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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

MITSUBISHI TANABE PHARMA CORPORATION, *et al.*, Plaintiffs, v. SANDOZ INC., *et al.*, Defendants.	Civil Action No. 17-5319 (FLW) (DEA) (CONSOLIDATED) (Filed Electronically)

FINAL JUDGMENT

NOW THEREFORE, IT IS HEREBY ORDERED, ADJUDGED, AND DECREED that:

1. This Court has jurisdiction over Plaintiffs Mitsubishi Tanabe Pharma Corporation, Janssen Pharmaceuticals, Inc., Janssen Pharmaceutica NV, Janssen Research and Development, LLC, and Cilag GmbH International (collectively, "Plaintiffs") and Defendant Zydus Pharmaceutical (U.S.A.) Inc. ("Zydus") and the subject matter of this action.

2. For the reasons set forth in the Court's March 22, 2021 Memorandum Opinion (D.I. 243), Final Judgment is entered in favor of Plaintiffs and against Zydus on all claims and counterclaims with respect to United States Patent No. 7,943,788 ("the '788 patent"), United

States Patent No. 8,222,219 ("the '219 patent"), and United States Patent No. 8,785,403 ("the '403 patent"). The manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of Zydus's Abbreviated New Drug Application ("ANDA") products that are the subject of ANDA Nos. 210541 and 210542 before the expiration of these patents would infringe claims 12 and 20 of the '788 patent, claim 22 of the '219 patent, and claim 26 of the '403 patent. Claims 12 and 20 of the '788 patent, claim 22 of the '219 patent, and claim 26 of the '403 patent are not invalid.

3. Pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of Zydus's ANDA Nos. 210541 and 210542 shall be no earlier than the latest date of expiration of the '788, '219, and '403 patents (currently July 14, 2027), including any periods of regulatory exclusivity, such as pediatric exclusivity under 21 U.S.C. § 355a, that the U.S. Food and Drug Administration ("FDA") may deem to apply in the future.

4. Pursuant to 35 U.S.C. § 271(e)(4)(B), Zydus and its affiliates, successors, partners, officers, agents, servants, employees, and attorneys, and other persons or entities in active concert or participation with any of them, are hereby enjoined from commercially manufacturing, using, offering to sell, or selling within the United States, or importing into the United States, the products that are the subject of ANDA Nos. 210541 and 210542 until the latest date of expiration of the '788, '219, and '403 patents (currently July 14, 2027). If Plaintiffs become entitled to new regulatory exclusivities, such as pediatric exclusivity under 21 U.S.C. § 355a, Plaintiffs may apply to the Court for further relief as may be appropriate, without prejudice to Zydus's right to object to such further relief. For the sake of clarity, nothing in this Judgment prohibits activity that falls within the 35 U.S.C. § 271(e)(1) safe harbor.

5. Within five days of the entry of this Final Judgment, Zydus shall inform the FDA of this Final Judgment and that, for ANDA Nos. 210541 and 210542, a Final Judgment has been entered that claims 12 and 20 of the '788 patent, claim 22 of the '219 patent, and claim 26 of the '403 patent are infringed and not invalid. Zydus shall provide confirmation of such communication to Plaintiffs within seven days thereof.

6. As the prevailing parties in this action, Plaintiffs may seek their costs subject to Paragraphs 7 and 8 in an amount to be determined by the Clerk of Court.

7. In the event that a party appeals this Final Judgment, any motion for attorney fees and/or costs, including any bill of costs or motion that this case is exceptional under 35 U.S.C. § 285, shall be considered timely if filed and served within 60 days after final disposition of any such appeal. The responding party shall have 45 days after filing and service of any such motion to respond, and the moving party shall have 21 days thereafter to file and serve a reply.

8. In the event that no party appeals this Final Judgment, any motion for attorney fees and/or costs, including any bill of costs or motion that this case is exceptional under 35 U.S.C. § 285, shall be considered timely if filed and served within 60 days after the expiration of the time for filing a notice of appeal under Fed. R. App. P. 3 and 4. The responding party shall have 45 days after filing and service of any such motion to respond, and the moving party shall have 21 days thereafter to file and serve a reply.

9. All pending motions and other outstanding requests for relief not specifically addressed herein are DENIED. This is a final, appealable judgment.

IT IS SO ORDERED this 5th day of April 2021.

/s/ Freda L. Wolfson
FREDA L. WOLFSON
United States Chief District Court Judge

FOR PUBLICATION

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

MITSUBISHI TANABE PHARMA CORPORATION, JANSSEN PHARMACEUTICALS, INC., JANSSEN PHARAMCEUTICA NV, JANSSEN RESEARCH AND DEVELOPMENT, LLC, and CILAG GMBH INTERNATIONAL, Plaintiffs, v. SANDOZ, INC., et al., Defendants.	Civil Action No. 17-5319 (FLW) (DEA) **REDACTED & AMENDED OPINION**

WOLFSON, Chief Judge:

This consolidated action was filed by Plaintiffs, Mitsubishi Tanabe Pharma Corp. ("MTPC"), Janssen Pharmaceuticals, Inc. ("JPI"), Janssen Pharmaceutica NV ("JNV"), Janssen Research and Development, LLC ("JRD"), and Cilag GmbH International ("Cilag")[1] (collectively, "Plaintiffs") against Defendant Zydus Pharmaceuticals (U.S.A.) Inc. ("Zydus" or "Defendant") for patent infringement in violation of section 271(e)(2) of Title 35 of the United States Code. In response, Zydus has filed a counterclaim seeking a declaratory judgment against Plaintiffs that the patents-in-suit are invalid.

Defendant is alleged to infringe the following claims of the corresponding United States Patents held by Plaintiffs: (1) claims 12 and 20 of United States Patent Number 7,943,788 ("the '788 Patent"); (2) claim 22 of United States Patent Number 8,222,219 ("the '219 Patent"); and (3)

[1] The Court refers to JPI, JNV, JRD, and Cilag, collectively, as "Janssen."

claim 26 of United States Patent Number 8,785,403 ("the '403 Patent") (collectively, the "asserted claims").[2] The patents-in-suit relate to the pharmaceutical composition and method of treatment encompassed by the drugs "Invokana" and "Invokamet" (together "the Invokana Products"), which are used to treat type 2 diabetes. Plaintiffs' infringement claims are based on Zydus's filing of Abbreviated New Drug Applications ("ANDA") with the Food and Drug Administration ("FDA") seeking approval to commercially manufacture and market generic versions of the Invokana Products prior to the expiration of the patents-in-suit.[3] Zydus has stipulated that its submission of the ANDAs and any commercial manufacture, use, offer for sale, sale, or importation of the ANDA products before expiration of the patents-in-suit would infringe the asserted claims. As its defense, Zydus contends that (1) the asserted claims of patents-in-suit are invalid as obvious; and (2) claims 12 and 20 of the '788 Patent are invalid under the doctrine of obviousness-type double patenting.

The Court conducted a six-day bench trial,[4] during which numerous experts testified as to the issues of obviousness and obviousness-type double patenting. In accordance with Federal Rule of Civil Procedure 52(a), the Court sets forth herein its findings of facts and conclusions of law. After consideration of all the evidence, the Court finds that the patents-in-suit are not invalid as obvious and that claims 12 and 20 of the '788 Patent are not invalid under the doctrine of

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2 The Court refers to the '788, '219, and '403 Patents, collectively, as the "patents-in-suit."

3 Zydus has agreed not to launch the products within the scope of the ANDAs at issue, *i.e.*, the generic equivalents of Invokana and Invokamet, until four months after the parties submitted their Proposed Findings of Fact and Conclusions of Law. (ECF No. 206.) The parties submitted their Proposed Findings of Fact and Conclusions of Law on November 23, 2020. (*See* Zydus Proposed Findings of Fact and Conclusions of Law ("DFOF"), ECF No. 221; Plaintiffs' Proposed Findings of Fact and Conclusions of Law ("PFOF"), ECF No. 220.)

4 In light of the ongoing COVID-19 pandemic, the bench trial was held remotely via Zoom.

obviousness-type double patenting. Based on Zydus's concession, the Court further concludes that the filed ANDAs infringe upon the patents-in-suit.

I. OVERVIEW

A. Parties

MTPC is the lawful assignee of the patents-in-suit. (Pretrial Order, Stipulation of Facts ("SOF") ¶ 1, ECF No. 144.) JPI, JRD, and Cilag are the exclusive licensees of the patents-in-suit, and JNV is an exclusive sublicensee of the patents-in-suit. (*Id.* ¶ 8.) JPI holds approved New Drug Application ("NDA") No. 204042 for canagliflozin tablets, which are prescribed and sold as Invokana, and approved NDA No. 204353 for canagliflozin and metformin hydrochloride tablets, which are prescribed and sold as Invokamet. (*Id.* ¶ 9.) Canagliflozin is in a class of compounds known as SGLT-2 inhibitors which are used in the treatment of type 2 diabetes.

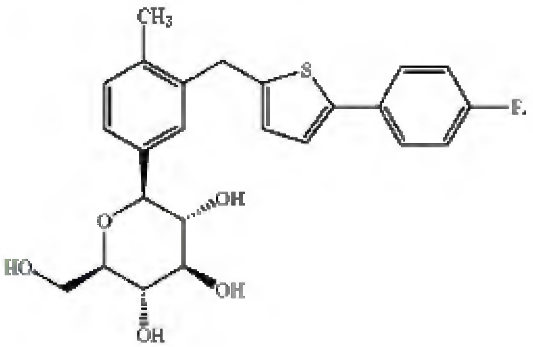
Zydus is a manufacturer and distributor of generic drugs. Zydus filed ANDA Nos. 210541 and 210542 with the FDA, seeking approval to commercially manufacture and market generic versions of the Invokana Products prior to the expiration of the patents-in-suit. (*Id.* ¶ 14.)

B. The Patents-in-Suit

1. The '788 Patent

The '788 Patent was issued by the United States Patent and Trademark Office ("USPTO") on May 17, 2011, and is entitled "Glucopyranoside Compound." (*Id.* ¶ 22; DTX-001.) The '788 Patent lists Sumihiro Nomura, Eiji Kawanishi, and Kiichiro Ueta as the named inventors. (SOF ¶ 23.) The '788 Patent was issued in connection with U.S. Patent Application No. 11/045,446 (the "'446 application"), which was filed on January 31, 2005, and was a continuation of International Application No. PCT/JP2004/011312, which was filed on July 30, 2004. (*Id.* ¶¶ 24–25.) Asserted claims 12 and 20 of the '788 Patent are directed to the compound now known as canagliflozin.

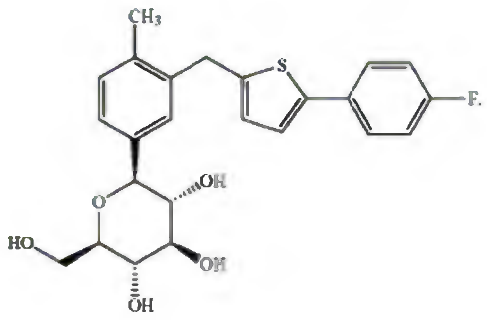
(*Id.* ¶¶ 26–27.) Specifically, claim 12 recites "1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluoro-phenyl)-2-thienylmethyl]benzene," which is the chemical name for canagliflozin. (*Id.* ¶ 26.) Claim 20 of the '788 Patent recites "[a] compound having the following structure," and depicts the chemical structure of canagliflozin:



(DTX-001, at 224:40-55.)

2. The '219 Patent

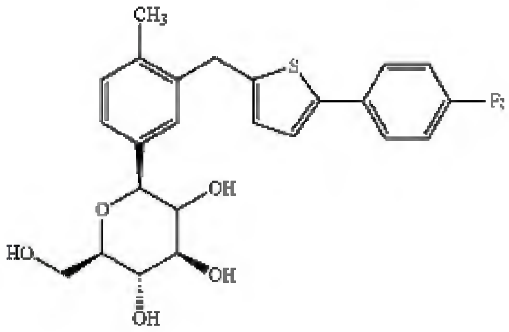
The '219 Patent was issued by the USPTO on July 17, 2012, and is titled "Glucopyranoside Compound." (SOF ¶ 28; DTX-002.) Like the '788 Patent, the listed inventors of the '219 Patent are Drs. Nomura, Kawanishi, and Ueta. (*Id.* ¶ 29.) The '219 Patent was issued in connection with U.S. Patent Application No. 13/174,814 ("the '814 application"), which was filed on July 1, 2011. (*Id.* ¶ 30.) The '814 application was filed as a division of U.S. Patent Application No. 13/005,757 ("the '757 application"), which was filed on January 13, 2011. (*Id.* ¶ 31.) The '757 application was filed as a division of the '446 application, which was issued as the '788 Patent. (*Id.*) Asserted claim 22 of the '219 Patent is directed to a method of treating or delaying the progression or onset of type 2 diabetes with the compound of the following structure, which is now known as canagliflozin:



(SOF ¶ 32; DTX-002, at 220:43-46.)

3. The '403 Patent

The '403 patent is titled "Glucopyranoside Compound" and was issued by the USPTO on July 22, 2014. (SF ¶ 33; DTX-003.) The '403 Patent lists Drs. Nomura, Kawanishi, and Ueta as the inventors. (SF ¶ 34.) The '403 Patent was issued in connection with U.S. Patent Application No. 13/494,602 (the "'602 application"), which was filed on June 12, 2012. (*Id.* ¶ 35.) The '602 application was a continuation of the '814 application. (*Id.* ¶ 36.) Asserted claim 26 of the '403 Patent is directed to a pharmaceutical composition comprising a biguanide compound and the compound of the following structure, which is now known as canagliflozin:



(SOF ¶ 37; DTX-003, at 221:25–26.)

C. The Invokana Products

Invokana, with canagliflozin as its active ingredient, was approved for use by the FDA in

March 2013. (PTX-1086.) It was the first SGLT[5] inhibitor to be approved in the United States.[6] (Williams Tr., at 1055:23–25.)[7] Invokamet was approved for use by the FDA in August 2014, and combines canagliflozin with metformin. (Brennan Dep. Tr., at 71:2–3; PTX-1085.) The Invokana Products act by inhibiting SGLT2 in the kidneys and suppressing glucose reabsorption. (*See* Bannister Demonstrative, at 7.) This leads to glucose being excreted in the urine in greater amounts, reducing blood glucose levels. (PTX-1086, at 7.) The Invokana Products also have the ability to inhibit SGLT1 and reduce the uptake of glucose from the gut. (Gavin Tr., at 757:–21.)

Clinical data has demonstrated that Invokana significantly reduces A1C, fasting plasma glucose levels, body weight, and systolic blood pressure in diabetic patients and that it is generally well tolerated. (*Id.* at 746:3–23; PTX-1086, at 9–14.) The Invokana Products are currently indicated: (1) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes; (2) to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease; and (3) to reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria. (Gavin Tr., at

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[5] SGLT refers to a sodium glucose transporter. (Bannister Tr., at 112:19–22.) SGLTs are present in the kidneys, which filter blood for the human body. (*Id.* at 112:23–24.) Waste filtered by the kidneys is generally shunted to the bladder and excreted in urine. (*Id.* at 112:25–113:3.) However, SGLTs reabsorb—or transport—glucose initially filtered by the kidney back into the blood. (*Id.* at 113:8–25.) There are two types of SGLTs—SGLT1 and SGLT2. SGLT2s are only present in the kidneys, while SGLT1s are responsible for shunting glucose in other parts of the body, including the gut and heart. (*Id.* at 114:17–22.)

[6] The FDA has since approved three additional SGLT inhibitors for use. In 2014, the FDA approved both dapagliflozin, marketed as Farxiga, and empagliflozin, marketed as Jardiance. (Williams Tr., at 1056:6–14.) In 2017, the FDA approved ertugliflozin. (*Id.* at 1056:14–16.)

[7] For ease of reference, the Court refers to the trial transcripts by the name of the expert testifying during that portion of the transcript.

743:10–19; PTX-1086, at 1; PTX-1085, at 1.)

D. Procedural History

On July 20, 2017, Plaintiffs filed the instant patent infringement action against Zydus arising from Zydus's filing of ANDA Nos. 210541 and 210542.[8] (SOF ¶ 14; ECF No. 1.) Zydus has stipulated that its submission of ANDA Nos. 210541 and 210542 to the FDA and any commercial manufacture, use, offer for sale, sale, or importation of Zydus's ANDA Products before the expiration of the patents-in-suit would infringe on the asserted claims, to the extent they are not found invalid. (SOF ¶ 17; ECF No. 100, at 2–3.) Rather, Zydus maintains that the patents-in-suit are invalid as obvious. As such, the sole issues presented at trial were (1) whether the patents-in-suit are invalid as obvious and (2) whether claims 12 and 20 of the '788 Patent are invalid for obviousness-type double patenting.

The Court held a six-day bench trial on September 24, 25, and 30; October 1 and 2; and November 5, 2020. At trial, Defendant presented four expert witnesses: Thomas T. Bannister, Ph.D.; DeForest McDuff, Ph.D.; Jonathan S. Williams, M.D., M.M.Sc.; and James T. Carmichael, Esq. Dr. Bannister was accepted without objection as an expert in molecular medicine and chemistry, drug discovery, and medicinal chemistry. (Bannister Tr., at 106:9–12, 107:18–22.) Dr. McDuff was accepted without objection as an expert in economics and commercial success. (McDuff Tr., at 406:1–3.) Dr. Williams was accepted without objection as an expert in the field

[8] This consolidated matter initially included as defendants Sandoz, Inc. ("Sandoz"), InvaGen Pharmaceuticals, Inc. ("InvaGen"), Aurobindo Pharma USA Inc. ("Aurobindo"), and Prinston Pharmaceutical Inc. ("Prinston"). The Court entered Consent Judgments of infringement with permanent injunctions lasting through patent expiration with respect to InvaGen, Prinston, and Aurobindo. (*See* ECF Nos. 99, 102, 172.) Sandoz was dismissed from this matter pursuant to a stipulation between Plaintiffs and Sandoz after Sandoz abandoned its last-remaining defense. (*See* ECF No. 129.) Sandoz, however, continues to challenge other patents covering the Invokana Products in a separate matter also proceeding in this District.

of clinical management and development of type 2 diabetes. (Williams Tr., at 1036:21–1037:24.) Mr. Carmichael was accepted as an expert in USPTO procedure. (Carmichael Tr., at 1274:19–1280:21.)

Plaintiff also presented four expert witnesses: Stephen G. Davies, Ph.D.; Raymond Sims; James R. Gavin III, M.D.; and Robert Stoll, Esq. Dr. Davies was accepted as an expert in medicinal chemistry. (Davies Tr., at 502:22–503:14.) Mr. Sims was accepted as an expert in intellectual property research and analysis regarding whether a patented product is a commercial success. (Sims Tr., at 935:14–23.) Dr. Gavin was accepted as an expert in the field of clinical management and development of type 2 diabetes treatment. (Gavin Tr., at 728:16–729:15.) Mr. Stoll was accepted as an expert in USPTO procedures, practices, and policy. (Stoll Tr., at 1194:21–1196:1.) Plaintiffs also presented testimony from Dr. Kawanishi, who is identified as the inventor of canagliflozin. (Kawanishi Tr., at 893:17–25.)

During trial, the Court denied Plaintiffs' motion for judgment as a matter of law pursuant to Federal Rule of Civil Procedure 52(c). (Trial Tr., at 432:2–3.) Limited closing arguments were presented on December 22, 2020.

II. OBVIOUSNESS

A. Findings of Fact

Because the question of obviousness is a factual question that is guided by legal principles, I make certain factual findings before setting forth my conclusions of law, *infra*. As such, this section contains the relevant factual background necessary for the Court to conduct its obviousness analysis. To the extent any finding of fact below is a conclusion of law, it is also adopted as a conclusion of law.

1. Medicinal Chemistry & Drug Discovery

Medicinal chemistry is a multidisciplinary approach which uses molecular biology, biochemistry, pharmacology, medicine, analytical chemistry, and organic chemistry to identify organic compounds that may treat diseases in humans. (Davies Tr., at 502:3–10.) In other words, the study of medicinal chemistry seeks "to understand how drug substances work." (Bannister Tr., at 112:9–11.) In that connection, the drug discovery process "is a data-driven, iterative process," that typically involves: (1) analyzing biological targets and known compounds in the prior art for a particular disease area; (2) selecting lead compounds for improvement based on known data; (3) identifying assays that can verify whether the compounds being developed have the desired effect; (4) identifying one portion of each selected compound to modify; (5) synthesizing, testing, and analyzing each modification to the selected lead compounds; (6) identifying a potentially promising compound for further biological development based on the testing results; (7) conducting further studies on that promising compound; and (8) advancing that compound to clinical development, if appropriate. (Davies Tr., at 511:4–514:9.)

The second step of that process, the selection of a lead compound, involves a discrete number of biological targets and their corresponding compounds because of limited time and resources. (*Id.* at 512:4–7, 650:15–24.) Once a lead compound is selected, the medicinal chemist investigates the effect of various structural modifications upon biological activity, usually through a lengthy, iterative, and labor-intensive program with the goal of finding an improved candidate molecule for further evaluation. (*Id.* at 512:4–513:18; Bannister Tr., at 313:21–315:8 (agreeing that "drug compound discovery is a highly iterative process" in which a medicinal chemist would "try [to] improve [a] starting compound").) The drug development process is "lengthy" because, *inter alia*, it is necessary to make modifications to one portion of the compound at a time to

determine if the change was helpful, harmful, or neutral. (Davies Tr., at 512:4–10, 514:14–21; Bannister Tr., at 314:23–315:18 (agreeing that "the goal of a medicinal chemist would be to try [to] improve [a] starting compound" by changing "one area of the molecule at a time").)

Bioisosterism, a relevant principle of medicinal chemistry, is the observation that, in certain cases, "one group of atoms take[s] the place of another group of atoms in a biologically active molecule [resulting in] roughly the same biological activity." (Bannister Tr., at 181:3–10; Davies Tr., at 655:19–25 (explaining that bioisosterism is a concept that permits you to "swap groups around in order to keep biological activity and change the other properties").) In other words, bioisosterism is the "idea that one substructure can be swapped out for another." (Bannister Tr., at 181:12–14.) The "two different collections of atoms [that can be swapped] are called bioisosteres." (*Id.* at 181:11–12.)

2. Type 2 Diabetes and its Treatment History

Diabetes mellitus, commonly referred to as "diabetes," is "a very complex and progressive metabolic disease." (Gavin Tr.,731:10.) There are four types of diabetes, the most common of which is type 2 diabetes. (*Id.* 731:11–12.) Type 2 diabetes is characterized by a state of insulin insensitivity and resistance. (Williams Tr., at 1040:25–1041:9.) While a person with type 2 diabetes may be able to produce a reduced amount of insulin, he or she will, over time, experience resistance to insulin's blood sugar-lowering action and/or inadequate functioning of β cells.[9]

Doctors diagnose type 2 diabetes through a variety of tests, including measuring blood sugar under certain conditions, such as fasting, or monitoring glycemic control "A1C" test. (Gavin Tr., at 732:17–25; Williams Tr., at 1044:9–13.) A1C is a measurement of the average blood glucose level in a patient over the previous few months. (Gavin Tr., at 732:12–736:3.)

[9] β cells are responsible for the production and release of insulin. (Gavin Tr., at 731:10–17.)

Once diagnosed, type 2 diabetes is generally treated in a stepwise manner. (Gavin Tr., at 736:9–19.) Typically, the initial recommendation is to incorporate diet and exercise into the patient's daily lifestyle. (*Id.*) Then, if necessary, a drug would be administered to control the patient's glucose levels. (*Id.*) A healthcare provider would introduce one drug at a time, beginning with metformin and then including additional agents, as necessary. (*See id.* at 736:9–737:16.) In the 2003 time-period, the most commonly used type 2 diabetes drugs included biguanides, sulfonylureas, α-glucosidase inhibitors, thiazolidinediones ("TZDs"), and meglitinides. (PTX-176, at 48–51.) However, the FDA-approved compounds in these classes of drugs each had certain shortcomings, including administration difficulties, weight gain, hypoglycemia, gastrointestinal side effects, negative psychological impact, and/or efficacy issues. (*See id.*) Accordingly, in 2003, additional tools were required to adequately manage type 2 diabetes and its complications. (*See id.*)

3. The POSA and the Problem to be Solved

The parties agree that the person of ordinary skill in the art (the "POSA") in this case would have had a graduate degree in medicinal chemistry, pharmacology, and/or a related field, with experience in the development of pharmaceutical compositions and an awareness of the antidiabetic drug field. (Bannister Tr., at 163:11–22; Davies Tr., at 516:17–21.) Additionally, a POSA would have had a "relatively low" level of creativity and would have had access to individuals having skills in chemistry and pharmacology, and would collaborate with them, as necessary. (*See* Bannister Tr., at 101:2224, 334:16–335:18; Davies Tr., at 502:510.)

Dr. Bannister and Dr. Davies further agreed that a POSA in this case would be "looking to positively alter the options for treating diabetes." (*See* Bannister Tr., at 280:11–14; Davies Tr., at 518:1–4 (explaining that the problem facing a POSA was "[t]o find an improved treatment, a better

drug, for the treatment of type 2 diabetes).)

4. Prior Art References

For the purpose of determining whether the patents-in-suit are obvious, the Court finds that the date of invention of the patents-in-suit occurred no later than October 29, 2003. (Kawanishi Tr., at 861:16–23.) October 29, 2003 is, therefore, the relevant date for determining the scope of prior art under 35 U.S.C. §§ 102(a), (e).[10] July 30, 2004, the earliest effective filing date for the patents-in-suit, is the relevant date for determining the scope of prior art under § 102(b).[11] In other words, references filed prior to July 30, 2003 may be considered prior art. *See* §§ 102(a), (b), (e). In this section, the Court discusses the key prior art references in this matter.

a) T-1095

In the 1990s, Tanabe Seiyaku ("Tanabe"), MTPC's predecessor, developed an analog of

[10] Because the patents-in-suit stem from patent applications that were filed before March 16, 2013, *i.e.*, before the passage of the Leahy-Smith America Invents Act ("AIA"), the Court refers to the pre-AIA version of 35 U.S.C. § 102. Pre-AIA section 102(a) provided that "[a] person shall be entitled to a patent unless the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent." 35 U.S.C. § 102(a) (2002). Pre-AIA section 102(e) provided that a person was not entitled to a patent if "the invention was described in (1) an application for a patent . . . by another filed in the United States before the invention by the applicant for a patent or (2) a patent granted on an application by another filed in the United States before the invention by the applicant for patent." *Id.* § 102(e).

[11] Pre-AIA section 102(b) provided that a person was not entitled to a patent if "the invention was patented or described in a printed publication in this or a foreign country or in a public use or on sale in this country, more than one year prior to the date of the application for patent in the United States." 35 U.S.C. § 102(b) (2002).

phlorizin,[12] known as T-1095, a potential anti-diabetic agent.[13] (Bannister Tr., at 125:23–26.) T-1095 is an O-glucoside, meaning that glucose is "attached through an oxygen atom to the rest of the molecule." (*Id.* at 126:3–18; *see also* Bannister Demonstrative, at 16.) According to Dr. Bannister, T-1095 was a "much improved phlorizin analog" because it remained metabolically stable. (*See* Bannister Tr., at 130:5–131:5.) As T-1095 was shown to be absorbed through the stomach, it could be given to animals orally. (*Id.* at 131:15–17.) Accordingly, "it actually became a clinical compound to be tested in humans and potentially be developed as a drug." (*Id.* at 131:17–19.)

Dr. Davies specifically observed that the T-1095 references highlighted two compounds: T-1095 and T-1095A. (Davies Tr., at 538:19–22.) Dr. Davies explained that:

> T-1095 is a prodrug for T-1095A. A prodrug is a derivative of a drug that is converted in the body to the drug itself. So where you have a compound that has good biological pharmaceutical activity but doesn't have, for example, good absorption profile, you can form what is called a prodrug. You can attach, temporarily, a group to that drug molecule that improves the, in this case, the absorption. But the body is able to, using its enzymes, take off that extra unit you put on, that temporary group you put on, to release the drug

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[12] Phlorizin is a natural compound that was shown to lower blood glucose in the 1930s. (*See* Bannister Tr., at 115:23–116:3.) Phlorizin, however, had certain limitations for use as an antidiabetic agent. (*Id.* at 118:14–17.) Notably, it needed to be injected into the blood, rather than be orally ingested, to have biological effect, and it was known to be metabolically unstable. (*Id.* at 118:14–120:15.)

[13] Tanabe's findings with respect to T-1095 are set forth in several publications, including Akira Oku, et al., *Antidiabetic ϵffect ϲf T-1095, an inhibitor ϲf Na+-glucose cotransporter in neonatally strϵptozotocin-treated rats*, 391 Eur. J. Pharmacol. 183 (2000); Akira Oku, et al., *T-1095, an Inhibitor ϲf Renal Na+-Glucose Cotransporters, May Provide a Novel Approach to Treating Diabetes*, 48 Diabetes 1794 (1999); Kenji Tsujihara, et al., *Na+-Glucose Cotransporter (SGL1) Inhibitors as Antidiabetic Agents. 4. Synthesis and Pharmacological Properties ϲf 4'-Dehydroxyphlorizin Derivatives Substituted on the B Ring*, 42 J. Med. Chem. 5311 (1999); and Kenji Tsujihara et al., *Na+-Glucose Cotransporter Inhibitors as Antidiabetics. I. Synthesis and Pharmacological Properties ϲf 4'Dehydroxyphlorizin Derivatives Based on a New Concϵpt*, 44 Chem. Pharm. Bull. 1174 (1996). The Court refers to these publications, collectively, as the "T-1095 references."

> inside the body.
>
> So in this case it shows the prodrug and the actual compound through oral administration. . . . It shows that they both induce urinary glucose excretion, and the prodrug increases it over the parent drug. So 1095 is better than 1095A, but the actual active species is the same.

(*Id.* at 538:22–539:12.) Tanabe, therefore, selected T-1095, the prodrug, "as a promising [candidate] for the treatment of diabetes." (*Id.* at 539:19–20; PTX-122, at 5314.) Indeed, as Dr. Davies observed, "[Tanabe] scientists had demonstrated that . . . long term treatment with T-1095 restored deterioration of diabetic states." (*Id.* at 633:2–6.) Further, "T-1095A had been selected for further evaluation and as a potential anti-diabetic agent and was expected to be used as therapy for patients with type 2 diabetes." (*Id.* at 636:3–12.)

b) Link

The Link reference[14] was published in 2000 and explored whether phlorizin can be made more stable by transforming it from an O-glucoside, a glucose with an oxygen linker, to a C-glucoside, a glucose with a carbon linker. (*See* Bannister Tr., at 132:9–133:8.) Link found, however, the C-glucosides were weaker than O-glucosides in terms of efficacy. (Davies Tr., at 545:14–16; *see also* Bannister Tr., at 133:21–134:1.) Accordingly, the Link authors concluded that the O-glucoside linkage was important to SGLT-inhibition activity. (Davies Tr., at 545:3–12.)

While the parties agree that the Link reference demonstrates that O-glucosides were more effective compounds, there is some disagreement as to whether Link demonstrates that C-glucosides are more metabolically stable than O-glucosides. Dr. Bannister testified that Link

[14] Link & Sorensen, *A method for preparing C-glycosides related to phlorizin*, 41 Tetrahedron Letts 9213 (2000).

demonstrated that C-glucosides were more stable because replacing an oxygen bond with a carbon bond, generally, makes the molecule more stable. (Bannister Tr., Vol. 1., at 133:12–20.) However, Dr. Bannister admitted that Link only "made what [are] presumably stable compounds" and that Link "doesn't describe the stability." (*Id.* at 136:16–18.) In that regard, Dr. Davies explained that "[t]here are many instances where replacing a CO bond with a CC bond will improve stability . . . it's not a given. It depends on what carbon bond you've made and where – where in the body you're putting the drug." (Davies Tr., at 662:14–17.) As such, the Court finds that the Link reference demonstrates only that O-glucosides were more effective at inhibiting SGLT activity. The Link reference would not, however, have taught a POSA that C-glucosides are more stable than O-glucosides as Link made no specific findings with respect to stability.

c) US '674

In 2001, U.S. Patent Application Publication No. 2001/0041674 ("US '674") disclosed that C-glucosides are metabolically stable and could have "potent anti-diabetic activities." (DTX-172, at 1 ¶ 14.) US '674 recognized that O-glucosides are subject to glucosidases when administered orally. (*Id.* at 1 ¶ 8.) Thus, US '674 posited that C-glucosides could "overcome the stability against glycosidases" and further observed that "it is not reported that C-glycosides [have] strong SGLT [inhibition], so far." (*Id.* at 1 ¶ 10.)

US '674 confirmed the findings of Link—that replacing the oxygen with a carbon atom does not produce a potent compound. (*See* Bannister Tr., at 141:22–142:3.) The compound disclosed in US '674 instead omitted a "spacer" in the carbon bond between the glucose and the A ring for a direct carbon-to-carbon bond, which permitted the compound to remain "biologically active." (*Id.* at 141:22–142:23.) The potency of the compounds disclosed in US '674 was supported with biological data showing an increase in "the amount of glucose that was going out

in the urine which necessarily means it decreases the amount of glucose in the blood." (*Id.* at 138:21–139:4.) However, as Dr. Davies highlighted, the biological activity reported in US '674 was based only on administration by intraperitoneal injection, not oral administration. (Davies Tr., at 669:1–670:80.)

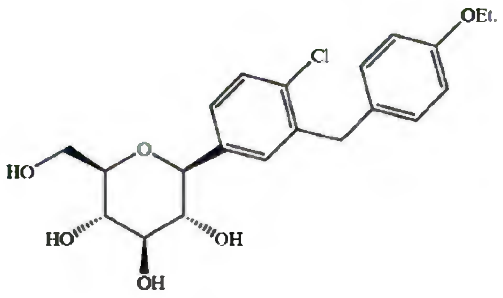
d) The BMS Patents

i. The '126 Patent

On July 2, 2002, US Patent No. 6,414,126 ("the '126 Patent") was issued to Ellsworth, *et al.*, and assigned to the Bristol Myers Squibb Company ("BMS"). (DTX-084.) The '126 Patent describes a family of C-glucoside compounds, which maintained the direct carbon link set forth in US '674, but modified the B and C rings of the molecule to attempt to formulate C-glucosides with greater potency. (*See* Bannister Tr., at 144:4–19.) Specifically, the '126 Patent states that "[t]he present invention relates to C-aryl glucosides which are inhibitors of sodium dependent glucose transporters found in the intestine and kidney (SGLT2) and to a method for treating diabetes, especially type II diabetes." (DTX-084 at 1.) The '126 Patent disclosed approximately 80 examples of C-glucosides and made "some broad claims about what different variables can be on different rings." (Bannister Tr., Vol.1, at 144:20–145:4.) The '126 Patent further provides a detailed description of a cell-based SGLT-2 inhibition assay. (DTX-084, at 35–36.)

ii. The '117 Patent

On February 4, 2003, US Patent No. 6,515,117 ("the '117 Patent") was issued to Ellsworth, *et al.*, with BMS as the assignee. (DTX-087.) The '117 Patent disclosed a single C-glucoside compound within the family reported in the '126 Patent, having the following structure:



(*Id.* at Abstract.) The '117 Patent described this structure as "[a]n SGLT2 inhibiting compound."[15] (*Id.*) The '117 Patent further set forth "[a] method for treating diabetes and related diseases employing an SGLT2 inhibiting amount of the above compound alone or in combination with another antidiabetic agent or other therapeutic agent." (*Id.*)

e) Patani

The Patani reference[16] was published in 1996, and reviews certain principles of bioisosterism. (*See* DTX-208.) Patani reviews "bioisosteric replacements which have been used to advance drug development." (*Id.* at 3148.) Specifically relevant here are Patani's teachings with respect to chloride and methyl groups, benzene rings and thiophene rings, and fluorine atoms and hydrogen atoms.

First, Patani states that "[w]hile the chlorine atom is often viewed to be isosteric[17] and

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15 Zydus refers to this structure as "dapagliflozin," which is the compound's marketing name. While a POSA at the time of invention would not have known the compound as dapagliflozin, the Court refers to the structure as its marketing name throughout the Opinion for ease of reference.

16 Patani & LaVoie, *Bioisosterism: A Rational Approach in Drug Design*, 96 Chem Rev. 3147 (1996).

17 Isosteric means that the molecules are the same size. (*See* Bannister Tr., at 207:3–5.)

isolipophilic[18] with the methyl group, it is very often selected as a bioisosteric replacement because of its ability to alter the metabolism." (*Id.* at 3154.) In that regard, Dr. Bannister testified that Patani "teaches us that chlorine and methyl are used interchangeably." (Bannister Tr., 193:25–194:2.) However, while Patani recognizes that chlorine and methyl are isoteric, it further states that "[t]he methyl substituents provide a site which is susceptible to metabolic degradation." (DTX-208, at 3154.) In other words,

> Patani is saying [that] it can be a good idea to change a methyl group to a chlorine, but it is not necessarily a good idea to change a chlorine to a methyl group, because a methyl group is susceptible to metabolic degradation, so you don't want to make a change that introduces instability into your molecule.

(Davies Tr., at 560:14–21; *see also* Bannister Tr., at 325:15–23 (agreeing that "[i]f there is a metabolic degradation, that means that the metabolic stability of the compound is adversely affected").)

Patani also teaches bioisosterism for benzene (methyl) rings and thiophene rings, observing that "[t]he classical bioisosteres benzene, thiophene, and pyridine resulted in analogues with retention of biological activity within different series of pharmacological agents." (DTX-208, at 3158.) Moreover, Patani states that fluorine and hydrogen atoms are often interchangeable as substituents: "[t]he substitution of hydrogen by fluorine is one of the more commonly employed monovalent isoteric replacements." (*Id.* at 3149.)

f) Sheridan

The Sheridan reference[19] was published in January 2002. (DTX-210.) Sheridan discloses

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[18] Dr. Bannister explained that "isolipophilic means greasy versus not greasy versus water-like." (Bannister Tr., at 207:6–7.)

[19] Robert P. Sheridan, *The Most Common Chemical Replacements in Drug-Like Compounds*, 42 J. Chem. Inf. Comput. Sci. 103 (2002).

a computation-based analysis of bioisosterism to "systematically identify candidate bioisosteres." (*Id.*) Graphically, Sheridan shows many "fragment pairs" and quantifies how well-matched they are, indicating the likelihood for successful replacement of one with the other. (*Id.* at 105–06.)

5. The Invention Story[20]

Dr. Kawanishi, an inventor of canagliflozin, testified at trial.[21] In December 2002, Dr. Kawanishi joined MTPC's "T-1095 backup project." (Kawanishi Tr., at 825:9–12.) The T-1095 backup project was a joint project with Janssen and sought an improved SGLT compound based on T-1095's poor performance in clinical trials. (*Id.* at 825:11–19.) During this project, MTPC scientists performed numerous modifications to both C-glucosides and O-glucosides to find a better SGLT inhibitor. (*See id.* at 843:9–848:23.) During this process, Dr. Kawanishi testified that MTPC would use other compounds from the literature as "reference compounds" to benchmark the progress of MTPC's own work. (*Id.* at 903:1–907:9.)

Dr. Kawanishi testified that around the fall of 2003, he began "making a plan to introduce to the aglycon portion of the molecule, a ring in addition to the A ring and B ring." (*Id.* at 853:5–9.) On or about, October 29, 2003, Dr. Kawanishi prepared a "Chem Draw" that memorialized his plan to synthesize and test forty analogs, which ultimately led to the discovery of canagliflozin. (*Id.* at 877:22–23.) Dr. Kawanishi shared his idea to add a third aryl ring to the compound with

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[20] The Court makes the following findings regarding the discovery of canagliflozin as useful background information. The Court does not, however, rely on Dr. Kawanishi's testimony in conducting its obviousness analysis because "[p]atentability shall not be negated by the manner in which the invention was made." 35 U.S.C. § 103; *see also Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012) ("The inventor's own path itself never leads to a conclusion of obviousness; that is hindsight.").

[21] Dr. Kawanishi was originally called to testify because, prior to trial, Zydus contested the date of invention. However, at trial, Zydus's counsel did not question Dr. Kawanishi regarding the date of invention nor does Zydus continue to contest the October 29, 2003 invention date.

his colleagues, who did not think that the SGLT activity would be maintained with this modification. (*Id.* at 856:19–25.) However, Dr. Kawanishi "felt strongly that SGLT activity is maintained, that a compound introducing a third ring maintains SGLT activity." (*Id.* at 857:18–21.) Based on this strong personal conviction, Dr. Kawanishi and two other researchers, Mr. Sugama and Mr. Yanagisawa, were permitted to implement Dr. Kawanishi's plan. (*Id.* at 857:19–58:5.) Thereafter, on November 13, 2003, Mr. Sugama first synthesized the compound known today as canagliflozin. (*Id.* at 859:16–22.)

B. Conclusions of Law

Zydus contends that the patents-in-suit are obvious over the compound disclosed in the '117 Patent, now known as dapagliflozin. Specifically, Zydus posits that a POSA would have selected dapagliflozin as a lead compound and would have been motivated to modify it to arrive at a "me too" drug. (DFOF ¶¶ 1–4.) Based on the principles of bioisosterism, Zydus maintains that a POSA would have had a reasonable expectation of success in modifying dapagliflozin to reach canagliflozin. (*Id.* ¶ 3.) Plaintiffs, on the other hand, argue that Zydus has failed to show, by clear and convincing evidence, that a POSA (1) would have selected dapagliflozin as a lead compound or (2) would have been motivated to modify dapagliflozin to reach canagliflozin.

1. The Legal Standard

35 U.S.C. § 103 provides that a patent may be invalidated if its claims are obvious in light of the prior art. More specifically, the pre-AIA version of section 103 provides that "[a] patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). As issued patents are entitled to a presumption of validity, 35

U.S.C. § 282(a), the party seeking to invalidate a patent must demonstrate obviousness by clear and convincing evidence. *Impax Labs., Inc. v. Aventis Pharms., Inc.*, 545 F.3d 1312, 1314 (Fed. Cir. 2008). Moreover, where, as here, "the examiner considered the asserted prior art and basis for the validity challenge during patent prosecution, that burden becomes particularly heavy."[22] *Id.* Whether a patent is invalid as obvious "is a question of law, based on the underlying factual findings." *K/S Himpp v. Hear-Wear Techs., LLC*, 751 F.3d 1362, 1364 (Fed. Cir. 2014).

The obviousness determination is centered on four factual inquiries, known as the *Graham* factors: "(1) the scope and content of prior art, (2) differences between claims and prior art, (3) the level of ordinary skill in pertinent art, and (4) secondary considerations such as commercial success and satisfaction of a long-felt need." *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009); *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 399 (2007); *Graham v. John Deere Co. of Kan. City*, 383 U.S. 1, 17 (1966). The Federal Circuit has explained that:

> Obviousness requires more than a mere showing that the prior art includes separate references covering each separate limitation in a claim under examination. Rather, obviousness requires the additional showing that a person of ordinary skill at the time of the invention would have selected and combined those prior art elements in the normal course of research and development to yield the claimed invention.

Unigene Labs., Inc. v. Apotex, Inc., 655 F.3d 1353, 1360–61 (Fed. Cir. 2011) (citations omitted).

Where the claims at issue involve a chemical compound, "*prima facie* obviousness under the third *Graham* factor generally turns on the structural similarities and differences between the claimed compound and the prior art compounds." *Otsuka Pharm. Co., Ltd. v. Sandoz, Inc.*, 678

[22] There is no dispute that the examiner considered the relevant prior art in the prosecution of the asserted claims.

F.3d 1280, 1291 (Fed. Cir. 2012). Indeed, Federal Circuit "case law demonstrates that whether a new chemical compound would have been *prima facie* obvious over particular prior art compounds typically follows a two-part inquiry." *Id.* "First, the court determines whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts." *Id.* (citing *Eisai Co. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008)). Second, the court must determine "whether the prior art would have supplied one of ordinary skills in the art with a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success." *Id.* at 1292 (citing *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007)). Importantly, when conducting this analysis, courts must avoid improperly relying on hindsight. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1070–71 (Fed. Cir. 2012).

2. Selection of a Lead Compound

The Federal Circuit has explained that a lead compound is "a compound in the prior art that would be most promising to modify in order to improve upon its . . . activity and obtain a compound with better activity." *Otsuka Pharm. Co.*, 678 F.3d at 1291 (alteration in original) (quoting *Takeda Chem. Indus.*, 492 F.3d at 1357). However, "[a]bsent 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." *Id.* Rather, "it is the possession of promising useful properties in a lead compound that motivates a chemist to make structurally similar compounds." *Daiichi Sankyo Co., Ltd. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010). Moreover, "the attribution of a compound as a lead compound must avoid hindsight bias; it must look at the state of that 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." *Id.* (emphasis in original). Indeed, "proving a reason to select a compound as a lead compound depends on more than just structural similarly, but also knowledge in the art of the functional properties and limitations of the prior art compounds." *Id.* In that regard, "[p]otent and promising activity in the prior art trumps mere structural relationships." *Id.* Thus, in determining whether a POSA would select a compound as a lead compound, the court must be "guided by evidence of the compound's pertinent properties," including "positive attributes such as activity and potency, adverse effects such as toxicity, and other relevant characteristics in evidence." *Otsuka Pharm.*, 678 F.3d at 1292 (citations omitted).

a) Testimony at Trial

Dr. Bannister, Zydus's medicinal chemistry expert, opined that a POSA would have selected the structure disclosed in the '117 Patent, otherwise known as dapagliflozin, as a lead compound. Dr. Bannister testified that a POSA would be interested in SGLT inhibition because it was a "promising biological mechanism" that had shown "promise in animals and even in people [of] lowering blood sugar." (*Id.* at 165:2–20.) In that connection, while Dr. Bannister understood there to be significant biological data concerning SGLT inhibitors in 2002 to 2003, there were no such existing drugs on the market. (*Id.* at 165:12–166:6.) Thus, in 2003, SGLT inhibitors were "just right" for development, meaning that there were "a lot of scientific advances to be made, lots of patients to be helped, [and] lots of money to be made."[23] (*Id.* at 168:2–5.)

Dr. Bannister opined that, among the SGLT-2 inhibitors known in 2003, a POSA would

[23] In explaining his analysis of lead compound selection, Dr. Bannister employed what he called "the Goldilocks principle." (Bannister Tr., at 166:21.) In other words, he testified that a POSA did not "want something that is . . . too hot, its already been explored exhaustively, not too cold, it's not some pie-in-the-sky idea." (*Id.* at 167:2–6.)

have selected dapagliflozin as a lead compound because, as a C-glucoside, it was not subject to the metabolic instability problem that had "plagued all the best compounds to date."[24] (*Id.* at 170:21–171:6.) While Dr. Bannister "admit[ted] that the BMS patents don't have numbers for a POSA to say . . . that compound is that potent," he noted that "a POSA knows how to test for the potency, based on the prior art or based upon the teachings of the '117 [Patent], with their assay." (*Id.* at 171:10–19.) Moreover, because the '117 Patent is only one compound, a POSA knows that "the chemistry works." (*Id.*) Most notably, Dr. Bannister concluded that because the '117 Patent focused on one compound, as opposed to the '126 Patent, a POSA would know that it is the best compound of those disclosed in the '126 Patent. (*Id.* at 172:4–14.)

Plaintiffs, however, contend that Dr. Bannister's opinion that a POSA would select dapagliflozin as a lead compound is based solely on hindsight. In that regard, Plaintiffs argue that Dr. Bannister provided no support for his "Goldilocks approach" to selecting a lead compound. Indeed, Plaintiffs' expert, Dr. Davies, provided a different perspective. Dr. Davies explained that

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[24] Zydus contends in its Proposed Findings of Fact and Conclusions of Law that MTPC's "internal documents dispel any doubt as to how [MTPC] identified dapagliflozin as a lead compound." (DFOF ¶ 107.) The Court, however, cannot consider such evidence in conducting its obviousness analysis because, as previously explained, "'[p]atentability shall not be negated by the manner in which the invention was made." 35 U.S.C. § 103. Recognizing this, Zydus argues there are several reasons why the Court may consider these internal documents, including to impeach the credibility of Dr. Kawanishi, to challenge the testimony of an alleged inventor concerning the conception date, or as evidence of inherency. (*See* DFOF ¶¶ 332–34.) Nevertheless, Zydus does not rely on any MTPC documents to support any challenge to the date of invention. Nor does Zydus make any legal argument regarding inherency. With respect to inherency, the Federal Circuit has explained that "the concept of inherency must be limited when applied to obviousness, and is present only when the limitation at issue is the 'natural result' of the combination of prior art elements." *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1195 (Fed. Cir. 2014). Zydus contends that SGLT inhibition activities of a compound are "inherent properties" and, therefore, "a POSA can easily ascertain such activity using routine prior art assay methods without undue experimentation." (DFOF ¶ 79.) However, as discussed *infra*, there is no dispute that a POSA would know how to conduct the assays necessary to determine the potency of dapagliflozin. Accordingly, to the extent Zydus relied on such materials at trial, the Court considers them only to weigh Dr. Kawanishi's credibility as a witness.

there were three categories of potential antidiabetic treatment options a POSA would have considered in selecting a lead compound at that time: (1) compounds that have been approved by a regulatory authority, such as the FDA; (2) compounds that had a demonstrated efficacy in humans, and (3) compounds for which there was preliminary activity data at the biological target. (Davies Demonstrative, at 10.) Dr. Davies opined that each of these categories of compounds would have been "just right" for development by a POSA. (*See* Davies Tr., at 519:9.)

Expanding on these three categories, Dr. Davies identified several FDA-approved therapies that existed in 2003 for treating type 2 diabetes, including α-glucosidase inhibitors, thiazolidinediones ("TZDs"), and meglitinides. (*Id.* at 520:3–524:8; Davies Demonstrative, at 12–15.) Dr. Davies highlighted that a POSA would continue to look in these areas, despite FDA approval, because the FDA-approved compounds did not solve all the problems, and "[t]here was still an unmet need to treat type 2 diabetes." (*Id.* at 524:3–8.) Next, the doctor highlighted that a POSA could have explored compounds that were in clinical trials and had shown some efficacy in humans, including non-TZD dual PPAR agonists, GLP-1 agonists, and DPP-4 inhibitors. (Davies Tr., at 524:17–530:3.) Third, the doctor explained that there were other type 2 diabetes treatment targets and mechanisms of action that were being actively pursued by the pharmaceutical industry during the relevant time-period, including protein-tyrosine phosphatase inhibitors, retinoid X receptor modulators, glycogen phosphorylase inhibitors, glucokinase activators, and glucocorticoid receptor antagonists. (*Id.* at 530:4–25.) Moreover, Dr. Davies identified certain compounds that would have been of greater interest to a POSA than dapagliflozin. (*See id.* at 540:3–541:10.)

Indeed, Dr. Davies observed that in 2003, while there was some data indicating that SGLT inhibitors were a potential treatment for type 2 diabetes, there was no clinical data demonstrating

such. (*See id.* at 531:12–25.) In that connection, the doctor testified that he reviewed articles from 2000 to 2003 regarding potential type 2 diabetes targets and found that they did not discuss SGLT inhibitors among promising examples being explored at the time. (*Id.* at 532:1–21.) Dr. Davies further explained that the literature from the relevant time-period that focused on SGLT inhibitors was more focused on the T-1095 compound. (*Id.* at 533:3–10.) In that regard, Dr. Davies disagreed with Dr. Bannister's opinion that a POSA would select dapagliflozin as a lead compound. Dr. Davies highlighted that the '117 Patent did not include the data necessary for a POSA to assess dapagliflozin's SGLT-2 inhibitor activity. (*Id.* at 541:17–24.) Notably, the doctor emphasized that in order to obtain the data, a POSA would have to make the '117 compound and set up the assay for SGLT2 activity, which "would take a significant amount of time." (*Id.* at 542:8–17.) In other words, if a POSA were focused on the '117 Patent, "they would need to first set up, validate, and run the tests just to find out what the potency was of the '117 Patent compound." (*Id.* at 542:24–543:6.)

b) A POSA Would Not Have Selected Dapagliflozin as a Lead Compound

Zydus contends that a POSA would have (1) understood that SGLT inhibitors were a promising class of compounds, and (2) would have selected dapagliflozin as a lead compound based on its stability and potency. As such, the Court first turns to whether a POSA would have pursued working with SGLT inhibitors as opposed to other classes of antidiabetic compounds. Dr. Bannister testified that SGLT inhibitors were a promising class of anti-diabetic agents because they were known to lower blood sugar in both humans and animals and, further, because there was biological data regarding both the T-1095 and US '674 compounds. (*See* Bannister Tr., at 165:1–15.) Moreover, Dr. Bannister opined that a POSA would be interested in SGLT-2 inhibitors because they presented a "huge commercial opportunity." (*Id.*) Thus, under Dr. Bannister's

"Goldilocks" approach, SGLT-2 inhibitors were "just right" for development because "nobody has done it . . . , there are scientific advances to be made, lots of patients to be helped, [and] lots of money to be made," if done right. (*Id.* at 168:2–5.)

This approach, however, fails to consider other compounds that were, in the 2002 to 2003 time-period, "just right" for further development. Put differently, there were several categories of compounds that a POSA would have been aware of in the relevant time-period and, further, that were "just right" for further development. For example, both Dr. Davies and Dr. Bannister agreed that "a POSA faced with a problem of trying to make an improved antidiabetic medication could also pursue an improvement against an existing therapy." (Bannister Tr., at 283:5–18; Davies Tr., at 519:18–524:8.) Notably, in 2003, there were several FDA-approved therapies that a POSA would be interested in improving. (*See* Davies Tr., at 519:18–524:8.) A POSA would have also been interested in compounds that had a demonstrated efficacy in humans, including dual PPAR agonists, GLP-1 receptor agonists, and DPP-4 inhibitors. (*See id.* at 524:14–16; Bannister Tr., at 281:1–283:4.)

While Dr. Bannister acknowledged that these different categories of compounds would have interested a POSA seeking to develop an improved antidiabetic agent, he failed to explain any reason why a POSA would solely focus on SGLT inhibitors. Indeed, Dr. Bannister admitted on cross examination that SGLT inhibitors would not have been the only focus of a POSA:

> Q: You agree that in the 2003, 2004 time period there were a number of ways to try and treat type 2 diabetes, correct?
>
> A: Yes.
>
> Q: For this reason, in deciding amongst the different targets that were possible for treating diabetes, SGLT compounds wouldn't necessarily be the only focus of a POSA. Do you agree?
>
> A: I would agree that there are other options, yes.

(*See* Bannister Tr., at 280:15–281:3.) When pressed as to whether he considered other categories of mechanisms in his lead compound selection analysis, Dr. Bannister stated that he did consider them, but found SGLT inhibitors to be more appealing and that some of the other compounds "fall into the too-hot-versus-too-cold concept." (*Id.* at 285:8–15.) The Court, however, finds this testimony lacks credibility as Dr. Bannister did not refer to any of those potential mechanisms during his direct testimony, nor did he indicate why those compounds were "too hot" or "too cold." (*See id.* at 280:15–285:19.) More importantly, Dr. Bannister does not give any cogent reason as to why other feasible compounds would have been less appealing that SGLT inhibitors.

Further, there was not a clear focus on SGLT inhibitors in the early 2000s that would have prompted a POSA to select an SGLT inhibitor as a lead compound. As Dr. Davies, who I find more credible, explained, his analysis of review articles from 2000 to 2003 regarding potential type 2 diabetes targets revealed that the industry did not discuss SGLT inhibitors among the numerous other compounds being explored at the time. (*See* Davies Tr., at 532:121, 534:4–12.)[25] In response, Zydus emphasizes that the prior art may point to more than one lead compound. (*See* Davies Tr., at 650:10–14); *see also Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 923 F. Supp. 2d 602, 654 (D. Del. 2013) ("[T]he Federal Circuit has rejected the notion that the 'prior art must point only to a single lead compound for further development efforts.'") (quoting *Altana Pharma AG v. Teva Pharms. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009))). It is true that a lead compound "may be one of a number of compounds that the [POSA] would have been motivated to select from the panoply of known compounds in the prior art, based on the lead

[25] For example, Dr. Davies highlighted three review articles in his trial testimony that made no mention of SGLT inhibitors: the Zhang reference, published in 2000, (PTX-240); the Sarabu reference, published in July 2003, (PTX-119); and the Morral reference, published in May 2003, (PTX-113).

compound's promising useful properties." *Bristol-Myers Squibb Co.*, 923 F. Supp. 2d at 654. On this point, however, Zydus has failed to show—by clear and convincing evidence—that a POSA would have been motivated to select SGLT inhibitors from the "panoply" of known antidiabetic agents that were in development in the early 2000s. *Accord id.*

Even assuming that a POSA would have selected an SGLT inhibitor as a lead compound, the Court further finds that Zydus has failed to show that a POSA would have selected dapagliflozin. There is no dispute that dapagliflozin is a C-glucoside compound that "possesses activity as inhibitors of [SGLT] found in the intestine and kidney of mammals and is useful in the treatment of diabetes." (DTX-087, at 4.) In other words, the "'117 Patent suggested that there was some biological activity against SGLT." (Davies Tr., at 645:25–646:3.) Zydus thus contends that a POSA would have selected dapagliflozin as a lead compound, because a POSA would have known that dapagliflozin was not subject to the metabolic instability problem that plagued other SGLT inhibitor compounds and would have surmised that dapagliflozin was potent. (Bannister. Tr., at 171:1–6.) I disagree.

First, it was Dr. Bannister's opinion that a POSA would know that dapagliflozin, as a C-glucoside, was not subject to the metabolic instability problem that had "plagued all the best compounds to date, save many [of] the '674 C-glucosides." (Bannister Tr., at 171:1–6.) In that connection, Dr. Bannister maintained that a POSA would not have selected an O-glucoside because, he concluded, all the O-glucosides in the prior art suffered from metabolic stability issues that would disrupt activity after oral administration. (*See, e.g.*, Bannister Tr., at 130:5–131:24.) However, that opinion is not supported by the prior art, which demonstrates that companies that were investigating SGLT inhibitors in the early 2000s, such as BMS, were, in fact, focused on O-glucosides during the relevant time-period. (*See* Davies Tr., at 550:18–551:5.) Indeed, Dr.

Bannister acknowledged that BMS described the efficacy of its O-glucosides and C-glucosides using the same disclosures in both sets of patents.[26] (*See* Bannister Tr., at 308:20–309:14; PTX-340.) Accordingly, it is not clear that a POSA would have been able to effectively distinguish BMS's C-glucoside and O-glucoside compounds to determine that the C-glucosides were more stable.

While Dr. Bannister opined that a POSA would have understood that C-glucosides had improved activity after oral administration compared to O-glucosides based on the findings of Link, US '674, and the BMS patents, (*see* Bannister Tr., at 141:15–144:3), none of those references disclosed activity data after oral administration. Notably, Link did not describe the stability of the tested C-glucosides and, further, showed that the tested C-glucosides were weaker than their corresponding O-glucosides. (Davies Tr., at 544:24–545:17; Bannister Tr., at 136:16–21; PTX-112.) US '674 also did not disclose improved oral activity since the *in vivo* experiment set forth in the patent application involved intraperitoneal administration of the compound.[27] (Davies 543:7–544:15.) Nor did US '674 compare its C-glucoside compounds to O-glucosides; that is, a POSA could not have known whether the C-glucoside compounds had improved activity. Moreover, there was no basis for Dr. Bannister's testimony that the BMS Patents were a "breakthrough" in solving the stability problems that had plagued SGLT-2 inhibitors; indeed, as Dr. Bannister admitted, "no prior art reference . . . calls BMS's C-glucoside work a breakthrough."

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[26] BMS disclosed a family of O-glucosides compounds in International Patent Application No. WO 2003/020737 ("WO '737"). (PTX-089.) WO '737 disclosed that the O-glucoside compounds reported by the application "are inhibitors of sodium dependent glucose transporters found in the intestine and kidney (SGLT2)" and included "a method for treating diabetes." (*Id.*)

[27] Intraperitoneal administration is done via injection into the body cavity and bypasses key metabolic processes implicated in oral administration, including those which occur in the gastrointestinal tract. (Davies Tr., at 543:7–544:15; Williams Tr., at 1091:2–14.)

(Bannister Tr., at 305:18–24.)

Second, a POSA similarly would have not known that dapagliflozin was a potent compound. Zydus contends that "[a] POSA would know, based on the compound synthesis and assays described in detail in the BMS Patents, how to make and test the potency of dapagliflozin." (DFOF ¶ 193.) The BMS Patents, however, do not actually disclose any information regarding the potency of dapagliflozin. (*See* Bannister Tr., at 289:2–21 (confirming that the '117 Patent did not disclose any *in vitro* data, selectivity data, or metabolic stability data).) Rather, a POSA would have had to run the assays set forth in the '117 Patent to test the potency of dapagliflozin. (*See* Bannister Tr., at 171:10–19.) Dr. Bannister testified that POSA would know how to follow the steps of the assay to test the biological activity of dapagliflozin and that the test would take a week or two. (*Id.* at 148:22–149:20.) However, in offering his opinion, Dr. Bannister seemingly failed to take into account that running such an assay would take "a significant amount of time" and resources for a POSA to make and test the compound. (Davies Tr., at 542:6–17.) In that regard, the Court does not find that a POSA would know that dapagliflozin was a potent compound, contrary to Dr. Bannister's opinion, without expending a significant amount of time and resources.

For these reasons, the Court finds that Zydus has not shown, by clear and convincing evidence, that a POSA would have selected dapagliflozin as a lead compound. While there is no dispute that dapagliflozin and canagliflozin are structurally similar, "[p]otent and promising activity in the prior art trumps mere structural relationships." *See Daiichi*, 619 F.3d at 1354. Here, a review of dapagliflozin's functional properties do not demonstrate that a POSA would have known that it was a promising SGLT-2 inhibitor or that it was especially potent in comparison to other known SGLT-2 inhibitors in the art, such as T-1095/T-1095A, for which there was considerably more available biologic activity data. More likely, a POSA at the time would have

had limited information as to the functional properties of dapagliflozin as the BMS Patents did not actually disclose the potency of the compound and, rather, simply suggested it had potential to act as an SGLT-2 inhibitor. Accordingly, the Court finds that the "lack of [available] pharmaceutical data" would not have led a POSA to select dapagliflozin as a lead compound, particularly under the clear and convincing standard. *See Merck Sharp & Dohme Corp. v. Sandoz Inc.*, No. 12-3289, 2015 WL 5089543, at *43 (D.N.J. Aug. 27, 2015) (citing *Daiichi*, 619 F.3d at 1354).[28]

3. Motivation to Modify & Reasonable Expectation of Success

Because Zydus has not shown by clear and convincing evidence that a POSA would select dapagliflozin as a lead compound, it has not set forth a *prima facie* case of obviousness. Nevertheless, for the sake of completeness, the Court will consider whether a POSA would have been motivated to modify dapagliflozin to arrive at canagliflozin. The relevant question on this inquiry is "whether the prior art would have supplied [a POSA] with a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success." *Otsuka*, 678 F.3d at 1292. "The motivation to modify that lead compound can come from any number of sources and need not necessarily be explicit in the art." *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 973 (Fed. Cir. 2014). Rather, the motivation to modify "may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself.'" *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1362 (Fed. Cir. 2007) (quoting *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1361 (Fed. Cir. 2006)).

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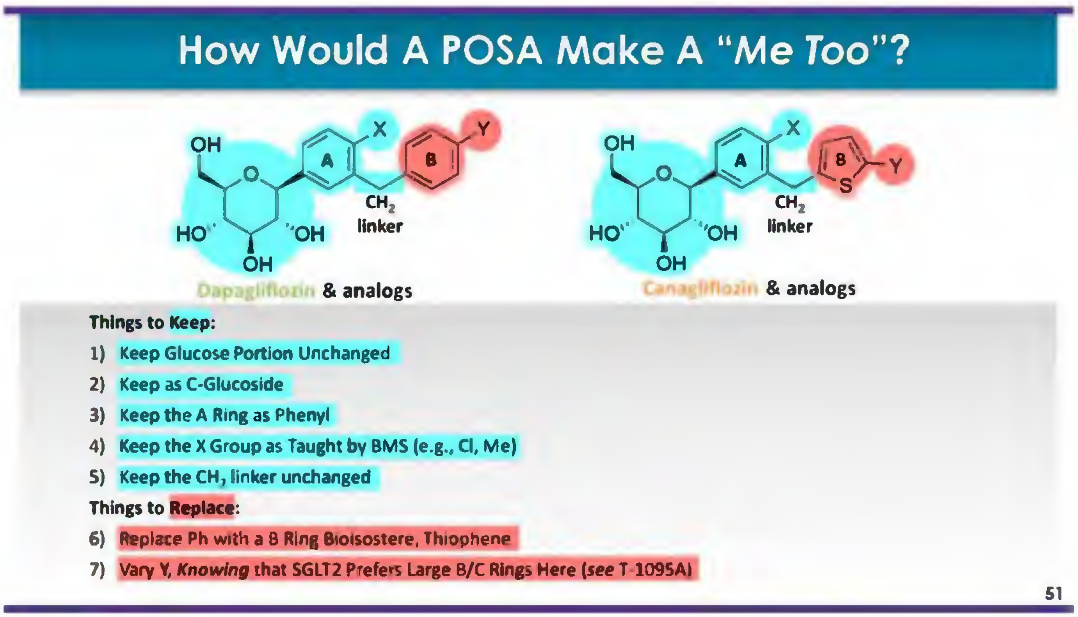
[28] Zydus contends that the fact that BMS took the extra effort to file a single compound patent covering dapagliflozin would suggest to a POSA that BMS considered dapagliflozin to be the "best" of the compounds covered by the '126 Patent. (DFOF ¶ 294.) That is not a reasonable inference, however, because the '117 Patent simply did not disclose the type of biologic activity data that would have prompted a POSA to choose dapagliflozin as a lead compound.

With respect to a reasonable expectation of success, "[i]t is sufficient to show that the claimed and prior art compounds possess a 'sufficiently close relationship . . . to create an expectation,' in light of the totality of the prior art, that the new compound will have 'similar properties' to the old." *Bristol Myers Squibb*, 752 F.3d at 973 (omission in original) (quoting *Otsuka Pharm.*, 678 F.3d at 1293). The prior art need not, however, contain "an explicit teaching that the claimed compound will have a particular utility." *Aventis Pharma*, 499 F.3d at 1301. Thus, in some circumstances, "[s]tructural similarity, alone, may be sufficient to give rise to an expectation that compounds similar in structure will have similar properties." *In re Merck & Co., Inc.*, 800 F.2d 1091, 1096 (Fed. Cir. 1986) (quoting *In re Payne*, 606 F.2d 303, 313 (C.C.P.A. 19789)).

a) Testimony at Trial

Dr. Bannister testified that a POSA would have a commercial "motivation to find something that would be comparable to" dapagliflozin, "this all-star of a compound that had just shown up." (*Id.* at 175:13–17.) He explained that a POSA would seek to modify dapagliflozin in a way to avoid the BMS Patents, while still maintaining its biological activity, essentially adopting the "strategy of developing a 'me too' drug." (*Id.* at 175:13–176:24.)

Fundamental to Dr. Bannister's opinion is the principle of bioisosterism, which according to Dr. Bannister, would be "well known to a POSA . . . by 2003." (*Id.* at 181:14–20.) Dr. Bannister went on to explain what parts of dapagliflozin a POSA would "keep" and what parts would be changed based on the "fundamental principles of bioisoster[ism]" to arrive at canagliflozin. (*Id.* at 189:22–25.) Dr. Bannister's analysis is described by the following demonstrative, which was presented at trial:



(Bannister Demonstrative, at 51.)

First, Dr. Bannister explained that a POSA would "keep the glucose portion [of the molecule] unchanged." (Bannister Tr., at 190:19.) A POSA would also, according to Dr. Bannister, keep the direct carbon-to-carbon bond between the glucose portion of the molecule and the A ring, keep the A ring as a phenyl, and keep the "carbon connector from the A ring to the B ring." (*Id.* at 191:1–194:17.) Once determining what to "keep" from dapagliflozin, Dr. Bannister indicated that a POSA would then make a "choice" of whether to make the "X Group" chlorine or methyl. (*Id.* at 191:19–192:25.) In that regard, Dr. Bannister testified that "chlorine and methyl are the two things you can most often swap out for one another" and that the two compounds can be used interchangeably. (*Id.* 192:24–25, 193:25–194:3.) Dr. Bannister went on to state that replacing chlorine with methyl is "not really a change. It's a choice. It's like one lump of sugar or two in your coffee this morning. Both are going to work. Both are going to give you a sweet drink." (*Id.* at 193:18–21.) Making the choice to use a 4-methyl, Dr. Bannister opined, would permit a POSA to "design around the prior art compound." (Bannister Tr., at 317:10–13.)

However, on cross examination, Dr. Bannister admitted that the BMS Patents claim dapagliflozin using both a 4-methyl and a 4-chlorine. (*Id.*)

Next, Dr. Bannister explained the steps a POSA would take to modify dapagliflozin. He opined that a POSA would not work through numerous theoretically possible options but, rather, would apply reasonable limiting principles in this process. (Bannister Tr., at 213:16–23.) Dr. Bannister suggested that the limiting principles a POSA would apply here were "obvious to try and easy to make." (*Id.* at 213:16–23.) Thus, according to the doctor, the first change the POSA would take is to do a bioisosteric swap in the B ring, because such a ring is "far away from the glucose" and the SGLT literature demonstrates that a "wide array of diversity is tolerated in the B ring." (*Id.* at 195:14–24, 217:7–10.) Based on Dr. Bannister's theory that a POSA would seek to design around the BMS Patents, he testified that "[the] best shot is to see whether something else [works] as a B ring." (*Id.* at 196:2–14.) In accordance with allegedly known bioisosteric replacements, Dr. Bannister opined that a POSA would be motivated to swap out the phenyl B ring in dapagliflozin for a thiophene B ring. (*Id.* at 184:2–13, 195:2–4.) A POSA would also be motivated to swap out the phenyl B ring because it was "easy to try" as the chemistry was known and laid out in the BMS Patents. (*Id.* at 185:16–187:17.)

According to Dr. Bannister, a POSA would next replace the ethoxy substituent on the thiophene B ring. (*Id.* at 196:15–24.) He emphasized that a POSA would need to replace the ethoxy substituent based on his knowledge that "multiple drugs [had] been withdrawn from the market that had a thiophene in them because of toxicity." (*Id.* at 242:2–7.) Dr. Bannister concluded that the solution to this issue is to add a substituent from a limited group at the Y position of the thiophene B ring. (*Id.* at 242:16–21.) In that regard, the doctor pointed out that the BMS Patents taught that 4-phenyl groups were suitable alternatives to 4-ethoxy groups as B ring

substituents. (*See* Bannister Demonstrative, at 74.)

The final change a POSA would make, according to Dr. Bannister, would be to add one or more fluorine (F) atoms to biologically active substances. (Bannister Tr., at 223:19–224:16.) Specifically, Dr. Bannister explained that a POSA would probably run a "fluorine scan," in which a fluorine is added to every possible position of a ring and tested for improvements. (*Id.* at 246:18–25.) Moreover, Dr. Bannister observed that the prior art would have motivated a POSA to add one or more F atoms to biologically active substances, given that the presence of the electron-withdrawing F atom often leads to improved drug-like properties. (*Id.* at 223:19–224:16.)

Finally, Dr. Bannister concluded that a POSA would have had a reasonable expectation that the modifications to dapagliflozin necessary to arrive at canagliflozin would result in a metabolically stable SGLT-2 inhibitor. (*Id.* at 163:5–10.) In explaining this conclusion, the doctor noted that while there is no guarantee that swapping out one bioisostere for another would not change the biological activity, a POSA "can have some confidence that it is likely or not likely to work depending on how often it has worked in the literature as a whole in the past." (*Id.* at 182:7–10.) Here, based on the "rank ordering of bioisosteres taught by Sheridan, [and] Patani," a POSA would have known whether the bioisosteres he planned to use would work. (*Id.* at 183:3–9.)

In contrast, Dr. Davies opined that a POSA would not "have been motivated to modify [dapagliflozin] to get to canagliflozin." (*Id.* at 555:14–17.) Specifically, Dr. Davies explained:

> I don't think a POSA would simply try to design around patents while maintaining activity. A POSA is in the business of finding an improved compound, not in finding a compound that just maintains activity. I don't think – Dr. Bannister proposes modifications that are not supported by his own prior art references. He ignores numerous other options that would have been considered by a POSA. And Dr. Bannister fails to identify prior art supporting a reasonable expectation of success, especially given the fact that he's proposing multiple simultaneous modifications with no testing of intermediates.

(*Id.* at 555:16–556:2.)

b) A POSA Would Not Have Been Motivated to Modify Dapagliflozin to Make Canagliflozin

i. A POSA Would Not Have Been Motivated to Design Around the BMS Patents

The Court begins with Zydus's contention that a POSA would have been motivated "to modify dapagliflozin in such a way as to avoid infringing the BMS Patents, while maintaining its biological activity." (DFOF ¶¶ 199–200.) In other words, Zydus maintains that a POSA would have been motivated to develop a "me too" drug. (*Id.*) Dr. Bannister described the "me too" strategy as taking a compound and "chang[ing] something that is relatively minor but is arguably not covered by [the patent] . . . and find out that it does exactly the same things." (Bannister Tr., at 175:22–176:6.) This approach, Dr. Bannister explained, does not necessarily result in a "better" compound but still makes a "new discovery" that can be taken to market and potentially be a commercial success. (*Id.* at 176:3–6.) To implement this strategy, Dr. Bannister concluded that a POSA would employ principles of bioisosterism to "circumvent a patent situation with potential competitors." (*Id.* at 177:11–22.) In support of this approach, Dr. Bannister relied on the Böhm reference,[29] which was a review article published in March 2002, and stated that bioisosteric replacements "could be attempted for various reason[s]," including "to circumvent a conflicting patent situation with potential competitors."[30] (DTX-192, at 43307.)

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[29] Böhm & Klebe, *Development of New Hydrogen-Bond Descriptors and Their Application to Comparative Molecular Field Analyses*, 45 J. Med. Chem. 1585 (2002). Dr. Bannister confirmed on cross-examination that he relied on the Böhm reference solely for the "fact that bioisosterism is a field of interest in the relevant time period." (Bannister Tr., at 318:1–20.)

[30] Dr. Bannister also pointed to the Nogrady reference for the general principle that "[v]ariations in ring structure are endless in drug synthesis, and are often used in the service of some other change or are introduced simply for patent-right purposes." (DTX-202, at 45945.) The

However, this theory of modification relies on a far too limited framing of the problem sought to be solved by the POSA. Indeed, Zydus's argument that a POSA would have wanted to make a "me too" compound is based on its underlying assumption that the problem the POSA sought to solve was to make a metabolically stable SGLT inhibitor. (DFOF ¶ 303.) However, both Dr. Davies and Dr. Bannister testified that the problem faced by a POSA was broader than seeking a stable SGLT-2 inhibitor; rather, a POSA would have been seeking to develop an improved antidiabetic agent. *See supra* § II.A.3. The Federal Circuit has explained that "[i]n considering motivation in the obviousness analysis, the problem examined is not the specific problem solved by the invention." *Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853, 859 (Fed. Cir. 2015). Indeed. "[d]efining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness." *Id.* Here, by framing the problem to be solved by a POSA as finding a metabolically stable SGLT-2 inhibitor with "roughly equal" properties to dapagliflozin, Zydus too narrowly focuses on the problem that was solved by the patents-in-suit and improperly relies on hindsight to suggest that a POSA would have been motivated to "circumvent" the BMS Patents. Thus, Zydus has failed to convince the Court that a POSA would have been motivated to "design around" the BMS Patents. Nevertheless, while the Court finds that Zydus has not shown that a POSA would have been motivated to design around the BMS Patents, I will briefly address each proposed change Zydus contends a POSA would have been motivated to make to dapagliflozin to reach canagliflozin.

Nogrady reference, however, was published in 2005, and therefore, does not reflect whether a POSA would have been motivated to make such replacements to design around a patent during the relevant time period.

ii. The Methyl to Chlorine Change

The first change that Dr. Bannister contends a POSA would have made to transform dapagliflozin to canagliflozin is to make the A ring substituent (denoted in Dr. Bannister's demonstrative as "X") a methyl, rather than a chlorine. Dr. Bannister testified that the Patani and Sheridan references taught that "chlorine and methyl are used interchangeably." (Bannister Tr., at 193:25–194:2.) Moreover, Dr. Bannister highlighted that the '126 Patent additionally taught that chlorine and methyl can be used "interchangeably" in the family of SGLT-2 inhibitors described in the '126 Patent. (*Id.* at 194:2–11, 192:16.) Indeed, while Dr. Davies contended that a POSA would not have known that methyl and chlorine could be used interchangeably because there was "no biological activity" disclosed in the '126 Patent, he agreed that the '126 Patent discloses "some examples that have the methyl and some that have chloro." (Davies Tr., at 698:16–20.)

Nevertheless, Plaintiffs maintain that a POSA would not have changed the A ring substituent to a methyl because the Patani reference specifically taught that switching a chlorine atom to a methyl may result in metabolic instability. (*See id.* at 559:23–561:2; Bannister Tr., at 325:20–23.) The Federal Circuit has explained that "a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). The Court, however, does not find that the Patani reference would have taught a POSA away from making the A ring substituent a methyl. The '126 Patent disclosed several compounds that used methyl in this manner. As Dr. Bannister explained at trial, these disclosures would suggest to a POSA that methyl may work in this location. The Court agrees. While there is some risk that switching a chlorine to a methyl *could* cause some instability, that instability is not a guarantee. Even so, a POSA would have seen the change used in the '126 Patent and reasonably surmised that, in this

context, chlorine and methyl could be used interchangeably. As such, the Court finds that Zydus has shown that a POSA would be motivated to change the A ring substituent from a chlorine to a methyl.

iii. The Thiophene to Phenyl Change

Zydus has not, however, shown that a POSA would have been motivated to change the phenyl B ring in dapagliflozin to a thiophene B ring. Dr. Bannister testified that the Sheridan reference taught that "thiophene is a[bio]isostere for phenyl, and the best one." (Bannister Tr., at 184:15–17.) Plaintiffs, however, argue that Dr. Bannister's alleged change of phenyl to thiophene does not have any support in the relevant prior art. Indeed, Plaintiffs highlight that Dr. Bannister failed to provide any prior art examples of thiophene being considered a bioisostere in the SGLT context and, further, Dr. Bannister admitted that none of the C-glucoside references, *i.e.*, the BMS Patents, describe a C-glucoside SGLT inhibitor that contains a thiophene ring at any location. (*Id.* at 336:21–25, 344:4–8.)

On that basis, the Court agrees that a POSA would not have been motivated to substitute the phenyl B ring in dapagliflozin with a thiophene B ring. Dr. Bannister's only support for this change is the "principles of bioisosterism." Fatally, Dr. Bannister referred to no prior art that would have suggested that replacing the phenyl with thiophene would have made a better compound, or that the new compound would have similar activity compared to the previous compound.[31] *See, e.g.*, *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, No. 08-335, 2011 WL

[31] Zydus contends that the proposed bioisosteric modifications provide clear and convincing evidence of motivation to modify because "the '126 Patent taught that certain known bioisosteres were, in fact, bioisosteric *in the context of the particular molecule being modified*." (DFOF ¶ 299 n.42 (citing *Mylan Pharm. Inc. v. Research Corp. Techs., Inc.*, 914 F.3d 1366, 1376 (Fed. Cir. 2019).) However, Zydus presented no evidence that a POSA would have known that thiophene is bioisosteric in the context of SGLT inhibitors, as no prior art taught as such, and *none* of the

3236037, at *4 (D. Del. July 28, 2011) (rejecting arguments "regarding the bioisosterism of thienyl and phenyl because bioisosterism gives no indication about whether the new compound will be better or worse than the previous compound, how well it will bind to the enzyme, or what the overall effect of the binding will be" (footnote omitted)), *aff'd* 689 F.3d 1368 (Fed. Cir. 2012). Put differently, a POSA would not have been motivated to make this change because he or she could not have predicted the effect the change would have on the compound without any indications from the prior art. As the Federal Circuit has emphasized, "predictability is a vital consideration in the obviousness analysis." *Otsuka*, 678 F.3d at 1298. Notably, "[i]n the context of drug development, data is a necessary prerequisite to predicting the impact of modifying a chemical compound." *UCB, Inc. v. Accord Healthcare, Inc.*, 201 F. Supp. 3d 491, 531 (D. Del. 2016), *aff'd*, 890 F.3d 1313 (Fed. Cir. 2018). In that regard, Zydus has not offered any evidence that shows a POSA would have been able to predict that replacing the phenyl B ring with a thiophene B ring would have improved the compound, let alone maintained the sought-after biological activity.

iv. The 4-Phenyl to 4-Ethoxy Change and Fluorination of the B Ring Substituent

The Court next considers the final two modifications proposed by Dr Bannister: (1) replacing the ethoxy substituent on the thiophene B ring to solve the toxicity problem created by adding thiophene to the compound; and (2) fluorinating the B ring substituent to "further mitigate the metabolic, toxicity, and oxidization issues associated with thiophene." (DFOF ¶ 304.) I reject both modifications proposed by Dr. Bannister in this context, because they are proposed solely to solve problems created by the addition of the thiophene B ring. In other words, these issues were

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compounds disclosed by the BMS Patents included thiophene. (*See* Davies Tr., at 612:12–21 ("The phenyl B ring is required in every single example in the '126 Patent.").)

not present in the dapagliflozin compound. As such, there is no reason a POSA would have made these modifications because he "would not have recognized the problem[s]," as they did not exist in the alleged lead compound. *See Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1357 (Fed. Cir. 2013); *see also Amerigen Pharms. Ltd. v. UCB Pharma GmbH*, 913 F.3d 1076, 1087 (Fed. Cir. 2019) (affirming no error in determination "that a person of ordinary skill would not have [made proposed modification] "to solve an undefined problem").

c) A POSA Would Not Have Had a Reasonable Expectation of Success

Finally, Zydus has not demonstrated by clear and convincing evidence that a POSA would have had a reasonable expectation of success that the modification proposed by Dr. Bannister would have yielded an improved antidiabetic agent. Zydus contends that the principle of bioisosterism, by definition, supports a reasonable expectation that the "new compound will have *similar properties* to the old." (DFOF ¶ 299 (quoting *Bristol Myers Squibb*, 752 F.3d at 972).) However, Zydus cannot rely on that principle here. As the Court discussed above, Zydus failed to show that a POSA would have known that thiophene is a bioisostere for phenyl *in the context of SGLT inhibitors* and, therefore, a POSA would not have had a reasonable expectation that making that replacement would have led to a stable and potent SGLT-2 inhibitor. Moreover, any reasonable expectation of success is belied by the fact that Dr. Bannister's analysis requires a POSA to have made multiple allegedly bioisosteric modifications to dapagliflozin. Dr. Bannister himself admitted that the prior art did not support making multiple, simultaneous bioisosteric changes to a compound. (*See* Bannister Tr., at 340:13–25, 341:8–17.) Accordingly, I find that Zydus has neither shown that a POSA would have been motivated to modify dapagliflozin to reach canagliflozin, nor that a POSA would have had a reasonable expectation of success. As such, Zydus has failed to make out a *prima facie* case of obviousness.

4. Objective Considerations

In determining whether a patent is invalid as obvious, a court must also consider secondary considerations of nonobviousness.[32] *KSR Int'l Co.*, 550 U.S. at 406–07. The Supreme Court has explained that this inquiry is broad and "invite[s] courts, where appropriate, to look at any secondary considerations that would prove instructive." *Id.* at 415. A court's evaluation of objective indicia of nonobviousness "is not just a cumulative or confirmatory part of the obviousness calculus but [rather] constitutes independent evidence of nonobviousness." *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008). Indeed, consideration of these criteria "help[s] inoculate the obviousness analysis against hindsight." *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1378 (Fed. Cir. 2012). As the obviousness inquiry is "expansive and flexible," *KSR Int'l Co.*, 550 U.S. at 419, there are a variety of secondary considerations that may be "utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented," including, but not limited to, "commercial success, long felt but unsolved needs, [and] failure of others." *Graham*, 383 U.S. at 17–18. In that regard, a court need not find that all factors are present to determine that the objective considerations support

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[32] While the Court finds that Zydus has not met its burden of proving obviousness, I must still consider the secondary considerations of nonobviousness. *See Apple Inc. v. Samsung Elecs. Co., Ltd.*, 839 F.3d 1034, 1048 (Fed. Cir. 2016) ("A determination of whether a patent claim is invalid as obvious under § 103 requires consideration of all four *Graham* factors, and it is error to reach a conclusion of obviousness until all those factors are considered."); *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 666–66 (Fed. Cir. 2000) ("[S]econdary considerations, when present, *must* be considered in determining obviousness." (emphasis added)); *Cephalon, Inc. v. Slayback Pharma Limited Liab. Co.*, 456 F. Supp. 3d 594, 601–02 (D. Del. 2020) (noting that "the safer course for a district court faced with an obviousness challenge (and looking to avoid reversal by the Federal Circuit) is to treat *Graham*'s 'invitation' to look at secondary considerations like a subpoena"). However, a failure to show that the objective considerations support a finding of nonobviousness, will not overcome a defendant's failure to make out a *prima facia* case of obviousness. *See Cephalon, Inc.*, 456 F. Supp. 3d at 611, 621 (finding that failure to show objective indicia of nonobviousness did not undermine conclusion that the asserted claims are not obvious).

a finding of nonobviousness. *See id.*

"Although secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion." *Apotex, Inc.*, 480 F.3d at 1372 (citing *Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988)). Indeed, the Federal Circuit has "often held [that] evidence of secondary considerations does not always overcome a strong prima facie showing of obviousness." *Asyst Techs., Inc. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008); *Sandt Tech., Ltd. v. Resco Metal & Plastics Corp.*, 264 F.3d 1344, 1355 (Fed. Cir. 2001) ("We see no error in the district court's conclusion in this case that the secondary considerations cannot overcome the strong evidence of obviousness presented.").

Here, the parties presented evidence as to unexpected properties, skepticism, long-felt, unmet need and failure of others, copying and acquiescence, and commercial success. In addition to finding that Zydus has failed to establish a prima facia case of obviousness, I further find that skepticism and commercial success support a finding of non-obviousness here.

a) Unexpected Properties

The Federal Circuit has explained that "[u]nexpected results are useful to show the improved properties provided by the claimed compositions are much greater than would have been predicted." *Millennium Pharms., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1368 (Fed. Cir. 2017) (quoting *Leo Pharm. Prods., Ltd.*, 726 F.3d at 1358). Thus, nonobvious may be demonstrated "when an invention 'yield[ed] more than predictable results.'" *Id.* (alteration in original) (quoting *Crocs, Inc. v. Intl Trade Comm'n*, 598 F.3d 1294, 1309 (Fed. Cir. 2010)). To that end, "the results must be shown to be unexpected compared with the closest prior art." *Id.* (quoting *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006)). However, unexpected results "do not necessarily guarantee that a new compound is nonobvious." *Bristol-Myers Squibb*, 752 F.3d at

977. In that connection, "[w]hile a 'marked superiority' in an expected property may be enough in some circumstances to render a compound patentable, a 'mere difference in degree' is insufficient." *Id.*

At trial, Plaintiff's expert Dr. Gavin opined that canagliflozin "has superior benefit compared to dapagliflozin." (Gavin Tr., at 750:13–17.) Specifically, Dr. Gavin testified that three studies demonstrated that canagliflozin has superior glycemic control, evidenced by reduced blood glucose levels upon oral administration:

(1) The peer-reviewed Zaccardi meta-analysis, which analyzed data from 38 randomized controlled clinical trials involving more than 23,000 participants, "to assess the comparative efficacy and safety of [SGLT-2] inhibitors in adults with type 2 diabetes." (PTX-238, at 783; Gavin Tr., at 763:7–764:17.) The data showed that the highest FDA-approved dose of canagliflozin reduced A1C and fasting plasma glucose levels to a statistically significant greater extent that the highest FDA-approved dose of dapagliflozin.[33] (Gavin Tr., at 763:7–764:17, 806:25–807:8; PTX-238 at 783, 791.) Based on this data, the Zaccardi meta-analysis concluded that "SGLT2 inhibitors improve cardiometabolic markets in patients with type 2 diabetes, with canagliflozin 300 mg generally performing better than other inhibitors." (PTX-238, at 791.)

(2) The Blonde cohort study, which analyzed data from type 2 diabetes patients taking either dapagliflozin or canagliflozin at their highest FDA-approved dosages. (PTX-182, at 1–2, 9.) The study concluded that patients taking canagliflozin had larger A1C reduction after six months and better A1C goal attainment. (Gavin Tr., at 762:9–24.) Moreover,

[33] Zydus suggests the fact that canagliflozin is used at a higher dose than dapagliflozin is relevant in determining whether there were unexpected results. (*See* DFOF ¶¶ 253–54.) Zydus, however, provides no scientific explanation for this assertion.

patients in the study who received 300 mg of canagliflozin were less likely to discontinue their treatment than those on 10 mg of dapagliflozin, which is critical for disease management. (*Id.* at 762:20–24.)

(3) Sha, a head-to-head Phase I study comparing canagliflozin and dapagliflozin, (Gavin Tr., at 751:16–18; PTX-231), which demonstrated that while both drugs "had similar effects on glucose excretion after dosing in the four-hour time frame, but canagliflozin was associated with a higher urinary glucose excretion and a greater renal threshold for glucose lowering for the rest of the day." (Gavin Tr., at 752:1–6.) Notably, the Sha study additionally found that canagliflozin provided the added benefit of delayed and reduced postprandial glucose excursion (change in blood glucose levels after a meal is consumed), while dapagliflozin did not. (Gavin Tr., at 752:7–15, 753:1–10, 757:10–25.)

Furthermore, Plaintiffs presented additional head-to-head studies between canagliflozin and other antidiabetic drugs, including sitagliptin, a DPP-4 inhibitor.[34] (Gavin Tr., at 758:11–25, 759:1–5, 760:7–10; PTX-1086.) This study showed that canagliflozin was statistically superior in lowering A1C levels in type 2 diabetes patients. (Gavin Tr., at 760:5–10.) In contrast, "dapagliflozin . . . was found to be inferior to sitagliptin." (*Id.* at 760:13–17.)

While the evidence highlighted by Plaintiffs demonstrates that canagliflozin has some benefits over dapagliflozin in the clinical setting, these benefits do not demonstrate a "marked superiority" over dapagliflozin. Rather, the differences between canagliflozin and dapagliflozin are one of degree. Canagliflozin and dapagliflozin, expectedly, have the same type of biologic activity. *See In re Merck & Co.*, 800 F.2d at 1099. In that connection, "[u]nexpected results that

[34] Because dapagliflozin was not approved by the FDA until after canagliflozin, it could not be used as the direct head-to-head comparator to demonstrate the efficacy of canagliflozin in a clinical trial. (Gavin Tr., at 750:18–751:6.)

are probative of nonobviousness are those that are 'different in kind and not merely in degree from the results of the prior art.'" *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013) (quoting *Grip Barbell Co. v. USA Sports, Inc.*, 393 F.3d 1317, 1322 (Fed. Cir. 2004)). Here, the difference between canagliflozin and dapagliflozin is one of efficacy and is not substantial. Accordingly, the Court does not find that this consideration does not support a finding of nonobviousness.

b) Skepticism

A court may also consider "[g]eneral skepticism of those in the art" as "'relevant and persuasive' evidence of nonobviousness." *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 885 (Fed. Cir. 1998) (quoting *Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 726 (Fed. Cir. 1990)). In other words, "[p]roceeding contrary to the accepted wisdom is . . . strong evidence of [non]obviousness." *Ruiz.*, 234 F.3d at 668. On this factor, Plaintiffs rely on the testimony of Dr. Gavin and Dr. Davies to support their assertion that "clinicians and researchers in the diabetes field were skeptical of the use of SGLT inhibitors as a potential type 2 diabetes treatment and, instead, focused on other drug categories." (PFOF ¶ 155.) In that regard, Dr. Gavin testified that in the 2003-time frame, a treatment "that depended on increasing the amount of glucose in the urine . . . was viewed generally as a counterintuitive approach" because clinicians had been taught "that the appearance of glucose in the urine was a sign of poor control in diabetes." (Gavin Tr., at 741:2–10.) Drs. Davies and Gavin additionally pointed to review articles from 2000 to 2003 documenting viable type 2 diabetes treatment targets which made no mention of SGLT inhibitors. (*See* Davies 532:1–21; Gavin Tr., at 738:1–740:18.)

Zydus, however, maintains that the research community was not skeptical of SGLT-2 inhibitors and argues that it was "a validated mechanism of action and promising treatment option

of type 2 diabetes." (DFOF ¶ 255.) Dr. Williams, Zydus's diabetes treatment expert, testified that "the research community had . . . validated SGLT as an important way of lowering blood sugar" and "that if you impaired SGLT, you could cause excretion of a greater amount of glucose into the urine, and at the same time lower blood glucose levels." (Williams Tr., at 1048:23–1049:3.) Thus, Dr. Williams opined that SGLT-2 inhibition was "an attractive area of research interest at that time." (*Id.* at 1049:4–6.) Moreover, Dr. Williams disagreed with Dr. Gavin's opinion that causing excretion of glucose in the urine would be viewed as counterintuitive. Rather, Dr. Williams observed that "people [who] have poorly controlled diabetes usually have higher glucose excretion in the urine," and the use of SGLT-2 inhibitors "take[s] advantage of that known physiologic phenomenon and . . . exploit[s] it to actually treat our patients with type 2 diabetes." (*Id.* at 1053:13–20.) Indeed, Dr. Williams opined that SGLT inhibition was an "attractive target" because it took "advantage of the knowledge and experience that you can get rid of glucose by using the kidney." (*Id.* at 1053:21–24.) Further, Zydus contends that the lack of skepticism was demonstrated by the medicinal chemistry community's exploration of SGLT inhibitors throughout the 1990s and 2000s, including Tanabe's work on T-1095 and BMS's development of dapagliflozin. (DFOF ¶ 257.)

Having heard competing testimony on this issue, I find that there was skepticism in the medicinal chemistry community regarding the development of SGLT inhibitors in the 2003 time-period. Drs. Davies and Gavin presented credible testimony that researchers in the type 2 diabetes community did not view SGLT inhibitors as a promising mechanism for treatment. (*See* Davies Tr., at 532:1–21, 534:4–12; Gavin Tr., at 738:1–140:18.) Most tellingly, Dr. Bannister, who had previously worked in the development of antidiabetic agents and kept up with relevant medicinal chemistry literature during 2003, could not recall whether he was aware of SGLT inhibitors during

the 2003 time-period. (*See* Bannister Tr., at 285:21–286:15.) Moreover, Dr. Williams lacked credibility on this issue. While the doctor claimed that SGLT inhibition was an "attractive" area of research, he pointed to no references to support that statement and admitted that the only SGLT inhibitor he was aware of during the relevant time period was T-1095; in fact, he was unaware of any companies that were developing SGLT-2 inhibitors prior to 2004. (*See* Williams Tr., at 1101:1–1102:5.)

Industry doubts about "whether or how a problem could be solved or the workability of the claimed solution" favors non-obviousness. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1335 (Fed. Cir. 2016). Here, the prior art presented at trial demonstrates that, in 2003, Plaintiffs and BMS were focused on SGLT inhibitors while others in the industry primarily focused on other compounds. Accordingly, the Court finds that there was, at the very least, some skepticism of SGLT inhibitors as antidiabetic agents, and that this consideration supports a finding of nonobviousness.

c) Long-Felt Need and Failure of Others

"Evidence is particularly probative of obviousness when it demonstrates both that a demand existed for the patented invention, and that others tried but failed to satisfy that demand." *In re Cyclobenzaprine Hydrochloride*, 676 F.3d at 1082–83. To show "satisfaction of long-felt need, one must establish that (1) a POSA recognized a problem that existed for a long period of time without a solution, (2) the long-felt need had not been satisfied by another before the claimed invention, and (3) the invention in fact satisfied the long-felt need." *Immunex Corp. v. Sandoz Inc.*, 395 F. Supp. 3d 366, 405 (D.N.J. 2019).

The parties do not dispute that in 2003, there was a "long-felt unmet need" for a metabolically stable SGLT-2 inhibitor. (*See* DFOF ¶ 259; PFOF ¶ 158.) There is similarly no

dispute that researchers studying SGLT inhibitors encountered many issues and dead ends and, furthermore, there were "a significant number[] of companies that did not achieve the goal of introducing a useful SGLT inhibitor." (Bannister Tr., at 249:10–19, 287:5–8.) However, the evidence presented by Plaintiffs does not demonstrate that this long-felt need was satisfied by canagliflozin. Indeed, there is no dispute that the '117 Patent, which disclosed the structure for dapagliflozin, was published on February 4, 2003, prior to the invention of canagliflozin and the filing of the patents-in-suit. (Bannister Tr., at 248:8–20.) In that regard, while there was an unmet need for an SGLT2 inhibitor, that need had been met by dapagliflozin prior to the invention of canagliflozin. As such, this consideration does not support a finding of nonobviousness.[35]

d) Copying & Acquiescence

Copying of an invention can also indicate nonobviousness. However, evidence of copying "in the ANDA context is not probative of nonobviousness because a showing of bioequivalence is required for FDA approval." *Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013); *see also Janssen Prods., L.P. v. Lupin Ltd.*, 109 F. Supp. 3d 650, 671–72 (D.N.J. 2014). Plaintiff, nevertheless, contends that the fact that at least 14 generic pharmaceutical companies are seeking to market generic Invokana Products may be considered objective evidence of nonobviousness. (PFOF ¶ 243.) In support of that contention, Plaintiffs cite *Metabolite Laboratories., Inc. v. Laboratory Corp. of America Holdings*, wherein the Federal Circuit found that extensive licensing of an invention supported a finding of nonobviousness. 370 F.3d 1354, 1368 (Fed. Cir. 2004). That case, however, is inapposite because it did not involve

[35] Plaintiffs' argument with respect to this factor highlights that canagliflozin was the first SGLT-2 inhibitor approved by the FDA for the treatment of type 2 diabetes. (PFOF ¶ 159.) However, it is of no moment that canagliflozin was approved for use before dapagliflozin. The Court's analysis of this factor, rather, focuses on whether there was already *an invention* that satisfied the unmet need.

pharmaceuticals or any ANDA. *See id.* at 1357. As such, I find that this consideration does not support a finding of nonobviousness.

e) Commercial Success

Commercial success is relevant to the obvious determination because "the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art." *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005). Thus, evidence of commercial success, along with "some casual relation or 'nexus' between an invention and commercial success of a product embodying that invention" is "probative of whether an invention was non-obvious." *Id.* However, if the commercial success is due to a feature "known in the prior art, the success is not pertinent." *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006).

The Court begins with several undisputed facts. The Invokana Products were launched in March 2013. [redacted]

Relevant to the parties' different interpretations of this data are several events that occurred following the launch of the Invokana Products. In 2014, the FDA approved additional SGLT-2 inhibitors: dapagliflozin, marketed as Farxiga, and empagliflozin, marketed as Jardiance.

(Williams Tr., at 1056:6–14.) In 2017, the FDA approved ertugliflozin. (*Id.* at 1056:14–16.) In 2016, Jardiance gained a new indication for treating patients with cardiovascular disease, which gave it a competitive advantage over the other SGLT-2 inhibitors on the market. (Sims. Tr., at 944:25–945:7.) Then, in May 2017, the FDA placed a black box warning, which is the strictest warning that can be put on a prescription drug product, about amputation risk, on the Invokana Products. (McDuff Tr., at 412:5–413:6.)[36] Finally, in 2018 and 2019, the Invokana Products received two new indications for cardiovascular disease and renal disease, respectively. (Sims Tr., at 947:24–948:10.)

In terms of raw sales revenue figures, the Invokana Products have been commercially successful. Federal Circuit case law provides that commercial success is "usually shown by significant sales in a relevant market." *Ecolochem, Inc. v. So. Cal. Edison, Co.*, 227 F.3d 1361, 1377 (Fed. Cir. 2000) (quoting *J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997)). [redacted] The fact that the Products have seen some decrease in sales as a result of the Black Box warning does not detract from these significant earnings. Indeed, in comparison to other products that courts have found to be a commercial success, the net sales of the Invokana Products are on par. *See Bristol-Myers Squibb*, 923 F. Supp. 2d at 677 (finding that $835 million of total revenue from sales in the United States and $3.8 billion in worldwide sales were "clearly not small numbers"). Moreover, as one court has aptly observed, "'[s]trong evidence of commercial success is not surprising in a case under the Hatch-Waxman Act,' because if the patented drug were not a commercial success, at

[36] The FDA removed the black box warning on August 26, 2020. (McDuff Tr., at 472:18–473:6.)

least to some degree, 'generic manufacturers would have little interest in offering their own versions of the drug.'" *Id.* (quoting *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, No. 99-38, 2001 WL 1397304, at *12 (S.D. Ind. Oct. 29, 2001)).

Nevertheless, Zydus further submits that the Invokana Products are not commercially successful because they have a low market share and have, allegedly, not been profitable for Janssen. Looking first to the question of market share, the testimony at trial demonstrated that in the branded market for second-line diabetes treatments, *i.e.*, excluding metformin, Invokana held a high of 15 percent market share, that eventually declined to 9 percent, which Mr. Sims testified was "still a significant share of that segment of the market." (Sims Tr., at 962:20–963:8.) Within the SGLT-2 inhibitor drug class, the Invokana Products have maintained a significant portion of the market as additional approved SGLT inhibitors have been launched. (Sims Tr., at 963:9–964:5; McDuff Tr., at 460:2–7.)

Finally, Dr. McDuff testified that the Invokana Products have only a one percent share of the non-insulin anti-diabetes drug products ("NIAD market") and a two percent share of the NIAD market excluding metformin. (McDuff Tr., at 423:20–426:7.) Zydus contends that the NIAD market figures should govern this Court's determination of market share in assessing the commercial success of the Invokana Products. I disagree. Zydus points to no case law, Federal Circuit or otherwise, to suggest that commercial success of a product is determined by the NIAD market, as a whole, as opposed to smaller subsets of the market. (DFOF ¶ 237.) Rather, I find that each of these figures is relevant to my determination of commercial success. *See Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc.*, 417 F. Supp. 2d 341, 386 (S.D.N.Y. 2006) (considering product's market share of oral antidiabetic drugs, as a whole, and smaller subset of TZD drug class). There is no dispute that at the time of the launch of the Invokana Products, and continued

to this day, the NIAD market is a crowded field. (*See* McDuff Tr., at 461:4–24.) Relative to that crowded market, the Invokana Products have maintained a strong market share among other SGLT-2 inhibitors.

The Court additionally heard evidence as to whether the Invokana Products have been profitable. At the outset, while evidence of profitability may be an indication of commercial success, *see Daiichi Sankyo Co., Ltd. v. Mylan Pharms. Inc.*, 670 F. Supp. 2d 359, 386 (D.N.J. 2009), the Court does not find that the analysis of profitability factors heavily into the commercial success analysis. In that connection, evidence of a product's sales and market share weighs more heavily on whether the product is obvious in light of the prior art. That is because the question of profitability depends on a number of internal factors, rather than a comparison to other similar products. For this reason, even if the Court were to consider the parties' positions with respect to profitability,[37] I do not find the argument persuasive.

Finally, Zydus contends that the Invokana Products are not successful because there is no nexus between the Product's performance and the patents-in-suit. The Federal Circuit has explained that "there is a presumption of nexus for objective considerations when the patentee

37 [redacted]

shows that the asserted objective evidence is tied to a specific product and that product 'is the invention disclosed and claimed in the patent.'" *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1329 (Fed. Cir. 2016) (quoting *J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997)). Here, there is no dispute that the Invokana Products are the embodiment of the invention disclosed in the patents-in-suit, *i.e.*, canagliflozin, and as such the presumption of nexus applies.[38]

However, the presumption of nexus may be rebutted by "evidence that shows the proffered objective evidence was 'due to extraneous factors other than the patented invention," including "additional features and external factors, such as improvements in marketing." *Id.* Zydus first contends that the discounting and marketing of the Invokana Products "demonstrate a lack of differentiation and lack of connection to the Patents-in-Suit." (DFOF ¶ 242.) While Dr. McDuff stated that the marketing spend for the Invokana Products was high "compared to typical drugs," he "did not do any comparison between the marketing and sales of Invokana compared to any other branded type 2 diabetes treatment." (McDuff Tr., at 463:16–464:5.) Moreover, Mr. Sims highlighted that the marketing for the Invokana Products has been "education related" and focused on risk/benefit profiles and clinical data, "rather than factors unrelated to the patent features of canagliflozin and its use in treating type 2 diabetes." (PFOF ¶ 172; Sims Tr., at 966:12–967:18.)

Next, Zydus contends that discounts and rebates for the Invokana Products substantially increased over time as the sales for the Products decreased relative to other SGLT-2 inhibitors on the market. (McDuff Tr., at 441:3–443:1.) Dr. McDuff testified that the discounting and pricing

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[38] Zydus, nevertheless, argues that Plaintiffs "fails to show how the Invokana Products' supposed success can be tied to anything particular about canagliflozin." (DFOF ¶ 240.) This argument, however, does not reflect Federal Circuit law which plainly provides that a nexus is presumed where, as here, the commercial products are the embodiment of the patents-in-suit. *See WBIP, LLC*, 829 F.3d at 1329.

data "shows that Invokana is not able to maintain its share of the market even though it is cutting prices [a]nd that indicates a lack of differentiation of the product compared to these competitors." (*Id.* at 442:23–443:1.) I do not find that this evidence overcomes the presumption of a nexus. While marketing and discounting may have played a role in the success of the Invokana Products, Zydus has "not negated the possibility that the merits of the claimed composition also drive prescriptions and sales," especially in light of the competitive nature of the diabetes prescription market. *See Intendis GMBH & Co. KG v. Glenmark Pharms. Ltd.*, 117 F. Supp. 3d 549, 593 (D. Del. 2015).

Ultimately, I find that the Invokana Products were commercially successful. The totality of the evidence presented on this issue demonstrates that the Invokana Products have been a commercial success for Janssen, and the products have made significant sales since their launch, despite the crowded market and the sales ramifications of the FDA's black box warning. Accordingly, this factor supports a finding of nonobviousness. While Zydus attempts to undermine the success of the Products, "[t]here is no requirement that the invention be the only successful product in its market niche or the most successful." *Takeda Chem. Indus.*, 417 F. Supp. 2d at 386. Accordingly, commercial success supports a finding of nonobviousness.

In sum, the Court finds that Zydus has not shown, by clear and convincing evidence, that the patents-in-suit are invalid as obvious. Zydus has failed to show, by clear and convincing evidence, that a POSA would have selected dapagliflozin as a lead compound or that a POSA would have been motivated to modify, or a reasonable expectation of modifying, dapagliflozin to reach canagliflozin. Moreover, objective indicia of nonobviousness, notably skepticism and commercial success, support the Court's finding of nonobviousness.

III. OBVIOUSNESS TYPE DOUBLE PATENTING

Finally, Zydus contends that claims 12 and 20 of the '788 Patent are invalid for obviousness-type double patenting because they are anticipated by, or obvious in view of, claim 22 of the earlier-expiring '219 Patent. Plaintiffs, however, maintain that the '219 Patent cannot serve as an obviousness-type double patenting reference and, even if it could, claims 12 and 20 of the '788 Patent are protected by the safe harbor set forth in 35 U.S.C. § 121. In support of its arguments on obviousness-type double patenting, Zydus relied on the testimony of Mr. Carmichael, an experienced patent examiner. Plaintiffs relied on the testimony of Mr. Stoll, also an experienced patent examiner.

A. The Relevant Prosecution History

The application that led to the '788 Patent was filed on January 31, 2005, claimed priority to an application filed on July 30, 2004, and was issued as the '788 Patent on May 17, 2011. (PTX-001.) On March 24, 2008, the PTO imposed a "restriction requirement," in which the PTO grouped the asserted claims into categories and directed MTPC to "elect" the category of claims to be examined first. (DTX-004, at 2464–79.) The PTO divided the claims into the following categories: (1) compounds, (2) methods of treatment, (3) processes for preparing/making the compounds, and (4) compositions comprising compounds and another therapeutic agent. (*Id.*; *see also* Stoll Demonstrative, at 703.) On April 24, 2008, MTPC responded to the restriction requirement and elected, with traverse,[39] the compound claim (canagliflozin, claim 10); the remaining claims were either cancelled or withdrawn.[40] (Stoll Tr., at 1210:1–1211:5.) On March

[39] Mr. Stoll explained that by filing the election "with traverse," MTPC indicated that it "does not agree with the restriction requirement." (Stoll Tr., at 1210:22–1211:1.)

[40] The examination of "unelected" or "withdrawn" claims is suspended until further notice but remain pending in the action. (Stoll Tr., at 1259:23–1260:4.) Conversely, a cancelled claim

3, 2009, MTPC cancelled the method of treatment claims in the '788 Patent application. (Stoll Tr., at 1248:4–11.) On May 17, 2011, the '788 Patent was issued. (DTX-001.) While, based on the date the application was filed, the '788 Patent would have expired on July 30, 2024, the PTO granted a priority term adjustment ("PTA") of 1,079 days pursuant to 35 U.S.C. § 154(b), based on delays caused by the USPTO during prosecution. (*See id.*) The '788 Patent, therefore, is set to expire on July 14, 2027.

The application that led to the '219 Patent was filed on July 1, 2011, claimed priority to the same application as the '788 Patent, and was issued as the '219 Patent on July 17, 2012. (PTX-002.) The '219 Patent had a shorter prosecution and, therefore, it was issued without a PTA. (*Id.*) Because the '219 Patent claimed priority to the same July 30, 2004 application as the '788 Patent, the '219 Patent will expire on April 11, 2025.[41] (PTX-005, at 698.)

B. Discussion

The doctrine of obviousness-type double patenting is a judicially created doctrine which "prohibits an inventor from obtaining a second patent for claims that are not patentably distinct from the claims of the first patent." *UCB, Inc.*, 890 F.3d at 1323 (quoting *In re Lonardo*, 119 F.3d 960, 965 (Fed. Cir. 1997)). The doctrine, thus, "prevent[s] the extension of the term of a patent, even where an express statutory basis for the rejection is missing, by prohibiting the issuance of the claims in a second patent not patentably distinct from the claims of the first patent." *Id.*

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is removed from the application entirely. (*Id.* a 1259:15–17; Carmichael Tr., at 1284:17–1285"3 ("A cancelled claim is no longer in the application, and it is not going . . . [to] have the same treatment as a withdrawn claim.").) Mr. Carmichael further expanded on the difference between withdrawn and cancelled claims, noting that the examiner must consider a withdrawn claim for rejoinder, "whereas the examiner does not need to consider a cancelled claim for rejoinder." (Carmichael Tr., at 1285:4–17.)

41 The '219 Patent was granted a 256-day patent term extension under 35 U.S.C. § 156, based on regulatory review delay. (PTX-005, at 698.)

(quoting *Otsuka Pharm. Co.*, 678 F.3d at 1297). In other words, "[p]rohibiting double patenting prevents a patentee from obtaining sequential patents on the same invention and obvious variants, to thereby effectively manufacture a timewise extension of its patent exclusivity through a later-expiring patent." *Novartis Pharms. Corp. v. Breckenridge Pharm. Inc.*, 909 F.3d 1355 (Fed. Cir. 2018). "The key purpose of obviousness-type double patenting is thus to prevent a patent owner from controlling the public's right to use the patented invention beyond the statutorily allowed patent term of that invention." *Id.*

At the outset, Plaintiffs contend that "the '219 Patent cannot serve as a proper basis for invalidating the '788 Patent's PTA under the judicially created obviousness-type double patenting doctrine." (PFOF ¶ 245.) Zydus, on the other hand, maintains that the Federal Circuit's decision in *Gilead Sciences, Inc. v. Natco Pharma Ltd.*, 753 F.3d 1208 (Fed. Cir. 2014), supports application of obviousness-type double patenting to this matter.

In *Gilead*, the Federal Circuit considered the narrow question of whether "a patent that issues after but expires before another patent qualif[ies] as a double patenting reference for that other patent." *Id.* at 1211–12. There, the plaintiff owned two patents, the written descriptions of which were substantially similar. *Id.* at 1210. Despite these similarities, the two patents were "not part of the same family of patents[,] were not before the same patent examiner," and had different priority dates. *Id.* The district court concluded that "'a later-issued but earlier-expiring patent' cannot 'serve as a double-patenting reference against an earlier issued but later-expiring patent.'" *Id.* at 1211. The Federal Circuit reversed, holding that "an earlier-expiring patent can qualify as an obviousness-type double patenting reference for a later-expiring patent *under the circumstances here*." *Id.* at 1217 (emphasis added). In that regard, the Federal Circuit highlighted that if the obviousness-type double patenting analysis was "limited by issuance date, inventors could

routinely orchestrate patent term extensions by (1) filing serial applications on obvious modifications of an invention, (2) claiming priority to different applications in each, and then (3) arranging for the application claiming the latest filing date to issue first." *Id.* at 1215. In that regard, the Federal Circuit was concerned that "the terms of such patents could be subject to significant gamesmanship during prosecution." *Id.* In other words, if such conduct were permitted, "inventors could potentially obtain additional patent term exclusivity for obvious variants of their inventions while also exploring the value of an earlier priority date during prosecution." *Id.*

Zydus contends that *Gilead* provides a bright-line rule: the expiration date of a patent governs the obviousness-type double patenting analysis. (*See* DFOF ¶ 340; Closing Statement, at 1355:5–15.) However, the Federal Circuit has since limited the holding of *Gilead*. In *Novartis AG v. Ezra Ventures LLC*, the court considered the question of whether an earlier issued patent that received a patent term extension ("PTE"), that caused it to expire after a later issued patent, was invalid for obviousness-type double patenting. 909 F.3d 1367 (Fed. Cir. 2018).[42] In *Ezra*, the plaintiff had received a PTE of the earlier-issued patent under § 156 for regulatory delays that prevented the patented product from entering the market. *See id.* at 1372–73. The *Ezra* Court determined "that obviousness-type double patenting does not invalidate a validly obtained PTE" where it is the "earlier-filed, earlier-issued [patent], not the later-filed, later-issued [patent], that has the later expiration date, due to a statutorily-allowed term extension under § 156." *Id.* at 1373,

[42] The Federal Circuit also limited the so-called "*Gilead* rule" in *Breckenridge Pharmaceutical Inc.*, 909 F.3d 1355. That case involved two patents, one issued before the Uruguay Round Agreements Act of 1994 ("URAA") and one issued after the URAA. The URAA changed how patent terms are calculated. In that regard, the earlier filed, pre-URAA patent expired *after* the later filed, post-URAA patent. *See id.* at 1357–58. Inherent in the *Breckenridge* decision is that "a change in patent term law should not truncate the term *statutorily assigned* to the pre-URAA" patent. *Id.* at 1357.

1374. In so holding, the court distinguished *Gilead*, noting that there was "no potential gamesmanship issue through structuring of priority claims" as there was in that case, and observed that *Gilead* was intended to prevent inventors from improperly securing a second, later expiring patent for the same invention. *Id.* at 1374–75. Finally, the *Ezra* court declined to permit "a judge-made doctrine" to "cut off a statutorily-authorized time extension." *Id.* at 1375.[43]

The Federal Circuit has not, however, had occasion to consider the instant situation: whether a later-filed, later-issued patent that expires before the earlier-filed, earlier-issued patent due to a statutorily allowed term extension under § 154(b), can act as an obviousness-type double patenting reference.[44] However, in light of the Federal Circuit's decisions in *Ezra* and *Breckenridge*, I find that the '219 Patent is not a proper reference to invalidate the '788 Patent under the principles of obviousness-type double patenting. Specifically, I find that, as in *Ezra*,

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[43] The Federal Circuit also considered the scope of *Gilead*'s holding in *AbbVie Inc. v. Mathilda & Terence Kennedy Institute of Rheumatology Trust*, 764 F.3d 1366, 1368 (Fed. Cir. 2014). *AbbVie*, however, has limited application here because, there, "the earlier-filed patent had an earlier issuance date and earlier expiration date." *Breckenridge*, 909 F.3d at 1366; *see also AbbVie*, 764 F.3d at 1368–70. *AbbVie* does, however, contain language that would suggest that obviousness-type double patenting does apply where the earlier-filed, but later-issued patent is extended based on a PTA. Indeed, in setting forth the principles underlying the doctrine, the *AbbVie* court noted that "[i]t is designed to prevent an inventor from securing a second, later expiring patent for the same invention." *Id.* at 1373. Thus, the *AbbVie* court stated that the doctrine still has continuing viability post-URAA because "[p]atents claiming overlapping subject matter that were filed at the same time still can have different patent terms due to examination delays at the PTO." *Id.* (citing 35 U.S.C. § 154(b)). This, however, was dicta and, further, did not impact the court's analysis as there was no PTA at issue in *AbbVie*. Moreover, the Federal Circuit has since, in *Ezra* and *Breckinridge*, distinguished the *AbbVie* decision. *See Breckenridge*, 909 F.3d at 1365–66; *Ezra*, 909 F.3d at 1375.

[44] The Court is only aware of one district court opinion addressing this issue: *Magna Electronics., Inc. v. TRW Automotive Holdings Corp.*, No. 12-654, 2015 WL 11430786 (W.D. Mich. Dec. 10, 2015). While the *Magna Electronics* court held that the "*Gilead*-rule" was applicable where an earlier-filed, earlier-issued patent expired after the later-filed, later-issued patent due to a PTA under § 154, that decision was rendered before the Federal Circuit decided *Ezra*. I therefore do not find *Magna Electronics* persuasive on this issue.

"[t]his case does not raise the traditional concern with obviousness-type double patenting of a patent owner 'extending his exclusive rights to an invention through claims in a later-filed patent that are not patentably distinct from claims in the earlier filed patent.'" *Ezra*, 909 F.3d at 1374. Here, both the '788 and '219 Patents are part of the same patent family and were filed as continuations of the '312 Application, which was filed on July 30, 2004. (*See* DTX-001; DTX-002.) Accordingly, absent the PTA granted to the '788 Patent, both the '788 Patent and the '219 Patent would have the same expiration date. (PFOF ¶ 188.) However, due to delays in the prosecution of the '788 Patent, it was extended by 1,079 days pursuant to section 154(b). (*See* DTX-001.) There is no dispute that this PTA was properly granted under section 154(b).[45] Unlike in *Gilead*, the granting of a PTA does not present the potential for gamesmanship by inventors to secure a second, later expiring patent for the same invention.[46] *See Ezra*, 909 F.3d at 1374–75. In

[45] Zydus attempts to distinguish *Ezra* because PTAs under section 154, unlike PTEs under section 156, are subject to terminal disclaimers. (DFOF ¶ 345.) In other words, if a patent is subject to a terminal disclaimer, a PTA cannot extend the patent's term beyond the terminal disclaimer. *See* 35 U.S.C. § 154(b)(2)(B). In that regard, Zydus suggests that the *Ezra* decision distinguishes PTEs and PTAs in the context of obviousness-type double patenting. This, however, is an incorrect reading of *Ezra*. The only mention of PTAs in *Ezra* is in the context of discussing an earlier decision that noted the different statutory conditions for granting these extensions and, further, that a PTA cannot extend the statutory term of a patent if a terminal disclaimer had previously been filed. *Ezra*, 909 F.3d at 1374 (citing *Merck & Co. v. Hi-Tech Pharmacal Co.*, 482 F.3d 1317, 1321–23 (Fed. Cir. 2007)). But even if the role of a terminal disclaimer affected the obviousness-type double patenting analysis, Zydus does not contend that a terminal disclaimer was required here.

[46] Zydus, in its post-trial submission, raised for the first time the issue of gamesmanship, contending that Plaintiffs engaged in gamesmanship by waiting to file the application for the '219 Patent after the '788 Patent had been issued. (DFOF ¶ 347.) The Court does not find that any gamesmanship was present here and, moreover, that gamesmanship does not factor into the application of the obviousness-type double patenting analysis. Rather, it is the "potential for gamesmanship" that courts have considered in determining whether the obviousness-type double patenting analysis applies in a certain situation. *See Ezra*, 909 F.3d at 1374 (noting that "[t]his case does not present the concerns that drove recent decisions of this court regarding obviousness-type double patenting in the post-URAA context").

other words, there is no concern that MTPC "sought to subsequently 'secur[e] a second, later expiring patent for the same invention" after the issuance of the '788 Patent. *See id.* at 1375. In that connection, but for the § 154(b) PTA, the '788 Patent would have expired before the '219 Patent. *See id.* Perhaps more importantly, however, the Court is swayed by the Federal Circuit's observation that "a judge made doctrine" should not be used to "cut off a statutorily-authorized time extension." *Id.* Agreeing with Zydus's position would mean just that.

In conclusion, the Court finds that the '219 Patent cannot be used as a reference against the '788 Patent for the purpose of obviousness-type double patenting analysis. Because I find that the '788 Patent is not invalid for obviousness-type double patenting, I need not consider the parties' argument with respect to whether the 25 U.S.C. § 121 safe harbor applies.

IV. CONCLUSION

For the foregoing reasons, the Court finds that (1) the patents-in-suit are not invalid as obvious and (2) that the '788 Patent is not invalid under the doctrine of obviousness-type double patenting. An appropriate Order follows.

DATED: March 22, 2021

/s/ Freda L. Wolfson
Freda L. Wolfson
U.S. Chief District Judge