Id.; EX1009 at 47:4-9 (Example 4), 47:22-28 (Example 5), 48:12-18 (Example 6), 50:6-11 (Example 10), 50:22-28 (Example 11), 51:6-10 (Example 12), 52:12-16 (Example 15).

One basis for obviousness is choosing something from a finite number of identified, predictable solutions, with a reasonable expectation of success. Here, DiMarchi and Lau both teach a small number of fatty acids that may be used as part of the albumin binding moiety, including primarily C8, C10, C12, C14, C16, C18, and C20 fatty acids, with special emphasis on C16, C18, and C20 fatty acids, as those were all utilized in the Examples of Lau, with the same AEEA-AEEA-γGlu spacer. EX1084 at ¶173. Further, it was established in the field that increasing the length of the fatty acid chain can enhance the half-life of glucagon-like peptide derivatives. *Id*. As one example, Madsen et al. examined the impact of fatty acid chain length on the half-life and duration of GLP-1 compounds. *Id*.; *see* EX1079. Specifically, Madsen assessed various peptide derivatives, all of which were derivatized at the lysine (K) at position 26 of the native GLP-1 sequence (corresponding to position 20 of the GLP-1 agonist compound sequence, discussed previously) with a spacer and an acyl group. *Id*.; EX1079 at 6126-6127. This is the same conjugation strategy discussed in Lau and Lorenz. EX1084 at ¶173. Additionally, Madsen utilized a γ-Glu spacer in Compounds 1-6, which was attached to fatty acids of varying lengths, including C10, C11, C12, C14, C16, and C18 fatty

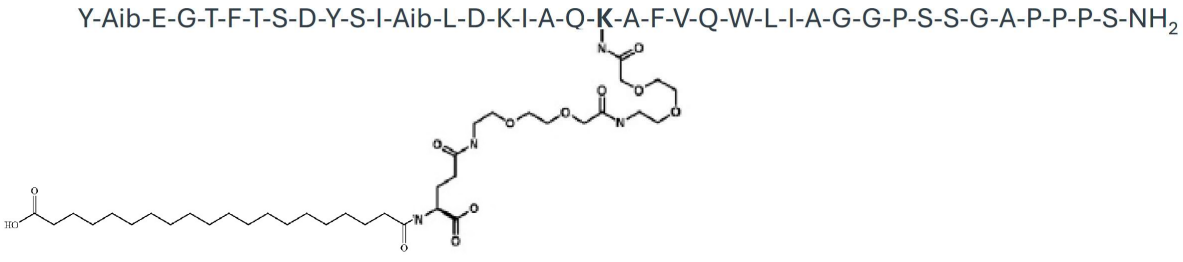
acids (corresponding to Compounds 1, 2, 3, 4, 5, and 6, respectively). EX1084 at ¶173; EX1079 at 6127. Madsen found that, as the length of the fatty acid attached to the spacer increases, the compound's half-life was prolonged, with half-life values of 0.8 hours for the C10 fatty acid; 5.1 hours for the C11 fatty acid; 7.6 hours for the C12 fatty acid; 9 hours for the C14 fatty acid; 16 hours for the C16 fatty acid; and 21 hours for the C18 fatty acid. *Id*. Consequently, a POSA would view the results of Madsen as evidence that increasing the length of the fatty acid is generally expected to prolong the half-life of the GLP-1 compounds. *Id*.

Based on the knowledge in the field, as exemplified by the disclosure of Madsen, a POSA would reasonably expect that the C16, C18, and C20 fatty acids described in Lau and DiMarchi could be utilized in the peptide rendered obvious by Alsina-Fernandez in view of DiMarchi and Lau, and that the use of any of these fatty acids would be expected to provide a prolonged half-life, similar to what was achieved with the use of a C18 fatty acid in the semaglutide compound. EX1084 at ¶174. Additionally, DiMarchi expressly explains that acylation or alkylation of the glucagon peptide "[i]ncreas[es] solubility and/or duration of action nor half-life in circulation,"[9] further supporting this expectation. *Id*.

[9] (DiMarchi), 8:12-14.

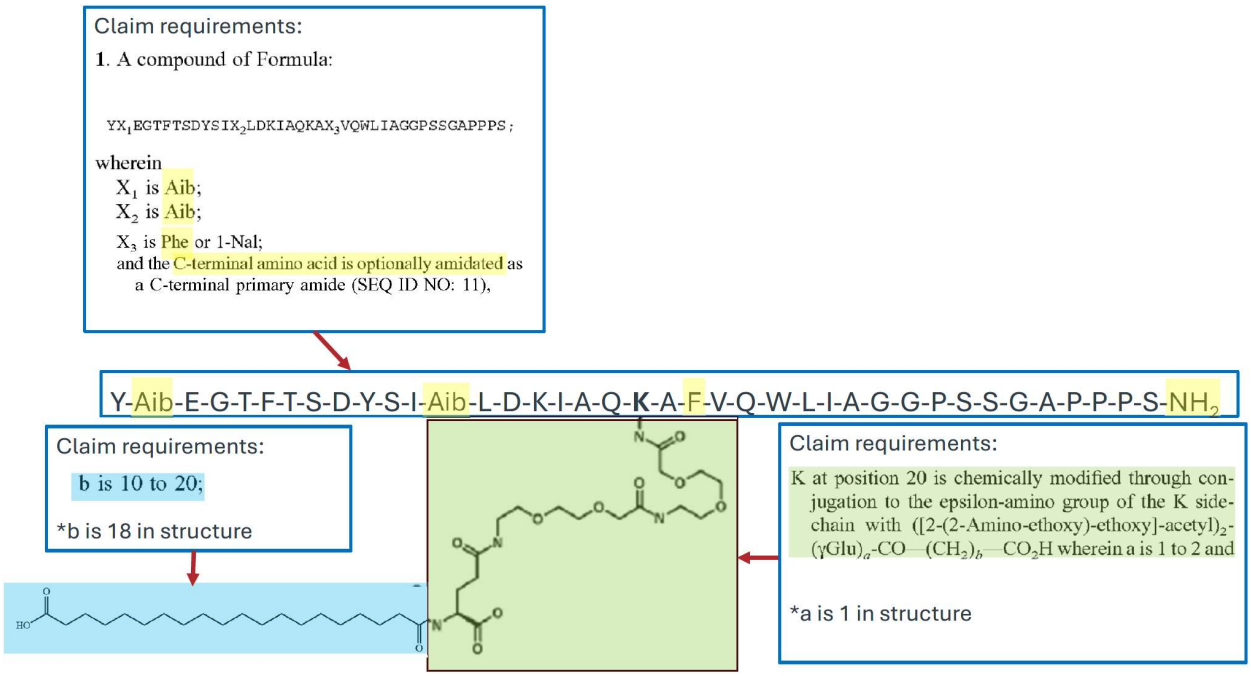
In view of these considerations, the acylation of the lysine (K) at position 20, with a spacer attached to a fatty acid (as was utilized in semaglutide) is precisely what was contemplated by DiMarchi and Lau, feeding both the motivation and reasonable expectation of success in utilizing this strategy to further modify the peptide of Alsina-Fernandez and DiMarchi. EX1084 at ¶175. Based upon the guidance provided by Lau (in view of Lorenz), and the explicit disclosure in DiMarchi discussing an acyl group attached via a spacer, a POSA would have been motivated to include the same AEEA-AEEA-γGlu spacer from semaglutide, attaching it to the amine of the lysine (K) amino acid at position 20, and using the spacer to attach a fatty acid, especially the C16, C18, and C20 fatty acids utilized in the Examples of Lau. *Id*.

To illustrate, Dr. Zhou provides the structure of the resulting peptide as understood by a POSA based on the teachings of Alsina-Fernandez in view of DiMarchi and Lau below. EX1084 at ¶176. For purposes of this illustration, Dr. Zhou included a C20 fatty acid (though the use of a C16 and/or C18 fatty acid would also be obvious design choices based on Lau):



Id.

A POSA would understand this peptide meets all the requirements of claim 1 as shown below by the annotations provided by Dr. Zhou. EX1084 at ¶177.



Id.

Accordingly, the combination of Alsina-Fernandez in view of DiMarchi and Lau renders obvious a peptide, as shown above, that meets each and every structural limitation of claim 1 as understood by a POSA. EX1084 at ¶178. In addition, a POSA would have been motivated to implement each of these substitutions/design strategies, and had a reasonable expectation of success in doing so, for all the reasons provided in the analysis above. *Id*. Therefore, claim 1 of the '780 Patent is obvious over Alsina-Fernandez in view of DiMarchi and Lau.

2. Claim 2

The compound of claim 1, wherein X_3 is Phe.

As discussed in the analysis of claim 1, the combination of Alsina-Fernandez in view of DiMarchi and Lau teaches a peptide having a Phe ("F") residue at position 22, which is the position of the claimed X_3. EX1084 at ¶¶179-181. Therefore, the proposed combination renders obvious claim 2.

3. Claims 4-6

Claim 4 - The compound of claim 2, wherein b is 14 to 18.

Claim 5 - The compound of claim 4, wherein b is 16 to 18.

Claim 6 - The compound of claim 5, wherein b is 18.

As discussed with respect to claim 1, the proposed combination teaches a peptide having a fatty acid attached to the AEEA-AEEA-γGlu spacer with a C20 fatty acid. When the peptide includes a C20 fatty acid, the "b" value for peptide is 18, corresponding to the 18 methylene units present in the C20 fatty acid. EX1084 at ¶¶1184, 188, and 192. Therefore, the proposed combination renders obvious claims 4, 5 and 6 as they all include "b" being 18 within their respect claim scope. *See* EX1084 at ¶¶182-185 (claim 4); ¶¶186-189 (claim 5) and ¶¶190-193 (claim 6)

4. Claim 7

The compound of claim 4, wherein a is 1.

As discussed with respect to claim 1, the proposed combination teaches a peptide having a [2-(2-amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu) spacer conjugated to the amino group side chain of the lysine (K) at position 20 of the sequence, meaning that there is a single γ-glutamyl group, and the "a" value for this compound is 1. EX1084 at ¶¶194-197. Therefore, the proposed combination renders obvious claim 7.

5. Claim 9

The compound of claim 4, wherein the C-terminal amino acid is amidated as a C-terminal primary amide.

As discussed previously, claim 4 is rendered obvious. Further, as discussed with respect to claim , the proposed combination teaches a peptide whereby the C-terminal amino acid is amidated as a C-terminal primary amide (-NH_2). EX1084 at ¶¶198-201. Therefore, the proposed combination renders obvious claim 9.

6. Claim 10

The compound of claim 1, wherein

X1 is Aib

X2 is Aib;

K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)2-(γGlu)1-CO—(CH2)18—CO2H;

X3 is Phe;

and the C-terminal amino acid is amidated as a C-terminal primary amide (SEQ ID NO: 3),

or a pharmaceutically acceptable salt thereof.

Claim 10 only varies from claim 1 in that the ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)$_1$ is limited to a single compound (i.e., "a is 1"); the number of methylene groups in the -CO-$(CH_2)_{18}$-CO_2H fatty acid limited to 18 (i.e., "b is 18"); and the C-terminal amino acid is amidated as a C-terminal primary amide (as opposed to the C-terminal being optionally amidated in claim 1). EX1084 at ¶204. For the same reasons provided above with respect claim 7 (requiring that "a is 1"), claim 6 (requiring that "b is 18"), and claim 9 (requiring that "the C-terminal amino acid is amidated as a C-terminal primary amide"), the proposed combination renders obvious claim 10. EX1084 at ¶¶202-205.

7. Claim 12

A pharmaceutical composition comprising the compound of claim 10 with a pharmaceutically acceptable carrier, diluent, or excipient.

The compound recited in claim 10 is obvious as discussed above. In addition, Alsina-Fernandez, DiMarchi, and Lau each expressly teach the peptide compounds described in their respective references would be developed as pharmaceutical formulations with a pharmaceutically acceptable carrier, diluent or excipient. EX1084 at ¶¶206-208; EX1007 at 5:4-5; EX1009 at 32:24-29; EX1017 at 17:22-23. Consequently, a POSA would have known to develop the peptide resulting from the combination of Alsina-Fernandez in view of DiMarchi and Lau as a pharmaceutical composition comprising the peptide and a pharmaceutically acceptable carrier, diluent or excipient, and would have had at least a reasonable expectation of success in doing so as this is standard practice in this field of art. EX1084 at ¶209. Indeed, it was already known that other similar peptides (e.g., exenatide, liraglutide, lixisenatide, semaglutide, etc.) had been successfully developed and approved by the FDA as pharmaceutical compositions. EX1084 at ¶¶143-144.

Therefore, the proposed combination renders obvious claim 12.

8. Claim 13

A method of treating type 2 diabetes mellitus, comprising administering to a patient in need thereof, an effective amount of the compound of claim 10.

The compound recited in claim 10 is obvious as discussed above. Alsina-Fernandez, DiMarchi and each expressly teach the peptide compounds described in their respective references would be administered for the treatment of diabetes mellitus. EX1084 at ¶¶211-213; EX1007 at 3:32 to 4:3; EX1009 at 38:3-4; EX1017 at 97:8-19. Consequently, a POSA would have administered an effective amount of the peptide resulting from the combination of Alsina-Fernandez in view of DiMarchi and Lau to a patient for the treatment of diabetes mellitus, and would have had at least a reasonable expectation of success in doing so. EX1084 at ¶¶214-215.

Therefore, the proposed combination renders obvious claim 13.

9. Claim 14

The method of claim 13, further comprising administering simultaneously, separately, or sequentially in combination with an effective amount of one or more agents selected from metformin,

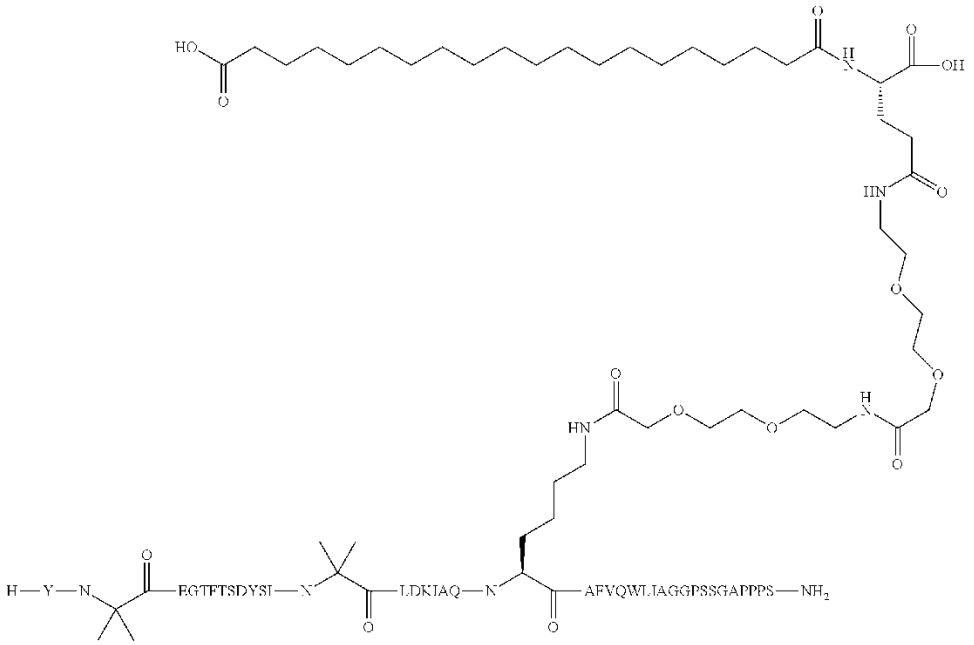
thiazolidinediones, sulfonylureas, dipeptidyl peptidase 4 inhibitors, and sodium glucose co-transporters.

The method recited in claim 13 is obvious as discussed above. Alsina-Fernandez teaches that his compound can include "other therapeutic agents" in addition to the GIP/GLP-1 peptide and that "[c]urrent treatment for diabetes includes insulin secretagogues, such as sulfonylureas." EX1084 at ¶¶216-219; EX1007 at 1:30-32 and 5:18-21. Further, DiMarchi teaches his peptide may be administered with other agents including "sulfonylureas," "biguanides such as metformin," or "thiazolidinediones." EX1017 at 100:23-30. Consequently, a POSA would have known additional therapeutic agents could be administered to a patient with type 2 diabetes mellitus with the peptide resulting from the combination of Alsina-Fernandez in view of DiMarchi and Lau including sulfonylureas, metformin, and thiazolidinediones, and would have had at least a reasonable expectation of success in doing so. EX1084 at ¶¶220-221

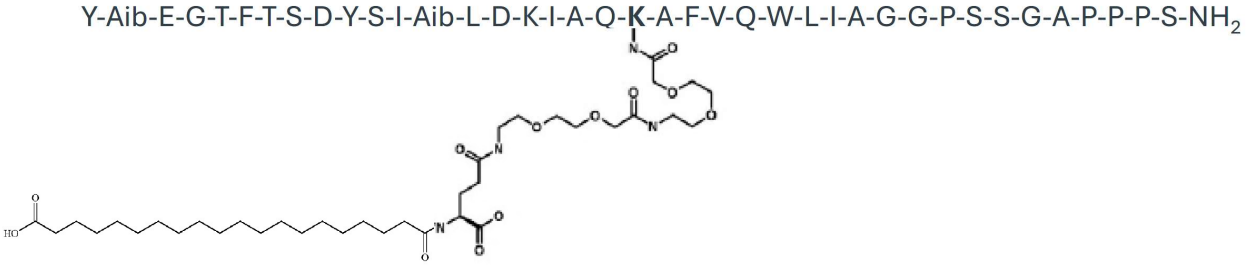
Therefore, the proposed combination renders obvious claim 14.

10. Claim 15

The compound of claim 1, wherein the Formula is:



As discussed in the analysis of claim 1, the resulting compound of the combination of Alisina-Fernandez, DiMarchi and Lau would have the following structure:



EX1084 at ¶¶222-224. While the orientation and labeling of the peptide in the illustration of this compound is different than what is provided in claim 15, a POSA

would know that this peptide is the same compound with the same chemical structure as what is recited in claim 15. EX1084 at ¶¶225-226.

11. Claims 16-18

> **16. A pharmaceutical composition comprising the compound of claim 15 with a pharmaceutically acceptable carrier, diluent, or excipient.**
>
> **17. A method of treating type 2 diabetes mellitus, comprising administering to a patient in need thereof, an effective amount of the compound of claim 15.**
>
> **18. The method of claim 17, further comprising administering simultaneously, separately, or sequentially in combination with an effective amount of one or more agents selected from metformin, thiazolidinediones, sulfonylureas, dipeptidyl peptidase 4 inhibitors, and sodium glucose co-transporters.**

Claims 16-18 are identical to claims 12-15 except that they depend from, and are directed to the administration of, the compound of claim 15, rather than the compound of claim 10. As already addressed, claims 10 and 15 are obvious over Alsina-Fernandez in view of DiMarchi and Lau. Consequently, claims 16-18 are obvious for the same reasons as stated for claims 12-15. *See* EX1084 at ¶¶227-231 (claim 16), ¶¶232-236 (claim 17) and ¶¶237-242 (claim 18).

XI. SECONDARY CONSIDERATIONS

The ’780 Patent does not provide evidence on its face or during prosecution of any secondary considerations to a POSA of non-obviousness that overcomes the prima facie obviousness of the Challenged Claims. EX1084 at ¶¶243-245.

The ’780 Patent states that “there remains a need” to provide a “balanced co-agonist” of GIP and GLP-1 receptors that is also selective against related glucagon receptors to provide weight loss. EX1001 at 2:27-33. However, a POSA would have recognized that is contrary to the other disclosure of the ’780 Patent, which explicitly cites to previous patent applications describing balanced co-agonists of GIP/GLP-1 also being selective against glucagon, including Alsina-Fernandez. EX1084 at ¶246; EX1001 at 1:55-57. As discussed with respect to claim 1, Alsina-Fernandez Example 2 provides a strong (picomolar) binding affinity for both GIP binding (*see* Ki value reported in Table 1 of 0.023 nM) and GLP-1 binding (*see* Ki value reported in Table 2 of 0.059 nM), while at the same time providing a substantially lower binding affinity for the glucagon receptor (*see* Table 3, reporting a Ki value of >23,600 nM). EX1007 at 13:6-10, 14:32-15:4, 16:22-25. A POSA would recognize that the similar binding affinities for GIP and GLP-1 (0.023 nM and 0.059 nM, respectively) represent a “balanced” co-agonism of GIP and GLP-1. EX1084 at ¶246. Alsina-Fernandez also states that GIP and GLP-1 co-agonist peptides described therein can be used for weight loss. EX1007 at 4:10-12, 4:23-24.

Consequently, the alleged "need" within the art was previously taught by the Alsina-Fernandez reference cited in the background of the '780 Patent. EX1084 at ¶246.

The '780 Patent also states that a need remained to provide a balanced GIP/GLP-1 co-agonist compound that delivers adequate stability against DPP-IV with low immunogenicity that supports once-weekly dosing. EX1001 as 2:34-41. However, the prior art disclosed known strategies to achieve these very outcomes. EX1084 at ¶247. DiMarchi teaches that adding a C-terminal extension peptide, such as GGPSSGAPPPS at the 29 position had previously been successfully appended to GLP-1 compounds to improve their potency and metabolic stability without inducing undue immunogenicity. *Id*; *see* EX1070 at Abstract; EX1071 at 1700-1701, Abstract. This same C-terminal motif GGPSSGAPPPS was also found in the FDA-approved GLP-1 receptor agonist exenatide, and associated with reduced clearance, improvement in half-life, and less susceptibility to undesirable DPP-IV cleavage. *Id*.; *see, e.g*., EX1053; EX1054,. Therefore, a POSA would not consider these features to be an unmet need. EX1084 at ¶247.

Moreover, it was also known in the art that GLP-1 compound semaglutide had a ~160 hour half-life allowing for once weekly dosing. EX1084 at ¶248; EX1076 at 4014. As discussed previously, Lau disclosed strategies to achieve this prolonged duration by conjugating fatty acids to a lysine at position 20. EX1084 at ¶248. Consequently, a POSA would not consider this to be an unmet need in the art. *Id*.

Additionally, Dr. Zhou reviewed all of the data provided in the '780 Patent, and concluded that, while the '780 Patent provides several comparisons to the semaglutide compound, by the '780 Patent's own admission, semaglutide is not a co-agonist of GIP and GLP-1 (but rather is selective for the GLP-1 receptor). EX1084 at ¶¶249-259; EX1001 at 8:23-26. Thus, none of the assessments provided in the '780 Patent compare the example peptides to the closest prior art, namely other GIP/GLP-1 receptor co-agonists despite the '780 Patent's admission the inventors were aware of other GIP/GLP-1 receptor co-agonists (including Alsina-Fernandez). EX1084 at ¶252; EX1001 at 1:55-57. At best, the data provided by the '780 Patent indicates that the claimed peptide compounds can be utilized as co-agonists of GIP and GLP-1, and generally provided binding affinities and other metabolic properties similar to those achieved with semaglutide. EX1084 at ¶260. However, none of the data in the '780 Patent demonstrates any unexpected result, much less any difference in kind, as compared to the closest prior art (i.e., other co-agonists of GIP and GLP-1). *Id*.

Additionally, to the extent that the co-agonists of GIP/GLP-1 described in the '780 patent provides any alleged "synergism," this synergism was expected based on the teachings of DiMarchi ("[i]n vivo data disclosed herein demonstrate that the combination of GIP agonist activity with GLP-1 agonist activity produces a greater effect on weight reduction than GLP-1 alone") and Finan ("co-agonism at

both of the receptors for the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)…[t]his unimolecular dual incretin…demonstrated enhanced antihyperglycemic and insulinotropic efficacy relative to selective GLP-1 agonists[,] [and] this superior efficacy translated across rodent models of obesity and diabetes"). EX1084 ¶261; EX1017 at 2:19-21; EX1061 at abstract.

Therefore, there is no evidence of secondary considerations overcoming the prima facie obviousness of the Challenged Claims. EX1084 at ¶262.

XII. CONCLUSION

Claims 1-2, 4-7, 9-10, 12-18 of the '780 Patent are obvious and Petitioner requests these claims be canceled.

Dated August 4, 2025,

Respectfully submitted,
/James P. Murphy/

James P. Murphy
Reg. No. 55,474
Polsinelli PC
1000 Louisiana Street
Suite 6400
Houston, Texas 77002
Tel: (713) 374-1600

Corey Casey
Reg. No. 66,950
Polsinelli PC
900 West 48th Place
Suite 900
Kansas City, Missouri 64112
Tel: (816) 572-4439
Attorneys for Petitioner

CERTIFICATE OF SERVICE UNDER 37 CFR § 42.6(e)(4)

The undersigned hereby certifies that a copy of the accompanying Petition for *inter partes* review, all accompanying exhibits, and the Power of Attorney is being served via FedEx Priority Overnight to the correspondence address of record for U.S. Patent No. 9,474,780 on August 4, 2025, upon the following:

Eli Lilly & Company
Patent Division
P.O Box 6288
Indianapolis, IN 46206-6288
United States

/Ericka McNeil/
Ericka McNeil
Polsinelli, PC
1000 Louisiana Street, Suite 6400
Houston, Texas 77002
Tele: (713) 374-1600