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 IPR2023-00724
Patent 10,335,462

PATENT OWNER'S RESPONSE

PROTECTIVE ORDER MATERIAL

Exhibit	Description
EX2033	September 24, 2012 NN9535-3819 Clinical Trial Report (produced as NN-OZEM-000064989) [UNDER SEAL]
EX2034	September 19, 2011 NN9535-3819 Safety Committee Meeting (produced as NN-OZEM-004435305) [UNDER SEAL]
EX2035	September 18, 2011 email from Lisbeth Vesterg Jacobsen to Christine Jensen (produced as NN-OZEM-004435304) [UNDER SEAL]
EX2036	NN9535-3819 CTR Workflow (produced as NN-OZEM-004437994) [UNDER SEAL]
EX2037	--intentionally omitted--
EX2038	March 11, 2010 email from Anne Flint to Nilas Ohrner, copying Christine Jensen (produced as NN-OZEM-004442969) [UNDER SEAL]
EX2039	March 11, 2010 draft Semaglutide Dose selection for phase 3 presentation (produced as NN-OZEM-004442970) [UNDER SEAL]
EX2040	November 26, 2010 draft Clinical Trial Protocol for NN9535-3819 (produced as NN-OZEM-004434630) [UNDER SEAL]
EX2041	November 26, 2010 email from Anne Flint to Christine Jensen et al (produced as NN-OZEM-004434628) [UNDER SEAL]
EX2042	--intentionally omitted--
EX2043	--intentionally omitted--
EX2044	--intentionally omitted--
EX2045	--intentionally omitted--
EX2046	May 20, 2010 DPComm Summary Sheet (produced as NN-OZEM-004338873) [UNDER SEAL]
EX2047	May 28, 2010 DPComm Clipping (produced as NN-OZEM-004338872) [UNDER SEAL]
EX2048	Drug Product Semaglutide B, 1.34 mg/ml, Description and Composition of the Drug Product [UNDER SEAL]
EX2049	Declaration of Devraj Chakravarty
EX2050	Declaration of Christine B. Jensen, Ph.D. [UNDER SEAL AND REDACTED COPIES]
EX2051	Declaration of Anne Flint [UNDER SEAL AND REDACTED COPIES]
EX2052	Declaration of Chloe Jiang
EX2053	Declaration of Smita Agarwal
EX2054	Declaration of Robin S. Goland, M.D.
EX2055	Declaration of Michael J. Blaha, M.D.
EX2056	Declaration of Patrick J. Sinko, Ph.D. [UNDER SEAL AND REDACTED COPIES]

administration of the active compound to alleviate the symptoms or complications…." EX1001, 5:16-27.[6]

VI. WO421 Is Not Prior Art to At Least '462 Claims 1-3

A. Legal Standards

"[A] document is prior art only when *published before the* ***invention*** *date*." *Mahurkar v. C.R. Bard, Inc.*, 79 F.3d 1572, 1576 (Fed. Cir. 1996). [redacted]

[6] At Institution, the Board found '462's claims do "not require any particular degree of efficacy." Inst.23. Petitioner and its experts, however, rely on numerous efficacy assertions to argue criticality and obviousness. *E.g.*, Pet.32, 34, 39-41, 46-47; EX1003, ¶¶324-325, 329-330, 367-369; EX1005, ¶¶68-71, 225, 227, 232-234. PO and its experts respond to those assertions. *E.g.*, EX2010, ¶299 n.4.

would have been changed based on results received (and that would still need to be analyzed) in the same month NCT773 began. EX2010, ¶414. Petitioner also ignores that ***1.0 mg was not disclosed*** in NCT657 or NCT773. EX2010, ¶415. Instead, Petitioner "explains" that 1.0 mg was "directly between" the NCT773 0.8 and 1.2 mg doses. Pet.57. That is not how POSITA select doses (EX2010, ¶416)—it is hindsight.

Next, Petitioner repeats its Ground 4 "obvious to try" and dose optimization arguments, again citing *Copaxone* (Pet.57), which is inapposite. §VIII.DVIII.D; EX2010, ¶417.

Additionally, as to claim 3, Petitioner fails to identify any "solution" teaching. §VIII.C; EX2010, ¶418. And as to claims 4-10, Petitioner relies on its defective Ground 3 arguments without explaining whether and how POSITA would have modified NCT657 and/or NCT773 using the '424 publication, and without providing motivation to combine or REOS explanations. Pet.58; EX2010, ¶419. For the reasons discussed regarding Ground 3, Petitioner fails to show claims 2-10 are obvious. §VIII.C; EX2010, ¶420.

F. Petitioner Fails to Address Objective Evidence of Non-Obviousness of Which Petitioner Is Aware

Petitioner's hand-waving at objective indicia—of which it and the rest of the world is aware of—speaks volumes. Pet.58-59; EX2018, 129:8-131:14

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(confirming Ozempic® practices claims 1-3); EX2056, §VI (Ozempic® practices claims 1-10). '462 covers Ozempic®, a remarkably-successful, world-renowned, treatment. To the extent the Board finds Petitioner has made out a *prima facie* case of obviousness, objective evidence of non-obviousness overcomes any such showing. *Leo*, 726 F.3d at 1357-58 ("Objective indicia 'can be the most probative evidence of nonobviousness in the record, and enables the court to avert the trap of hindsight.'").

1. Nexus

Nexus is presumed where, as here, "the patentee shows that the asserted objective evidence is tied to a specific product and that product embodies the claimed features, and is coextensive with them." *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373 (Fed. Cir. 2019); *id.* at 1374 ("perfect correspondence" not required). Here, 1.0 mg Ozempic® is "essentially the claimed invention." *Id.*; *see also* EX2056, §VI (1.0 mg Ozempic® embodies claims 1-10 of '462); EX2054, ¶¶39-46; EX2018, 129:8-131:14. And any unclaimed features are not, *e.g.*, described as "critical." *Fox Factory*, 944 F.3d at 1374-75. Thus, the presumption applies.

Even if the Board were to disagree about the presumption, PO has "prove[n] nexus by showing that the evidence of secondary considerations is the 'direct result of the unique characteristics of the claimed invention.'" *Fox Factory*, 944 F.3d at

1373-74. As demonstrated by the evidence cited for each of the factors below (*see also, e.g.*, EX2054, ¶¶ 46-59, 93), PO's objective evidence here is tied to Ozempic®'s unique characteristics claimed in the '462: (1) administering semaglutide (2) once-weekly at (3) 1.0 mg (4) to treat patients with T2D. Thus, presumption or not, there is nexus.

2. Commercial Success

Demonstrating an invention's commercial value ("commercial success"), weighs in favor of non-obviousness. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1337 (Fed. Cir. 2016). Ozempic® has enjoyed ***immense*** commercial success since its 2018 launch, increasing each year and generating more than ***$19 billion in net sales*** in the U.S. *See* EX2300, ¶74. Ozempic® attained "blockbuster" status—more than $1 billion in annual sales—the first full year after launch. *See id.*. Specifically, prescriptions and dollar sales for the 1.0 mg dose of Ozempic® have generated an estimated [redacted] prescriptions from launch to November 2023, comprising have generated an estimated [redacted] of Ozempic®'s total sales and [redacted] of Ozempic®'s total prescriptions for the same time period. *Id.* ¶¶85-87.Petitioner's experts confirm Ozempic®'s commercial success. EX2019, 131:21; EX2018, 123:12-124:3.

Ozempic®'s success is despite the T2D space being extremely crowded when Ozempic® launched and being increasingly crowded as new drugs have been

introduced. *See* EX2300, ¶¶36-70 (describing drugs available in the T2D space). As of Ozempic®'s launch, over 20 non-insulin drugs were approved to treat T2D, and 6 more have been approved since. *See id.* Nevertheless, Ozempic®'s share of total U.S. dollar sales among competitor treatments continues to rise. *Id.* ¶¶75-76.

This success has been driven in substantial part by '462. Ozempic® 's promotional materials emphasize '462's benefits: efficacy, safety/tolerability, and convenience and compliance. *See* EX2300, ¶¶94-105; *see also, e.g.*, EX2302, EX2303, EX2306. The promotional efforts and expenditures for Ozempic® are [redacted] other T2D drugs that most directly compete with Ozempic® (i.e., GLP-1 agonists, DPP-4 inhibitors, and SGLT2 inhibitors) at similar points in their lifecycles. EX2300, ¶¶106-10. Nor is Ozempic®'s commercial success due to the success of other Novo Nordisk T2D products such that patients who formerly used other Novo Nordisk products (*e.g.*, Victoza®) newly began using Ozempic®. *Id.* ¶¶110-12; EX2323, 7-9; EX2315, 7-9. Finally, Ozempic®'s commercial success is not due to pricing strategies. EX2300, ¶¶113-16. Novo Nordisk priced Ozempic® [redacted] competitor products [redacted] EX2334, 74-78, and offered rebating that was [redacted]—other competitor products, EX2300, ¶115

There is also no evidence that other patents served as "blocking" patents to reduce marketplace incentives to develop the claimed inventions. *See* EX2300,

¶¶117-120. A so-called "blocking patent" is an earlier patent infringed by the practicing of a later patent that "may deter non-owners and non-licensees from investing the resources needed to make, develop, and market such a later, 'blocked' invention." *Acorda Therapeutics, Inc. v. Roxane Lab'ys, Inc.*, 903 F.3d 1310, 1337 (Fed. Cir. 2018). "[T]he mere existence …of blocking patents does not, without more, 'necessarily detract from evidence of commercial success….'" *Id.* at 1338. Here, Petitioner may assert two patents covering the compound semaglutide—'343 and '122—are blocking patents. The '343 issued only a few short months before '462's latest priority date creating only a "small window of time" that could potentially disincentivize innovation relative to the large time that existed prior. EX2300, ¶120; EX2487, 1. The '122, in turn, issued after '462's latest priority date (July 1, 2012), so cannot have disincentivized innovation leading to '462. EX2300, ¶120; EX2488, 1. Accordingly, the'343's and '122's existence do not substantially diminish the significant commercial success associated with '462, embodied by Ozempic®.

3. Unexpected Results

The ***significant reductions in HbA$_{1c}$*** and ***weight loss*** in T2D patients using Ozempic® is unexpected in comparison to previously-available medications for treating T2D, including the closest prior art—other GLP-1 analogues (or, as Petitioner seems to suggest, semaglutide *but with no data*). EX2054, ¶¶57-76.

Allgenesis Biotherapeutics, Inc. v. Cloudbreak Therapeutics LLC, IPR2020-01438, Pap.29, 73-77 (Feb. 15, 2022) (comparative efficacy and safety data between claimed and prior art methods demonstrated unexpected results). Once-***weekly 1.0 mg*** Ozempic® provides superior HbA_{1c} ***and*** weight loss as compared to once-***daily*** liraglutide at 1.2 or 1.8 mg.[45] EX1001, Figs. 1, 5; EX2054, ¶¶61-63, 65, 76; *Amgen Inc. v. Sandoz Inc*., 66 F.4th 952, 964 (Fed. Cir. 2023) Ozempic® was also superior for glucose control and weight loss versus ***higher doses of other once-weekly*** GLP-1 analogues—dulaglutide (0.75 and 1.5 mg) and exenatide ER (2.0 mg). EX2054, ¶¶65-73. POSITA would not have expected these superior outcomes using '462's claimed method. *Id.* ¶¶74-78. Indeed, before '462's invention POSITA would have expected these weight loss results to be possible ***only with bariatric surgery***. *Id.* ¶77. And Ozempic® was far superior in HbA_{1c} reduction versus other T2D treatments, including insulin, and weight loss—and most other therapies caused ***weight gain***. *Id.* ¶¶50-59, 64-65, 40-49.

In addition to the HbA_{1c} reduction and weight loss results, treatment of diabetes with 1.0 mg once-weekly semaglutide has also demonstrated both ***unexpected kidney protective benefits*** and ***unexpected cardiovascular benefits***—

[45] These results were also surprising and unexpected for semaglutide, for which *no* prior results were available. EX2011; EX2054, §§VIII.A, VIII.F.3.

neither of which were known prior to ’462. *See* EX2011, ¶¶44-46, 57; EX2055, ¶¶33, 39, 44; EX2056, §VII. These results would not have been expected as there was ***no data*** regarding kidney protection or cardiovascular outcomes for semaglutide at this dose and administration until well after any priority date for ’462.

Clinical trial data comparing 0.5 mg once-weekly semaglutide, 1.0 mg once-weekly semaglutide, and 1.8 mg daily liraglutide in T2D patients revealed “the largest magnitude of [***kidney***] protective effects [was] observed for semaglutide 1.0mg.” EX2015, 8; EX2011, ¶¶47-51; EX2056, §VII. Further trials evaluating 1.0 mg once-weekly semaglutide showed surprising results with impressive reductions in several markers of chronic kidney disease. EX2011, ¶¶52-56. And although some kidney disease markers likely improved via reduction in HbA_{1c}, body weight, and blood pressure, there is *additional* benefit from the claimed method that “does not appear to be explained or accounted for by changes in these parameters alone.” EX2013, 9; EX2011, ¶¶55-56. Most recently, Novo ***stopped a Phase IIIb trial*** directed to effects of semaglutide on ***kidney*** outcomes ***due to the superior efficacy*** of 1.0mg once-weekly semaglutide versus placebo. EX2011, ¶¶58-62; EX2056, §VII. The trial was stopped because patients receiving 1.0mg once-weekly semaglutide had ***such*** unexpected improvements that it would have

been ***unethical*** to continue administering placebo to patients in the placebo arm. *Id.* ¶¶62-63. Such stoppage is "very rare." *Id*.

1.0 mg once-weekly semaglutide also remarkably demonstrated superiority as compared to placebo on ***cardiovascular*** *endpoints* in a clinical trial designed simply to show cardiovascular <u>*safety*</u> for 1.0mg once-weekly subcutaneous semaglutide. EX2055, ¶¶34-36; EX2056, §VII. Once-weekly semaglutide showed a 26% reduction in major adverse cardiovascular events (MACE), including a statistically significant 39% decrease in nonfatal stroke. *Id.* (citing EX2101, 8-10). For 1.0mg once-weekly semaglutide specifically, the MACE reduction was 29% (p=0.06). *Id.* ¶37 (citing EX2102, 44). This MACE reduction was particularly notable compared to the already-impressive 13% reduction in MACE seen with 1.8mg daily liraglutide, the allegedly closest prior art.[46] *Id.* ¶38. Further, the reduction in nonfatal stroke appears *more robust (and clinically relevant) for semaglutide*. *Id.* ¶38 (citing EX2110, 2); *see also id.* ¶41. These results were also surprising and unexpected in view of previously-completed research with DPP-4 inhibitors which had shown ***no*** benefit to reduction in MACE. *Id.* ¶43 (citing EX2105, 2, 11).

[46] *See* n.36.

The clinical trial data also trended towards ***greater benefit for 1.0mg once-weekly semaglutide*** in the components of MACE. Most notably, the data show a 38% reduction in myocardial infarction with the claimed dose (p=0.09) versus a 12% reduction with 0.5 mg once-weekly semaglutide (p=0.62). *Id.* ¶37 (Blaha) (citing EX2102, 45-47). The claimed dose also showed more benefit on other intermediate cardiovascular outcomes that are highly important in everyday clinical practice. *Id.* (citing EX2102, 101-04). The cardiovascular outcomes benefits seen with the claimed dose are unlikely to be explained solely by reduction in HbA1c, blood pressure, or weight, and were seen across essentially all subgroups of patients—regardless of baseline BMI, gender, age, or cardiovascular risk. *Id.* ¶¶40, 42; EX2110, 3-6; EX2111, 3; EX2100, 3, 9-10.

Thus, across HbA1c and weight loss, chronic kidney disease, and cardiovascular outcomes, 1.0mg once-weekly semaglutide has demonstrated surprising and unexpected results, underscoring nonobviousness.

4. Long-Felt Need

Prior to ’462 and Ozempic® there was a long-felt need for a safe, effective, and tolerable once-weekly T2D treatment that significantly reduced HbA_{1c} and caused significant weight loss, an important treatment component. EX2054, ¶¶79-83, 40-58; *see also* EX1003, ¶323 (“semaglutide was an option that would be

provided as a once weekly injection, a significant improvement in the eyes of patients"); EX1005, ¶¶ 80-81 (discussing "[f]urther research"; "once weekly dosing for GLP-1 receptor agonists ***in development… could*** 'improve compliance, and… offer an improved throughout-the-day glycemic control compared with the currently available GLP-1R agonists (exenatide and liraglutide)'" and "'[n]ausea may best be avoided by a long half-life…'"), 262 ("GLP-1-receptor agonists, such as… liraglutide, produced gastrointestinal problems at higher doses."). Many available therapies were effective at lowering blood sugar but caused weight gain. EX2054, ¶80. And the then-available GLP-1 analogues did not cause weight loss that meaningful impacted T2D, and had, *e.g.*, lack-of-adherence or insufficient blood sugar management issues. *Id.* ¶¶81-82. Ozempic® satisfied this long-felt need. *Cyclobenzaprine*, 676 F.3d at 1082-83; EX1003, ¶323 ("once weekly injection [was] a significant improvement in the eyes of patients"); EX2018, 20:2-21:14 (Bantle); EX2010, ¶¶178-191.

5. Industry Praise

Ozempic® is now a household name. EX2080. It has been widely praised by patients, clinicians, prominent medical journals, and the media—all of which evidence nonobviousness. *Lassen Therapeutics 1, Inc. v. Singapore Health Servs. Pte Ltd.*, PGR2019-00053, Pap.10, 33-36 (Feb. 6, 2020). Ozempic®'s trial results have been praised in numerous medical journals, including the Lancet Diabetes

Endocrinology. *See* EX2082; EX2083; EX2084; EX2085; EX2101; EX2054, ¶¶84-85, 62-74. And the *New Yorker* and *NY Times* published prominent articles describing the impact Ozempic® has had on medicine. EX2080, 1; EX2081, 2; EX2054, ¶¶86-87.

Bantle confirmed that he is aware of patients praising Ozempic®, yet did not take this into account in forming his opinions. EX2018, 125:4-19.

Further, the impressive and unexpected cardiovascular outcomes discussed above in §VIII.F.3 have brought a "paradigm shift" in treating and managing T2D. EX2055, ¶¶45-46; EX2056, §VII. Clinical practice guidelines now recommend using a small set of GLP-1 receptor agonists with demonstrated cardioprotective benefits—namely semaglutide, liraglutide, and dulaglutide—in the treatment of diabetes. *Id.* ¶¶47-51 (citing EX2090, 10, 26; EX2091, 11; EX2092, 11, 14, 16; EX2087, 14 (guidelines)). The American College of Cardiology recognizes there is a "potential for clinically relevant heterogeneity within the class" based on different patient risks and concerns and specifically recommends that if a patient is being treated with once-weekly semaglutide, that the 1.0mg dose be used for cardiovascular benefit. *Id.* ¶48 (citing EX2092, 11, 14). And modeling suggests that semaglutide may provide a greater reduction in MACE among T2D patients than dulaglutide. *Id.* ¶52 (citing EX2095, 1, 5-6). This paradigm shift in treatment has been the driving force in the creation of cardiometabolic clinics staffed with

cardiologists who have the expertise to treat both T2D and atherosclerotic cardiovascular disease. *Id.* ¶53 (citing EX2088, EX2089, EX2093).

6. Skepticism

Industry skepticism weighs in favor of nonobviousness. *Neptune Generics, LLC v. Eli Lilly & Co.*, 921 F.3d 1372, 1377-78 (Fed. Cir. 2019). In 2012 there were (and still are) few once-weekly GLP-1 analogues available to treat T2D and POSITA would have been skeptical others would be approved. EX2054, ¶88. Even after Ozempic® was approved, POSITA would have remained skeptical that the reported clinical trial results would be obtainable in practice. *Id.* ¶¶89-90. Ozempic® overcame this skepticism and far exceeded its clinical trial results. *Id.* ¶¶89-92; *see also* §VIII.F.3. The industry's skepticism was misplaced.

IX. Conclusion

Petitioner has failed to show that '462 is anticipated or obvious. The patentability of '462 should be confirmed.

Respectfully submitted by: Dated: January 17, 2024

/*J. Steven Baughman*/
J. Steven Baughman (Reg. No. 47,414)