

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 IPR2023-00723
Patent 8,129,343

**PATENT OWNER'S PRELIMINARY RESPONSE
UNDER 37 C.F.R. § 42.107**

LIST OF EXHIBITS

Exhibit	Description
EX2001	Excerpt of Defendants’ Initial Invalidity Contentions, <i>In re: Ozempic (Semaglutide) Patent Litigation</i> , No. 1:22-cv-01040-CFC, (D. Del. Oct. 20, 2022)
EX2002	J. Lau, P. Bloch, et al., “Discovery of the Once-Weekly Glucagon-Like Peptide-1 (GLP-1) Analogue Semaglutide,” <i>Med. Chem.</i> , 58:7370-7380 (2015)
EX2003	U.S. Patent No. 10,335,462
EX2004	B. Furman, N. Pyne, P. Flatt & F. O’Harte, “Targeting B-cell cyclic adenosine monophosphate for the development of novel drugs for treating type 2 diabetes mellitus,” <i>J. Pharmacy and Pharmacology</i> , 56:1477-1492 (2004)
EX2005	WO98/32466
EX2006	U.S. Patent No. 6,528,486
EX2007	WO00/69911
EX2008	Excerpt of Plaintiffs’ Initial Responses to Defendants’ Initial Invalidity Contentions, <i>In re: Ozempic (Semaglutide) Patent Litigation</i> , No. 1:22-cv-01040-CFC, (D. Del. Dec. 21, 2022)
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I. Introduction

Patent Owner Novo Nordisk A/S (“PO”) submits this §42.107¹ Preliminary Response to the above-captioned Petition (“Petition”/“Pet.”). The Board should deny institution because Petitioner fails to meet its burden to establish unpatentability, including by failing to articulate clearly the arguments and evidence on which Petitioner purports to rely, and failing to show liraglutide would have been a lead compound. Petitioner also fails to show obviousness of Claims 1-6 (“Challenged Claims”/“Claims”) of U.S. Pat. 8,129,343 (“’343 Patent”/“’343”). Petitioner concedes semaglutide (the GLP-1 analogue covered by the Claims) is novel, arguing only that semaglutide, the active ingredient in PO’s revolutionary once-weekly drug Ozempic®—which generated nearly \$3 billion in 2021 sales and over \$8.5 billion in 2022—was somehow obvious.

Petitioner’s Grounds 1 and 2 rest on a flawed lead-compound analysis that ignores the wide array of therapeutic approaches and potential leads a skilled artisan would have had to choose from. Instead, Petitioner zeroes in on liraglutide—a decision based on a hindsight-driven search for compounds structurally similar to the claimed invention. This directly contravenes Federal Circuit precedent. *E.g.*,

¹ Unless stated, all statutory and regulatory citations are to 35 U.S.C./37 C.F.R., as context indicates, and all emphases/annotations are added.

Otsuka Pharm. Co., v. Sandoz, Inc., 678 F.3d 1280, 1292 (Fed. Cir. 2012); *Sanofi-Aventis U.S., LLC v. Dr. Reddy's Lab 'ys, Inc.*, 933 F.3d 1367, 1375 (Fed. Cir. 2019). To start, Petitioner asserts liraglutide would have been selected as the “lead compound” because of its half-life and efficacy, but ignores the multitude of other compounds in Petitioner’s own art with **longer** half-lives, **greater** potency, **or both**. Petitioner itself acknowledges in litigation that “[n]umerous other GLP-1 derivatives would have been candidates,” EX2001, 5, conceding here “[m]any would have worked” as a starting point. Pet.31. This confirms Petitioner failed to demonstrate liraglutide is a lead because Petitioner failed to show POSITA “would have had a **reason to select** [liraglutide] **over**” these “[m]any” other GLP-1 analogue candidates. *See, e.g., Daiichi Sankyo Co. v. Matrix Lab 'ys, Ltd.*, 619 F.3d 1346, 1353-54 (Fed. Cir. 2010).

Even if liraglutide were shown to be a proper lead, Petitioner fails to address Petitioner’s own art, which contradicts Petitioner’s proposed rationale for modifying liraglutide, and ignores the innumerable other modifications available to POSITA. While Petitioner attempts to suggest POSITA would have selected “three” particular substantive changes to liraglutide² from a multitude of known alternatives (including

² What Petitioner tries to call “**three**” proposed changes (Pet.6) are at least **four**:

Petitioner proposes modifying both the (1) length (from C₁₆ to C₁₈) and (2) type

others Petitioner’s own art recommends) to “reach semaglutide” (Pet.42), this unsupported argument contradicts the teachings and data in Petitioner’s own art—which Petitioner simply ignores. At bottom, the art clearly demonstrates that each liraglutide modification Petitioner claims was obvious was, in fact, disfavored by the art, a mismatch for liraglutide, or, at most, one in a sea of potential alterations. Petitioner further fails to support its assertion about reasonable expectation of success (“REOS”) with anything beyond a conclusory and unsupported assertion by its expert, entitled to no weight.

Ultimately, Petitioner seeks to stitch together a patchwork of unrelated excerpts from a disparate collection of references in a hindsight-based effort to recreate semaglutide from the prior art. This improper mixing-and-matching of prior-art snippets to track Petitioner’s theory, ignoring those that don’t, is legally insufficient.

And Petitioner’s purported “Ground 3”—“Obviousness over *the prior art* and *common drug development principles*”—is a breathtakingly impermissible catch-all that fails to identify what references it relies on, what limitations are allegedly disclosed in particular references, or how one reference is modified by

(monoacid to diacid) of liraglutide’s fatty acid, incorrectly labeling *two* changes as *one*. Pet.6, 39-40.

another (if at all). Pet.51-59. Instituting this Petition and forcing PO to respond to such a grab-bag of arguments with no meaningful notice of what it must defend against (or what Petitioner might later argue was supported by this vague catch-all) would be highly prejudicial and a denial of due process. The Board has made clear that including improper grounds like Ground 3 provides sufficient reason to deny institution. *Adaptics Ltd. v. Perfect Co.*, IPR2018-01596, Pap.20, 15-19 (Mar. 6, 2019) (informative) (“*Adaptics*”). And to the extent it is considered on any “merits,” Ground 3’s “obvious-to-try” theory clearly fails: even a small handful of Petitioner’s own references disclose, at minimum, ***millions of combinations*** of modifications, and Petitioner again offers merely a conclusory REOS assertion. *Infra*, §§VI.C-VII.

Finally, the Board should deny institution under §325(d). Petitioner’s grounds, largely resting on references sharing common authorship, simply recycle art considered, or are cumulative of art considered, during prosecution. And in claiming “material error,” Petitioner merely asserts the Examiner—using the same liraglutide art—failed to make the precise obviousness argument Petitioner urges here. Petitioner has not shown entitlement to institution based on the same or substantially the same art and arguments.

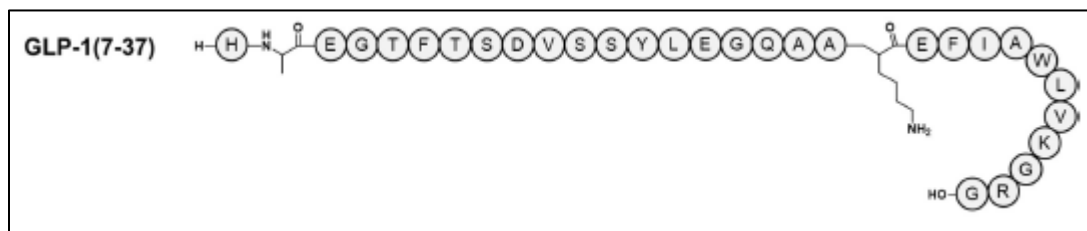
Institution should be denied.

II. Claims Are Directed To A Novel, Non-Obvious Invention

Before '343's inventions, there were various approved type 2 diabetes treatments, but with significant disadvantages. For example, sulphonylureas, glinides, biguanides, and insulin sensitizers were approved, but had limited efficacy and side effects like weight gain. EX1011, 1. Insulin was very effective but required multiple doses per day and presented a serious hypoglycemia risk. *Id.* "GLP-1" (glucagon-like peptide 1) was discovered in 1983 and initially described as an "incretin" ("promoting glucose-dependent insulin release" upon food ingestion). *Id.* Later, GLP-1—"found to lower plasma glucagon in a glucose-dependent manner, decrease the rate of gastric emptying, [and] promote fullness/satiety and stimulate insulin biosynthesis, as well as proliferation of β -cells"—was being investigated, but it, too, presented challenges. *Id.* For example, GLP-1 had a half-life under two minutes, and was "metabolized by dipeptidyl peptidase IV (DPP-IV) and rapidly cleared by the kidneys." *Id.*

After years of work, multiple GLP-1 analogues with different structures and approaches were being clinically investigated—some for potential once-daily administration. EX1010, 2. One of these was PO's compound, liraglutide (below). *Id.* But as of the priority date, *none* were FDA approved, a majority of each analogue's clinical data was not yet public (*see* EX1010, 2-5), and researchers continued searching.

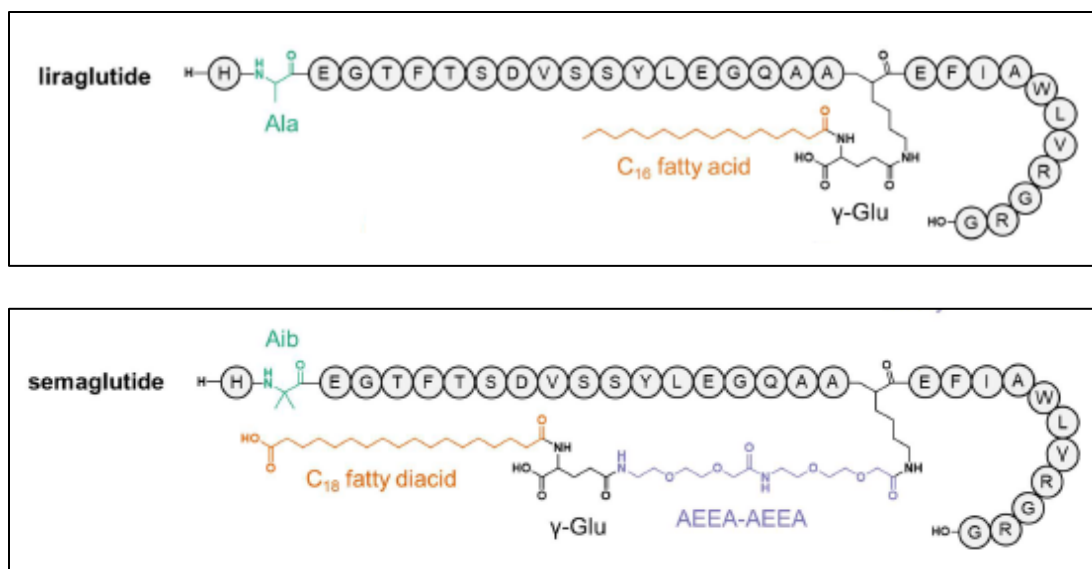
The Claims of '343, "Acylated GLP-1 Compounds" (claiming priority to a March 23, 2005 provisional), are directed to semaglutide, and formulations and methods of treatment with semaglutide. EX1002, 1, 66-70; Pet.10. Semaglutide is a "GLP-1(7-37)"³ analogue with multiple changes from native human GLP-1(7-37) (below). EX2002⁴, 2, 5. Semaglutide has a non-natural amino acid, aminoisobutyric acid, substituted at position 8 ("Aib⁸"). *Id.* Semaglutide also has a complex structure modifying GLP-1's lysine ("Lys") at position 26, consisting of a di-aminoethylethanolamine ("di-AEEA") spacer bonded to a gamma glutamic acid ("γ-Glu"), which is bonded to a "C₁₈"⁵ dicarboxylic fatty acid. *Id.* In addition, semaglutide has an arginine ("Arg") substituted for the native lysine at position 34. *Id.*



³ “GLP-1(7-37)” reflects that amino acids at positions 1-6 were cleaved from the 37-position parent, GLP-1(1-37). EX1010, 1. (GLP-1(7-37)’s first position is numbered “7.” *Id.*)

⁴ EX2002 and EX2004 appear in regularly published journals.

⁵ “x” in “C_x” identifies the number of carbons in a fatty-acid chain.



Pet.32, 35.

Semaglutide's structural differences from native GLP-1 led to a **greatly increased half-life**—165 hours for semaglutide versus *under 2 minutes* for GLP-1 and 8 hours for liraglutide—and far greater **effectiveness** over previously-attempted longer-acting GLP-1 analogues. Pet.18; EX2002, 1-2, 5. These differences from GLP-1 surprisingly allowed PO's commercial products with semaglutide as the only active ingredient—Ozempic® for diabetes and Wegovy® for chronic weight management—to be **dosed once-weekly** in a **lower dose** than analogues (like liraglutide) delivered daily, while providing greater blood glucose control and weight loss than liraglutide. As a result, patients need to inject significantly less frequently, and with less GLP-1 analogue (1.0mg/week semaglutide for diabetes, versus 8.4mg/week (1.2mg/day) liraglutide) to achieve a better outcome. EX2003, Figs. 1-5.

'343's Examiner initially rejected the pending genus claims as obvious over the "Knudsen Patent"⁶ (EX1012) and Larsen. EX1004, 41-46. PO then returned to its conditionally elected species claims for semaglutide (EX1004, 32-33, 68), and the Examiner allowed '343. EX1004, 25.

III. Petitioner's References Identify Thousands of Compounds and Potential Modifications

A. Knudsen 2004 (EX1010)

Knudsen 2004—cited on '343's face—is an article by a Novo Nordisk researcher discussing several GLP-1-based compounds under development with varying half-lives and dosing frequencies, including two exendin-4 analogues, exenatide (a.k.a. synthetic extendin-4) and ZP10, and natural GLP-1 analogues including liraglutide, CJC-1131, Albugon, and BIM-51077. EX1010, 2-4; EX1002, 1. Notably, Knudsen 2004 discloses that, *e.g.*, CJC-1131 has a half-life ***16-26 times longer*** than liraglutide's (*10-12 days* versus *11-15 hours*) and Albugon has a half-life 4-6 times longer than liraglutide's (*3 days* in monkeys versus *11-15 hours* in humans). EX1010, 4.

⁶ Knudsen—lead inventor of EX1012, a Ground 1-2 secondary reference—is an author on both of Petitioner's primary references (EX1010, EX1011).

B. Knudsen 2001 (EX1011)

Knudsen 2001, co-authored by Knudsen, discusses GLP-1 analogues for treating type 2 diabetes. EX1011, 1. Knudsen 2001 recognizes the significant investigation still needed to identify and test GLP-1 analogues with the potential for once-daily administration, and reports negative impacts of various potential GLP-1 modifications. EX1011, 3-4. For example, although ignored by Petitioner, Knudsen 2001 discloses compound 16, an analogue with a C₁₈ acid and γ -Glu spacer (two semaglutide features), “led to a ***significant loss of activity*** compared to C₁₆..., C₁₄... and C₁₂.” EX1011, 4 (C₁₈ analogue 3x less active than C₁₆, which is 3x less active than C₁₄ and C₁₂). Further, diacids, “could be ***no longer than a C₁₄... before a loss in potency***... compared to the γ -Glu spacer monoacid series... ***was seen.***” *Id.* (C₁₆ diacid 2x less active than C₁₄ diacid).

Knudsen 2001 discloses, *e.g.*:

- at least two GLP-1 analogues (compounds 4, 20), modified at a different amino acid or with a GABA-spacer instead of γ -Glu,

yielding *substantially longer half-life than liraglutide* (compound 5);

Cpd.	Plasma t _{1/2} (h)
1(GLP-1)	1.2
4	20 ± 2
5	14 ± 2
7	13
8	12 ± 1
18	15 ± 3
20	31 ± 4
21	8.8 ± 1

- at least six GLP-1 analogues (compounds 3, 4, 6, 8, 9, 17, 18) with *higher potency than liraglutide* (a lower EC₅₀ value indicates higher potency); and

Table I: GLP-1 compounds and their potency measured using the cloned human GLP-1 receptor expressed in baby hamster kidney cells.

Cpd.	Parent peptide	Acyl site	Acyl substituent	Potency (EC ₅₀ , pM)
1	GLP-1(7-37)	-	None	55 ± 19
2	K8R26,34-GLP-1(7-37)	K8	γ-Glu-C16	1260 ± 210
3	K18R26,34-GLP-1(7-37)	K18	γ-Glu-C16	35.2 ± 6.2
4	K23 R26,34-GLP-1(7-37)	K23	γ-Glu-C16	30.1 ± 3.3
5	R34-GLP-1(7-37)	K26	γ-Glu-C16	61.0 ± 7.1
6	K27R26,34-GLP-1(7-37)	K27	γ-Glu-C16	36.3 ± 0.3
7	R26-GLP-1(7-37)	K34	γ-Glu-C16	121 ± 26
8	K36R26,34-GLP-1(7-36)	K36	γ-Glu-C16	36.4 ± 2.1
9	R26,34-GLP-1(7-38)	K38	γ-Glu-C16	53.0 ± 2.8
14	R34-GLP-1(7-37)	K26	C16-diacid	154 ± 66
15	R34-GLP-1(7-37)	K26	C14-diacid	72 ± 0.7
16	R34-GLP-1(7-37)	K26	γ-Glu-C18	194 ± 24
17	R34-GLP-1(7-37)	K26	γ-Glu-C14	22.0 ± 7.1
18	R34-GLP-1(7-37)	K26	γ-Glu-C12	27.3 ± 8.4
19	Des-amino-H7R34-GLP-1(7-37)	K26	γ-Glu-C16	687 ± 129
20	R34-GLP-1(7-37)	K26	GABA-C16	84.4 ± 22.1
21	R34-GLP-1(7-37)	K26	β-Ala-C16	113 ± 3
22	R34-GLP-1(7-37)	K26	Iso-Nip-C16	410 ± 120

- at least one GLP-1 analogue (compound 4 (acylated at position 23)) with both *substantially longer half-life and higher potency than liraglutide*.

EX1011, 4-5 (Tables I-II).

Lastly, while semaglutide has a position 8 Aib substitution at the N-terminus, Knudsen 2001 recognizes that “[d]esamino His⁷ represents one of the more potent suggestions to a modification giving metabolic stability,” that “*considerably more potent* compounds could be obtained *by not modifying the N-terminus* when a combination with acylation was desired,” and that “any amino acid substitution poses a *risk of immunogenicity*.” EX1011, 4-5. Knudsen 2001 selected compound 5—with *no* N-terminus modification—for development over analogues with N-terminus modifications. *Id.* Finally, while Petitioner urges a position 8 substitution to protect against DPP-IV degradation, Knudsen 2001 chose liraglutide because it *already had substantial protection against DPP-IV cleaving* through acylation *without* needing any position 8 substitution. *Id.*

C. Knudsen Patent (EX1012)

The Knudsen Patent, “Derivatives of GLP-1 Analogs” (issued July 31, 2001), is assigned to PO. It was expressly considered during examination, and discloses *thousands* of GLP-1 analogues—describing *each* as a “preferred embodiment” (*e.g.*, EX1012, cols.20-167), and recognizing 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. *E.g.*, EX1012, 9:21-19:59. The Knudsen Patent discloses:

- multiple GLP-1 analogues with *greater half-life than liraglutide*

(Example 37), including Exs.11-14, 32 and 34 (EX1012, 192:30-60

(Table 1));

TABLE 1									
Test com- pound*)	Hours after sc. Administration								
	0.75	1	2	4	6	8	10	12	24
GLP-1 (7-37)		100	9	1					
Exam- ple 25	73	92	100	98	82	24	16	16	16
Exam- ple 17	76	71	91	100	84	68	30		9
Exam- ple 43		39	71	93	100	91	59	50	17
Exam- ple 37		26	38	97	100	71	81	80	45
Exam- ple 11	24	47	59	71	100	94	100		94
Exam- ple 12	36	54	65	94	80	100	85		93
Exam- ple 32	55	53	90	83	88	70	98	100	100
Exam- ple 14	18	25	32	47	98	83	97		100
Exam- ple 13	15	22	38	59	97	85	100		76
Exam- ple 38	60	53	100	66	48	39	25	29	0
Exam- ple 39	38	100	70	47	33	33	18	27	14
Exam- ple 40	47	19	50	100	51	56	34	14	0
Exam- ple 34	19	32	44	84	59	66	83	84	100

and

- multiple GLP-1 analogues *more potent than liraglutide*, including, *e.g.*, Exs.16, 26, 30, 38-40, and 43 (EX1012, 193:35-46).

Test Compound*)	EC ₅₀ , pM	Test Compound*)	EC ₅₀ , pM
GLP-1(7-37)	61	Example 31	96
Example 45	120	Example 30	41
Example 43	24	Example 26	8.8
Example 40	55	Example 25	99
Example 39	5.1	Example 19	79
Example 38	54	Example 16	3.5
Example 37	60		

D. Dong (EX1013)

Dong discloses testing of GLP-1(7-36)⁷ analogues designed and synthesized to improve half-life. EX1013, 6. Dong states GLP-1 is cleaved *in vivo* in two places—between positions 8-9 (by DPP-IV) and 34-35—reducing its half-life. *Id.* Attempting to increase half-life, Dong synthesized GLP-1 analogues with substitutions at position 8, 35, 26, 34 and/or 31. While Petitioner proposes substitutions at position 8 but *not* positions 31 and 35 to reach semaglutide, Dong reports half-life is improved when two to five substitutions are *made together*, including the “representative analogue,” compound 4, which includes 2 substitutions: Aib⁸ and Aib³⁵ (a combination of substitutions absent in

⁷ Petitioner does not address that Dong’s data pertains to a different form of GLP-1, (7-36), let alone explain why data and modifications from (7-36) would translate to (7-37). Pet.23-24, 36-37; *infra*, §VI.B.2.a.

semaglutide). *Id.* Dong also reports Aib^{8,35} results in a half-life of 9.76 hours, whereas Aib⁸ alone (as in semaglutide) resulted in a poorer half-life of only 4.52 hours—the second shortest of *any* GLP-1(7-36) analogue Dong tested. *Id.* And Dong’s conclusion notes compound 4, Aib^{8,35} (not found in semaglutide), was “significantly more efficacious than hGLP-1” (native human GLP-1). *Id.*, 7.

E. Bridon (EX1014)

U.S. Patent 6,514,500, “Long Lasting Synthetic Glucagon Like Peptide” (“Bridon,” issued February 4, 2003), is assigned to ConjuChem, Inc. EX1014, 1. Related publication WO00/69911, claiming priority to the same provisional (60/159,783) and sharing (in relevant part) Bridon’s specification, is cited on ’343’s face. EX1002, 1; EX2007.

Bridon discloses analogues “capable of forming covalent bonds with one or more blood components [such as albumin] to form a conjugate,” so that, when administered, they form a “peptidase stabilized therapeutic peptide.” EX1014, 1 (Abstract). Bridon explains the covalent bond to albumin formed upon administration (a bond *not* formed when liraglutide or semaglutide interacts with albumin) extends “[t]he activity of the modified ITPs compound... for days to weeks.” EX1014, 21:17-27.

Further, while Bridon discloses numerous GLP-1 analogues, it emphasizes its “invention relates... especially [to] GLP-1(7-36) amide[s].” EX1014, 1:61-67,

51:1-68:6. Semaglutide is not a GLP-1(7-36) amide, nor does Petitioner contend it is.⁸ EX2002, 5.

Bridon discloses numerous types of linker-reactive groups that could be used to covalently bind blood components such as albumin, and further discloses that, in “preferred embodiments,” the albumin-binding substituent attached to Bridon’s linker is “a maleimido-containing group such as (GMBA or MPA)” (not a fatty acid incapable of covalently binding albumin, as in liraglutide and semaglutide). EX1014, 3:10-20, 9:15-18. And Bridon claimed only one GLP-1 analogue, which had no linker, and instead was substituted directly on ϵ -position of Lys³⁷ with MPA. EX1014, cls.1-2.

IV. Claim Construction

No terms require construction for considering institution. *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).

V. §314(a) Discretionary Denial: Ground 3 Fails to Identify “With Particularity” Each Reference and Combination on Which the Challenge is Based, and Its Extraordinary, Prejudicial Impropriety Requires Denial

Petitioner purports to identify “Ground 3” as “Obviousness *over the prior art and common drug development principles* (under *KSR*).” Pet.5. But generally invoking the “prior art” with unspecified “common drug development principles”

⁸ See n.7.

ignores the “particularity” petitions require (*e.g.*, §312(a)(3); §42.104(b)(4)), and Petitioner’s extraordinarily overreaching attempt to proceed to trial *without specifying the prior art and arguments actually at issue* in “Ground 3” denies PO due process and any meaningful opportunity to respond—and requires denial of the Petition as a whole. *See, e.g., Adaptics*, 20-21 (denying institution where “catch-all” ground not “reasonably bounded in scope”).

Like *Adaptics*, Petitioner’s Ground 3 “attempts to require [PO] to address whether each limitation is taught not only by *each*” reference, “but [also] by *each* of these references *in combination with one or more of the other references* asserted in the proceeding.” *Id.*; *see also EnergySource Minerals, LLC v. TerraLithium LLC*, IPR2019-01607, Pap.10, 13-17 (May 4, 2020) (denying institution where “catch-all” ground lacked particularity); *InVue Sec. Prods., Inc. v. Mobile Tech., Inc.*, IPR2019-00078, Pap.7, 14-15 (May 1, 2019) (denying institution for lack of particularity where grounds included “Known Prior Art in Section IV,” consisting of 16 references); *ADT LLC v. Vivint, Inc.*, IPR2022-00634, Pap.7, 13-15 (Oct. 4, 2022) (denying institution where one ground lacked particularity and petitioner failed to explain interplay between its two references). The result is that PO is left to guess which reference (if any) is the primary reference, which (and how many) are secondary reference(s), and how and why the primary reference (whatever it may be) is to be modified by any secondary

reference(s) (whatever they may be). *Cf., e.g., John Crane, Inc. v. Finalrod IP, LLC*, IPR2016-01827, Pap.6, 13-14 (Jan. 31, 2017) (denying institution where petitioner failed to show how and why specific teachings would have been combined). “If a petition fails to state its challenge with particularity... the patent owner is forced to shoot into the dark. The potential for unfairness is obvious.” *Cuozzo Speed Techs., LLC v. Lee*, 579 U.S. 261, 296 (2016) (Alito J., concurring-in-part); *see also* §312(a)(3). Ground 3 is a particularly egregious example: instituting trial and requiring PO to defend against this vague invocation of unspecified “art” and “principles” would unquestionably prejudice PO and deprive it of basic due process, requiring PO to guess blindly at Petitioner’s arguments while effectively empowering Petitioner to argue whatever it wants going forward.

Like *Adaptics*, Petitioner relies on “voluminous additional exhibits containing substantive disclosures relating to the [Claims’] subject matter” (*Adaptics*, 22), in addition to “common drug development principles” (Pet.5). *E.g.*, Pet.viii-xvi (identifying over 110 exhibits), Pet.62-65 (citing multiple declarations, in turn citing many references and internally cross-referencing multiple other citation-containing sections). As just one example of Ground 3’s breadth, the first full paragraph of Petition page 57 cites three declarations from different Petitioner experts, including, *e.g.*, five paragraphs of Dr. Flatt’s (EX1020 ¶¶263-267) that in turn cite 19 different references and cross-reference seven other sections of his

declaration (each including more citations). It is not possible to tell which combination(s) Petitioner may be asserting in Ground 3, let alone which portions of which references Petitioner relies on. Indeed, neither Petitioner nor Dr. Flatt identifies which, whether, or how any of these references are combined with one another. *ADT*, IPR2022-00634, Pap.7, 14-15 (noting lack of particularity would prejudice owner if IPR instituted); *John Crane*, IPR2016-01827, Pap.6, 13-14. This prevents Petitioner from meeting its burden for Ground 3.

Moreover, given Ground 3's extraordinary vagueness—denying any meaningful opportunity to respond—the Board should, as before, exercise its §314(a) discretion to deny institution of the entire Petition based on this improper “catch-all” ground. *Adaptics*, 24; *see also EnergySource*, IPR2019-01607, Pap.10, 13-17; *Jiangsu Sainty Sumex Tools Corp. v. Milwaukee Elec. Tool Corp.*, IPR2021-00373, Pap.19, 23-24 (July 6, 2021) (denying institution where combinations included “one or more of” five references “in combination with one or more of common knowledge [or] common sense,” explaining this “approach [] raises a formidable number of possible... combinations”).

VI. Grounds 1-2: Petitioner's Lead Compound Analysis Is Legally Deficient

Grounds 1 and 2 fail. Both require starting with liraglutide as lead compound, but Petitioner's analysis is insufficient to meet its burden to establish liraglutide as a lead. Petitioner then argues only the particular modifications that

would result in semaglutide would have been obvious, ignoring the overwhelming number of other potential modifications described in the art, including some detailed and recommended in Petitioner's own exhibits. Finally, Petitioner asserts REOS in making these modifications, but based on nothing more than its expert's conclusory say-so, which should be given no weight, and fails to address the interplay among its multiple proposed modifications. Petitioner thus fails to meet its burden at each mandatory step.

A. Petitioner's Lead Compound Analysis Fails

To satisfy the "lead-compound framework" on which Petitioner expressly conditioned Grounds 1 and 2 (Pet.5), Petitioner must identify an appropriate lead: "the analysis... requires [Petitioner] to demonstrate... [POSITA] would have had a *reason to select* [its] proposed lead compound or compounds *over other compounds in the prior art.*" *Daiichi*, 619 F.3d at 1354; *Sawai USA, Inc. v. Astellas Pharma Inc.*, IPR2018-00079, Pap.7, 19-22 (May 4, 2018) ("*Sawai*") (denying institution where "Petitioner provides no persuasive explanation why [POSITA] would have focused on pharmacophore A to the exclusion of pharmacophore B" for a lead); *Takeda Chem. Indus. Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007) (challenger's "obviousness argument clearly depends on a preliminary finding that [POSITA] would have selected compound b

as a lead”). But Petitioner’s lead-compound analysis fails to make this required showing concerning other compounds Petitioner admits were known.

In co-pending litigation Petitioner argues “[n]umerous other GLP-1 derivatives would have been candidates” (EX2001, 5), and asserts “[m]any would have worked” as a starting point. Pet.29. Taken at its word, Petitioner failed to demonstrate liraglutide is a lead by failing to show POSITA “would have had a **reason to select** [liraglutide] **over**” these “[m]any” other candidates. *See, e.g., Daiichi*, 619 F.3d at 1353-54 (upholding rejection of proposed “second-generation ARB” leads over “**other** second-generation ARBs”); *see also Takeda*, 492 F.3d at 1359-60 (upholding rejection of proposed lead, noting “art disclose[s] a broad selection of compounds any one of which could have been selected as a lead... for further investigation” and district “court found nothing in the... art to narrow the possibilities... to [the proposed lead]”).

Lead-compound analysis requires identification and analysis of the known “*pertinent properties*” of potential leads—the known prior-art compounds. *Otsuka*, 678 F.3d at 1292 (“In determining whether [POSITA] would have selected a prior art compound as a lead, *the analysis is guided by evidence of the compound’s pertinent properties.... Absent a reason or motivation based on such prior art evidence, mere structural similarity between a prior art compound and the claimed compound does not inform the lead compound selection.*”); *Daiichi*,

619 F.3d at 1353-54 (analysis depends on “knowledge in the art of the functional properties and limitations of the prior art compounds”); *Sawai*, 12 (similar). Here, Petitioner cannot meet its burden because it failed to identify (let alone thoroughly analyze) the complete array of pertinent properties POSITA would have considered. While Petitioner elsewhere mentions two properties, half-life and potency,⁹ it fails to show how these would support its argued choice of liraglutide over other GLP-1 analogues: lead-compound analysis cannot hand-pick certain properties and ignore others.¹⁰ *E.g.*, *Daiichi*, 619 F.3d at 1353.

Even if, *arguendo*, POSITA could properly have considered only half-life and potency (ignoring acknowledged drawbacks such as solubility (Pet.33)), Petitioner ignores the significantly **greater potency** and **longer half-lives** of

⁹ Petitioner’s own submissions confirm POSITA were concerned with properties beyond these two that Petitioner ignores—*e.g.*, Pet.31 (solubility); EX1011, 3-5 (PK profile, metabolic stability, ability to formulate, immunogenicity); EX1010, 4-5 (side effects, PK profile); EX1031, 11 (administration routes).

¹⁰ *E.g.*, Petitioner admits a drawback of liraglutide (and other analogues) related to formulation, but does not explain why or how POSITA would have weighed this—simply noting it as a characteristic that *would have had to be overcome*. Pet.33-34; EX1024, ¶79.

numerous ***non***-liraglutide GLP-1 analogues in Petitioner's own art. POSITA

would not have made this mistake: "proving a reason to select... a lead compound

depends on... knowledge in the art of the functional properties and limitations of the prior art compounds." *Daiichi*, 619 F.3d at 1354. Petitioner ignores its own

references confirming other analogues with, *e.g.*:

- ***greater potency than liraglutide***, including Knudsen 2001's compounds 3-4, 6, 8-9, and 17-18; and Knudsen Patent's Exs.16, 26, 30, 38-40 and 43;
- ***substantially longer half-lives than liraglutide***, including Knudsen 2001's compounds 4, 20; Knudsen Patent's Exs.11-14, 32 and 34; and Knudsen 2004's Albugon (3 days in monkeys) and CJC-1131 (10-12 days); and
- ***both greater potency and substantially longer half-lives than liraglutide***, including Knudsen 2001's compound 4.

EX1010, 2; EX1011, 4-5; EX1012, 192:30-60 (Table 1), 193:35-46; EX1013, 6.

Petitioner never addresses why liraglutide, with ***less-favorable potency and half-***

life, would have been selected as a lead over such compounds that were clearly

superior in one or both. *See* Pet.26-31, 44-46. For this reason, Grounds 1 and 2

fail: "***Potent and promising activity in the prior art trumps*** mere structural

relationships." *Daiichi*, 619 F.3d at 1353-54 (upholding rejection of proposed

leads over other compounds “demonstrat[ing] *greater potency* and... more thoroughly studied”); *Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000) (affirming failure to “show the required motivation for selecting” lead where asserted motivation was *activity* but others had *greater activity*).

B. Even if Liraglutide Were Selected as a Lead, Petitioner Fails to Establish “Motivation To Combine”

Even if, *arguendo*, Petitioner had established liraglutide as a proper lead, Petitioner failed to show it would have been obvious to modify liraglutide to arrive at semaglutide. “Any compound may look obvious once someone has made it and found it to be useful, but working backwards from that compound, with the benefit of hindsight,... does not render it obvious.” *Sanofi-Aventis*, 933 F.3d at 1375. Petitioner’s obviousness argument—premised on its erroneous assertion that only “three” “trivial” changes were necessary to transform liraglutide into the claimed semaglutide (Pet.2)—is nothing more than a hindsight path backwards from ’343. In addition to casting at least four changes as “three,”¹¹ Petitioner ignores **(1) its own references suggesting many other types and locations of modifications, (2) the wide variety of options for implementing those “three” types and locations of changes, and (3) the *negative* impacts Petitioner’s references report for the**

¹¹ See n.2.

modifications required to reach semaglutide from liraglutide. The Board has similarly denied institution where “the sheer number of modifications needed and the large number of possible substitution options suggest... a hindsight reconstruction... rather than a reasoned basis for modifying” the lead to arrive at the invention. *Sawai*, 22-25 (rejecting argument based on asserted lead with “four structural differences”); *see also Par Pharm. Inc. v. Novartis AG*, IPR2016-00084, Pap.73, 35 (Jan. 11, 2018) (“*Par Pharm.*”) (rejecting lead-compound argument where POSITA “would have been faced with a large number of decision points [and o]nly by making the ‘right’ choice at each step would the skilled artisan arrive at” the claimed compound); *Mylan Pharms. Inc. v. UCB Pharma GmbH*, IPR2016-00514, Pap.38, 39 (July 19, 2017) (“The sheer number of possibilities available to [POSITA] at each stage of the process speaks to the nonobviousness of the final product.”); *Mylan Pharms. Inc. v. Nissan Chem. Indus., Ltd.*, IPR2015-01069, Pap.24, 7 (Oct. 20, 2015) (denying institution where multiple modifications (each with many possibilities) were needed to go from lead to claimed invention).

1. Petitioner Ignores The Numerous Types and Locations of Potential Modifications to Liraglutide Other than Those in Semaglutide

Liraglutide and semaglutide differ in four significant respects. To reach semaglutide, Petitioner improperly ignores all other sites of GLP-1 ripe for

modification, and a huge number of other types of known, available modifications POSITA would have considered at each—and combinations thereof.

Compared to native GLP-1,¹² semaglutide has amino acid substitutions at positions 8 and 34, and an acylated position 26. EX2002, 5. However, Petitioner’s Knudsen 2004’s structure activity relationship (“SAR”) figure for GLP-1(7-37) discloses *23 of the 31 positions may be modified*, including six positions that “may be derivatized with long fatty acid.” EX1010, 3. Petitioner’s Knudsen Patent identifies modifications at nearly every position, including deleting amino acid 8 entirely. EX1012, 9:21-16:49. And (at 62) it discloses analogues with modifications at positions 8, 17-19, 23, 26-27, 34, and 36—it includes *over 70 pages* of these analogues. *E.g.*, EX1012, 20:3-167:62. Petitioner’s Dong reference identifies five sites for modification on GLP-1(7-36)—positions 8, 26, 31, 34, 35—and provides half-life and potency data for analogues with each of these changes. EX1013, 6. Petitioner’s Bridon discloses acylating GLP-1(7-37)’s position 37.

¹² Petitioner’s art acknowledges many POSITA at the time were working from a *different* GLP-1 agonist, exenatide, not GLP-1 itself or liraglutide. EX1010, 3-4 (*e.g.*, Lilly & Amylin’s AC2993, Zealand’s ZP10, Weizmann Institute’s extendin-4 prodrug). Indeed, Dr. Flatt’s article reported data indicating Exendin-4 was the most promising analogue tested, including over liraglutide. EX2004, 7.

EX1014, 26:40-32:30. And, Petitioner's expert, Dr. Flatt, published a 2004 paper identifying multiple *other* types of modifications with promising results, including, *e.g.*, substitutions at positions 7 and 9 (although neither he nor Petitioner addresses them) and others at position 8. EX2004, 7. For example, he reported on position 7 modifications that "ha[d] been shown to be completely resistant to DPP IV and human plasma degradation, as well as exhibiting potent receptor binding, cAMP production and insulin secretory activity in-vitro." EX2004, 6.

Petitioner simply ignores the overwhelming majority of these alternatives, arriving at semaglutide based only on hindsight. In doing so, Petitioner also ignores its own stated rationale: while, *e.g.*, Petitioner asserts POSITA would have sought to *minimize* the number of changes to native GLP-1, it never explains why POSITA would have maintained liraglutide's arginine-lysine substitution in GLP-1's position 34, or why POSITA would have changed GLP-1's position 8 to an artificial Aib when its art stated one should *not*. *E.g.*, Pet.19, 47; EX1020, ¶182; EX1011, 4 ("considerably more potent compounds could be obtained by *not* modifying the N-terminus when a combination with acylation [is] desired"). The Board has denied institution for similar failures to "explain sufficiently why [POSITA] would have maintained the predetermined [changes] and only modified [one site]," *Gilead Scis., Inc. v. Regents of the Univ. of Minn.*, IPR2017-01753, Pap.42, 14 (Apr. 22, 2020) ("*Gilead*"), and should do so again here.

Given the numerous types, locations, and combinations of potential modifications, Petitioner's analysis fails to meet its burden because Petitioner never addresses why POSITA would have been motivated and found it obvious to pluck *only the specific changes that would yield semaglutide* from the multitude of known (and, indeed, suggested) alternatives. Petitioner's choice to ignore potential changes resulting in something other than semaglutide is fatal, violating the directive that lead-compound analysis "must avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to select and then modify a lead compound to arrive at the claimed invention." *Daiichi*, 619 F.3d at 1354 (italics original).

2. Even Focusing on the Types of Modifications Needed to Arrive at Semaglutide, Petitioner Ignores The Numerous Options for Implementing Them

Petitioner's own references disclose a vast array of options for each of Petitioner's "three" chosen types of modifications. *See also infra*, §VII; *supra*, n.2. Petitioner fails to sufficiently explain why POSITA would have selected the precise modifications needed *to arrive at semaglutide*. The only way Petitioner can jump from liraglutide to semaglutide is through "hindsight reconstruction... rather than a reasoned basis for" each modification. *Sawai*, 24-25; *Par Pharm.*, 35-36; *Mylan Pharms.*, IPR2016-00514, Pap.38, 39; *Mylan Pharms.*, IPR2015-

01069, Pap.24, 7. PO addresses each of Petitioner's types/categories of proposed modifications below.

(a) **N-Terminus (Position 8) Modifications**

GLP-1 (7-37)'s position 8 is at its N-terminus. *E.g.*, EX1013, 6. Liraglutide and semaglutide are both ***acylated*** derivatives of GLP-1. EX1010, 2; Pet.32, 35. Petitioner's Knudsen 2001 taught that one of liraglutide's distinguishing characteristics was *already achieving "quite a substantial protection against DPP-IV... by acylation alone," without* needing to modify the N-terminus. EX1011, 4-5. Indeed, Knudsen 2001 *tested* N-terminus modifications on liraglutide and concluded they create ***considerably less potent*** compounds when combined ***with acylation*** and posed a ***risk to immunogenicity***. EX1011, 4-5. Petitioner simply ignores ***its own art's*** clearly documenting the benefits of an ***unmodified*** N-terminus and liraglutide's ***already-existing "quite... substantial protection" against DPP-IV cleavage*** to argue POSITA starting with liraglutide would have been motivated to ***modify*** its N-terminus to protect against ***DPP-IV cleavage***. Pet.36-37; EX1011, 5.¹³ Petitioner fails, *e.g.*, to (1) explain why POSITA would have been motivated to modify liraglutide's N-terminus given the expected

¹³ Petitioner's proposal to alter liraglutide's distinguishing characteristics further undercuts its arguments for selecting liraglutide as lead. *Daiichi*, 619 F.3d at 1356.

considerable loss in potency and (2) establish an *acylated* GLP-1 analogue *already reported to be DPP-IV resistant* would nevertheless have needed protection against DPP-IV or been expected to benefit from it using an Aib⁸ substitution.¹⁴

Life Spine, Inc. v. Globus Med., Inc., IPR2022-01603, Pap.8, 40 (June 12, 2023) (denying institution where petitioner “has not articulated sufficient reasoning to explain why a POSITA would modify [its base reference] to address a concern [it] already addresses via a different mechanism.”); *Google LLC v. Jawbone Innovations, LLC*, IPR2022-00889, Pap.12, 20 (Nov. 14, 2022) (denying institution where petitioner failed to explain “motivat[ation] to solve a problem [the reference] already solves.”); *Bioeq IP AG v. Genentech, Inc.*, IPR2016-01608, Pap.11, 12-14 (Feb. 22, 2017) (“*Bioeq*”) (denying institution where petitioner failed to address competing effect in reference).

Petitioner’s basis for proposing Aib⁸ substitution is that Dong reported Aib⁸-modified GLP-1 analogues¹⁵ with longer half-lives than unmodified ones. Pet.36. But this ignores Dong’s teaching that *multiple* modifications are preferred, not just *one* at position 8. And, unlike liraglutide, *Dong’s GLP-1 analogues were not*

¹⁴ Petitioner ignores Knudsen 2000, which discloses N-terminus modifications yielding, at best, only modest 3-4 minute half-life increases. EX1034, 1.

¹⁵ See n.7.

acylated; Petitioner never explains why POSITA would have been motivated to use Dong's N-terminus modifications on (acylated) liraglutide notwithstanding Knudsen 2001's teachings this **combination** of features results in "**considerably**" **less potent compounds**. EX1011, 4. Petitioner certainly points to no art teaching that, despite Knudsen 2001's explicit negative disclosures about this combination, POSITA would still choose to modify GLP-1 with **both** position 26 acylation and Aib⁸ substitution. Petitioner treats drug design as if multiple modifications directed to the same goal (here, DPP-IV resistance) would necessarily be better than one. But drug design is far more nuanced, and Petitioner offers no basis to assert any hoped-for benefit in DPP-IV resistance would be expected to overcome any expected drop in potency. EX1011, 4; *Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 996 (Fed. Cir. 2009) ("to the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable."); *Sawai*, 24-25.

Further, even ignoring the acylation distinction, Petitioner's proposed modification **contradicts Petitioner's stated goal of achieving a long half-life**: the (single) Aib⁸ substitution Dong tested led to **the second lowest half-life of the**

eight alternatives tested. EX1013, 6.¹⁶ Petitioner’s attempts to snip isolated prior-art teachings fail: a party “may not selectively point to one portion of an exhibit to buttress its argument, while disregarding another part... that undermines its contention.” *Gilead*, 25; *In re Wesslau*, 353 F.2d 238, 241 (C.C.P.A. 1965) (“impermissible... to pick and choose... only so much of [reference] as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to [POSITA].”); *CSL Behring LLC v. Bioverative Therapeutics Inc.*, IPR2018-01313, Pap.10, 25-27 (Jan. 9, 2019) (“*CSL*”); *Immunex Corp. v. Sandoz Inc.*, 964 F.3d 1049, 1066-67 (Fed. Cir. 2020) (affirming no motivation to combine because “POSA would be deterred from pursuing the claimed combination by concerns of stimulating inflammation and aggregation,” which ran counter to argued motivation to treat autoimmune disorders); *Bioeq*, 12-14 (denying institution where petitioner failed to address temperature change in reference, which was a known competing effect).

¹⁶ Dong further states the “***resulting analogs bearing modifications at both positions 8 and 35... have much longer plasma half-life than mono-substituted compounds***” and “***retain receptor potency*** of the native hGLP-1.” EX1013, 6-7. Nevertheless, Petitioner (improperly using semaglutide as a hindsight roadmap) does not suggest POSITA would modify position 35.

Petitioner also points to Knudsen 2004’s supposed identification of position 8 as one that “may be modified....” Pet.33. But Petitioner’s citation here is to a figure showing **GLP-1 itself** (which is not acylated), **not liraglutide** (which is). EX1010, 3. And Knudsen 2004 identifies *many other positions that may be modified*, which Petitioner ignores. *Id.*

Finally, while Petitioner points to half-life and potency as the motivations for this Aib⁸ modification (Pet.32-34), Petitioner does not account for Knudsen 2001’s teaching that combining an N-terminus modification with acylation led to *considerably less potent* compounds. EX1011, 4. And Petitioner fails to address other recommended options, like CJC-1131’s D-Ala⁸ modification,¹⁷ while hand-picking other motivations (*e.g.*, improving “spacing” and “solubility”) to argue the other modifications needed to reach semaglutide—but failing to address how, *e.g.*, motivations regarding solubility or spacing (albumin binding) might impact or conflict with its argument for this Aib⁸ substitution.

¹⁷ Petitioner never explains why POSITA would not look to CJC-1131’s different position 8 substitution, when Petitioner elsewhere argues CJC-1131 was “especially pertinent art” with a “very long half-life” and POSITA would look to its AEEA spacer to improve liraglutide. Pet.36-37, 40-41; EX1030, 4-5.

Even when Petitioner *does* acknowledge tensions between its motivations, it urges contradictory choices. Petitioner argues, *e.g.*, POSITA would choose Aib⁸ over Aib^{8,35} despite Aib⁸'s *poorer half-life* because Aib⁸ had *better potency* (Pet.36-37 (citing EX1020, ¶¶178-180)), but Petitioner elsewhere argues POSITA would choose a C₁₈ diacid over a C₁₆ monoacid to *improve half-life* while *ignoring* expected *negative impacts on potency*. Pet.39-42 (citing EX1020, ¶¶215-225); EX1011, 4. Petitioner cannot have it both ways, and its inconsistencies confirm Petitioner's failure to demonstrate the obviousness of its proposed liraglutide modifications. *Immunex*, 964 F.3d at 1066-67; *Bioeq*, 12-14.

(b) Spacer Modifications

Liraglutide and semaglutide each have a spacer¹⁸ or spacers connecting the amino-acid backbone to the fatty-acid chain. Liraglutide has a γ -Glu spacer between its GLP-1 backbone's position 26 and its fatty-acid chain. EX1011, 4 (Table 1, compound 5). Semaglutide *adds two new AEEA spacers* ("*di-AEEA*") attached to each other *between* a position 26 lysine and the γ -Glu spacer. EX2002, 5.

Observing that a spacer increases the distance between the peptide chain (here, the amino-acid backbone) and the fatty-acid chain, Petitioner asserts POSITA would have been motivated to lengthen liraglutide's spacer—but fails to

¹⁸ Also referred to as a "linker." EX1022, ¶100 n.6.

establish the length of *liraglutide*'s spacer actually caused any detriment or, even if too short, *how long* its spacer would need to be to resolve whatever those issues might be. Pet.35-37. Petitioner's generic argument that using a spacer was "tried and true" ignores that *liraglutide already included a spacer*. Pet.37; *Life Spine*, IPR2022-01603, Pap.8, 40; *Google*, IPR2022-00889, Pap.12, 20. Petitioner notes *liraglutide* uses a spacer and other spacers *could* be used (Pet.34-35), but this also does not establish motivation. *Adidas AG v. Nike, Inc.*, 963 F.3d 1355, 1359 (Fed. Cir. 2020) ("The obviousness inquiry does not merely ask whether a skilled artisan *could* combine the references, but instead asks whether 'they *would have been motivated* to do so.'").

Petitioner observes "others had suggested tweaking *liraglutide*'s spacer length to improve activity." Pet.35 (citing EX1030). But EX1030 actually says "the site of attachment to albumin is of importance and that the *linker position and length* in [*liraglutide*] *could* be suboptimal" with respect to "intrinsic activity" *as compared to CJC-1131's*. EX1030, 5. Petitioner fails to acknowledge its proposed linker modification *does not rely on* CJC-1131's linker position (modified at position 37, *i.e.*, "attached to the COOH-terminus"), length (a *single* AEEA spacer, not *two* AEEA spacers *plus* a γ -Glu spacer), or protraction mechanism (covalent binding to albumin *in vivo*). EX1030, 5; EX1010, 2, 4 (Table 1). Further, Petitioner repeatedly argues a spacer would be used to

attenuate interference between the GLP-1 receptor and albumin (which binds to the fatty-acid chain). Pet.36; EX1020, ¶203; EX1022, ¶¶105-106, ¶¶108-111. But Petitioner never establishes there *is* any interference between the GLP-1 receptor and albumin *in liraglutide*, and thus fails to establish that, as Petitioner claims, “[l]engthening the spacer attenuates this problem.” Pet.36.¹⁹ And, Petitioner elsewhere touts the half-life of the Knudsen Patent’s Ex.11, which *does not have any spacer*. Pet.41; EX1012, 177:32-37. Even assuming additional spacing were needed, Petitioner does not establish why two AEEA linkers in its proposed position would have created sufficient space to “attenuate[]” whatever supposed “problem” might have existed. Pet.36.

Even if Petitioner had established an issue with liraglutide’s spacer, Petitioner does not provide sufficient support to explain why POSITA would have made the multitude of choices required to end up with semaglutide’s specific spacers at this particular location, including at least the (1) choice of AEEA as a

¹⁹ Instead of providing actual *data* indicating some problem to be solved with liraglutide’s spacer length, or how long would be “long enough” to solve it (*e.g.*, if “[l]engthening” is just *better* (Pet.35-36), why not 100 (or 1,000) spacers?), Petitioner provides only a cartoonish discussion of 737s (Pet.36), confirming it has nothing substantive to offer.

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.

Petitioner asserts AEEA is hydrophilic, motivating POSITA to add AEEA to liraglutide's γ -Glu spacer (which has a negative charge) to make the compound more water-soluble. Pet.38. However, Petitioner fails to address the interplay of this change (including Petitioner's motivation to *add* AEEA to γ -Glu rather than *replace* it) with its implementation of a fatty-acid chain using a diacid which, according to Petitioner, would *already have added a negative charge*. See Pet.34-39; EX1024, ¶80. Petitioner does not sufficiently explain why POSITA would have found it important or helpful to *maintain* the γ -Glu spacer's negative charge, *add* two hydrophilic AEEA spacers, and add a negatively-charged diacid. While Petitioner ellipsizes its cited art, which discloses using a glutamyl spacer *or* diacids to increase the negative charge (Pet.22-23 (citing EX1011, 3)), Petitioner neither asserts nor establishes a benefit of using *both*. Petitioner has thus failed to establish why POSITA would have *added* two AEEA spacers rather than, *e.g.*, *replaced* liraglutide's spacer with di-AEEA.

Petitioner also fails to provide sufficient support for selecting AEEA.

Petitioner asserts the art “reported that di-AEEA was generally ‘helpful in enhancing binding to target molecule[s]’ and ‘should routinely be tested’ for inclusion in new peptides.” Pet.37 (citing EX1045, 125:4-8, 130:30-34). But those quotes relate to testing peptides targeting *different receptors* (VEGF/KDR), ***not GLP-1 receptors***. EX1045, 1, 130:30-34. Nor does that art address the impact of combining AEEA linkers with a γ -Glu spacer.

Petitioner’s admissions elsewhere further undermine its arguments for AEEA: “A POSA would have also expected that ***any hydrophilic, chemically unreactive linker*** (e.g., PEG-like AEEA) would have worked, ***with the exact identify left to convenience or cost considerations***.” Pet.58. Petitioner nowhere compares liraglutide’s *existing* linker with the “convenience or cost” of *adding two AEEA molecules*. And Petitioner’s admission that *no single PEG spacer* was preferred (*id.*) further undercuts its suggestion POSITA would choose *two AEEA spacers not even mentioned* in Knudsen 2004 or the Knudsen Patent—Petitioner’s relied-upon references to argue spacers other than liraglutide’s γ -Glu spacer “can be used” and would be “tolerate[d].” Pet.38. Further, while Knudsen 2004 notes spacers *other than γ -Glu* “can be used,” it does not address Petitioner’s proposed *adding spacers to γ -Glu*. EX1010, 3; *see Adidas*, 963 F.3d at 1359.

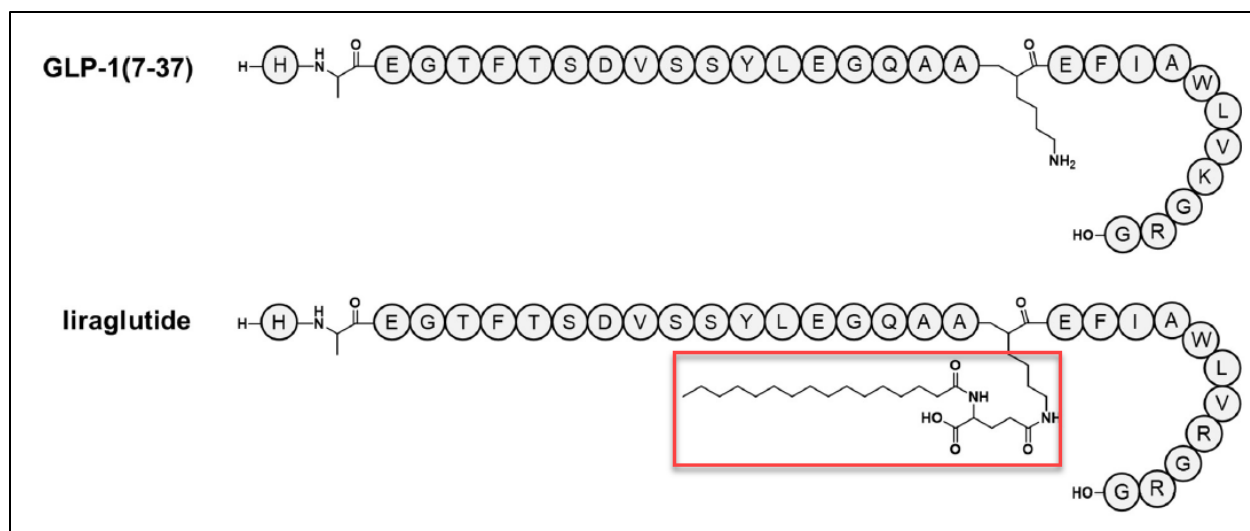
Even assuming POSITA would have modified liraglutide using an AEEA linker, Petitioner fails to establish why *two* AEEA linkers (as required by all claims) would have been preferable, let alone two *in this particular location and configuration*, with both AEEA molecules attached to each other and placed between position 26 and the γ -Glu spacer. More specifically, Petitioner fails to explain why, according to its suggestions about the huge sizes of albumin and the GLP-1 receptor versus liraglutide, POSITA would have been motivated to use only two linkers rather than, *e.g., some larger number of* AEEA linkers (which would fall outside the scope all claims). Indeed, Petitioner seems not to know of any reason POSITA would have chosen two AEEA linkers, as opposed to some other number, since its Petition offers *none*. And to the extent Petitioner meant (but failed) to make some sort of routine-optimization argument about the number of spacers (Pet.6, 37), it made no showing regarding the “optimal” number of AEEA spacers.

Additionally, while Petitioner points to AEEA as being “preferred” in Bridon (EX1014), the di-AEEA spacer example there (amongst many other AEEA examples) is used *in a different position* (37) and *without a γ -Glu spacer*. EX1014, 28:55-60 (Ex.5), 31:45-47 (Ex.7). Indeed, Petitioner offers no more than a conclusory assertion regarding specifically positioning the di-AEEA *between position 26 and γ -Glu*. Pet.39.

Petitioner tries to justify using a di-AEEA spacer at liraglutide's position 26 (instead of Bridon's position 37) by arguing "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." Pet.38-39. But elsewhere Petitioner asserts these peptides are easily assembled at the "push of a button," and Bridon itself discloses *replacing* the GLP-1 backbone's position 37 *with a lysine, then* attaching the di-AEEA spacer. Pet.38; EX1014, 28:55-60 (Ex.5), 31:45-47 (Ex.7). Petitioner fails to explain why POSITA would have chosen Bridon's di-AEEA spacer while ignoring Bridon's teachings about its attachment at position 37 (not 26) and, *e.g.*, the fact that Bridon's spacer is not also attached to a γ -Glu spacer. *Gilead*, 25; *Wesslau*, 353 F.2d at 241; *CSL*, 25-27.

(c) Fatty Acid Modifications

Petitioner proposes two separate modifications to liraglutide's fatty-acid chain—increasing its length, and changing from monoacid to diacid—to *increase half-life*. Pet.39-42. But as Petitioner's diagram makes clear, one of liraglutide's distinguishing features is a γ -Glu-C₁₆ monoacid structure acylated to Lys²⁶. Pet.32:



Petitioner itself asserts liraglutide's fatty-acid chain (which Petitioner proposes modifying) was one of the changes to GLP-1 that contributed to liraglutide's favorable properties: "[Liraglutide's] γ -L-Glu spacer *and fatty acid*-modified Lys²⁶ imparted a long half-life via albumin binding and *gave particularly good activity*." Pet.46; *see also id.* ("Knudsen 2001 disclosed a series of GLP-1 analogues, [and] said that liraglutide 'was selected as the best compound' among them"). Petitioner does not even try to square its selection of liraglutide and its particular features (like liraglutide's fatty-acid chain) with Petitioner's proposal to *modify* the very features that distinguished liraglutide from GLP-1. *Daiichi*, 619 F.3d at 1356. POSITA "would not select [liraglutide] as [a] lea[d] only to disregard one of [its] distinguishing characteristics." *Id.* For this reason alone, Petitioner's arguments fail.

Petitioner does not address its references' teachings that a C₁₈ diacid would negatively impact liraglutide. Petitioner argues POSITA would have

known a C₁₈ diacid “would have worked *better* than liraglutide’s C₁₆ monoacid,” and thus been motivated to substitute C₁₈ for liraglutide’s C₁₆ in view of Knudsen 2004 or the Knudsen Patent. Pet.39-42. But Petitioner fails to address contradictory disclosures in its own references.

For example, Knudsen 2001 teaches a *C₁₈ monoacid with a γ -Glu spacer “led to a significant loss of activity compared to C₁₆.” EX1011, 4. And, within the diacid series, “the *diacid could be no longer than a C₁₄... before a loss in potency...* compared to the γ -Glu spacer *monoacid* series... ***was seen.***” EX1011, 4. Petitioner fails to address these teachings or explain why Knudsen 2001 does not teach away from using any diacid longer than C₁₄ or monoacid longer than C₁₆. Pet.39-42, 49-50; *Millenium Pharms., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1366 (Fed. Cir. 2017); *Takeda*, 492 F.3d at 1358-59 (affirming teach-away where compound “singled out” for having two “undesirable” effects).*

Petitioner also ignores the contradictory teachings in its Markussen reference. EX1038. Markussen taught 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.*” EX1038, 3 (Table 1), 5. While Markussen concerns insulin, rather than GLP-1, it contradicts Petitioner’s unsupported assertion that POSITA expected C₁₈ fatty acids would always work better than C₁₆. Pet.39-42.

Petitioner's own cited art thus "consistently teaches that the type of modification proposed by Petitioner" is not desirable, and its Petition fails for this reason, as well. *Gilead*, 21 (denying institution where proposed modification was contrary to art's teachings); *CSL*, 25-27; *Takeda*, 492 F.3d at 1358-59; *Bioeq*, 12-14 (denying institution where petitioner failed to address competing effect in cited reference).

Petitioner's Arguments Regarding Knudsen Patent Ex.11 Fail to Support Motivation to Combine. Petitioner's cherry-picked compound from Knudsen Patent Ex.11 uses a C₁₈ diacid and has a longer half-life than liraglutide, but does not support its motivation to combine. Pet.41. Indeed, ***Exs.32 and 34 and had the best half-lives of all GLP-1 derivatives in Table 1 (better than liraglutide or Ex.11), but do not use a C₁₈ diacid.*** *Id.*, 95 (Ex.32 uses two C₁₄ diacids ("carboxytridecanoyl") and Ex.34 uses C₁₆ diacid ("carboxypentadecanoyl"); neither has a γ -Glu spacer). Further, the Knudsen Patent discloses fatty acids in lengths C₄-C₄₀—a total of 37 *length options*. And, *for each length, there were many varieties of fatty acids to choose from* (plus various amino acid positions to substitute with various fatty acids, with and without various types of linkers), including monoacids versus diacids, and many types of each. EX1012, 16:56-68, 19:1-59. Petitioner fails to provide sufficient reasoning for POSITA to have selected a C₁₈ diacid specifically, particularly given

Petitioner's admission other options "would work well" and "the choice of a particular lipophilic fatty acid would have been a matter of 'optimization'...." Pet.41-42.

Even assuming, *arguendo*, POSITA motivated to extend half-life would have looked to Ex.11, Petitioner does not address how *other* differences in Ex.11 that Petitioner does not propose changing in liraglutide, including how its proposed fatty acid modification might have interacted with the spacer, would have impacted POSITA's decisions. *See supra* §VI.B.2. For example, Petitioner ignores potency, and Knudsen 2000 teaches "[a] C16 γ -Glu-spaced monoacid and the corresponding C18 *decreases potency* from 36 to 116 pM." EX1034, 4; EX1011, 4.

C. Petitioner Fails To Establish REOS In Creating Semaglutide

Petitioner asserts, in one unsupported sentence, that the "prior art taught that the three modifications would work, individually and synergistically, to improve the properties of GLP-1 analogues." Pet.46, 42. But Petitioner has not even shown REOS for the four *individual changes it argues* (*supra* n.2), let alone that POSITA "would have reasonably expected that *all of the [proposed] modifications as a whole* would have been successful. The combination of 'several sequential modifications' is not obvious where there is no reason in the prior art to make the subsequent modification." *Mylan Pharms. Inc. v. AstraZeneca AB*, IPR2015-01340, Pap.79, 44-46 (Aug. 18, 2017) (FWD) ("Mylan"); *Pfizer Inc. v. Teva*

Pharms. USA, Inc., 555 F. App'x 961, 971 (Fed. Cir. 2014) (nonprecedential) (where, as here, “drug discovery” is “complicated, unpredictable, and largely conducted through trial and error,” REOS in making modification can be “precluded... even if [challenger is] able to establish that the prior art taught [the modification]”) (internal quotations omitted); *cf.* Pet.42.

1. Petitioner Fails to Show REOS For Individual Modifications

Di-AEEA- γ -Glu spacer. Petitioner points to no art disclosing a di-AEEA spacer with a γ -Glu and conclusorily asserts POSITA would have REOS because it is a “predictable use of [a] prior art element[s] according to [its] established function[.]” Pet.39. But as Petitioner’s own art demonstrates, different spacers impact half-life and potency differently. *See*, EX1011, 4 (Table 1). For example, compounds 5 and 20-22 in Knudsen 2001 are all acylated at site 26 and have a C₁₆ monoacid but use different linkers. *Id.* Those differences lead to dramatically different potencies. *Id.* (EC₅₀ values ranging from 61-410 pM). Petitioner fails to grapple with these teachings in asserting predictability.

Fatty Acid Modifications. Petitioner’s own references teach use of a C₁₈ diacid negatively impacts GLP-1 analogues’ potency compared to a C₁₆ monoacid. Knudsen 2001 teaches that a C₁₈ acid with a γ -Glu spacer “led to a significant loss of activity compared to C16.” EX1011, 4. And, within the diacid series, “the diacid could be no longer than a C14... before a loss in potency... compared to the

γ -Glu spacer monoacid series... was seen.” *Id.*; *see also* EX1034, 2. Petitioner simply ignores this (later) Knudsen 2001 article teaching **both** of Petitioner’s modifications to liraglutide’s fatty acid were disfavored, relying instead on a reference in the (earlier) Knudsen Patent to C₁₈ diacid as a “preferred species.”

Pet.41. But the Knudsen Patent disclosed **hundreds** of preferred fatty-acid embodiments. EX1012, 16:56-67, 19:1-59. Petitioner’s argument, even if credited, means POSITA would have needed to test *each of those hundreds of options, and in a multitude of combinations with numerous other changes* required to arrive at semaglutide, all the while not knowing which, if any, might work to achieve a longer-lasting compound retaining liraglutide’s “therapeutic properties” (Pet.42). Petitioner concedes as much in its nonsensical suggestion that this massive undertaking was mere “optimization.” Pet.42. Petitioner’s argument is also contradicted by the fact that the Knudsen Patent itself actually landed on *liraglutide* (not the changes required for semaglutide) in the face of the other “preferred fatty acids,” because liraglutide worked best **without a C₁₈ diacid**. EX1012, cl.14; EX1011, 4. Petitioner fails to explain why POSITA would have had REOS in achieving a long-lasting GLP-1 analogue that retained liraglutide’s “therapeutic properties” (Pet.46) but modified liraglutide with a **C₁₈ diacid**, given Petitioner’s own liraglutide art showing a **C₁₆ monoacid** was preferable and—specifically in liraglutide—resulted in better potency.

N-terminus. Petitioner's Knudsen 2001 references teaches the *combination of an N-terminus modification and fatty acid acylation could negatively impact potency*. EX1011, 4. Knudsen 2001 discloses compound 19 differs from compound 5, liraglutide, only by an N-terminus modification. *Id.* Specifically, compound 19 has a Desamino His⁷ modification which "represents one of the more potent suggestions to a modification giving metabolic stability." *Id.* Knudsen 2001 states that, "as seen when comparing **19** (687 pM) to **5** (68 pM), *considerably more potent compounds could be obtained by not modifying the N-terminus* when a *combination with acylation* was desired." EX1011, 4. Petitioner fails to explain why POSITA would have had REOS achieving a long-lasting GLP-1 analogue that retained liraglutide's "therapeutic properties" (Pet.42) using Aib⁸ to *modify (acylated) liraglutide's N-terminus*, in view of Knudsen 2001's (1) data demonstrating the negative impact of N-terminus modification *on liraglutide specifically* and (2) express general disclosure that N-terminus modification combined with acylation negatively impacts potency. *Id.* Petitioner never confronts these contrary teachings.

* * *

Petitioner's cited cases are inapposite. In support of REOS for the Aib⁸ modification to result in an "analogue [having] a longer half-life than liraglutide" (Pet.37) "while retaining its therapeutic properties" (Pet.42 (argued for "each of the

... modifications’’)), Petitioner points to *KSR*’s statement that using both would be a “predictable use of [a] prior art element[] according to [its] established function[.]” Pet.34; *see also* Pet.39 (citing *KSR* for an unspecified REOS for spacer modification). Again, as discussed, this is contradicted by Petitioner’s references, which taught that N-terminus modifications and spacers had dramatic negative **potency** impacts that Petitioner ignores. *E.g.*, EX1011, 4. These modifications were not “predictable.”²⁰ And Petitioner’s reliance on *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012), for REOS for the fatty acid modification is similarly misplaced, as it is not a lead-compound case. *Id.* For a lead-compound argument, as Petitioner presses here, there must be evidence “to suggest making the specific molecular modifications” to the lead. *Takeda*, 492 F.3d at 1360-61. Petitioner’s suggestion of a massive trial-and-error investigation for the multitude of possible combined changes involving a fatty acid is certainly not the required “specific molecular modification[.]” *Id.*

2. Petitioner Fails to Show REOS For Its Argued Combination of Modifications

Petitioner also fails to show POSITA would have REOS that its particular proposed *combination* of changes—out of millions of possible choices—would

²⁰ To the extent, *arguendo*, they *were*, these references indicate Petitioner’s changes would have been expected to **negatively** impact potency.

have led (as Petitioner argues (Pet.42)) “to... semaglutide.” *Institut Pasteur & Universite Pierre Et Marie Curie v. Focarino*, 738 F.3d 1337, 1346 (Fed. Cir. 2013) (“[T]he expectation-of-success analysis must match the highly desired goal, not switch to a different goal that may be a less challenging but also less worthwhile pursuit.”). Petitioner identifies *no art* that motivated Petitioner’s four modifications to be made in a single analogue, or REOS that these *combined* changes would result in a successful analogue, let alone semaglutide. *Mylan*, 44-46; *see also Takeda*, 492 F.3d at 1362.

Petitioner’s rote assertion that “POSA would have reasonably expected the changes to work together, synergistically, to improve the same properties” (Pet.42) is insufficient. *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). Petitioner’s experts add nothing, and their conclusory opinions deserve no weight. *Xerox Corp. v. Bytemark, Inc.*, IPR2022-00624, Pap.9, 15-16 (Aug. 24, 2022) (precedential). Petitioner’s total failure to show any “reason in the prior art to make the subsequent modification[s]” *in combination*, or any indication semaglutide’s superior properties would have been expected to result from doing so, is an independent reason to deny institution. *See, e.g., Sawai*, 24-25; *Mylan*, 44-46; *see also Par Pharm*, 35-36; *Mylan Pharms.*, IPR2016-00514, Pap.38, 39; *Mylan Pharms.*, IPR2015-01069, Pap.24, 7.

VII. Ground 3: Petitioner's Obvious-To-Try Analysis Fails

Petitioner's Ground 3²¹ lacks sufficient particularity to permit a meaningful, detailed response. *See supra* §V. However, even at a generalized level, Petitioner's grab-bag of Ground 3 theories fails. Petitioner's obviousness theory depends on its assertion there were "a finite number of identified, predictable solutions." Pet.57. But Petitioner failed to show *both* that there were a finite

²¹ Petitioner's assertion that lead-compound analysis is not required here runs counter to Federal Circuit cases. For example, in *Takeda* the Federal Circuit considered how *KSR* bears on obviousness analysis in chemical compound cases, and emphasized: "in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound." 492 F.3d at 1356-57 ("That test... is consistent with the legal principles enunciated in *KSR*"); *Daiichi*, 619 F.3d at 1352 ("Proof of obviousness based on structural similarity requires clear and convincing evidence that a medical chemist of ordinary skill would have been motivated to select and then to modify a prior art compound (e.g., a lead compound) to arrive at a claimed compound with a reasonable expectation that the new compound would have similar or improved properties compared with the old."; discussing *KSR*).

number of solutions *and* that the solutions used to make semaglutide were predictable. *Supra*, §VI.B-C; *Apple Inc. v. Universal Secure Registry, LLC*, IPR2018-00808, Pap.9, 9 (Oct. 9, 2018) (denying institution where petitioner did not support “skeletal” assertion there were “finite number” or “otherwise... define the range of possible solutions”).

As explained, even assuming POSITA started with liraglutide, Petitioner’s own references disclose numerous other modifications at and in addition to those at positions 8 and 26, which Petitioner ignores. *Supra*, §V.I.B.1.

N-terminus. Petitioner asserts there “were a finite number of conservative (i.e., small) amino-acid substitutions that were known” to “give better metabolic stability against DPP-IV.” Pet.57. But Dong discloses *three* amino acid substitutions (EX1013, 6), Dr. Flatt’s article discloses *six* additional substitutions at position 8, *seven* options at position 7, and *six* at position 9 (EX2004, 7), and the Knudsen Patent discloses deleting positions, 7, 8, and/or 9 altogether (*three* more options) (EX1012, 12:39-44). This is a total of *at least 25 unique individual modifications*, even setting aside the additional possibilities and permutations for Petitioner’s other modifications.

Fatty acids. Petitioner asserts “POSA would have been motivated to attach a long-chain fatty acid” to increase the duration of action; “there [were] a limited number of candidates that would have been expected to work”; and the “exact

length of a fatty acid and *whether a carboxylic acid were present*” were “two factors [known] to impact fatty acid/albumin interactions.” Pet.57-58. By Petitioner’s logic, the Knudsen Patent alone discloses ***at least*** 74 options: lengths from “4-40,” which can each be either monoacid or diacid. EX1012, 16:56-61 (“lipophilic substituents preferably comprises 4-40 carbon atoms...”). Even assuming POSITA would have tested only fatty acids longer than liraglutide’s C₁₆ (an assumption that Petitioner does not sufficiently support), there would still be **48** monoacids and diacids 17-40 carbons in length. And, Knudsen 2004 discloses at least **6 positions** where this fatty-acid chain could attach (EX1010, 3; *see also* Pet.63 (acknowledging “limited number of positions”)) resulting in a total **288 combinations** in just these two references.

Spacers. Petitioner asserts the spacer and its length were both result-effective variables. Pet.58. Petitioner argues “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.” Pet.58. Even crediting Petitioner’s logic that one would ignore peptide spacers (despite the Knudsen Patent ***recommending*** them as ***preferred species*** (EX1012, 18:25-33 (disclosing 36 *more* options for dipeptide spacers))), it leaves the ***entire class*** of ***PEG-like*** spacers to choose from, with *potential permutations for each spacer identified* (e.g., AEEA and ***di***-AEEA). As POSITA would have known,

there are—at a minimum—tens of thousands of different “chemically unreactive” “PEG-like” spacers. For example, WO98/32466 discloses two forms of halogenated PEGs by formula, one of which is “X-PEG-Y,” where “X” is “an activating group,” and the publication lists 42 preferred embodiments (36 activating groups and any of the six halogens), where “PEG” is “ $-(\text{-CH}_2\text{CH}_2\text{O-})_m\text{-CH}_2\text{CH}_2\text{-}$,” m is “equal or greater than 1,” and “Y” may be any of the six halogens. EX2005, 9:23-12:10. Even assuming “ m ” is 25 or less, that is 6,300 preferred embodiments just for “halogenated PEGs”—far from a “limited range of options” or a “finite number of identified, predictable solutions.” Pet.57; *KSR*, 550 U.S. at 421.

Total combinations. Conservatively, relying on a subset of Petitioner’s references and a subset of “PEG-like” spacers POSITA had to choose from, there are *millions of combinations in Petitioner’s supposedly “finite number” of options*: (25 DPP-IV options)*(288 fatty acid combinations)*(6,300 spacer choices)=45,360,000. Obvious-to-try is inapplicable here. *KSR*, 550 U.S. at 421. The law “recognizes an important distinction between combining known options into ‘a finite number of identified, predictable solutions,’ and ‘merely throwing metaphorical darts at a board’ in hopes of arriving at a successful result.” *Leo Pharm. Prods., Ltd v. Rea*, 726 F.3d 1346, 1356-57 (Fed. Cir. 2013); *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d

1063, 1072-73 (Fed. Cir. 2012); *Sanofi-Aventis Deutschland GmbH v. Glenmark Pharms. Inc., USA*, 748 F.3d 1354, 1359 (Fed. Cir. 2014); *Proctor & Gamble*, 566 F.3d at 996.

Petitioner's two cases do not support its approach. Pet.57-59. *KSR* allows an "obvious to try" approach only when there is "a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions." 550 U.S. at 421. As discussed, Petitioner does not show there were, in fact, "a finite number of identified, predictable solutions."

In Petitioner's *Application of Boesch*, 617 F.2d 272 (C.C.P.A. 1980), the court affirmed the Solicitor's conclusion finding the "optimum value of a result effective variable," the Nv value, was obvious, as the alloy was disclosed, the equation was known, and it was known a smaller Nv value was better. *Id.* at 276. That analysis does not apply here, where testing the millions of combinations of potential modifications to a protein, where the impact of each is unknown, is not simply optimizing a "result effective variable." For example, Knudsen 2001 taught modifying liraglutide's N-terminus greatly **decreased** potency, longer fatty acids **decreased** potency, and using a longer diacid **decreased** potency. EX1011, 4. Yet, unexpectedly, the combination of these changes along with a di-AEEA spacer led to **increased** potency. EX2002, 2, 5.

VIII. Grounds 1-3: Objective Evidence of Non-Obviousness

Even if, *arguendo*, Petitioner had met its burden of showing *prima facie* obviousness, Petitioner has not shown it can overcome the objective evidence of non-obviousness *that Petitioner knows of*, yet largely ignores. EX2008, 2-3; Pet.60-62; *see Merck Sharp & Dohme Corp v. Genentech, Inc.*, PGR2021-00039, Pap.10, 31, 35-38 (July 24, 2021) (denying institution where purported evidence to overcome surprising results was merely prophetic suggestion that therapies “may be synergistically combined”); *Dish Network LLC v. Sound View Innovations, LLC*, IPR2020-00969, Pap.20, 29-32 (Nov. 25, 2020); *Stryker Corp. v. KFX Med., LLC*, IPR2019-00817, Pap.10, 28-29 (Sept. 16, 2019) (“We have cautioned petitioners in prior proceedings that *petitions may be denied if they do not address known evidence of secondary considerations.*”). While PO intends, if instituted, to address Petitioner’s other misstatements and present evidence on a range of additional objective indicia that confirm ’343’s non-obviousness, here PO focuses on Petitioner’s unsupported and inconsistent *unexpected results* and *long-felt need* arguments, which are legally and factually erroneous.

1. The Results Were Unexpected

Petitioner asserts—in a grand total of three sentences—that semaglutide’s long half-life was expected in view of liraglutide (Pet.57, 60) because the general “types of modifications” Petitioner argues were known to “extend half-life,” and

any increase would differ only in “degree, not kind.” Pet.60. Not so. It is undisputed that semaglutide’s half-life is approximately **7 days: 11-15 times longer than liraglutide** and nearly **4,800 times longer than native GLP-1**. EX2002, 1; *Amgen Inc. v. Sandoz Inc.*, 66 F.4th 952, 963-64 (Fed. Cir. 2023) (finding “20-fold difference [in potency], when an otherwise two-fold difference would have been expected..., suffices to support a finding of an unexpected result”). Petitioner points to *no art* suggesting the combined modifications would result in semaglutide’s dramatic and synergistic improvement yielding an **11-15 times greater** half-life than liraglutide’s.

Neither Petitioner nor its experts even *asserts* this extent of half-life increase was predicted or expected. And Petitioner identifies no reference suggesting the proposed modifications would, in any GLP-1 analogue, *combine* to result in anything near semaglutide’s **165-hour** half-life. EX2002, 1; *Mylan*, 44-45; *see also Takeda*, 492 F.3d at 1362.

These unexpected results are commensurate with ’343’s claims, which are directed to semaglutide. *See* Pet.60. And Petitioner itself argues semaglutide’s longer half-life is a result of its claimed chemical structure. Pet.60. There is thus nexus between the unexpected results for semaglutide and ’343’s claims, which undisputedly claim semaglutide. Pet.60.

Finally, Petitioner’s suggestion (Pet.60) that unexpected results can be ignored if they are not identified in the patent or prosecution is simply *wrong*. *Forest Lab ’ys, LLC v. Sigmapharm Lab ’ys, LLC*, 918 F.3d 928, 937 (Fed. Cir. 2019); *Sanofi-Aventis Deutschland*, 748 F.3d at 1360. Indeed, unexpected results do not even need to be appreciated at the priority date, so long as they were *unexpected* then. *Id.*

Petitioner thus knew of but failed to overcome the compelling evidence of unexpected results.

2. Long-Felt Need

Petitioner asserts there was no long-felt need for semaglutide because it was “satisfied by other diabetes treatment options disclosed in the prior art.” Pet.61. But Petitioner contradicts itself: “[a]s of the priority date, other diabetes treatments faced waning interest from the scientific community—too many side effects, too little efficacy.” Pet.28. Petitioner also argues “liraglutide’s half-life allowed for at best once-daily administration, but that was inconvenient and risked patient noncompliance.” Pet.30. Petitioner’s internal contradictions belie its attempt to show obviousness.

IX. Institution Should Be Denied Under §325(d)

This is precisely the type of IPR that §325(d) and *Advanced Bionics, LLC v. MED-EL Elektromedizinische Gerate GmbH* (IPR2019-01469, Pap.6, 8-9 (Feb. 13,

2020) (precedential) (“*AB*”)) were meant to prevent. Petitioner’s references include **only** art expressly applied or considered by the Examiner, or substantially similar to and cumulative of that art. And Petitioner fails to show any error in the Examiner’s application of those references, instead conclusorily asserting she “fail[ed] to perform any sort of lead-compound analysis...” (Pet.68), which Petitioner argues would yield “liraglutide as a lead.” Pet.26. Petitioner fails to square this with its extended argument that lead-compound analysis is not even required. Pet.51-59. And substantively, the Examiner **explicitly considered and issued a rejection** based on the Knudsen Patent—a reference Petitioner itself asserts is “**specifically directed to liraglutide....**” Pet.68. Thus, Petitioner’s complaint about what the Examiner did and did not say about the Knudsen Patent is legally insufficient: it improperly “equates [a] silence in discussing relevant prior art to a material error.” *See Microsoft Corp. v. AlmondNet, Inc.*, IPR2022-01319, Pap.9, 11 (Jan. 30, 2023) (“*AlmondNet*”) (exercising §325(d) discretion where art was before Examiner, not concealed, and only argument of error was that “references in the Petition ‘were not substantively considered during [prosecution]’”); *AB*, 9. Just as the Office expressly found this art had been overcome, the Board should reject Petitioner’s obviousness arguments here resting on the same Knudsen Patent and other cumulative art. EX1004, 42-46; *Becton, Dickinson and Co. v. B. Braun Melsungen AG*, IPR2017-01586, Pap.8, 22-23 (Dec.

15, 2017) (precedential as to §III.C.5, first paragraph) (“*Becton*”); *see Motorola Mobility LLC v. Maxell, Ltd.*, IPR2022-01287, Pap.11, 16 n.8 (Feb. 2, 2023).

Revisiting the same and substantially similar art and arguments already overcome during prosecution would waste the Board’s limited resources and unfairly burden PO.

A. Advanced Bionics Part One

AB part one considers whether the same or “substantially the same” art or arguments “previously were presented to the Office” (*AB*, 8; *see Becton*, 17-18), and is satisfied here. Petitioner asserts it “provides new prior art (and testimony) never considered by the Examiner.” Pet.66. But in fact, each of Petitioner’s references was either substantively discussed and applied, expressly considered, or cumulative of references that were.

First, all Grounds rely on the Knudsen Patent (EX1012), which the Examiner affirmatively applied in an obviousness rejection. EX1004, 42-45.

Indeed, the Examiner expressly relied on the same Knudsen Patent teachings Petitioner cites here: (1) “GLP-1 analogs” with “a more protracted profile of action than the parent peptides”; (2) “modified amino acid[s]”; (3) “derivatives at Lys 26”; (4) “lipophilic substituents (B) including, e.g., HOOC(CH₂)_mCO- wherein m is an integer from 4 to 24,” including where m is 16 (*i.e.*, a C₁₈ fatty diacid); (5) “lipophilic substituents are attached to the parent by means of a spacer” that “forms

an amide bond with an amino group of the GLP-1 moiety”; and (6) “treat[ment of] diabetes and obesity.” EX1004, 42-45; Pet.19-20, 33-34 (“use of amino acid substitutions, including non-natural ones”), 34-35 (“extended... half-life,” “lipophilic group,” and “spacers”), (“lipophilic substituent was meant to extend the half-life”), 41 (“HOOC(CH₂)₁₆CO—’ (C₁₈ diacid”), 44 (“treat type-2 diabetes”), 49 (C₁₈ diacid), 58 (“spacers”); *see also* EX1003, 48 (discussing same Knudsen Patent teachings). Like Petitioner, the Examiner asserted “it would have been obvious... to select GLP-1 analogs, spacers and lipophilic substituents from amongst those taught by Knudsen... because Knudsen et al. teach such combinations produce analogs with a satisfactory protracted profile of action.” EX1004, 44 (further discussing “derivates at Lys 26”). But the Examiner correctly dropped this obviousness argument when considering the final, as-issued claim language, while Petitioner has not.

In addition to the Knudsen Patent, Petitioner’s Knudsen 2004 reference (EX1010, Grounds 1 and 3) is also cited on ’343’s face (EX1002, 2). Further, a publication (WO00/69911) claiming priority to the same provisional application as Petitioner’s Bridon reference (EX1014, Grounds 1-3) with the same di-AEEA spacer disclosures Petitioner relies on here is also expressly discussed in ’343’s specification and cited on ’343’s face. EX1002, 1 (WO00/69911), 1:35-38; EX2007, 3:1-8, 5:10-18, 52:20.

Second, Petitioner *never addresses* whether its purportedly “new” art is *cumulative* of the Knudsen Patent and the other art before the Examiner. Instead Petitioner simply asserts it is “new” and that no art “was ever identified as teaching the newly claimed di-AEEA spacer....” Pet.66. But proper *AB* part one analysis ***requires*** consideration of “[p]reviously presented art includ[ing] art made of record by the Examiner, and art provided to the Office by an applicant, such as on an ...IDS[or] in the prosecution history of the challenged patent,” along with art that is “***cumulative***” of those references. *AB*, 7-8; *Ivantis, Inc. v. Sight Scis., Inc.*, IPR2022-01533, Pap.14, 13-14 (Mar. 27, 2023) (*AB* part 1 satisfied where asserted reference cumulative of reference considered but not discussed); *Keysight Techs., Inc. v. Centripetal Networks, Inc.*, IPR2022-01421, Pap.9, 9-10 (Mar. 22, 2023); *Becton*, 22-23. Petitioner simply *failed to do so* and *AB* Part One is met for this reason alone. *Autel Intelligent Tech. Corp. v. Orange Elec. Co.*, IPR2021-01545, Pap.8, 17, 20-23, 27 (Apr. 8, 2022) (denying institution under §325(d) where petitioner failed to “persuasively identify any specific, substantial difference between [petitioner’s reference] and the Third Reexamination’s prior art”); *Darfon Elecs. Corp. v. Shipman*, IPR2022-01008, Pap.11, 14 (Dec. 2, 2022) (denying institution under §325(d), noting “Petitioner does not address whether the proffered art is cumulative...”); *Alarm.com, Inc. v. Vivint, Inc.*, IPR2022-00728, Pap.6, 20-22 (Nov. 1, 2022) (concluding art cumulative).

Further, the required analysis Petitioner omitted confirms significant overlap between Petitioner's relied-upon disclosures and the disclosures and art the Examiner expressly considered:

The Knudsen References. The lead inventor of the (cited and asserted) **Knudsen Patent** authored **Knudson 2004** (Grounds 1 and 3, cited on '343's face) and co-authored **Knudsen 2001** (Grounds 2 and 3), along with two co-inventors on the Knudsen Patent. Petitioner confirms their overlap, relying on Knudsen 2001 and Knudsen 2004 for many of the same Knudsen Patent teachings identified by the Examiner and overcome during prosecution. Pet.17-20, 22-24, 28-30 (longer half-life and treatment of type 2 diabetes), 33-34 (amino acid substitutions), 39 (spacer and fatty acid), 34-35 (spacer), 41 (C₁₈ fatty diacid), 46 (half-life, spacer, and C₁₈ fatty diacid), 49-50 (fatty diacid), 57-58 (same), 58 (spacer).

Petitioner additionally treats the Knudsen references as interchangeable, referring to and relying on Ground 1's Knudsen 2004 arguments and for Knudsen 2001 in Ground 2 (Pet.44-50), and repeatedly citing to all three together (*e.g.*, "Exs. 1010-1012" (Knudsen references), "Exs. 1010-1013" (Knudsen references and Dong), "Exs. 1010-1014" (Knudsen references, Dong, and Bridon)) as collectively supporting Petitioner's assertions. *E.g.*, Pet.27-28, 33-34, 37, 39, 63-64.

Dong. Grounds 1-3 rely on Dong for its alleged Aib⁸ teaching. Pet.5.

Petitioner never addresses whether Dong is cumulative of references considered during prosecution, but it plainly is. Petitioner acknowledges the Examiner's rejection citing Knudsen Patent in view of Larsen (EX2006) (Pet.13), stating Larsen "teach[es] GLP-1(7-37) having at least one modification consisting of, e.g., alpha-amino-isobutyric (*Aib*) **at position 8** and a lipophilic substituent." EX1004, 45-46. The rejection further states "[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to change the amino acid at position 8 of the GLP-1(7-37) analog for Aib as taught by Larsen." *Id*. And in litigation Petitioner cites another PO reference (Deacon, cited on '343's face) for the same teaching. Pet.36-37; EX2001, 2-4, 6; EX1002, 1; EX1072, 1, 4-5; EX2001, 6. Dong is cumulative.

Bridon. Bridon is also cumulative. WO00/69911, claiming priority to the same provisional as Bridon and containing the same di-AEEA spacer disclosures Petitioner relies on here, was cited on '343's face. EX1002, 1; EX1004, 7, 125, 232; EX2007, 3:1-8, 5:10-18, 52:20.

Thus, each and every reference relied on by Petitioner was either before the Examiner or cumulative of art that was. Petitioner simply ignores this, making no attempt to explain away how its Petition clearly duplicates the art and issues the Examiner already considered.

Third, Petitioner’s assertion that the arguments here are new—even if, *arguendo*, it were credited—is irrelevant and need not be reached: *AB* part one is met where art *or* arguments were previously presented. *Microsoft Corp. v. ThroughPuter, Inc.*, IPR2022-00757, Pap.10, 20 (Nov. 1, 2022). Nevertheless, Petitioner’s arguments are *not* new. Laying out substantially the same argument now followed and repeated by Petitioner, the Examiner argued the claims were obvious over the teachings of the Knudsen Patent (including the same teachings Petitioner argues) and Larsen (repeated here by Petitioner through art cumulative of Larsen), but then allowed the claims of ’343 (limited to semaglutide) over those teachings. EX1004, 25; *Gator Bio, Inc. v. Sartorius Bioanalytical Instruments, Inc.*, IPR2023-00215, Pap.19, 17-19 (June 20, 2023) (exercising §325(d) discretion where petitioner’s arguments “significantly overlap[ped] with those previously considered by the Office”).

Petitioner alleges its arguments are “new” because it applies “two distinct modes of analysis.” Pet.67. But Petitioner cites no caselaw supporting its assertion that different discussion “modes” render arguments “new” for §325(d) (Pet.67), and Petitioner’s arguments here—under both its purported lead-compound analysis and, to the extent it can be understood, its “KSR” Ground—are the same arguments addressed during prosecution, *and PO’s responses are the same*: no art taught or suggested the combination of the claimed amino acid

backbone, spacers, and fatty acid side chain. Thus, this case is different from Petitioner's *Aquestive Therapeutics, Inc. v. Neurelis, Inc.*, IPR2019-00451, Pap.8, 37-39 (Aug. 13, 2019), where the Board determined "there will likely be differences in the manner in which Patent Owner distinguishes [asserted art] from its invention due to differences in disclosure between [asserted art] and [previously presented] art." *Id.*, at 38-39. Finally, Petitioner's criticism of the Examiner's analysis as "only... a top-down approach to obviousness" looking to GLP-1 analogues and "high-level modifications" from the Knudsen Patent and Larsen is at best strikingly un-self-aware, as *this describes Petitioner's own argument* for invalidity here: a hindsight approach based on a GLP-1 analogue and a "bucket of possible options" from the Knudsen Patent and duplicative secondary art. Pet.66-67.

B. Advanced Bionics Part Two

AB part two considers whether a petitioner has shown the Office erred in a manner material to the Claims' patentability. *AB*, 8-10. "If a condition in the first part of the framework is satisfied and the petitioner fails to make a showing of material error, the Director generally will exercise discretion not to institute *inter partes* review." *Id.*, 8-9. "***If reasonable minds can disagree regarding the purported treatment of the art or arguments, it cannot be said that the Office erred in a manner material to patentability.***" *Id.*, 9.

Petitioner's *AB* part two argument rests on the unsupported assertion that "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." Pet.68.

To begin, Petitioner's "lead-compound" complaint conflicts with its own arguments that lead-compound analysis *is not required* and presents "a too-high burden" for obviousness, "**violat[ing]...*Graham* and *KSR***." Pet.51-56. Thus, according to Petitioner's own reasoning, *not* using the lead-compound analysis made it *easier* for the Examiner to *reject* '343's claims—surely not an "error" "material to patentability" under *AB* part two. Moreover, while Petitioner asserts a failure to perform lead-compound analysis Petitioner says would yield "liraglutide as a lead" GLP-1 analogue (Pet.26), Petitioner fails to square this with the Examiner's affirmative use of the same Knudsen Patent Petitioner says is "specifically directed to liraglutide..." (Pet.68) to issue a rejection based on its GLP-1 analogue teachings. Again, this is not material error. *See, e.g., AlmondNet*, Pap.9, 11; *AB*, 9 (no material error "[i]f reasonable minds can disagree regarding the purported treatment of the art or arguments").

Petitioner further argues the Examiner "should have recognized that both the Knudsen Patent and Knudsen 2004 taught a structurally similar compound

(liraglutide) to” semaglutide, and, to “fill a perceived gap,” “should have been able to identify prior art describing the routine use of di-AEEA spacers to modify liraglutide.” Pet.68-69. Again, Petitioner fails to show error, let alone material error.

To start, Petitioner ignores that, while reviewing the art (including the Knudsen Patent) in examining the broader genus claims, the Examiner was aware of semaglutide as the elected species, and thus knew the significance of prior art disclosures with alleged structural similarities to semaglutide. *E.g.*, EX1004, 41 (PO “indicat[ing various] claims ...read on *the elected species [semaglutide]*.”); Pet.12.

Petitioner also does not explain how it was material error for the Examiner to begin by considering, selecting among, and combining the broader teachings of the Knudsen Patent—which Petitioner asserts was “specifically directed to liraglutide,” but also contained a “broader disclosure of various options for different GLP-1 analogues” (Pet.68-69)—rather than starting with liraglutide alone. Here the Examiner argued starting with a GLP-1 structure from the Knudsen Patent that, in described configurations, already included features *beyond liraglutide’s* that are included in semaglutide—such as “HOOC(CH₂)_mCO- wherein m is an integer from 4 to 24” including where m is 16 (*i.e.*, a C₁₈ fatty diacid)—and then combining with Larsen, which disclosed an Aib⁸ substitution.

EX1004, 42-46. *Supra*, §IX.A. Tellingly, Petitioner (by starting, instead, with liraglutide) found itself arguing a POSITA would have had to ***borrow and add to liraglutide this same C₁₈ fatty diacid disclosure from this other GLP-1 structure*** the Examiner relied on as her starting point in the Knudsen Patent. Pet.41.

Whether starting with these broader teachings of the Knudsen Patent with more of semaglutide's features or, instead, just liraglutide, no art disclosed "the routine use of di-AEEA spacers *to modify liraglutide*." Pet.69. Petitioner does not identify *even a single reference* that disclosed "modify[ing] *liraglutide* with a di-AEEA spacer." Pet.69. Petitioner's Bridon reference, its only reference disclosing di-AEEA, discloses its use with GLP-1 (none with an Aib⁸ substitution) or its derivative exenatide and is directed to a very different approach to extending half-life—*e.g.*, (1) its di-AEEA spacer is linked to a different amino acid location (37 rather than 26); (2) it does not disclose a γ -Glu spacer (as in semaglutide); (3) its di-AEEA spacer is bound to a maleimide (not a fatty acid, as in semaglutide); and (4) maleimide creates a covalent bond to albumin (rather than reversibly binding to albumin as does semaglutide's C₁₈ diacid). *Supra*, §VI.B.2.b.

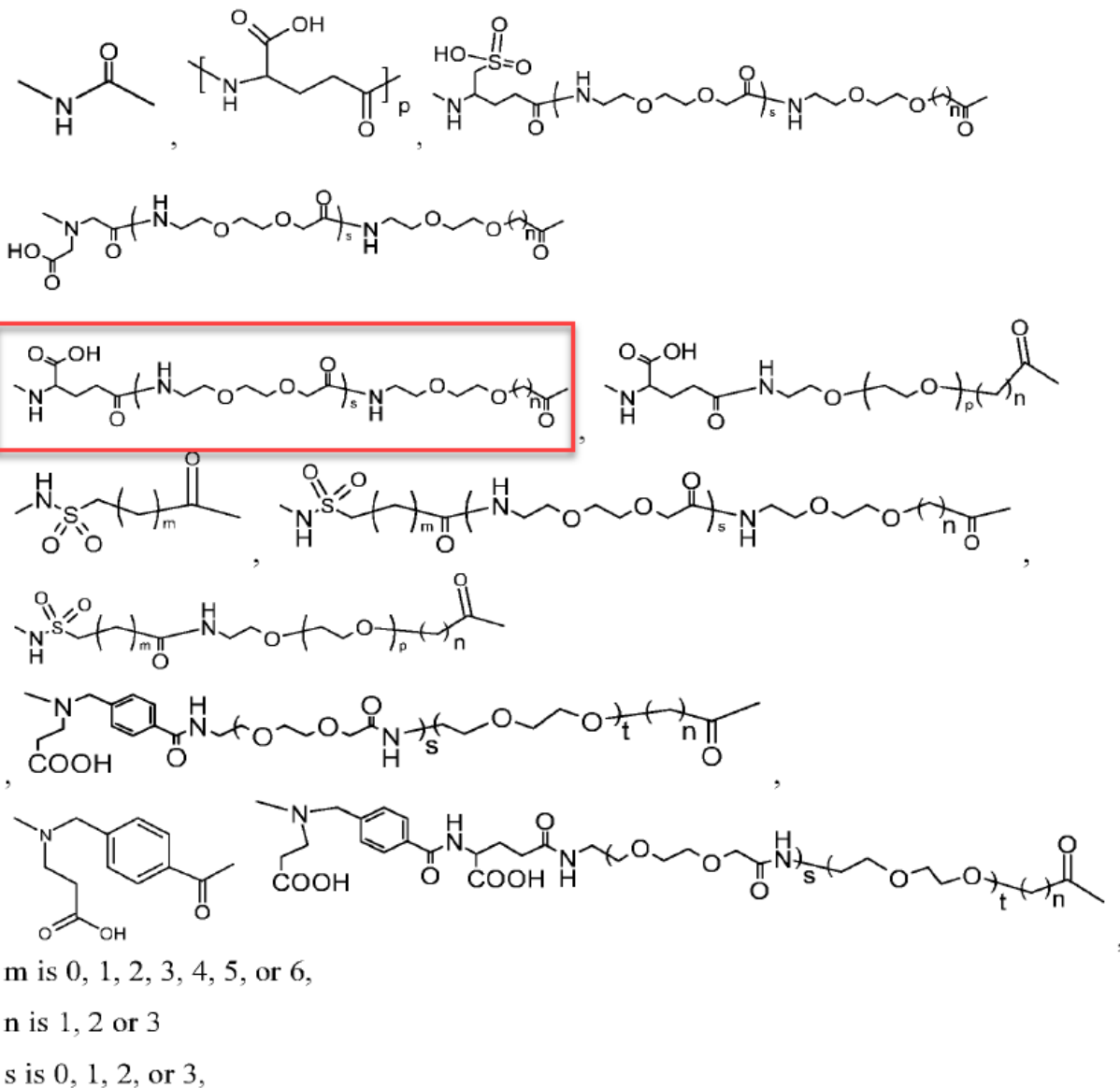
Furthermore, Bridon is cumulative of WO00/69911, which has the same di-AEEA spacer teachings and is discussed in '343's specification. *Supra*, §IX.A; EX1002, 1:35-38. Petitioner provides no evidence WO00/69911 was "overlooked"; it simply disagrees with the Examiner's conclusion that semaglutide

was not obvious in view of disparate teachings from multiple references disclosing GLP-1 analogues. *AlmondNet*, Pap.9, 11 (exercising §325(d) discretion where art was before Examiner, not concealed, and only argument of error was that references in “Petition ‘were not substantively considered during [prosecution]’”); *Monolithic Power Sys., Inc. v. Volterra Semiconductor LLC*, IPR2020-01348, Pap.19, 11-13 (Mar. 4, 2021) (exercising §325(d) discretion, noting it was “difficult to suggest that the Examiner merely ‘overlooked’” reference discussed in challenged patent’s specification); *Agrinomix, LLC v. Mitchell Ellis Prods., Inc.*, IPR2017-00525, Pap.8, 10-11 (June 14, 2017) (denying institution under §325(d) where reference “discussed in the Specification”). It was plainly not error to conclude Bridon’s disparate teachings (also in WO00/69911) were inapplicable to the analogues in the Knudsen Patent. *Supra*, §VI.B.2.b.

Petitioner’s cases are inapposite. In *Weatherford U.S., L.P. v. Eventure Global Technology, Inc.*, IPR2020-01684, Pap.16, 18-19 (Apr. 14, 2021), as Petitioner asserts, the Board found the examiner erred by overlooking art and knowledge satisfying “*amended* claimed features made to distinguish [Examiner’s cited references] and the disclosures of [additional art].” Pet.68. Here, in contrast, the Examiner made no such error in following up on an amendment: the original genus claims and elected species before the Examiner *already included* the di-

AEEA- γ -Glu spacer at issue. *See* EX1004, 78-79, 32-33; *id.*, 79:

and B and U' together is the acylated moiety, where U' is selected from



And in *10X Genomics, Inc. v. Bio-Rad Labs., Inc.*, IPR2021-00133, Pap.11, 15-19 (May 14, 2021), the Board was “persuaded” of error by petitioner’s argument the examiner “failed to reinstate [a prior] rejection when subsequent amendments to the claims during prosecution materially altered [their] scope....”

Here, in contrast, claim scope was not broadened, and the Examiner was *already aware of semaglutide as the elected species* at the time of her rejections. EX1004, 41, 68.

Petitioner has not shown any material error, and fails to meet its *AB* part two burden. *Eyenovia*, 19 (Nov. 8, 2022) (exercising §325(d) discretion, finding petitioner failed to show material error where no rejection was issued over IPR references but each was before examiner or cumulative); *Google LLC v. Valtrus Innovations Ltd.*, IPR2022-01197, Pap.9, 23 (Jan. 3, 2023) (exercising §325(d) discretion where petitioner failed to discuss with specificity how examiner erred with respect to reference); *Ivantis*, IPR2022-01533, Pap.14, 19 (exercising §325(d) discretion where “Petitioner does not sufficiently demonstrate or explain why a different conclusion should be reached based on the same disclosures in the same references that were cited during prosecution.”).

Both parts of the *AB* analysis confirm the Board should exercise its § 325(d) discretion to deny institution.

X. Conclusion

Petitioner has failed to show there is a reasonable likelihood it will prevail, and institution should be denied. In addition, or alternatively, the Board should exercise its discretion to deny the Petition under §§325(d) and/or 314.

Respectfully submitted by:

Dated: July 6, 2023

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CERTIFICATE OF WORD COUNT

The undersigned certifies that the foregoing PATENT OWNER'S PRELIMINARY RESPONSE UNDER 37 C.F.R. §42.107 complies with the type-volume limitation in 37 C.F.R. §42.24(c)(1). According to the word-processing system's word count, the brief contains 13,933 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a)(1).

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of PATENT OWNER'S PRELIMINARY RESPONSE UNDER 37 C.F.R. §42.107 has been served in its entirety by causing the aforementioned document to be electronically mailed to the following attorneys of record for the Petitioner listed below:

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