IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ASTRAZENECA AB,

Plaintiff;

v.

ZYDUS PHARMACEUTICALS (USA) INC.,

Defendant.

Civil Action No. 18-664-RGA

TRIAL OPINION

Michael P. Kelly, Daniel M. Silver, Alexander M. Joyce, MCCARTER & ENGLISH LLP, Wilmington, DE; Charles E. Lipsey, Ryan P. O'Quinn, FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP, Reston, VA; Jill K. MacAlpine, Matthew Hlinka, FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP, Washington, D.C.; John D. Livingstone, M. David Weingarten, Megan L. Meyers, FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP, Atlanta, GA.

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October 15, 2021

ANDREWS, U.S. DISTRICT JUDGE:

On May 1, 2018, AstraZeneca AB brought this action against Zydus Pharmaceuticals, Inc. for infringement of U.S. Patent Nos. 6,414,126 ("the '126 patent") and 6,515,117 ("the '117 patent") under 35 U.S.C. § 271(e)(2)(A). (D.I. 1). I held a four-day bench trial. (D.I. 152–155).[1] By trial, the parties had narrowed the dispute to the validity of claims 1–3, 14, and 16 of the '117 patent. (D.I. 135, ¶5; Tr. at 2:22-3:1; *see* D.I. 66 at 2).

Before me is the issue of the validity of the asserted claims. Zydus argues that each of the asserted claims is invalid for obviousness. (D.I. 160). I have considered the parties' post-trial submissions. (D.I. 158, 159, 160, 161, 163, 164).

I. BACKGROUND

The '117 patent is directed to compounds and methods for treatment of diabetes and related diseases through inhibition of sodium dependent glucose transporters (SGLT2) found in the intestine and kidney. (D.I. 1-2 at 1:10–14). AstraZeneca owns NDA No. 202293 for Farxiga (dapagliflozin) tablets for the treatment of diabetes and related diseases. (D.I. 1 at 8). The '117 patent is listed in the Orange Book for Farxiga. (*Id.*). Zydus filed ANDA No. 211582 seeking FDA approval for manufacture, use, and sale of a generic dapagliflozin tablet. (*Id.* at 6). Zydus sent its Paragraph IV certification to AstraZeneca on March 20, 2018. (*Id.* at 4). AstraZeneca then filed this action alleging infringement by Zydus's ANDA submission. (*Id.*); 35 U.S.C. § 271(e)(2)(A).

II. ASSERTED CLAIMS

Claims 1–3 of the '117 patent recite a "pharmaceutical composition" and various permutations of the composition: complexed with pharmaceutically acceptable salts,

[1] I cite to the trial transcript as "Tr." The trial transcript is consecutively numbered.

stereoisomeric compositions, or a prodrug ester. (D.I. 1-2, '117 patent, 25:32–67). The core pharmaceutical composition recited by the claims is shown below:

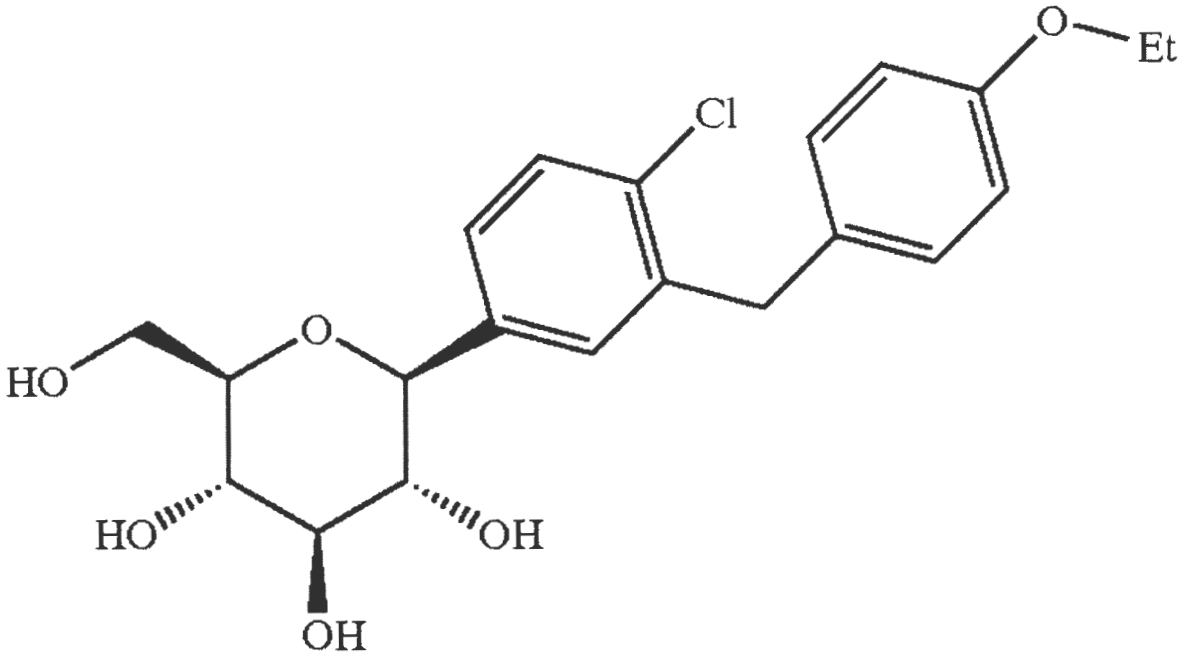


Fig. 1 – Pharmaceutical composition in Claims 1-3 of the '117 Patent (PTX0242 at 183)

Claims 14 and 16 of the '117 patent teach methods for treatment of diabetes and related diseases using a "therapeutically effective amount" of the composition defined in claim 1. (*Id.* at claims 14, 16). The relevant claims provide:

> 14. A method for treating or delaying the progression or onset of diabetes, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, hyperlipidemia, obesity, hypertriglyceridemia, Syndrome X, diabetic complications, atherosclerosis or hypertension, or for increasing high density lipoprotein levels, which comprises administering to a mammalian species in need of treatment *a therapeutically effective amount of a compound as defined in claim 1*.
>
> 16. A method for treating type II diabetes which comprises administering to a mammalian species in need of treatment *a therapeutically effective amount of a compound as defined in claim 1* alone or in combination with another antidiabetic agent, an agent for treating the complications of diabetes, an anti-obesity agent, an

antihypertensive agent, an antiplatelet agent, an anti-atherosclerotic agent and/or a hypolipidemic agent.

(PTX0242 at 26:57–67; 27:16–24).

III. LEGAL STANDARD

A patent claim is invalid as obvious under 35 U.S.C. § 103 "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103; *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406-07 (2007). "Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined." *KSR*, 550 U.S. at 406 (internal citation and quotation marks omitted).

A court is required to consider secondary considerations, or objective indicia of nonobviousness, before reaching an obviousness determination, as a "check against hindsight bias." *In re Cyclobenzaprine Hydrochloride Extended–Release Capsule Patent Litig.*, 676 F.3d 1063, 1078-79 (Fed. Cir. 2012). "Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17–18 (1966).

Zydus has the burden of proving obviousness by clear and convincing evidence.

IV. ANALYSIS

Zydus argues that the asserted claims are invalid as obvious. For the following reasons, I find each asserted claim not obvious.

A. Findings of Fact

1. A person of ordinary skill in the art is a pharmaceutical chemist with a Ph.D. and several years of experience in research and development of new pharmaceutical compositions, including experience in synthetic organic chemistry and structure activity relationship (SAR) analysis. (D.I. 161, ¶ 1, D.I. 159, ¶ 22). The POSA would either have a basic knowledge of the disease to be treated, as well as the relevant assays for evaluating a drug candidate for that disease, or work with a medical doctor with drug development training for that disease. (D.I. 161, ¶ 1, D.I. 159, ¶ 22).

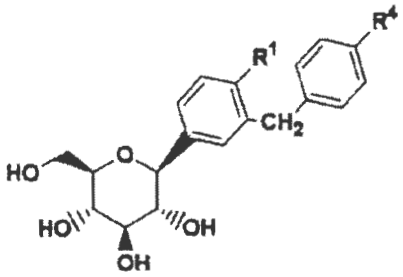
2. The '117 patent has a priority date of May 20, 2002. (PTX0242 at 170).

3. Zydus's proffered references—WO '128 (DTX007), Hongu (PTX0073), and Kees (DTX010)—are prior art. (D.I. 135-1, Ex. A, ¶¶ 41, 46, 52).

4. WO '128 discloses eighty structurally similar compounds as prospective SGLT2 inhibitors. (DTX007). Twenty-five of these fall within the genus Formula IB, which the patentee designates as the "[m]ost preferred" set of embodiments. (*Id.*). The Formula IB genus has preferred chemical moieties at certain positions, as shown below in Fig. 2:

Most preferred are compounds of formula I of the structure IB

IB



where R^1 is hydrogen, halogen or lower alkyl and R^4 is lower alkyl, $R^{5a}O$, $-OCHF_2$, or $-SR^{5e}$. It is preferred that R^1 be linked *para* to the glucoside bond and the R^4 substituent be linked at the *para* position.

Fig. 2 – WO '128 Formula IB Compounds (DTX007 at 12)

5. WO '128 does not provide data of comparative biological activity (i.e., SGLT2 inhibition) for any of its listed compounds, nor does it indicate why its Formula IB compounds are preferred candidates for development.

6. Hongu teaches away from replacing the methoxy at the 4-position on the distal ring (R^4 Fig. 2) with a heavier moiety because it shows decreased biological activity when the methoxy is replaced with larger distal alkoxy groups. (PTX0073 at 7) ("As the alkyl or alkoxy group became larger, the activity tended to be reduced.").

7. Kees teaches away from replacing the methoxy at the 4-position on the distal ring with a larger alkoxy moiety because it shows decreased biological activity for compounds with larger alkoxy groups. (DTX010 at Table 1). The preferred compound in Kees is an ethyl group at the R^4 position rather than an alkoxy. (*Id.* at Table 2).

8. SAR analysis is an iterative approach to rational drug design used by POSAs to optimize a potentially therapeutic molecule by evaluating whether changes to its chemical structure affect the molecule's desired therapeutic property, which is typically a change in biological activity. (Tr. at 264:8–266:6). The molecular scaffold (i.e., the core structure) that is chosen for iterative permutation during SAR is called the "lead compound." (D.I. 161 at ¶¶ 15, 20-21).

9. Because WO '128 does not evaluate the activity of its compounds, including those in Formula IB, it is not an SAR study. (Tr. at 307:23–308:2, 356:22–357:21). WO '128 does not identify a lead compound because it did not test for favorable activity or pharmacological characteristics that would have identified a compound as such.

10. Based on the lack of biological activity data in WO '128 and the teaching away from the use of larger alkoxy groups at the 4-distal position by Hongu and Kees, a POSA would not have been motivated to swap the distal 4-methoxy in WO '128's Example 12 with an ethoxy (which would otherwise yield the molecule claimed in the '117 patent).

11. Given the lack of available biological data for candidate SGLT2 inhibitors and the unpredictability of changes in biological activity due to modification of chemical structure, a POSA would not have had a basis to expect dapagliflozin to exhibit better glucose-reducing effects than the closest prior art, such as Example 12.

B. Conclusions of Law

Claims 1–3 of the '117 patent recite the same core chemical compound. "For a chemical compound, a prima facie case of obviousness requires structural similarity between claimed and prior art subject matter . . . where the prior art gives reason or motivation to make the claimed compositions." *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1377 (Fed. Cir. 2006) (internal quotations omitted). Structural similarity between the prior art and the patented compound is insufficient, on its own, to show motivation to combine. *Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007) ("Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.").

Based on my factual findings—specifically the lack of biological data available for the closest prior art, WO '128, and the teaching away of prior art from inserting an ethoxy into the 4-distal position—Zydus has not presented clear and convincing evidence of obviousness.

First, Zydus argues that a POSA would have been motivated to select Example 12 of WO '128 as a lead compound. (D.I. 160 at 4). Going through WO '128, Zydus identifies a number of preferred substituents that would have found their way into the various positions required to form Example 12. (*Id.* at 4-5). These include, for example, selecting a lead compound with a 4-methoxy substituent because that moiety was most represented at the R^4 position. (*Id.* at 6) (citing D.I. 161 Finding of Fact 21 (in turn citing Tr. 93:25–94:12, 95:8–11)). Zydus also argues that disclosure of biological data is not required to show a POSA's motivation to select Example 12 as a lead compound because the '117 patent itself does not disclose biological data to do so. (D.I. 160 at 12).

Zydus's arguments do not address, however, the premise that identification of a lead compound requires some indication that the preferred scaffold is likely to yield a biologically active compound upon modification. No such activity data is reported in WO '128 for a POSA to make a choice of lead compound based on the contents therein. As to Zydus's argument that the '117 patent also does not provide any biological data, this is not an appropriate comparison because sixteen of the patent's seventeen claims rely on a single molecular structure. A POSA could reasonably infer that the compound identified in claims 1–16 is the lead candidate for further development; the same cannot be said for any one of eighty species in WO '128, none of which are presented with any biological activity data. Even the Formula IB genus, which the authors of WO '128 designate their "[m]ost preferred" group, has twenty-five members. Without additional data to differentiate between the species in Formula IB, a POSA would not have known which structure to choose as a lead compound.

Second, Zydus argues the "one small, conservative change" from a methoxy to an ethoxy at the 4-distal position that is required to go from Example 12 of WO '128 to dapagliflozin would have been obvious to a POSA. (*Id.* at 7). Specifically, it argues that upon selection of the lead compound, a POSA would naturally seek to make a spectrum of small changes, which would include "the common replacement of methoxy with ethoxy." (*Id.* at 8–9) (citing Tr. 99:22–100:19). Because the change is small and in the normal course of a POSA's conduct of SAR, Zydus argues that there would be a reasonable expectation of success. (*Id.* at 9).

Zydus's argument presupposes that a POSA would have been able to identify Example 12 as the appropriate lead compound, which I have already noted I do not think is the case. Even supposing it were, however, I do not think Zydus has shown clear and convincing evidence that a POSA would have been motivated to make the required change from a methoxy to an ethoxy at

the R^4 position. Neither Hongu nor Kees supports the shift from methoxy to ethoxy. Moreover, Dr. Gribble's testimony that a POSA would have made the required change in due course "as part of the iterative process of SAR" seems to have some hindsight bias. (Tr. at 100:15–19). On the other hand, I find credible Dr. Batchelor's testimony that a POSA would not have automatically considered making the required change because none of the eighty compounds shown in WO '128 had an ethoxy at the R^4 position. (Tr. at 317:9–25).

Third, Zydus argues that the prior art does not teach away from substitution of the ethoxy at the R^4 position. (D.I. 160 at 10–11). Pointing to Hongu and Kees, Zydus argues that neither reference clearly teaches that a larger alkoxy group is likely to produce less favorable results. (*Id.*). Dr. Batchelor's testimony, Defendant argues, conceded, "Hongu alone may not be sufficient to teach a POSA away from larger alkyl groups." (*Id.* at 11) (citing Tr. at 385:1–23).

I have already found that both Hongu and Kees teach away from substitution of the ethoxy for the methoxy at the R^4 position because Hongu disfavors larger alkoxy groups at that position and Kees presents an ethyl group, which is not an alkoxy, as its most preferred group. Even were that not the case, Zydus's arguments misconstrue its burden of proof. It is not sufficient for Zydus to show that Hongu and Kees did not teach away from making the necessary modification to render dapagliflozin obvious; Zydus needed to show by clear and convincing evidence that a POSA would have had an *affirmative* reason to make that change. No such reason was given.

I therefore find that Zydus has not shown by clear and convincing evidence that claims 1–3 of the '117 patent are invalid as obvious. Because method claims 14 and 16 rely on the same chemical compound as claims 1–3, dapagliflozin, and both parties' arguments for those method

claims on their analysis of the obviousness of the dapagliflozin (D.I. 160 at 1; D.I. 158 at 18), I also find claims 14 and 16 of the '117 patent not obvious.

The parties dispute various purported secondary considerations of non-obviousness, primarily "unexpected results." (D.I. 158 at 28-37; D.I. 160 at 13-19). The disputed secondary considerations cannot help Zydus. Because Zydus has not made the case for obviousness by clear and convincing evidence (without consideration of the disputed factors), I do not need to consider them, and I therefore do not reach them.

V. CONCLUSION

For the foregoing reasons, I find that Zydus has failed to prove any of the asserted claims are obvious. As Zydus raises no other invalidity theories, I find each of the asserted claims infringed. (D.I. 135-1, Ex. A, ¶ 38).

The parties shall submit a final judgment consistent with this memorandum opinion within one week.