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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte ISAN CHEN,
JEFFREY H. HAGER, EDNA CHOW MANEVAL,
MARK R. HERBERT, and NICHOLAS D. SMITH

Appeal 2020-000990
Application 15/094,113
Technology Center 1600

Before FRANCISCO C. PRATS, JOHN G. NEW, and DAVID COTTA, *Administrative Patent Judges*.

PRATS, *Administrative Patent Judge*.

DECISION ON APPEAL

Pursuant to 35 U.S.C. § 134(a), Appellant[1] appeals from the Examiner's decision to finally reject claims 1, 2, 5, 6, 19–21, and 28–36. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

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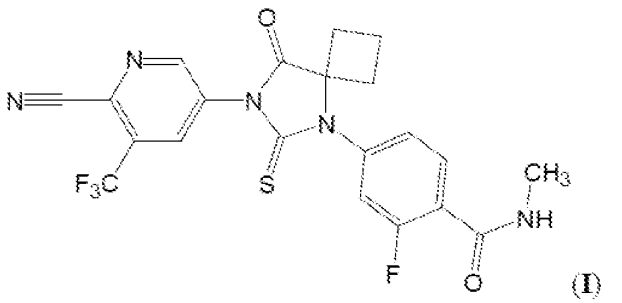
[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identifies Aragon Pharmaceuticals, Inc., a wholly-owned subsidiary of Johnson & Johnson, as the real party in interest. Appeal Br. 1.

STATEMENT OF THE CASE

The sole rejection before us for review is the Examiner's rejection of claims 1, 2, 5, 6, 19–21, and 28–36 under 35 U.S.C. § 103(a) as being unpatentable over Szmulewitz[2] (Final Act. 4–6;[3] Ans. 4–7)[4].

Claim 1 is representative and reads as follows:

> 1. A method of treating metastatic castration-resistant prostate cancer, non-metastatic castration-resistant prostate cancer, metastatic castration-sensitive prostate cancer, non-metastatic castration-sensitive prostate cancer or high-risk localized prostate cancer in a male human patient comprising orally administering the compound of Formula (I), or a pharmaceutically acceptable salt thereof,
>
> 
> (I),
>
> to a human male patient in need of such treatment at a dose of about 30 mg per day to about 480 mg per day, in combination with:
>
> (a) abiraterone acetate; and
>
> (b) a corticosteroid.

Appeal Br. 12.

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[2] US 9,289,436 B2 (issued Mar. 22, 2016).
[3] Final Action entered October 5, 2018.
[4] Examiner's Answer entered September 17, 2019.

DISCUSSION

The Examiner's Prima Facie Case

The Examiner cited various teachings in Szmulewitz as suggesting treatment of prostate cancer with all of the therapeutic agents recited in Appellant's claim 1, including the compound of Appellant's Formula (I) (also known as ARN-509 (*see* Spec. ¶ 61)), abiraterone acetate, and a corticosteroid. Ans. 4–6. The Examiner also noted Szmulewitz's teaching that leuprolide and goserelin were useful for treating prostate cancer. *Id.* 4.

Based on the identified teachings, the Examiner concluded that Szmulewitz "*renders obvious* a composition comprising . . . ARN-509[] in combination with abiraterone acetate (tradename Zytiga) and a corticosteroid (e.g., prednisone) wherein the dosage of composition components may vary and the composition is used for treating various prostate cancer conditions." Ans. 7.

Analysis

As stated in *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992):

> [T]he examiner bears the initial burden . . . of presenting a *prima facie* case of unpatentability. . . .
>
> After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of argument.

In the present case, having carefully considered all of the evidence and arguments presented by Appellant and the Examiner, Appellant does not persuade us that the Examiner's conclusion of obviousness as to Appellant's claim 1 is not supported by a preponderance of the evidence.

Szmulewitz describes "a method of treating castration-resistant prostate cancer in a subject comprising administering to said subject a glucocorticoid receptor (GR) antagonist." Szmulewitz 3:30–33. Szmulewitz thus describes treating a patient encompassed by Appellant's claim 1. *See* Appeal Br. 12 (claim 1 reciting "[a] method of treating metastatic castration-resistant prostate cancer" as well as "non-metastatic castration-resistant prostate cancer").

As required by Appellant's claim 1, Szmulewitz's GR antagonist may be a corticosteroid. *See* Szmulewitz 3:42–44 ("The GR antagonist may be beclometasone, betamethasone, budesonide, ciclesonide, flunisolide, fluticasone, GSK650394, mifepristone, mometasone, or triamcinoclone."). [5] Szmulewitz also discloses that the corticosteroid prednisone was known to be useful for treating prostate cancer in combination with abiraterone acetate, one of the therapeutic agents recited in Appellant's claim 1. *See id.* 14:7–11 ("On Apr. 28, 2011, the U.S. Food and Drug Administration approved abiraterone acetate in combination with prednisone to treat patients with late-stage (metastatic) castration-resistant prostate cancer patients who have received prior docetaxel (chemotherapy).").

As required by Appellant's claim 1, the subject receiving Szmulewitz's GR antagonist may also "currently be[]treated with an androgen receptor (AR) antagonist, such as . . . ARN-509." Szmulewitz

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[5] At the time of Appellant's earliest priority date beclometasone, betamethasone, budesonide, flunisolide, fluticasone, and triamcinoclone were well known corticosteroids. *See* US 6,241,969 B1 (issued June 5, 2001) at 6:8–30 (listing beclometasone, betamethasone, budesonide, flunisolide, fluticasone, and triamcinoclone as exemplary corticosteroids useful in in corticosteroid formulations).

3:38–39. As noted above ARN-509 is the compound of Appellant's Formula (I) recited in Appellant's claim 1. *See* Spec. ¶ 61.

Although Szmulewitz does not expressly describe administering ARN-509 at the dose of about 30 mg per day to about 480 mg per day recited in Appellant's claim 1, Szmulewitz discloses that it was known in the art to optimize the dosage of medicaments used to treat prostate cancer. *See* Szmulewitz 23:21–24 ("Some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject."). Szmulewitz, moreover, suggests that any of the therapeutic agents described in its disclosure may be administered at wide dosage ranges. *See id.* 21:45–58 ("A patient may be administered a single GR antagonist *or a combination of compounds described herein* in an amount that is, is at least, or is at most 0.1 . . ., 500 mg/kg/day (or any range derivable therein)." (emphasis added)).

We therefore agree with the Examiner that, given the absence of evidence of unexpected results, the ARN-509 dosage recited in claim 1 would have been obvious to a skilled artisan. *See Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004) ("Where 'the difference between the claimed invention and the prior art is some range or other variable within the claims . . ., the [applicant] must show that the particular range is critical, generally by showing that the claimed range achieves unexpected results.'") (quoting *In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990)).

As required by Appellant's claim 1, the subject receiving Szmulewitz's GR antagonist "may be treated with a second prostate cancer

therapy . . . [which] may be an androgen synthesis inhibitor, such as . . . abiraterone." Szmulewitz 3:46–51.

Thus, given the teachings in Szmulewitz that ARN-509, abiraterone acetate, and a corticosteroid, would be useful in combination for treating castration-resistant prostate cancer, we agree with the Examiner that a skilled artisan had a good reason for, and a reasonable expectation of success in, administering all of those agents to treat either metastatic or non-metastatic castration-resistant prostate cancer, as recited in Appellant's claim 1. We therefore also agree with the Examiner that the process of Appellant's claim 1 would have been obvious in view of Szmulewitz.

Appellant's arguments do not persuade us to the contrary.

In particular, given Szmulewitz's express disclosure that its GR antagonist can be administered to a patient that is treated with an AR antagonist, such as ARN-509, as well as an androgen synthesis inhibitor, such as abiraterone (*see* Szmulewitz 3:37–51), Appellant does not persuade us that the Examiner failed to identify a reason for combining ARN-509 and abiraterone when treating prostate cancer, or that the Examiner's reasoning was based on improper hindsight. *See* Appeal Br. 5–7; Reply Br. 7–8. The fact that Szmulewitz lists ARN-509 and abiraterone among other therapies does not negate that fact that Szmulewitz expressly describes ARN-509 and abiraterone as being useful in combination with other agents when treating prostate cancer. *See Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) (species claim held obvious where it recited one of 1200 possible combinations of embodiments disclosed by reference and where reference suggested no preference for claimed embodiment); *see also id.*

808 (That a reference "discloses a multitude of effective combinations does not render any particular formulation less obvious.").

Appellant, moreover, fails to identify any persuasive evidence of record supporting its assertion that a skilled artisan would have viewed ARN-509 and abiraterone as being potentially incompatible (*see* Appeal Br. 6), despite Szmulewitz's express suggestion that combining an AR antagonist such as ARN-509 and an androgen synthesis inhibitor such as abiraterone would be useful for treating prostate cancer (*see* Szmulewitz 3:37–51). Appellant's assertion as to the potential for increased side effects when combining ARN-509 and abiraterone is therefore unsupported attorney argument entitled to little, if any, probative weight. *See Johnston v. IVAC Corp.*, 885 F.2d 1574, 1581 (Fed. Cir. 1989) ("Attorneys' argument is no substitute for evidence.").

Appellant also does not persuade us that Szmulewitz teaches away from using a corticosteroid in its methods. *See* Appeal Br. 7–9; Reply Br. 3–5. We acknowledge, as Appellant contends, that administration of GR antagonists is central to Szmulewitz's prostate cancer treatments. *See* Szmulewitz, abstract ("Methods are directed to the treatment of subjects with prostate cancer, in particular those with castration resistant prostate cancer, with glucocorticoid receptor antagonists."); *see also id.* 3:30–33 ("In one aspect of the invention, there is provided a method of treating castration-resistant prostate cancer in a subject comprising administering to said subject a glucocorticoid receptor (GR) antagonist.").

As noted above, however, Szmulewitz expressly discloses that its GR antagonist can be any of a number of known corticosteroids, including for example beclometasone, betamethasone, budesonide, flunisolide,

fluticasone, and triamcinoclone. *See* Szmulewitz 3:42–44. Appellant does not persuade us, therefore, that Szmulewitz teaches away from using corticosteroids in its methods, or that Szmulewitz teaches away from treating prostate cancer with a corticosteroid in combination with ARN-509 and abiraterone, as recited in Appellant's claim 1.

We acknowledge, as Appellant contends (*see* Appeal Br. 8–9; Reply Br. 3–5), that Szmulewitz distinguishes between a standard treatment of prostate cancer using a GR agonist such as prednisone (a corticosteroid), and the use of GR antagonists for treating prostate cancer, which Szmulewitz describes as its invention. *Compare* Szmulewitz 2:17–29 (questioning the efficacy of prednisone, "a GR agonist," in treating prostate cancer) *with id.* 28:18–21 (Szmulewitz noting that its experimental data in cancer cell lines "suggest that increased GR expression and activity antagonizes AR inhibition and sustains tumor cell survival") *and id.* 28:50–54 ("[T]he inventors believe that a GR inhibitor will synergize with second generation AR-inhibitors, such as MDV3100, and delay the onset of CRPC [(castrate resistant prostate cancer)] progression in patients treated with the combination compared to patients treated with MDV3100 alone.").

However, the fact that the inventors in Szmulewitz describe GR antagonists as their preferred alternative to a more conventional GR agonist treatment does not negate the fact that Szmulewitz discloses the combination of a corticosteroid (prednisone) and abiraterone acetate, two of the three ingredients recited in Appellant's claim 1, as an FDA-approved prostate cancer treatment. *See* Szmulewitz 14:7–11. And, as noted above, Szmulewitz further discloses that ARN-509 was a known AR antagonist

useful for treating prostate cancer in combination with other agents. *See id.* 3:37–39.

Given these teachings, Appellant does not persuade us that the Examiner erred in determining that a skilled artisan, even advised of Szmulewitz's preference for GR antagonists, had motivation for combining ARN-509 with the FDA-approved abiraterone/prednisone treatment known in the art. *See In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004) ("[O]ur case law does not require that a particular combination must be the preferred, or the most desirable, combination described in the prior art in order to provide motivation for the current invention."). Indeed, given Szmulewitz's express teaching that its GR antagonist can be any of a number of known corticosteroids, including for example beclometasone, betamethasone, budesonide, flunisolide, fluticasone, and triamcinoclone (*see* Szmulewitz 3:42–44), Appellant does not persuade us that Szmulewitz teaches away from using corticosteroids in its methods, or that Szmulewitz teaches away from treating prostate cancer with a corticosteroid in combination with ARN-509 and abiraterone, as recited in Appellant's claim 1.

Appellant also does not persuade us that the Examiner's characterization in the Final Action of ARN-509 as a GR antagonist undermines the Examiner's conclusion that the ARN-509 dosage of about 30 mg per day to about 480 mg per day recited in Appellant's claim 1 would have been obvious to a skilled artisan. *See* Appeal Br. 9–10. In response to this argument the Examiner contends that that "initial reference to ARN-509 as the glucocortico[i]d receptor (GR) . . . was an obvious typographical error as indicated by the referenced portion of Szmulewitz et al which specifically

state[s] that ARN-509 is an androgen receptor (AR) substance (column 3, lines 38-39)." Ans. 16. Appellant does not reply to the Examiner's contention directly. *See* Reply Br. *generally*.

In any event, as noted above, Szmulewitz discloses that it was known in the art to optimize the dosage of medicaments used to treat prostate cancer. *See* Szmulewitz 23:21–24 ("Some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject."). Szmulewitz, moreover, suggests that any of the therapeutic agents described in its disclosure may be administered at wide dosage ranges. *See id.* 21:45–58 ("A patient may be administered a single GR antagonist *or a combination of compounds described herein* in an amount that is, is at least, or is at most 0.1 . . ., 500 mg/kg/day (or any range derivable therein)." (emphasis added)). Appellant does not persuade us, therefore, that the Examiner erred in determining that the ARN-509 dosage recited in Appellant's claim 1 would have been obvious to a skilled artisan. *See Iron Grip Barbell v. USA Sports*, 392 F.3d at 1322 ("Where the difference between the claimed invention and the prior art is some range or other variable within the claims . . ., the [applicant] must show that the particular range is critical, generally by showing that the claimed range achieves unexpected results.") (internal quotations omitted)).

Appellant also does not persuade that the Examiner reversibly erred in characterizing Appellant's claim 1 as reciting a "composition" rather than a process (Reply Br. 2), or in characterizing Szmulewitz's primary therapeutic agent as a GR "substance" rather than a GR antagonist (*see id.* 3; *see also* Ans. 4–6). To the contrary, for the reasons discussed above, we agree with

the Examiner that the teachings of Szmulewitz would have provided a skilled artisan with a good reason for, and a reasonable expectation of success in, treating either metastatic or non-metastatic castration-resistant prostate cancer, as recited in Appellant's claim 1, using the combination of agents recited in the claim, at the claimed dosages. We therefore affirm the Examiner's rejection of claim 1 for obviousness over Szmulewitz. Because they were not argued separately, claims 2, 19, 20, and 32–36 fall with claim 1. *See* 37 C.F.R. § 41.37(c)(1)(iv) (2018).

Appellant argues claims 5, 6, and 21 as a separate claim grouping. Appeal Br. 10. We select claim 21 as representative of this group of claims. *See* 37 C.F.R. § 41.37(c)(1)(iv).

Claim 21 recites "[t]he method of claim 1, further comprising administering a therapeutically effective amount of a gonadotropin-releasing hormone [GnRH] agonist or antagonist to the male human patient." Appeal Br. 17. Appellant's Specification explains that, "[i]n some embodiments, the GnRH agonist or antagonist is leuprolide . . . ." Spec. 28

Appellant contends that the Examiner "failed to identify any disclosure in Szmulewitz that teaches or suggests *further* combination with a GnRH agonist or antagonist (claim 21) such as leuprolide (claim 5) or goserelin acetate (claim 6)." Appeal Br. 10. Instead, Appellant contends, "the Examiner appears to rely on a disclosure of leuprolide and goserelin as potential combination agents with a GR antagonist at col. 3, lines 47-49." *Id.* (citing Final Act. 4).

We are not persuaded. As noted above, Szmulewitz's GR antagonist may be any one of a number of known corticosteroids, including for example beclometasone, betamethasone, budesonide, flunisolide,

fluticasone, and triamcinoclone. *See* Szmulewitz 3:42–44. And, in addition to ARN-509 and abiraterone, Szmulewitz describes administering its GR antagonist prostate cancer treatment to a subject "currently being treated with androgen deprivation therapy, such as with leuprolide goserelin." Szmulewitz 3:35–36. Appellant does not persuade us, therefore, that the Examiner erred in finding that Szmulewitz would have suggested including a GnRH agonist or antagonist such as leuprolide in a corticosteroid/ARN-509/abiraterone combination therapy for treating prostate cancer. Accordingly, we also affirm the Examiner's rejection of claim 21 over Szmulewitz. Because they were argued in the same claim grouping, claims 5 and 6 fall with claim 21. *See* 37 C.F.R. § 41.37(c)(1)(iv).

Appellant argues claims 28–31 as a separate claim grouping. Appeal Br. 10. We select claim 29 as representative of this group of claims. *See* 37 C.F.R. § 41.37(c)(1)(iv).

Claim 29 recites "[t]he method according to claim 1, wherein the [ARN-509], or a pharmaceutically acceptable salt thereof and abiraterone acetate and the corticosteroid are administered at the same time." Appeal Br. 18. As to claim 29, Appellant argues that the Examiner "references the disclosure in Szmulewitz relating to routes of administration and frequency of administration of a ***GR antagonist***." Appeal Br. 10 (citing Final Act. 4–5). We are not persuaded.

As noted above, Szmulewitz teaches that its GR antagonists, which may be corticosteroids, may be administered to a patient that "is currently being treated" with an AR antagonist such as ARN-509. Szmulewitz 3:38. Szmulewitz also discloses combining its GR antagonists "with a second prostate cancer therapy [which] . . . may be abiraterone . . . ." *Id.* 3:47–51.

Szmulewitz explains further that "[t]he second prostate cancer therapy may be given prior to said GR antagonist, after said GR antagonist, or at the same time as said GR antagonist." *Id.* at 3:54–56.

Given Szmulewitz's disclosure that its GR antagonist, which may be a corticosteroid, and its second prostate cancer therapy, which may abiraterone, can be administered at the same time, we are not persuaded that the Examiner erred in finding that Szmulewitz would have suggested administering those agents at the same time, as recited in Appellant's claim 29. Moreover, given Szmulewitz's disclosure that its GR antagonist can be administered to a patient receiving ARN-509, we discern no error in the Examiner's determination that it also would have been obvious to administer ARN-509 at the same time as the other agents. We therefore affirm the Examiner's rejection of claim 29 over Szmulewitz. Because they were argued in the same claim grouping, claims 28, 30, and 31 fall with claim 29. *See* 37 C.F.R. § 41.37(c)(1)(iv).

DECISION SUMMARY

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
1, 2, 5, 6, 19–21, 28–36	103(a)	Szmulewitz	1, 2, 5, 6, 19–21, 28–36	

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). *See* 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED