UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte CONSTANTIN EFTHYMIOPOULOS

Appeal 2014-008350
Application 08/737,141
Technology Center 1600

Before DEMETRA J. MILLS, ERIC B. GRIMES and LORA M. GREEN, *Administrative Patent Judges*.

MILLS, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134. The Examiner has rejected the claims for obviousness. We have jurisdiction under 35 U.S.C. § 6(b).

STATEMENT OF CASE

The following claim is representative.

14. A method for treating a human suffering from an infection by an influenza virus, wherein the method comprises administering to the human, an effective amount of 5-acetamido-2,3,4,5-tetradeoxy-4-guanidino-D-glycero-D-galacto-non-2-enopyranosonic acid, wherein the 5-acetamido-2,3,4,5-tetradeoxy-4-guanidino-D-glycero-Dgalacto-non-2-enopyranosonic acid is administered by *inhalation through the mouth alone*. [Emphasis added.]

Examiner Cited References

Von Itzstein et al. ("Von Itzstein I"), WO 91/16320, published Oct. 31, 1991.
Von Itzstein et al. ("Von Itzstein II"), AU-27242/92, published April 29, 1993.

Everard et al., *Comparison of nebulized deposition in the lungs of healthy adult following oral and nasal inhalation*, 48 Thorax 1045–1046 (1993).

Ganderton et al., Dry Powder Inhalers, *Advances in Pharmaceutical Science*, Academy Press, London,165–191 (1992).

Harry Smith and Cliver Sweet, *Lessons for Human Influenza from Pathogenicity Studies with Ferrets*, reviews of infectious diseases, 10 Reviews of Infectious Diseases 56–75 (1988).

Appellant Cited References

Hayden et al., *Anti-influenza virus activity of the neuraminidase inhibitor 4-guanidino-Neu5Ac2en in cell culture and in human respiratory epithelium*, 25 Antiviral research 123–131 (1994).

Belser et al., *The ferret as a model organism to study influenza A virus infection*, 4 Disease Models & Mechanisms 575–579 (2011), http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3180220/?report=printable..

Bergstrom et al., *Deposition and Disposition of [^{11}C]Zanamivir Following Administration as an Intranasal Spray*, 36 (Suppl. 1) Clinical Pharmacokinetics 33–39 (1999).

Cass et al., *Pharmacoscintigraphic Evaluation of Lung Deposition of Inhaled Zanamivir in Healthy Volunteers,* 36 (Suppl. 1) Clinical Pharmacokinetics 21–31 (1999).

Chandler et al., *Synthesis of the potent influenza neuraminidase inhibitor 4-guanidino Neu5Ac2en. X-Ray molecular structure of 5-acetamido-4-amino-2,6-anhydro-3,4,5-trideoxy-D-erythro-L-gluco-nononic acid*, J. Chem. Soc. Perkin Trans. I 1173–1180 (1995).

Kaiser et al., *Short-Term Treatment with Zanamivir to Prevent Influenza: Results of a Placebo-Controlled Study*, 30 Clinical Infectious Diseases 587–9 (2000).

Grounds of Rejection

Claims 14–30, 32, 34–38, and 43–65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Von Itzstein II in view of Von Itzstein I, in further view of Everard, Ganderton, and applicants' admission at page 3, lines 20–33 of the Specification. (Ans. 2.)

FINDINGS OF FACT

The Examiner's findings of fact are set forth in the Answer at pages 2–5. The following facts are highlighted.

1. Von Itzstein II discloses substituted derivatives of alpha-D-neuraminic acid and their use as antiviral agents, including use against influenza virus. (Page 1A.) The closest disclosed

derivative to the compound recited in claim 1 includes an additional methyl group but is otherwise identical. (Page 3, ll. 19–26 (formula I); page 5, ll. 1–3.)

2. Von Itzstein II discloses that the neuraminic acid compounds may be administered "in a form suitable for administration by inhalation". (Page 8, ll. 19–20.)
3. "Intranasal" is defined as occurring within or administered through the nose."[1]
4. Von Itzstein II states that neuraminidase inhibitors may be administered by any of the methods and formulations employed in the art for intranasal administration. (Von Itzstein II, page 10.)
5. Von Itzstein II states that, "in general the compounds may be administered in the form of a solution or a suspension or as a dry powder." (*id.*)
6. Von Itzstein I discloses the claimed neuraminidase inhibitor compound and its use as an antiviral agent for treating influenza. (Page 8, ll. 12–13, 17–20.)

Discussion

BACKGROUND

We acknowledge for the record our prior Decisions in this case dated March 10, 2006 (Appeal No. 2006-0150) and March 22, 2011 (Appeal No. 2010-000780). We also acknowledge the dismissal of the Appeal of the

[1] http://dictionary.reference.com/browse/intranasal

2011 Decision in Civ. Act. No. 11-944 (JEB) from the United States District Court for the District of Columbia dated Aug. 2012 for this case.

PRINCIPLES OF LAW

In making our determination, we apply the preponderance of the evidence standard. *See, e.g., Ethicon, Inc. v. Quigg*, 849 F.2d 1422, 1427 (Fed. Cir. 1988) (explaining the general evidentiary standard for proceedings before the Office). The Board "determines the scope of claims in patent applications not solely on the basis of the claim language, but upon giving claims their broadest reasonable construction 'in light of the specification as it would be interpreted by one of ordinary skill in the art.'" *Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005) (quoting *In re Am. Acad. of Sci. Tech. Ctr.*, 367 F.3d 1359, 1364 (Fed. Cir. 2004)).

"In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a *prima facie* case of obviousness. Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant." *In re Rijckaert*, 9 F.3d 1531, 1532 (Fed. Cir. 1993) (citations omitted). In order to determine whether a prima facie case of obviousness has been established, we consider the factors set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966): (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the relevant art; and (4) objective evidence of nonobviousness, if present.

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007).

"[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991). Moreover, a showing of unexpected results must be commensurate in scope with the breadth of the claims. *In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983); *see also In re Greenfield*, 571 F.2d 1185, 1189 (CCPA 1978) ("[O]bjective evidence of non-obviousnesss must be commensurate in scope with the claims.").

The teachings of a reference are not limited to the specific examples disclosed therein. *In re Mills*, 470 F.2d 649, 651 (CCPA 1972); *In re Chapman*, 357 F.2d 418, 424 (CCPA 1966) ("A reference can be used for all it realistically teaches, and is not limited to disclosures in its specific illustrative examples."). Obviousness is determined in view of the sum of all of the relevant teachings in the art, not isolated teachings in the art. *See In re Kuderna*, 426 F.2d 385, 389 (CCPA 1970); *see also In re Shuman*, 361 F.2d 1008, 1012 (CCPA 1966).

ISSUE

The Examiner's position

The Examiner finds that Von Itzstein II discloses administering an adjacent homolog of the claimed compound by inhalation for treating influenza infection. (Ans. 3.) The Examiner acknowledges that Von Itzstein II does not specifically teach inhalation of the compound through the mouth. (*Id.*) The Examiner further finds that Von Itzstein I teaches the claimed compound administered to the respiratory tract by intranasal delivery, such as by a powder inhaler. (*Id.*) The Examiner concludes that, "it would have been prima facie obvious to a person of ordinary skill in the art, at the time

the claimed the invention was made, to employ the claimed compound for treating influenza by inhalation of the compound through mouth." (Ans. 4.)

The Examiner finds that

> inhalation is understood in the art as: drug in suitable dosage form (solution, suspension or powder) is delivered to the respiratory tract by ***inhaling the drug*** either through the nasal or mouth. At the time the claimed invention was made, inhalers, such as diskhaler®, Tuberhaler®, rotahaler® (for dry powder) and various metered dose inhalers (MDI) (for liquid) are old and well-known in the art and most of them are through mouth. See, e.g., Ganderton et al. pages 176-184 and applicants' admission at page 3, lines 20-34. Ganderton et al. reveal that lactose is a commonly used carrier for dry powder inhalation. See, pages 173-174. Everard et al. reveal that oral inhalation and nasal inhalation are different in the deposition of the drug. Oral inhalation delivers more drugs to the lungs and nasal inhalation delivers more drug to the upper respiratory tract. Ganderton et al. also reveals that many other factors, such as particle size, inspiratory flow rate, the mouth piece, may affect the deposition of the drug. Therefore, Everard shows that the route of inhalation is one of result affecting parameters.

(Ans. 4–5.)

Appellant's position

Appellant contends that:

1. At the time of the invention, the person of ordinary skill in the art would reasonably have expected that drug delivery to treat influenza infection in the upper respiratory tract ("URT") of humans suffering from an infection by an influenza virus would be required for clinical effectiveness. As such, in view of the evidence and submissions presented by Appellant, successful therapeutic treatment of an influenza infection by delivering a drug to the lower respiratory tract

("LRT") by inhalation through the mouth alone in accordance with the claimed invention, without targeting the URT infection in humans suffering from an infection by an influenza virus, would not have reasonably been expected. (Appeal Br. 7.)

2. Appellant argues that he has provided

> unexpected results including related expert opinion testimony regarding the successful therapeutic treatment of an influenza infection by delivering a drug to the LRT by inhalation through the mouth ***alone*** in accordance with the claimed invention, ***without*** targeting the URT infection in humans suffering from an infection by an influenza virus. (Appeal Br. 7.)

3. Appellant argues that

> the Examiner's statement that von Itzstein II teaches a method of treating influenza viral infection in an animal, particularly, human, by administering a composition comprising a compound defined by general formula (1), which encompasses the claimed compound, ***by inhalation or insufflation*** (emphasis added), is misleading. What von Itzstein II actually describes is administering the compounds of formula (1) by ***any*** route. In other words, von Itzstein II does not focus on inhalation and insufflation only. (Appeal Br. 9.)

4. Appellant argues that Von Itzstein II never discloses inhalation by mouth (Appeal Br. 10) and is silent about formulations for oral inhalation or insufflation (Appeal Br. 11).
5. Appellant argues that Von Itzstein I discloses that intranasal delivery is the only route of administration, to the exclusion of all others. (Appeal Br. 11.)
6. Appellant argues that the fact that Von Itzstein I reveals influenza virus infects the lung and teaches that the claimed compound reduced viral titer in the lungs does not mean that Von Itzstein I

administered the claimed compound by oral inhalation alone. (Appeal Br. 13.) Appellant argues that Example 22 of Von Itzstein I shows administration of a drop of liquid in the nasal cavity which is not inhalation. (Appeal Br. 13.)

7. Appellant argues that the Examiner has ignored the teachings of Smith and Sweet. (Appeal Br. 14.)
8. Appellant relies on the Declaration of Frederick G. Hayden[2] as evidence of non-obviousness of the claimed invention.
9. Appellant argues that the mouse model used in Example 22 of Von Itzstein I is not an accurate influenza model, as shown by Belser. (Appeal Br. 16).
10. Appellant argues that no expectation of success can be established based on the methyl homologue of Von Itzstein II because evidence of record (Chandler) establishes that the claimed compound has been shown, in one instance, to be approximately 2,400X more active than the methyl homolog of Von Itzstein II, providing unexpected results for the claimed compound. (Appeal Br. 19.)
11. Appellant argues that the Hayden Declaration establishes that, at the time of the invention, there were uncertainties regarding the initial sites of influenza virus acquisition and spread within the respiratory tract in natural influenza illness. (Appeal Br. 31.)

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[2] Declaration under 37 C.F.R. § 1.132 of Frederick G. Hayden, filed March 15, 2013.

The Issues are: Does the evidence cited by the Examiner support a prima facie case of obviousness? Has Appellant provided sufficient comparative evidence in view of the closest prior art, showing unexpected results of use of the claimed compound to treat influenza as disclosed in Von Itzstein I via inhalation through the mouth alone?

ANALYSIS

We find that the Examiner has presented a prima facie case of obviousness of the claimed method. The Examiner has provided evidence that it was known in the art at the time of the invention that the claimed compound could be used to treat influenza. (FF7.) Von Itzstein II evidences that it was known in the art at the time of the invention that neuraminidase compounds known to treat influenza, including compounds closely related to the claimed compound, could be administered by inhalation. Thus, we agree with the Examiner that it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to administer the known (claimed) compound by inhalation, including inhalation through the mouth.

With respect to the issue as to whether the Examiner has established a prima facie case of obviousness, Appellant argues that, at the time of the invention, the person of ordinary skill in the art would reasonably have expected that drug delivery to treat influenza infection in the upper respiratory tract ("URT") of humans suffering from an infection by an influenza virus would be required for clinical effectiveness. (Appeal Br. 7.)

Appellant argues that

> the Examiner's statement that Von Itzstein II teaches a method of treating influenza viral infection in an animal, particularly,

> human, by administering a composition comprising a compound defined by general formula (I), which encompasses the claimed compound, ***by inhalation or insufflation*** (emphasis added), is misleading. What von Itzstein II actually describes is administering the compounds of formula (1) by ***any*** route. In other words, Von Itzstein II does not focus on inhalation and insufflation only.

(Appeal Br. 9.) Appellant argues Von Itzstein II never discloses inhalation by mouth (Appeal Br. 10) and is silent about formulations for oral inhalation (Appeal Br. 11).

We are not persuaded. "A reference can be used for all it realistically teaches, and is not limited to disclosures in its specific illustrative examples." *In re Chapman*, 357 F.2d 418, 424 (CCPA 1966). Obviousness is determined in view of the sum of all of the relevant teachings in the art, not isolated teachings in the art. *See In re Kuderna*, 426 F.2d 385, 389 (CCPA 1970); *see also In re Shuman*, 361 F.2d 1008, 1012 (CCPA 1966). Here, Von Itzstein I discloses use of the claimed compound to treat influenza (FF7) and Von Itzstein II discloses treating influenza with, among other compounds, a compound identical to the one claimed but for an additional methyl group (FF1) and administering it by inhalation (FF2).

Notwithstanding the fact that Von Itzstein II does not focus on inhalation only, Von Itzstein II mentions inhalation as being among the forms of administration that can be used effectively with its influenza treatment compounds. That disclosure is entitled to a presumption of enablement. *In re Antor Media Corp.*, 689 F.3d 1282, 1288 (Fed. Cir. 2012) ("[A] prior art publication cited by an Examiner is presumptively enabling barring any showing to the contrary by a patent applicant."). In addition, inhalation can only be carried out via the nose or the mouth. Since Von

Itzstein II does not limit its disclosure to nasal inhalation, it is reasonably understood to disclose inhalation by either the nose alone, mouth alone, or both.

Regarding Von Itzstein I, Appellant argues that intranasal delivery is the only route of administration disclosed, to the exclusion of all others. (Appeal Br. 11.) Appellant argues that the fact that Von Itzstein I reveals influenza virus infects the lung and teaches that the claimed compound reduced viral titer in the lungs after inhalation does not mean that Von Itzstein I administered the claimed compound by oral inhalation alone. (Appeal Br. 13.) Appellant argues that Example 22 of Von Itzstein I shows administration of a drop of liquid in the nasal cavity which is not inhalation. (Appeal Br. 13.)

We are not persuaded. Von Itzstein I discloses that the claimed compound may be intranasally administered (page 10, ll. 14–17) and Von Itzstein II discloses that closely related compounds may be administered in a variety of ways, including intranasally and by inhalation (FF2, FF5). When the disclosures of the references are considered together, we conclude that it would have been obvious to a person of ordinary skill in the art to administer the claimed compound by inhalation, including inhalation through the mouth. Appellant's focus on Von Itzstein I's Example 22 is misplaced because, while that example shows that intranasal administration is effective, it does not show that oral inhalation is not.

Appellant argues that Chandler provides evidence that rebuts the Examiner's assumption that a structural homolog of a known compound is prima facie obvious (Appeal Br. 19). Appellant argues that Chandler shows

that the claimed compound is "is superior by orders of magnitude in the *in vitro* assays when compared to the methyl homolog" (*id.*).

This argument is not persuasive because the rejection on appeal does not rely on Von Itzstein II's methyl homolog to show the obviousness of the claimed compound, it relies on Von Itzstein I's disclosure of the identical compound. It is therefore irrelevant to the basis of the rejection whether the claimed compound would have been obvious based on its methyl homolog.

In sum, we find that the preponderance of the evidence supports a prima facie case of obviousness. To repeat: Von Itzstein I discloses the claimed compound and its use in treating influenza, but does not teach administering it by inhalation through the mouth. Von Itzstein II teaches treatment of influenza using very closely related compounds, and teaches that they can be administered a number of ways, including by inhalation. Based on these teachings, which are presumed to be enabled, it would have been obvious to administer the compound taught by Von Itzstein I by inhalation through the mouth with a reasonable expectation that doing so would be effective in treating influenza.

"In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a *prima facie* case of obviousness. Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant." *In re Rijckaert*, 9 F.3d at 1532. "[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *In re Baxter Travenol Labs.*, 952 F.2d at 392.

Thus, a prima facie case of obviousness having been established, to show unexpected results, the appropriate comparison by Appellant is that of

the claimed invention with that of the closest prior art. In other words, it is a comparison of the effectiveness of the claimed compound administered only by oral inhalation (Appellant's claim 14), as compared with the effectiveness of intranasal administration of the compound of Von Itzstein I (the claimed compound).

Appellant relies on the Hayden Declaration, and references cited therein, as evidence of unexpected results (Appeal Br. 23–34). Dr. Hayden pointed to a study in which the claimed compound was administered by oral inhalation and its efficacy was measured (Hayden Declaration ¶¶4–6, citing the Hayden reference[3]). Dr. Hayden points out that the study compared placebo to two modes of administering the claimed compound: by oral inhalation alone, or by oral inhalation in combination with intranasal spray, and concluded that "adding intranasal administration of zanamivir did not obviously improve" the results found for oral inhalation alone (*id.* at ¶5).

As even Dr. Hayden acknowledges, however, "this study was not designed to compare directly the effects of zanamivir administration by oral inhalation alone to the effects of zanamivir administration by intranasal administration alone" (*id.* at ¶6). That is, the study was not designed to be, and is not, a comparison of the claimed invention (inhalation by mouth) with the closest prior art (intranasal administration). The study presented in the Hayden reference therefore does not show that the claimed method achieves results that are unexpectedly superior to the closest prior art method.

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[3] Hayden et al., *Efficacy and Safety of the Neuraminidase Inhibitor Zanamivir in the Treatment of Influenzavirus Infections*, 337 NEW ENGLAND J. MED. 874–880 (1997).

Dr. Hayden also points to a study (Hayden Declaration ¶9, citing Bergstrom et al.[4]) investigating the deposition and disposition of radio-labeled zanamivir when administered as a nasal spray, and another study (Hayden Declaration ¶10, citing Cass et al.[5]) investigating the deposition of zanamivir when administered by oral inhalation, contending that those references demonstrate that "the clinical effectiveness of administering zanamivar by the oral inhalation route to treat and to prevent naturally occurring influenza virus infection was uncertain" (Hayden Declaration ¶ 11).

Regardless of what parts of the respiratory tract are primarily targeted by oral inhalation and by intransasal administration, however, Von Itzstein II would have provided a skilled artisan with a reasonable expectation that both routes of administration would be effective for administering a neuraminidase inhibitor (Von Itzstein II 3:3-17) for treatment of influenza virus (FF1), including the neuraminidase inhibitor disclosed by Von Itzstein I (FF7). The results reported by Bergstrom and Cass do not provide a basis for reasonably doubting that Von Itzstein is enabling for what it discloses, especially since they were not published until after the effective filing date of the instant application.

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[4] Bergstrom et al., *Deposition and Disposition of [^{11}C] Zanamivir following Administratin as an Intranasal Spray*," 36 Suppl. Clin. Pharmacokinet. 33-39 (1999).

[5] Cass et al., "*Pharmacoscintigraphic Evaluation of Lung Deposition of Inhaled Zanamivir in Healthy Volunteers*," 36 CLIN. PHARMACOKINET. 21–31 (1999).

Appellant further relies on paragraph 7 of the Hayden Declaration, which discusses Kaiser.[6] Dr. Hayden concluded from Kaiser that

> From this study, we concluded that short-term administration of intranasal zanamivir was ineffective in providing *prophylactic* activity against development of symptomatic influenza. After presumed exposure to influenza virus, the rate of symptomatic influenza during 5 days of prophylaxis was 6% for the placebo group and 6% for the intranasal administration group, that is, intranasal zanamivir failed to show any protective benefit. However, for the two groups receiving treatment with orally inhaled zanamivir, the rate of influenza was substantially although not statistically significantly reduced, ranging from 2%-3% *(see* Kaiser et al., page 588, second column, "Discussion.") The results of this study supported a difference in protection between intranasal zanamivir and orally inhaled zanamivir.

Again, the study presented by Kaiser does not show that the claimed method is unexpectedly superior to the one made obvious by Von Itzstein I and Von Itzstein II. First, as Dr. Hayden concedes, the study results in Kaiser were not found to be statistically significant. (Hayden Declaration ¶ 7.) In addition, the Kaiser study was limited to prophylactic prevention of infection as opposed to treatment of infection, while appealed claims 14–30, 32, and 34–38 are directed to methods of treating influenza virus infection.

Appellant separately argues claims 43–65, which are directed to methods of treating a human susceptible to influenza virus infection; i.e., preventing infection (Appeal Br. 34–37). Here, as well, we do not find Appellant's arguments persuasive. As the Examiner pointed out (Ans. 3), Von Itzstein II suggests starting treatment before the time of infection (Von

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[6] Kaiser et al., "*Short-Term Treatment with Zanamivir to Prevent Influenza: Results of a Placebo-Controlled Study*," 30 CLIN. INFECT. DIS. 587-589 (2000).

Itzstein II 7:27–30) and therefore makes obvious a method of treating a human susceptible to influenza virus infection. Kaiser's results—showing no statistically significant difference in preventing infection between intranasal and inhaled zanamivir—do not show any unexpected superiority for the claimed method over the prior art.

On balance, Appellant has not provided sufficient comparative evidence with the closest prior art and thus has not rebutted the Examiner's prima facie case of obviousness by a preponderance of the evidence. The obviousness rejection is affirmed.

CONCLUSION OF LAW

The cited references support the Examiner's prima facie obviousness rejection, which has not been rebutted by Appellant by a preponderance of the evidence. Appellant has failed to present comparative evidence to rebut the Examiner's prima facie case of obviousness. The obviousness rejection is affirmed.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

kmm