at 670 (Table 1), 671. Dong, however, focuses on the benefits of the bi-substituted analogs, and in particular, compound 4 ($Aib^{8,35}$), which advanced to clinical trials. *Id.* at 671; *see* also Ex. 1020 ¶ 178 (Dr. Flatt's testimony that Ipsen Biopharmaceuticals elected to take the $Aib^{8,35}$ analog (Dong's compound 4) into clinical trials). In particular, Dong states that, "analogs bearing modifications at both positions 8 and 35 . . . have much longer plasma half-life than mono-substituted compounds,' while "retain[ing] receptor potency of the native hGLP-1." *Id.* at 670–671 (Table 1). Of these, Dong reports that "representative analog, compound **4,** is significantly more efficacious than hGLP-1 *in vivo,* and is effective in lowering blood glucose in the *db/db* mouse model of type 2 diabetes." Ex. 1013, 671. Petitioner does not adequately explain why one of ordinary skill in the art would have chosen to modify position 8 but not position 35 as suggested by Dong.

In particular, Petitioner contends that one of ordinary skill in the art would have viewed Dong's compound 3, bearing only the Aib^{8} modification as "more promising" than any of the bi-substituted compounds such as compound 4. Pet. 33 (citing Ex. 1020 ¶¶ 178–180). In this respect, Dr. Flatt points to the K_i (inhibition constant) data reported in Dong's Table 1. Ex. 1020 ¶¶ 179–181. According to Dr. Flatt, "the Aib^{8} analogue had a significantly lower K_i than all other analogues, including the $Aib^{8,35}$ analogue." *Id.* ¶ 180. As such, Dr. Flatt opines that one of ordinary skill in the art "would have understood the data from Dong to suggest that the Aib^{8} analogue would actually be a *more* potent and efficacious analogue than the other analogues, including the $Aib^{8,35}$ analogue." Dr. Flatt thus opines that one of ordinary skill in the art would have been motivated to modify liraglutide with the Aib^{8} substitution with the expectation of "enhanced

DPP-4 resistance (i.e., a longer half-life) and improved receptor binding (i.e., a potentially more efficacious drug)." *See id.* ¶ 181.

On the record before us, however, Dr. Flatt's assessment of the relative benefit one of ordinary skill in the art would have accorded the higher K_i of mono-substituted compound 3 as compared to the "much longer plasma half-life" of Dong's bi-substituted compounds is at odds with Dong's selection of bi-substituted compound 4 for clinical trials. *See* Ex. 1013, 670–671 (Table 1).

We are also skeptical of Dr. Flatt's assertion that one of ordinary skill in the art would have recognized that Dong's substitution of Aib for alanine at position 8 "would complement and work synergistically with liraglutide's [other] properties," including the fatty acylation of Lys^{26}. *See* Ex. 1020 ¶ 181. In this respect, Patent Owner notes that, unlike liraglutide, Dong's GLP-1 analogs were not acylated, whereas Knudsen 2001 counseled *against* N-terminal modifications in the context of acylation. Prelim. Resp. 28–30, 46 (citing Ex. 1011, 680–681). In addressing such combinations, Knudsen 2001 states, for example, that "Desamino His^7 represents one of the more potent suggestions to a modification giving metabolic stability (81). Nevertheless, as seen when comparing **19** (687 pM) to **5** [liraglutide] (68 pM), considerably more potent compounds could be obtained by not modifying the N-terminus when a combination with acylation was desired." *Id.* at 680. As such, we are unpersuaded on the record before us that one of ordinary skill in the art would have had a reasonable expectation that the Aib^8 modification would be beneficial or otherwise "complement and work synergistically with" the acylated Lys^{26} of liraglutide or semaglutide. *See* Ex. 1020 ¶ 181.

We also understand Knudsen 2001 considered—and rejected—modifications to liraglutide at Ala^{8}, stating that

> Amino acid substitutions in position 8 can give better metabolic stability against DPP-IV. However, since quite a substantial protection against DPP-IV was obtained by acylation alone, and since any amino acid substitution poses a risk of immunogenicity, and since compound **5** [liraglutide] was equipotent with GLP-1 and had the half-life required to be dosed once daily, [liraglutide] was selected for clinical development.

Id. at 681.

Taken together, we are not persuaded that Petitioner has shown sufficiently that one of ordinary skill in the art would have been motivated to substitute Aib, for alanine at position 8 of liraglutide.

(2) Adding a di-AEEA spacer at Lys^{26}

Liraglutide comprises an albumin-binding fatty acid bound to Lysine 26 via a γ-glutamyl spacer. *See, e.g.*, Ex. 1010, 4130; Ex. 1011, 681. According to Petitioner, it would have been obvious to add exactly two additional spacers (serial AEEA moieties) between the γ-glutamyl spacer and the peptide backbone at amino acid 26 to further separate the receptor-binding peptide backbone from the albumin-binding fatty acid. Pet. 34–36. As summarized by Patent Owner, this step alone requires one of ordinary skill in the art to make a multitude of choices encompassing:

> (1) choice of AEEA as a spacer type, (2) number of AEEA spacers (two) and decision to connect those spacers *to each other*, (3) decision to *add* the two AEEA spacers to liraglutide's spacer rather than *replace* it, (4) decision to place both AEEA spacers *between* the position 26 lysine and γ-glu spacer, and (5) decision to attach the spacers to position 26 rather than other locations the art disclosed.

Prelim. Resp. 35-36. Considering the evidence of record, and for substantially the reasons set forth on pages 35–39 of the Preliminary Response, Petitioner has not shown sufficiently that one of ordinary skill in the art would have been motivated to add a di-AEEA spacer between the γ-glutamyl spacer and the peptide backbone of liraglutide with a reasonable expectation of success. We highlight the following issues.

Relying on the testimony of Drs. Flatt and Soares, Petitioner's primary reason for inserting a di-AEEA spacer is that "the bulkiness of both albumin and the GLP-1 receptor means the two interfere with each other at short distances," whereas "[l]engthening the spacer attenuates this problem." *Id.* at 35–36 (citing Ex. 1020 ¶ 203; Ex. 1022 ¶ 105). But as Patent Owner points out, liraglutide *already included* a γ-glutamyl spacer, and neither Petitioner, nor its declarants provide credible evidence that one of ordinary skill recognized a steric interference "problem" between the GLP-1 receptor and albumin in liraglutide. *See* Prelim. Resp. 34–35. As evidence to the contrary, Patent Owner points us to Petitioner's focus on the compound disclosed in the Knudsen Patent's Example 11 ($Arg^{34}Lys^{26}$ (N^{ε}-(ω-carboxyheptadecanoyl))-GLP-1(7-37)-OH), which exhibits a longer half-life than liraglutide yet does not have a spacer. *See id.* at 35 (citing Pet. 41); Ex. 1012, 177:32–57, 192:30–60; Ex. 1020 ¶ 213.

At best, Petitioner relies on Holst's[19] statements regarding "the high biological activity [of CJC-1131] in spite of the presence of the albumin moiety," which "contrasts strikingly to [liraglutide], the intrinsic activity of

[19] J.J. Holst, *The Incretin Approach for Diabetes Treatment Modulation of Islet Hormone Release by GLP-1 Agonism*, 53 (suppl. 3) DIABETES S197 (2004) ("Holst") (Ex. 1030).

which is clearly lowered by albumin binding (by 2–3 orders of magnitude), suggesting that the site of attachment to albumin is of importance and that the linker position and length in [liraglutide] could be suboptimal." *See* Pet. 35 (citing Ex. 1020 ¶ 201; Ex. 1022 ¶ 107); Ex. 1030, S201. We, nevertheless, agree with Patent Owner that Holst's comparison provides insufficient motivation to add the di-AEEA spacer at Lys^{26} as required by the claims. Whereas the C16 acyl chain attached to liraglutide's Lys^{26} non-covalently, and reversibly, associates with albumin after injection, CJC-1131 contains a reactive maleimide moiety at Lys^{34} that forms a permanent covalent bond with albumin. *See* Ex. 1030, S200–S201; Ex. 1010, 4129, 4131; Ex. 1020 ¶¶ 88–89. As such, the two analogs interact with albumin via different mechanisms and at different places along the GLP-1 peptide chain.

In addition to its assertion that one of ordinary skill in the art would have been motivated by Holst's conjecture to "tweak[]" liraglutide's spacer length to improve activity, Petitioner points to Bridon, which refers to AEEA as "a preferred linking group,"[20] and discloses exemplary GLP-1 analogs having di-AEEA moieties—albeit not associated with Lys^{26}, a γ-glu spacer, or a fatty acyl chain as found in either liraglutide or semaglutide. *See* Pet. 35 (citing Ex. 1030, S200); 37–38 (citing, e.g., Ex. 1014, 3:19–20, 28:56–30:67 (Example 5), 31:45–32:22 (Example 7)); *see also* Prelim. Resp. 38 (Patent Owner noting that, as compared to liraglutide and semaglutide,

[20] Bridon describes a vast array chemical classes of linking groups including the class of poly ethoxy amino acids. Ex. 1014, 3:10–20. Read in context, it is not clear whether Bridon's reference to AEEA as "a preferred linking group" indicates a general preference, or that AEEA is a merely a preferred linking group within the class of poly ethoxy amino acids. *See id.*

Bridon uses di-AEEA "***in a different position*** (37) and ***without a γ-glu spacer***").

Petitioner further points to Sato's[21] disclosure regarding the use of spacers between KDR and VEGF/KDR binding peptides and a labeling moiety such as biotin. Pet. 37 (citing Ex. 1045, 125:4-8, 130:30-34; Ex. 1020 ¶¶ 197–199; Ex. 1022 ¶¶ 103-104). According to Sato,

> modifications within the scope of the invention include introduction of linkers or spacers between the targeting sequence of the KDR or VEGF/KDR complex binding peptide and the detectable label or therapeutic agent. Use of such linkers/spacers may improve the relevant properties of the binding peptide (*e.g.*, increase serum stability, etc.). These linkers may include, but are not restricted to, substituted or unsubstituted alkyl chains, polyethylene glycol derivatives, amino acid spacers, sugars, or aliphatic or aromatic spacers common in the art.

Ex. 1045, 54:3–10. In one set of experiments, Sato inserted a "JJ" spacer between the KDR binding sequence and biotin, which enhanced target binding. *See id.* at 123:23–124:2, Fig. 3. According to Dr. Flatt, the "JJ" spacer is di-AEEA. *See* Ex. 1020 ¶¶ 197. Sato concludes that including a "spacer between the binding sequence and biotin can be helpful in enhancing binding to target molecule by multiple mechanisms. First, it could help reduce the steric hindrance between four biotinylated peptide[s] after their binding to single avidin molecule. Second, it could provide extra length necessary to reach multiple binding sites available on a single cell." Ex. 1045, 124:2–8. Elsewhere, Sato broadly teaches that "[a]ddition of a hydrophilic spacer between the peptide and the group used for attachment to the particle should routinely be tested with new targeting molecules as it

[21] WO 03/074005 (Ex. 1045).

improves the binding for both of the peptides evaluated here." *Id.* at 129:31–33. But as Patent Owner points out, Sato does not discuss peptides targeting GLP-1 receptors nor address the effect of combining multiple AEEA linkers with a γ-glu linker. *See* Prelim. Resp. 37.

Petitioner further argues that "GLP-1 analogs had solubility problems that interfered with formulation." Pet. 38 (citing Ex. 1093, 3:21–24; Ex. 1034, 1; Ex. 1020 ¶ 204; Ex. 1022 ¶¶ 111–112; Ex. 1024 ¶¶ 79, 85–86). As we understand the argument, Petitioner contends that one of ordinary skill in the art would have been motivated to add two polar, but uncharged AEEA moieties to liraglutide because their hydrophilicity, in conjunction with the existing negative charge of the γ-glutamyl linker, would further help with solubility. *Id.* (citing Ex. 1020 ¶ 204–205; Ex. 1022 ¶¶ 111–112, 118; Ex. 1034 ¶¶ 79, 85–86). Petitioner does not explain adequately why one of ordinary skill would look to AEEA in particular for this purpose—let alone two copies of AEEA—as opposed to any number of other known hydrophilic, or even charged, spacers. Nor, as Patent Owner points out, does Petitioner address why one of ordinary skill in the art would have been motivated to modify liraglutide by adding "two hydrophilic AEEA spacers *and* add a negatively-charged diacid." *See* Prelim. Resp. 36.

As to the placement of the two AEEA spacers relative to liraglutide's γ-glu linker, Petitioner merely asserts that "a POSA would have been more inclined to retain the glutamyl-fatty acid linkage that worked in liraglutide and was described as important to liraglutid's properties. Pet. 39 (citing Ex. 1020 ¶¶ 204–205; Ex. 1022 ¶¶ 105-107, 118; Exs. 1010–1012, 1034). As evidence of this position, Dr. Flatt points to Markussen's finding that changing the position of a charged moiety on the *insulin beta chain* affects

its binding to albumin. Ex. 1022 ¶ 205 (citing Ex. 1038, 287). According to Mardussen:

> The spatial position of the negative charge of the C-terminus of the B-chain is of importance for the binding to albumin. When the charge is moved closer to the fatty acid substitution in Lys^{B29} by deletion of residue Thr^{B30}, the affinity for albumin increases. Possibly, the charge mimics the carboxylate group of a fatty acid and thereby enhances binding to albumin. When the fatty acid is substituted in position Phe^{B1} there is no negative charge in the vicinity, and the binding constant becomes lower by a factor of 4. The atomic structure of HSA is known, but the fatty acid binding sites have not been identified. Binding of the Lys^{B29} fatty acid acylated analogues to the insulin receptor excludes concurrent binding to albumin (data not reported). Since Lys^{B29} is not a participant in receptor binding, it appears likely that the exclusion of albumin by the receptor is due to competition for space rather than for specific binding sites on the insulin molecule.

Ex. 1038, 287 (internal footnote numbers omitted). On this record Petitioner's declarant does not persuade us that one of ordinary skill in the art would have applied the above observations regarding insulin to the construction of GLY-1 analogs. Moreover, Dr. Flatt's assertion that Knudsen 2000 confirmed the importance of "retain[ing] the glutamate carboxylate group near the fatty acid," appears to merely suggest the importance of net negative charge—whether provided by the "L-glutamoyl spacer or with diacides"—and says nothing about the positioning of the charge generally or the γ-glu spacer in particular. Ex. 1020 ¶ 205 (citing Ex. 1034, 1664).[22] As such, we agree with Patent Owner that Petitioner's

[22] Petitioner's assertion, that "Knudsen 2000 disclosed an 'enhanced effect on binding to albumin' when the glutamyl spacer was used," refers to the same teaching regarding the effect of increased negative charge and is likewise unavailing. *See* Pet. 41 (citing Ex. 1034, 1663; Ex. 1020 ¶ 224).

explanation for why a person of ordinary skill in the art would have elected the specific positioning of di-AEEA is insufficiently supported. *See* Prelim. Resp. 38.

(3) Substituting the C16 Mono-acid with a C18 Di-acid

Petitioner contends that one of ordinary skill in the art would have been motivated to substitute the C16 mono-acid of liraglutide with a C18 di-acid as required by the challenged claims. Pet. 39–42. As noted above, this involves both the modification of liraglutide's carbon chain as well as the number of carboxylic acid residues attached to that chain.

(a) C16 to C18

Liraglutide's association with albumin reduces the rate of kidney clearance and, thus, increases the in vivo half-life of the active peptide. As explained by Holz, "[f]atty acylation confers . . . an ability to noncovalently bind via hydrophobic interactions with serum albumin, thereby slowing renal clearance and dramatically extending the circulating half-life" of various GLP-1 analogs. Ex. 1031, 2478.[23] According to Petitioner, one of ordinary skill in the art would have recognized that because lipophilic moieties bind the plasma albumin fatty acid binding sites, the longer, more lipophilic C18 carbon chain would "work better," i.e., bind more tightly to albumin and, thus, extend the half-life of the GLP-1 analog. *See id.* at 40 (citing e.g., Ex. 1020 ¶¶ 87–95, 117, 131–134, 137–138, 143-147, 211, 214–24; Ex. 1022 ¶¶ 124–127, 129–133, 135–140, 127). But given the Knudsen Patent's disclosure of a vast array of cyclic, branched, and straight chain

[23] G.G. Holz, *Glucagon-Like Peptide-1 Synthetic Analogs: New Therapeutic Agents for Use in Treatment of Diabetes Mellitus*, 10 CURRENT MED. CHEM. 2471 (2003) ("Holz").

lipophilic substituents, including those with up to 40 carbon atoms, it is unclear why under Petitioner's "more is better" theory, one of ordinary skill in the art would select a single straight chain moiety of precisely 16 carbons. *See* Ex. 1012, 16:56–19:59; Pet. 41–42 (referencing Ex. 1012, 16:56–58, 19:1–59). Nor, as Patent Owner points out, does Petitioner address Markussen's teaching that "the albumin affinity of acylated insulin increased as the fatty-acid chain length increased from 10 to 14 carbon atoms, but that ***increasing it further*** (*e.g.*, to 16) '***failed to improve binding any further***.'" Prelim. Resp. 41 (citing Ex. 1038, 3 (Table 1), 5). Markussen, although admittedly directed to insulin rather than GLP-1, would appear to suggest that, in the context of associating a peptide or protein to albumin, one of ordinary skill in the art would not have necessarily expected that a C18 fatty acid is better than C16 fatty acid.

(b) Mono-acid to Di-acid

Petitioner further contends that one of ordinary skill in the art would have realized that albumin binds to negatively charged carboxylic groups of mono- and di-acids via its many positively charged amino acids. *Id.* at 40–41. Accordingly, Petitioner posits, one of ordinary skill in the art would have been motivated to substitute the mono-acid of liraglutide with a di-acid with the expectation that the increased negative charge would provide stronger albumin binding. *Id.* at 41–42. (citing Ex. 1020 ¶¶ 216–218; Ex. 1022 ¶¶ 129–139; Ex. 1024 ¶¶ 80–85). As support, Petitioner points to data in the Knudsen Patent showing that the GLP-1 analog of Example 11 ($Arg^{34}Lys^{26}$ (N^{ε}-(ω-carboxyheptadecanoyl))-GLP-1(7-37)-OH), has longer half-life than the liraglutide of Example 37 ($Arg^{34}Lys^{26}$(N^{ε}-(γ-glutamyl(N^{α}-hexadecanoyl)))-GLP-1(7-37)-OH.). *Id.* at 41 (citing Ex. 1012, 177:33–57, Claim 10, 192:30–60, Table 1); Ex. 1020 ¶¶ 213–215.

Petitioner infers, without adequate support from its declarants, that one of ordinary skill in the art would have attributed the difference in half-life to the C18 di-acid in Example 11 as compared to the C16 mono-acid in liraglutide, as opposed to, for example, liraglutides's γ-glu linker. Pet. 41 (citing Ex. 1020 ¶¶ 214–215, Ex, 1022 ¶¶ 134–135); *see also*, *id.* at 46 ("[Liraglutide's] γ-L-Glu spacer and fatty acid-modified Lys^{26} imparted a long half-life via albumin binding and gave particularly good activity"); Ex. 1020 ¶¶ 204–205 (Dr. Flatt's testimony indicating that the negatively-charged γ-glu spacer contributes to liraglutide's binding to albumin). We find unhelpful Petitioner's failure to address how one of ordinary skill in the art would have viewed the comparison of the Knudsen Patent's Examples 11 and 37 in light of this additional difference. Moreover, as Patent Owner points out, the Knudsen Patent's Examples 32 and 34 had better half-lives than either Example 11 or liraglutide "***but do <u>not</u> use a C_{18} diacid***" and, thus, call into question Petitioner's logic in selecting a linear C18 fatty acid and a diacid. *See* Prelim. Resp. 42; Ex. 1012, 185:32–53 (Example 32, $Lys^{26,34}$-bis(N^{ε}-(ω-carboxytridecanoyl))-GLP-1(7-37)-OH, 186:26–48 (Example 34, $Arg^{26,34}Lys^{38}$ (N^{ε}-(ω-carboxypentadecanoyl)-GLP-1(7-38)-OH), 192 (Table 1)

We also find Petitioner's analysis incomplete for failing to address Knudsen 2001's express teaching that "[w]ithin the γ-glu spacer monoacid series (**5**, 16-18), derivatization with a C18 acid (**16**, 194 pM) led to a significant loss of activity compared to C16," and "[w]ithin the diacid series (**14, 15**), the diacid could be no longer than a C14 (**15,** 72 pM) before a loss in potency **(14,** 154 pM), compared to the γ-glu spacer monoacid series (**17, 18,** 22-27 pM) was seen." *See* Ex. 1011, 680. As such, Petitioner has not explained how, in seeking to modify liraglutides C18 mono-acid, one of

ordinary skill in the art would have weighed Knudsen 2001's express caution regarding loss of potency, against the alleged suggestion in the earlier Knudsen Patent that a C18 di-acid might be more stable. *See also* Prelim. Resp. 41 (noting that "Petitioner fails to address these teachings or explain why Knudsen 2001 does not teach away from using any diacid longer than C_{14} or a monoacid longer than C_{16}").

Considering the record before us, Petitioner has not shown sufficiently that one of ordinary skill in the art would be motivated to make the required modification with a reasonable expectation of success.

(4) Hindsight and Reasonable Expectation of Success

One of ordinary skill in the art seeking to modify liraglutide would need to undertake at least four discrete steps to arrive at semaglutide—some of which entail multiple options and decision points for each step (e.g., the selection and placement of di-AEEA, and whether to replace, or add to, the existing γ-glu linker). As discussed above, we find Petitioner's justification for these individual steps problematic. Taken as whole, and considering the vast number of modifications suggested in the art—and indeed, the large number of amino acids suggested as cites for modification—Petitioner has failed to meet its burden of demonstrating why a skilled artisan would have been motivated to make all of the identified substitutions and no others to arrive at the claimed subject matter. *See e.g.*, Ex. 1010, 4130 (Figure 3) (identifying amino acids available for derivatization (Ser^{18}, Gln^{23}, Lys^{26}, Glu^{27}, Lys^{34}, and Arg^{36}) or modification (Ala^{8})); Ex. 1011, 680–681 (identifying desamino His^{7} as "one of the more potent suggestions to a modification giving metabolic stability,"); Ex. 1012 at, *e.g.*, 9:21-19:59; 192:30–60 (Table 1), 193:35–46 (disclosing numerous GLP-1 analogs, including those with greater half-lives or potency than liraglutide, and

teaching that each could be further modified, including with amino acid substitutions and/or acylation at multiple positions, numerous fatty acid options for the acylation, and numerous spacer options for linking the fatty and amino acids); Ex. 1013, 670–671 (disclosing that GLP-1 analogs bearing modifications at both positions 8 and 35 maintain efficacy but "have much longer plasma half-life than mono-substituted compounds").

On pages 43–53 of the Preliminary Response, the reasoning with which we agree and adopt, Patent Owner casts much the same argument discussed above in terms of Petitioner's failure to establish a reasonable expectation of success for the changes individually, and in combination. In contrast to Petitioner's assertion that one of ordinary skill in the art "would have reasonably expected the changes to work together, synergistically, to improve the same properties" (Pet. 42 (citing Ex. 1020 ¶ 226; 1022 ¶ 151; Ex. 1024 ¶ 86), Patent Owner points, for example, to evidence in the art showing that modifications to GLP-1 are often unpredictable. Citing the prior art of record, Patent Owner notes, for example, that different linkers can lead to dramatically different potencies (Prelim Resp. 44 (citing Ex. 1011, 680 (Table 1)); that potency can be sensitive to acylation position and inversely correlated with fatty acid length (*id.* at 44–45 (citing Ex. 1011, 680); and that N-terminal modification in combination with fatty acid acylation could negatively impact potency (*id.* at 46 (citing Ex. 1011, 677, 680))). We agree with this assessment of the evidence in the art.

(5) Secondary Considerations

Petitioner contends that any evidence of secondary considerations would fail to overcome its assertions of obviousness. Pet. 59. Petitioner preemptively asserts that there is no evidence of unexpected results, teaching away, long-felt but unmet need, commercial sales, industry skepticism,

skepticism, or probative evidence of copying. *Id.* at 60–62. Of these, Patent Owner addresses only unexpected results and long-felt need in the Preliminary Response. *See* Prelim. Resp. 54–56. With respect to the former, Patent Owner points out that "[i]t is undisputed that semaglutide's half-life is approximately . . . ***11–15 times longer than liraglutide***." *Id.* at 55 (citing Ex. 2002, 7370).[24] And with respect to long-felt need, Patent Owner points to Petitioner's statements that "[non-GLP-1] diabetes treatments faced waning interest in the scientific community," and "liraglutide's half-life allowed for at best once-daily administration, but that was inconvenient and risked patient compliance." *Id.* at 56 (quoting Pet. 28, 30).

On the present record, however, we need not rely on the limited evidence of secondary considerations with respect to any of the Grounds.

(6) Conclusion as to Ground 1

For the reasons set forth above, Petitioner does not show sufficiently that it would have been obvious to modify liraglutide with a reasonable expectation of success so as to arrive at semaglutide, the compound recited in the challenged claims.

2. Ground 2: Obviousness over Knudsen 2001, Knudsen Patent, Dong and Bridon

As Ground 2, Petitioner challenges claims 1–6 as obvious in view of Knudsen 2001, Knudsen Patent, Dong and Bridon. Pet. 5, 44–50. Patent Owner opposes. Prelim. Resp. 18–48. Petitioner's arguments in support of Ground 2 are substantially similar to those based on Knudsen 2004 in Ground 1, but with a focus on the earlier-published, and largely duplicative,

[24] J. Lau et al., *Discovery of the Once-Weekly Glucagon-Like Peptide-1 (GLP-1) Analogue Semaglutide*, 58 MED. CHEM., 7370–80 ("Lau") (2015).

Knudsen 2001 article. For essentially the same reasons as discussed with respect to Ground 1, Petitioner does not show sufficiently that it would have been obvious to modify liraglutide so as to arrive at semaglutide with a reasonable expectation of success. *See, e.g.,* Prelim. Resp. 18–48 (Patent Owner's combined argument opposing Grounds 1 and 2).

3. Ground 3: Obviousness in view of Knudsen 2004, Knudsen 2001, Knudsen Patent, Dong, Bridon

As Ground 3, Petitioner challenges claims 1–6 as obvious in view of Knudsen 2004, Knudsen 2001, Knudsen Patent, Dong and Bridon. Pet. 5, 51–59. Patent Owner opposes. Prelim. Resp. 49–53.

Despite addressing the same art asserted in Grounds 1 and 2 under the lead compound approach, Petitioner frames Ground 3 as rooted in "common drug development principles (under *KSR*)." Pet. 5, 51; *see* Reply 1 (Petitioner's assertion that "Ground 3 relies on the same prior art as Grounds 1 and 2 . . . [t]he only difference is the analytical framework for a POSA's motivation").

Petitioner thus argues that we should dispense with the first prong of Federal Circuit's requirement for new chemical cases, wherein a challenger must show the required motivation for selecting a lead compound. *See* Pet. 51–52 (citing, e.g., *Yamanouchi*, 231, F.3d at 1345; *Otsuka* 678 F.3d at 1292; *Daiichi Sankyo*, 619 F.3d at 1354). As an initial matter, rejecting the selection of a lead-compound is not helpful insofar we ***agree*** with Petitioner that one of ordinary skill in the art would have selected liraglutide as a lead compound. *See* Section II.E.1.a, *supra*.

Petitioner also urges that, rather than apply the second prong of the lead compound framework, we instead apply the more general principles of *KSR*. In particular, Petitioner argues that requiring challengers to show "that

the prior art would have suggested making the *specific* molecular modifications necessary to achieve the claimed invention," the lead compound framework "places a too-high burden on patent challengers." Pet. 55–56 (citing *Takeda*, 492 F.3d at 1356). Petitioner fails to establish, however, in what way the Board's application of the Federal Circuit's lead compound framework is "inconsistent with *KSR*," or that our reviewing Court's long-established framework is otherwise inapplicable to the present dispute. *See* Pet. 51–56; *see also* Prelim Resp. 49, n.21 (discussing why the Federal Circuit's lead-compound approach is consistent with *KSR*).

Further, and for substantially the reasons discussed under the lead compound inquiry of Section II.E.b, Petitioner does not adequately explain why one of ordinary skill in the art would have been motivated "to combine . . . elements in the fashion claimed by the patent at issue." *KSR*, 550 U.S. at 418. Downplaying the focus on motivation to make specific modifications, Petitioner suggests that the ordinarily skilled artisan would arrive at semaglutide's precise combination of features "through routine trial-and-error" by "testing 'a finite number of identifiable, predictable solutions.'" *See* Pet. 56–57 (citing *KSR*, 550 U.S. at 241).

We do not find Petitioner's argument availing on the present record. Rather, we agree with, and adopt, Patent Owner's explanation for why Petitioner has not adequately demonstrated that the potential solutions were either finite or reasonably predictable. *See* Prelim. Resp. 49–53. In sum, given the vast number of potential GLP-1 modifications suggested in the art of record, and the evidence that many of their effects were unpredictable alone or in combination with other modifications, Petitioner's argument reduces to impermissible hindsight. *See* Section II.E.1.B.4, above.

For the above reasons. Petitioner does not show sufficiently that one of ordinary skill in the art would have found semaglutide obvious under Ground 3.

4. Denial under §325(d)

Applying the "two-part framework" described in *Advanced Bionics, LLC v. MED-EL Electromedizinishe Geräte GmbH*, IPR2019-01469, Paper 6 at 8–10 (Feb. 13, 2020) (precedential), Patent Owner argues that we should exercise our discretion to deny institution because all of Petitioner's asserted references were previously presented to the Office or are cumulative of that art, and that the Petition fails to establish any error in the Examiner's application of those references. Prelim. Resp. 56–70; Sur-reply 3–5. Petitioner disagrees. Pet. 63–69; Reply 1–5. Because we deny the Petition on its merits, we need not decide whether to exercise our discretion to deny institution. *See also, Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1367 (Fed. Cir. 2016) (explaining that "the PTO is permitted, but never compelled, to institute an IPR proceeding").

III. CONCLUSION

Petitioner has not demonstrated a reasonable likelihood that at least one claim of the '343 patent is unpatentable.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, Petitioner's request for an *inter partes* review of claims 1–6 of the '343 patent under the present Petition is *denied* and no trial is instituted.

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