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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte HECTOR F. DELUCA,
LORI A. PLUM, and MARGARET CLAGETT-DAME

Appeal 2017-010188
Application 14/710,744
Technology Center 1600

Before RICHARD M. LEBOVITZ, JEFFREY N. FREDMAN, and JOHN E. SCHNEIDER, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal[1],[2] under 35 U.S.C. § 134 involving claims to a method of reducing serum parathyroid hormone levels in a subject having primary hyperparathyroidism and exhibiting elevated serum parathyroid hormone levels. The Examiner rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

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[1] Appellants identify the Real Party in Interest as the Wisconsin Alumni Research Foundation (*see* App. Br. 1).

[2] We have considered and herein refer to the Specification of May 13, 2015 ("Spec."); Final Office Action of May 13, 2016 ("Final Act."); Appeal Brief of Jan. 1, 2017 ("App. Br."); Examiner's Answer of May 23, 2017 ("Ans."); and Reply Brief of July 24, 2017 ("Reply Br.").

Statement of the Case

Background

"'Hyperparathyroidism' refers to a disorder of the parathyroid glands in which the parathyroid glands exhibit overactivity. 'Primary' hyperparathyroidism means the disorder originates in the parathyroid glands themselves in contrast to 'secondary' hyperparathyroidism which means the disorder results subsequent to another underlying disease" (Spec. ¶ 3). "In primary hyperparathyroidism, the parathyroid glands become overactive and release excessive parathyroid hormone (PTH) into the blood stream. One of the primary functions of PTH is to increase serum calcium levels" (*id.* ¶ 4). "[E]xcessive serum PTH results in excessive serum calcium levels or 'hypercalcemia,' which presents a number of health risks" (*id.* ¶ 5).

"In order to reduce PTH secretion directly, a calcimimetic also may be administered to treat primary hyperparathyroidism. A calcimimetic is an agent that mimics the effect of calcium on the calcium receptors (CaRs) in the parathyroid gland" (*id.* ¶ 9). "[N]ew vitamin D analogs that can be used to treat primary hyperparathyroidism are highly desirable" (*id.* ¶ 11). The Specification teaches that "a highly potent active vitamin D analog (AVD), namely, 2-methylene-19-nor-(20S)-1α,25-dihydroxyvitamin D_3, otherwise referred to as '2MD' is shown to suppress PTH production in patients having primary hyperparathyroidism without increasing serum calcium or serum phosphate" (*id.* ¶ 11).

The Claims

Claims 1, 3, 4, and 6–9 are on appeal. Independent claim 1 is representative and reads as follows:

> 1. A method of reducing serum parathyroid hormone levels in a subject having primary hyperparathyroidism and exhibiting elevated serum parathyroid hormone levels, the method comprising administering a therapeutically effective amount of 2-methylene-19-nor-(20S)-1α,25-dihydroxyvitamin D_3 or a pharmaceutically acceptable salt thereof to the subject wherein the serum parathyroid hormone levels in the subject are reduced without inducing hypercalcemia in the subject.

The Issues

A. The Examiner rejected claims 1, 3, 4, 6, and 9 under 35 U.S.C. § 103(a) as obvious over Shevde,[3] Khan,[4] and Taniegra[5] (Final Act. 4–7).

B. The Examiner rejected claims 7 and 8 under 35 U.S.C. § 103(a) as obvious over Shevde, Khan, Taniegra, and Michis-Troussard[6] (Final Act. 7–9).

A. 35 U.S.C. § 103(a) over Shevde, Khan, and Taniegra

The Examiner finds Shevde teaches "2MD is a potent bone-selective analog of [1, 25-dihydroxy-vitamin D3] effective in treating bone loss diseases" but acknowledges that Shevde "does not teach treatment of primary hyperparathyroidism" (Final Act. 5).

The Examiner finds Khan teaches "primary hyperparathyroidism is associated with bone loss" and that the "calcium receptor allows calcium to act with parathyroid hormone (PTH) and 1,25-dihydroxy-vitamin D3 in

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[3] Shevde et al., *A potent analog of 1α,25-dihydroxyvitamin D_3 selectively induces bone formation*, 99 PROC. NAT'L ACAD. SCI. USA 13487–91 (2002).
[4] Khan et al., *Primary hyperparathyroidism: pathophysiology and impact on bone*, 163 CMAJ 184–7 (2000).
[5] Taniegra, *Hyperparathyroidism*, 69 AM. FAMILY PHYSICIAN 333–9 (2004).
[6] Mischis-Troussard et al., *Primary hyperparathyroidism with normal serum intact parathyroid hormone levels*, 93 QJ MED. 365–7 (2000).

maintaining calcium homeostasis" (Final Act. 5–6). The Examiner finds Khan teaches "when extracellular calcium binds to the calcium receptor in the parathyroid cell, PTH secretion and parathyroid cell growth are inhibited" (*id.* at 6). The Examiner acknowledges that "[n]either Shevde nor Khan teach serum parathyroid hormone levels in primary hyperparathyroidism patients" (*id.* at 6).

The Examiner finds Taniegra teaches "that persistent hypercalcemia and an elevated serum parathyroid hormone level are the diagnostic criteria for primary hyperparathyroidism" and that "in the diagnosis and treatment of hyperparathyroidism that one should check for signs and symptoms of hypercalcemia and manage crisis if present" (Final Act. 6).

The Examiner finds it obvious

> to have administered 2MD to patients with primary hyperparathyroidism with elevated parathyroid hormone levels. One would have been motivated to do so because 1) Shevde teaches that 2MD is a potent bone-selective analog of [1, 25-dihydroxy-vitamin D3] effective in treating bone loss diseases by inducing substantial bone growth both in vitro and in vivo, 2) Khan teaches that primary hyperparathyroidism is associated with bone loss, and 3) Taniegra teaches that patients with primary hyperparathyroidism have elevated parathyroid hormone levels and persistent hypercalcemia that should be managed and monitored.

(Final Act. 6–7).

The issue with respect to this rejection is: Does the evidence of record support the Examiner's conclusion that Shevde, Khan, and Taniegra renders treatment of patients "having primary hyperparathyroidism and exhibiting elevated serum parathyroid hormone levels" with 2MD obvious as required by claim 1?

Findings of Fact

1. Shevde teaches:

> We report here on the properties of 2-methylene-19-nor-(20S)-1α,25-$(OH)_2D_3$ (2MD), a highly potent analog of 1,25$(OH)_2D_3$ that induces bone formation both *in vitro* and *in vivo*. Selectivity for bone was first demonstrated through the observation that 2MD is at least 30-fold more effective than 1,25$(OH)_2D_3$ in stimulating osteoblast-mediated bone calcium mobilization while being only slightly more potent in supporting intestinal calcium transport. 2MD is also highly potent in promoting osteoblast- mediated osteoclast formation in vitro, a process essential to both bone resorption and formation.

(Shevde 13487, abstract).

2. Figure 1a of Shevde is reproduced below:

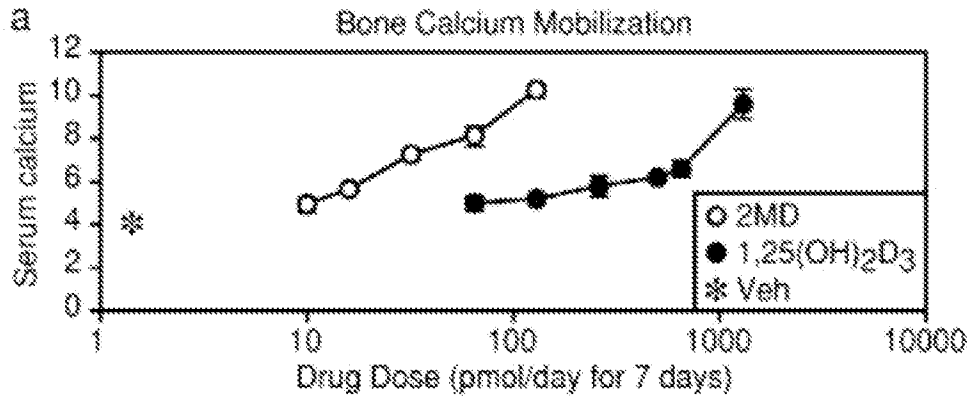

Figure 1a shows animals were treated with "the indicated doses of either 1,25$(OH)_2D_3$ or 2MD" and "(a) Twenty-four hours after the final dose . . . blood was taken to determine serum calcium levels (mg/dl)" (Shevde 13488, col. 2).

3. Khan teaches "[p]rimary hyperparathyroidism has been associated with bone loss, especially at cortical skeletal sites" (Khan 184, abstract).

4. Khan teaches "discovery of the calcium receptor that allows calcium to act with PTH and 1,25-dihydroxy-vitamin D_3 in maintaining calcium homeostasis" (Khan 184).

5. Khan teaches "[w]hen extracellular calcium binds to the calcium receptor in the parathyroid cell, PTH secretion and parathyroid cell growth are inhibited" (Khan 184).

6. Taniegra teaches "[p]ersistent hypercalcemia and an elevated serum parathyroid hormone level are the diagnostic criteria for primary hyperparathyroidism. Other causes of hypercalcemia are rare" (Taniegra 333, abstract).

7. Taniegra teaches "[c]onfirmed hypercalcemia: check for signs and symptoms of hypercalcemia; manage crisis if present" (Taniegra 336, Figure 2).

8. Taniegra teaches "no medical therapies are available to effectively cure primary hyperparathyroidism. In postmenopausal women, estrogen may reduce PTH-stimulated bone resorption. The effects of newer oral bisphosphonates, calcimimetics, and raloxifene are being studied. Medications may be tried in symptomatic patients who have severe concurrent illness but are poor surgical candidates" (Taniegra 339, col. 1).

Principles of Law

A prima facie case for obviousness "requires a suggestion of all limitations in a claim," *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) and "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007).

Analysis

Appellants contend "claim 1 was amended to recite a method of administering 2MD to a specific class of subjects, which are subjects having primary hyperparathyroidism and exhibiting elevated serum PTH levels" (App. Br. 5). Appellants contend "a patient group having primary hyperparathyroidism and exhibiting elevated serum parathyroid hormone levels is a distinct patient group and is not the same as a patient group having primary hyperparathyroidism and exhibiting bone loss" (*id.* at 9). Appellants contend "[a]dministering a therapeutically effective amount of 2MD to this specific class of patients without inducing hypercalcemia is not taught or suggested in the art, explicitly or inherently" (*id.* at 8). Appellants contend regarding the primary prior art reference cited, Shevde, that:

> Even if Shevde discloses the use of 2MD for bone formation, Shevde does not disclose that 2MD can be administered at a therapeutically effective dose such that serum PTH levels are reduced without inducing hypercalcemia in a subject having primary hyperparathyroidism. Rather, Shevde discloses that 2MD can be administered to increase bone mass in ovariectomized rats in vivo at a dose that resulted only in a slight increase in serum calcium levels.

(App. Br. 10).

The Examiner finds "the combination of references teaches the instant patient population of subjects having both 1) primary hyperparathyroidism, and 2) elevated parathyroid hormone levels" (Ans. 9). The Examiner finds "while the two patient populations are not entirely the same, the rejection is maintained as it reads on the instant patient population as Appellant admits the patient populations overlap in scope" (*id.* at 10). The Examiner finds "a reduction in serum parathyroid hormones and avoidance of hypercalcemia

would naturally flow from practicing the prior art method of the above aforementioned references, which render obvious administration of 2MD" (*id.* at 11).

We agree with Appellants that the patient populations disclosed in Shevde, Khan, and Taniegra differ from the patient population recited in claim 1 who must have "primary hyperthyroidism and exhibiting elevated serum parathyroid levels" and where effective treatment with 2MD reduces parathyroid levels without inducing hypercalcemia.

In *Perricone*, the Federal Circuit distinguished between the topical application of a lotion to skin generally to prevent sunburn, and the topical application of a lotion to treat sunburned skin, finding that the "issue is not . . . whether [the prior art] lotion if applied to skin sunburn would inherently treat that damage, but whether Pereira discloses the application of its composition to skin sunburn. It does not." *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1378 (Fed. Cir. 2005).

Similar to *Perricone*, claim 1 does not require administration of 2MD to patients with hyperparathyroidism generally, but rather limits administration to a specific subset of patients who not only meet the general requirement of elevated serum parathyroid hormone levels disclosed by Taniegra (FF 6) but further limits the patient population to those for whom administration of 2MD will not induce hypercalcemia. As Appellants point out, "Shevde discloses that 2MD can be administered to increase bone mass in ovariectomized rats *in vivo* at a dose that resulted only in a slight increase in serum calcium levels", and further note that Shevde does not show that these 2MD levels necessarily result in reducing elevated parathyroid hormone levels (*see* App. Br. 10; *see, e.g.,* Figure 1A of Shevde (FF 2)).

Appellants argue that based on 2MD's calcimetic properties, it would be expected that it would induce hypercalcemia (see App. Br. 10–11; FF 2). In response to these arguments, the Examiner has not established that the ordinary artisan would have expected that 2MD not induce hypercalcemia, and therefore has not established that the particular patient population at issue would have been obvious based on the prior art.

We also note, regarding the Examiner's argument that the treatment would "naturally flow from practicing the prior art method" (Ans. 11) that as in *Perricone*, the issue is not whether 2MD would inherently treat the patient population of claim 1, but rather whether the combination of Shevde, Khan, and Taniegra suggest treatment of the particular patient subpopulation required by claim 1. The claim is a method claim, not a product claim, and therefore the intended patient population is not an "intended use" recitation but rather is a limitation of the claim. We note that "every limitation positively recited in a claim must be given effect in order to determine what subject matter that claim defines." *In re Wilder*, 429 F.2d 447, 450 (CCPA 1970).

Conclusion of Law

The evidence of record does not support the Examiner's conclusion that Shevde, Khan, and Taniegra renders treatment of patients "having primary hyperparathyroidism and exhibiting elevated serum parathyroid hormone levels" with 2MD obvious as required by claim 1.

B. 35 U.S.C. § 103(a) over Shevde, Khan, Taniegra, and Michis-Troussard

Having reversed the obviousness rejection of claim 1 for failing to render the patient population required by claim 1 obvious for the reasons given above, we also find that the further combination with Michis-Troussard does not address this issue and therefore does not render the rejected claims obvious for the same reasons.

SUMMARY

In summary, we reverse the rejection of claims 1, 3, 4, 6, and 9 under 35 U.S.C. § 103(a) as obvious over Shevde, Khan, and Taniegra.

We reverse the rejection of claims 7 and 8 under 35 U.S.C. § 103(a) as obvious over Shevde, Khan, Taniegra, and Michis-Troussard.

REVERSED