UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/407,498	12/12/2014	András Varró	DAN-134	8124

12495 7590 06/15/2020

Jason D. Voight
3312 N. Kensington St.
Arlington, VA 22207

EXAMINER	
RAMACHANDRAN, UMAMAHESWARI	

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
06/15/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

jason.voight@gmail.com
jason.voight@voightip.com

UNITED STATES PATENT AND TRADEMARK OFFICE

_____

BEFORE THE PATENT TRIAL AND APPEAL BOARD

_____

Ex parte ANDRÁS VARRÓ, PÉTER MÁTYUS, ISTVÁN BACZKÓ, GYÖRGY FALKAY, NORBERT JOST, ISTVÁN LEPRÁN, ANITA SZTOJKOV-IVANOV, LÁSZLÓ VIRÁG, and NORBERT BUZÁS

_____

Appeal 2019-005815
Application 14/407,498
Technology Center 1600

_____

Before FRANCISCO C. PRATS, ELIZABETH A. LAVIER, and RACHEL H. TOWNSEND, *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 reject claims 5–11. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

---

[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant states that the real party in interest Szegedi Tudományegyetem. Appeal Br. 2.

STATEMENT OF THE CASE

The following rejections are before us for review:

(1) Claims 5–11 under 35 U.S.C. § 103(a) as being unpatentable over Varro 1,[2] Varro 2,[3] Tieleman,[4] and Letelier[5] (Ans. 4–8);

(2) Claims 5–9 under 35 U.S.C. § 103(a) as being unpatentable over Tieleman, Letelier, and Varro 2 (Ans. 8–10); and

(3) Claims 5–9 under 35 U.S.C. § 103(a) as being unpatentable over Tieleman, Letelier, Nattel,[6] and Varro 2 (Ans. 10–13).

Appellant's claim 5, the sole independent claim on appeal, is representative and reads as follows:

> 5. A method for the treatment and/or reducing the incidence of atrial fibrillation, said method comprising orally administering to a human or animal a pharmaceutical composition comprising a compound selected from the group consisting of desethylamiodarone [(DEA)] and pharmaceutically acceptable salts, hydrates and solvates thereof, together with pharmaceutically acceptable excipients, vehicle and/or carrier.

---

[2] András Varró et al., *Antiarrhythmic effect of desethylamiodarone in conscious rats*, 39 J. PHARM. PHARMACOL. 483–484 (1987).
[3] A. Varro et al., *Long-term cardiac electrophysiological effect of desethylamiodarone in dog cardiac muscle*, 22 EUR. HEART J. 55 (Abstr. Suppl., abstract P415) (2001).
[4] Robert G. Tieleman et al., *Efficacy, Safety, and Determinants of Conversion of Atrial Fibrillation and Flutter With Oral Amiodarone*, 79 AMERICAN J. CARDIOL. 53–57 (1997).
[5] Luz M. Letelier et al., *Effectiveness of Amiodarone for Conversion of Atrial Fibrillation to Sinus Rhythm*, 163 ARCH. INTERN. MED. 777–785 (2003).
[6] Stanley Nattel et al., *The antiarrhythmic efficacy of amiodarone and desethylamiodarone, alone and in combination, in dogs with acute myocardial infarction*, 77 CIRCULATION 200–208 (1988).

Appeal Br. 15.

OBVIOUSNESS—
VARRO 1, VARRO 2, TIELEMAN, AND LETELIER

The Examiner's Prima Facie Case

In rejecting Appellant's claims 5–11 over Varro 1, Varro 2, Tieleman, and Letelier, the Examiner cited Varro 1 and Varro 2 as evidence that desethylamiodarone (DEA) was known in the art to be useful for treating cardiac arrhythmias. Ans. 5–6. In particular, the Examiner noted the teaching in Varro 1 that DEA is a metabolite of amiodarone (AMIO) that appears in plasma and accumulates in cardiac muscle during chronic treatment of cardiac arrhythmias with AMIO. *Id.* at 5. The Examiner also specifically noted Varro 1's teaching that the electrophysiological effects of DEA are very similar to the effects of AMIO. *Id.*

In Varro 2, the Examiner noted the teaching of "the possibility that DEA treatment alone would be effective and may be a less dangerous antiarrhythmic treatment than that of AMIO (see P 415)." Ans. 6.

The Examiner conceded that Varro 1 and Varro 2 differ from the rejected claims in that "Varro 1 explicitly demonstrate[s] the anti-arrhythmic activity of DEA but do[es] not teach the arrhythmia to be treated as atrial fibrillation." Ans. 6.

As evidence that it would have been obvious to orally administer DEA to treat atrial fibrillation as recited in Appellant's claims, the Examiner cited Tieleman as disclosing that, when chronically administering AMIO to treat atrial fibrillation, plasma levels of the metabolite DEA were more important than levels of the parent compound, AMIO. Ans. 7. The

Examiner cited Letelier as evidence that AMIO was known to be useful for treating atrial fibrillation in an oral dosage regimen. *Id.*

Based on the references' combined teachings, the Examiner concluded that it would have been obvious to orally administer DEA to treat atrial fibrillation. *See* Ans. 7–8.

Analysis

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

> [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.

Having carefully considered all of the arguments and evidence advanced by Appellant and the Examiner, Appellant does not persuade us that a preponderance of the evidence fails to support the Examiner's conclusion of obviousness as to Appellant's representative claim 5.

As seen above, representative claim 5 recites treating and/or reducing the incidence of atrial fibrillation by orally administering a pharmaceutical composition that contains DEA, or pharmaceutically acceptable salts, hydrates, and solvates thereof, together with a pharmaceutically acceptable excipient, vehicle, and/or carrier. Appeal Br. 15.

As explained in Letelier, atrial fibrillation is "the most commonly encountered arrhythmia." Letelier 777. Letelier discloses, moreover, that AMIO "is effective for converting AF [(atrial fibrillation)] to sinus rhythm in a wide range of patients." *Id.*

Tieleman, similar to Letelier, discloses that chronic oral administration of AMIO is an effective treatment for atrial fibrillation. *See* Tieleman 53 ("[AMIO] loading is safe and is still able to convert refractory atrial fibrillation or flutter.") (Abstract).

Although neither Letelier nor Tieleman discloses treating atrial fibrillation patients with DEA as recited in Appellant's claim 5, Tieleman discloses that the therapeutic antiarrhythmic effects of chronic oral administration of AMIO are positively correlated with plasma levels of DEA, the metabolite of AMIO. *See* Tieleman 53 ("Conversion is related to increased [DEA] plasma levels and concomitant treatment with verapamil. Because prolonged loading may increase [DEA] plasma concentrations, this may enhance efficacy and obviate the need for electrical cardioversion."); *see also id.* at 56 ("The present study showed that for conversion of atrial fibrillation, plasma concentrations of [DEA] were more important than those of the parent compound.").

Given Tieleman's determination that, when treating atrial fibrillation by chronic oral administration of AMIO, the plasma concentration of DEA was more important to the therapeutic effect than the plasma concentration of AMIO, we agree with the Examiner that a skilled artisan had a good reason for administering DEA, instead of AMIO, when treating atrial fibrillation. The teachings in Varro 1 and Varro 2 bolster that finding.

Specifically, turning first to Varro 2, the reference describes a study of chronic oral administration of DEA to dogs and, based on the results of the study, "[i]t was concluded that chronic DEA treatment exerts electrophysiological changes similar to those seen after long-term AMI[O] treatment." Varro 2 at 55. Varro 2 states that its conclusion "further argues

for the important role of the metabolite during chronic AMI[O] administration, and raises the possibility that DEA treatment alone would be an effective and may be a less dangerous antiarrhythmic treatment than that of AMI[O]." *Id.*

Given Varro 2's teaching that chronic oral administration of DEA exerts therapeutic antiarrhythmic effects similar to those of AMIO, as well as its teaching that DEA treatment would possibly be an effective and less dangerous antiarrhythmic treatment than AMIO, we agree with the Examiner that a skilled artisan, viewing Varro 2 alongside the teachings discussed above in Tieleman and Letelier, had a good reason for, and a reasonable expectation of success in, chronic oral administration of DEA, instead of AMIO, as a treatment for atrial fibrillation (the most commonly encountered arrhythmia).

The obviousness of oral administration of DEA to treat atrial fibrillation, including chronic administration of the drug, is further bolstered by the teachings of Varro 1. Varro 1 discloses a study of the effects of intraperitoneal administration of DEA to rats having experimentally induced arrhythmias, among them ventricular fibrillation. *See* Varro 1 at 483–484.

Varro 1 discloses that its study was prompted by previous investigations finding that chronic AMIO administration results in the appearance of DEA in plasma and accumulation of DEA in cardiac muscle. Varro 1 at 483. Varro 1 also notes that previous "[e]lectrophysiological studies indicate that [DEA] delayed repolarization of cardiac muscle both in-situ and in-vitro." *Id.* (citations omitted). Based on those previous investigations, Varro 1 hypothesized that "it is likely that the effects of

[DEA] contribute to the strong antiarrhythmic efficacy of the chronic [AMIO] administration." *Id.*

To confirm its hypothesis that DEA contributes to the strong antiarrhythmic effect of chronic AMIO administration, Varro 1 pretreated rats with DEA, then induced arrhythmias (including ventricular fibrillation) in the rats by ligating a coronary artery, and examined the results. *See* Varro 1 at 483–484. Varro 1 discloses that its results "show that DEA pretreatment improved the survival in the acute phase of arrhythmias caused by coronary ligation in conscious rats" and that the "antiarrhythmic effects were produced by a dose of [DEA] comparable with that of [AMIO] we have already reported to be effective in the present model." *Id.* at 484 (citation omitted). Based on the results of its experiments, Varro 1 concluded that "[a]lthough the antiarrhythmic effect of [DEA] needs to be examined in other species, including man, we assume that it contributes to the antiarrhythmic effect seen after chronic [AMIO] administration." *Id.* at 484.

Given Varro 1's teaching that DEA contributes to the antiarrhythmic effect seen after chronic AMIO administration, as well as its teaching that DEA exerts electrophysiological effects similar to the effects of AMIO, we agree with the Examiner that a skilled artisan, viewing Varro 1 alongside the teachings discussed above in Varro 2, Tieleman, and Letelier, had a good reason for, and a reasonable expectation of success in, chronic oral administration of DEA, instead of AMIO, as a treatment for atrial fibrillation (the most commonly encountered arrhythmia). Accordingly, for the reasons discussed, we agree with the Examiner that the process recited in

Appellant's representative claim 5 would have been prima facie obvious to a skilled artisan.

Appellant's arguments do not persuade us to the contrary. We acknowledge, as Appellant contends, that none of the cited references expressly describes treating atrial fibrillation by orally administering DEA. *See* Appeal Br. 5–6. We also acknowledge Appellant's contention that "[t]he prior art does not provide any indication or suggestion that DEA has the role of treatment of atrial fibrillation or can be used as the medicament for the treatment of atrial fibrillation." *Id.* at 7.

As discussed above, however, both Varro 1 and Varro 2 teach that DEA is as effective as AMIO for treating arrhythmias, including by chronic oral administration, and DEA exerts similar electrophysiological effects on the heart as AMIO. As also discussed above, Varro 2 in particular expressly suggests that "DEA treatment alone would be an effective and may be a less dangerous antiarrhythmic treatment than that of AMI[O]." Varro 2 at 55. And, as also discussed above, Tieleman teaches that when treating atrial fibrillation with chronically administered oral AMIO, the plasma concentrations of DEA are more important to the therapeutic effect than the plasma concentrations of AMIO. *See* Tieleman 56. Appellant does not persuade us, therefore, that a skilled artisan treating atrial fibrillation by chronic oral administration of AMIO as taught for example in Tieleman and Letelier, lacked a good reason for, or a reasonable expectation of success in, chronically administering oral DEA, instead of AMIO.

We acknowledge Appellant's contention that a skilled artisan, absent evidence to the contrary, might hypothetically expect that not all metabolites would be as useful as their parent compound. *See* Appeal Br. 7. However,

given the express teachings in Tieleman, Varro 1, and Varro 2 as to the therapeutic effect of DEA, we are not persuaded that a skilled artisan lacked a *reasonabl*e expectation that chronic oral administration of DEA would treat atrial fibrillation. *See In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009) ("Obviousness does not require absolute predictability of success. . . . For obviousness under § 103, all that is required is a reasonable expectation of success.") (quoting *In re O'Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988) (emphasis removed)).

We are not persuaded, moreover, that the Nattel reference would have undermined the reasonable expectation of success provided by the combination of references discussed above, nor are we persuaded that Nattel teaches away from treating atrial fibrillation by chronic oral administration of DEA. *See* Appeal Br. 7–8.

Nattel describes a study of the effects of intravenous administration of both AMIO and DEA to dogs having experimentally induced ventricular arrhythmias. *See* Nattel 200–201.

Nattel notes that "[p]lasma and myocardial drug concentrations were similar to those measured during long-term [AMIO] therapy in man." Nattel 200 (abstract); *see also id.* at 207 ("The plasma and myocardial drug concentrations achieved in our dogs were in the same range as concentrations occurring with long-term oral [AMIO] treatment.").

Nattel discloses that "[b]oth [AMIO] and [DEA] suppressed ventricular arrhythmias in a dose-dependent fashion. The metabolite [(DEA)], however, was more potent with a 50% effective concentration for suppression of premature ventricular complexes of 1.4 mg/liter compared with 4.6 mg/liter for the parent compound." Nattel 200 (abstract); *see also*

id. at 207 ("In our experiments, the antiarrhythmic potency of [DEA] was about three times that of [AMIO] based on plasma concentration.").

Nattel concluded that its experiments "suggest that the accumulation of [DEA] that occurs with long-term oral [AMIO] therapy contributes importantly to the antiarrhythmic effects of the drug, and may account for the gradual increase in antiarrhythmic action during the course of [AMIO] therapy." Nattel 200 (abstract).

Nattel, thus, teaches that DEA accumulation is important to the therapeutic antiarrhythmic effect of chronic AMIO treatment, and that DEA can exert a more potent effect than AMIO. Accordingly, rather than teaching away from the claimed invention, Nattel bolsters the suggestion from the collective teachings of Varro 1, Varro 2, Tieleman, and Letelier discussed above that chronic oral administration of DEA would be a suitable treatment for atrial fibrillation.

Appellant contends that the following discussion in Nattel teaches away from orally administering DEA to treat atrial fibrillation (Appeal Br. 8):

> Extrapolation of the results of intravenous drug administration in dogs to the effects of long-term oral drug therapy in man requires great caution. The plasma and myocardial drug concentrations achieved in our dogs were in the same range as concentrations occurring with long-term oral amiodarone treatment. ***Single-dose intravenous [AMIO] is known to be much more effective against supraventricular than ventricular arrhythmias. This may be due to the greater effect of [AMIO] compared with its metabolite [(DEA)] on slow-channel function.***

Nattel 207 (emphasis added).

The passage in Nattel cited by Appellant, however, does not criticize, discredit, or even specifically discuss whether oral administration of DEA would be expected to be useful for treating atrial fibrillation. Appellant does not persuade us, therefore, that the quoted language in Nattel is sufficient to teach away from the claimed invention. *See DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009) (A reference "does not teach away . . . if it merely expresses a general preference for an alternative invention but does not criticize, discredit, or otherwise discourage investigation into the invention claimed.") (internal quotations omitted) (citation omitted).

Appellant, moreover, fails to explain specifically how or why Nattel's teaching regarding *single dose* AMIO administration, or AMIO's greater effect on slow-channel function as compared to DEA, would have discouraged investigation into treating atrial fibrillation by *chronic* oral administration of DEA, as suggested by the teachings of Varro 1, Varro 2, Tieleman, and Letelier discussed above. If anything, Nattel's teaching that AMIO exerts more potent effects against supraventricular (i.e., atrial) arrhythmias bolsters the suggestion from Tieleman, Varro 1, and Varro 2 that DEA, having similar therapeutic effects to AMIO, would also be effective against supraventricular arrhythmias such as atrial fibrillation.

In sum, for the reasons discussed, Appellant does not persuade us that the Examiner erred in determining that the process recited in Appellant's representative claim 5 would have prima facie obvious to a skilled artisan.

Appellant does not persuade us, moreover, that it has advanced objective evidence of nonobviousness sufficient to outweigh the prior art evidence of prima facie obviousness advanced by the Examiner. In

particular, we are not persuaded that Appellant's evidence as to long-felt need is entitled to significant probative weight. *See* Appeal Br. 10 (citing Varro Decl.);[7] Reply Br. 1–2.

Appellant "emphasizes that there has been a long-felt need not just for a treatment of AF [(atrial fibrillation)], but for a *better* treatment of AF with fewer adverse side-effects than exhibited by [AMIO] (see, e.g., specification page 1, lines 12-14, 31)." Appeal Br. 10.

We acknowledge the Specification's disclosure that "AMIO — which has a very complex mode of action inhibiting cardiac sodium, calcium, potassium currents and beta adrenoceptors — also exerts serious extracardiac adverse effects like pulmonary fibrosis, hepatotoxicity, photodermatosis, cornea deposits etc. which greatly limit its clinical use (Tisdale et al, 1995)." Spec. 1.

Establishing long-felt need, however, "requires objective evidence that an art-recognized problem existed in the art for a long period of time ***without solution***." *Ex parte Jellá*, 90 USPQ2d 1009, 1019 (BPAI 2008) (precedential; emphasis added); *see also Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966) (secondary considerations include "long felt ***but unsolved*** needs") (emphasis added).

The fact that it may have been known for a long time that AMIO treatment of atrial fibrillation had significant side effects does not establish that the need for a lower side effect atrial fibrillation treatment was unsolved. In that regard, we are not persuaded that Appellant has shown

[7] Declaration of Dr. Andras Varró under 37 C.F.R. § 1.132 (signed February 21, 2017).

sufficiently that effective treatments for atrial fibrillation having little or few side effects, or at least fewer than AMIO, were not available in the prior art.

We acknowledge the Varro Declaration's assertion that "many have sought to find a treatment with fewer or less severe adverse side effects" than AMIO, as evidenced by an "enclosed [] list of hundreds of published research articles wherein effects of AMIO such as thyroid dysfunction, pulmonary toxicity; hepatocellular toxicity, liver injury and drug-drug interactions have been studied and reported." Varro Decl. ¶ 3.

The Varro Declaration, however, includes no specific discussion of any of the articles in the cited list. Nor does the Varro Declaration include any specific explanation as to how or why any of the articles in the cited list establishes that the prior art had failed to solve the need for a reduced side effect treatment for atrial fibrillation. Absent some specific evidence-based explanation as to *why* the articles in the list cited in the Varro Declaration support the assertions made in the declaration, we are not persuaded that the conclusory assertions in the declaration are sufficient to establish that the asserted need was unsolved, or that significant efforts had failed to solve the problem. *See In re Allen*, 324 F.2d 993, 997 (CCPA 1963) (An allegation of a long felt but unsolved problem in the art "is not evidence of unobviousness unless it is shown . . . that the widespread efforts of skilled workers having knowledge of the prior art had failed to find a solution to the problem.").

In sum, for the reasons discussed, we find that Appellant's evidence as to long-felt but unsolved need is not entitled to significant probative weight. Similarly, we find that Appellant's evidence of unexpected results is not sufficient to outweigh the prior art evidence of obviousness advanced by the Examiner.

Appellant contends that "Examples 1 to 4 of the present application . . . demonstrate that oral administration of DEA has unexpectedly higher therapeutic efficacy than oral administration of amiodarone, and unexpectedly lower toxic side effect to the liver, lung and other tissues of patients." Appeal Br. 11. Regarding unexpected results, the Varro Declaration states as follows:

> [C]ontrary to the prior art disclosures, the data of the present application establishes for the first time that in addition to being significantly more effective, DEA shows markedly decreased side effects when administered daily. In fact, half the dose of DEA needs to be administered relative to AMIO to achieve the same clinical effects. These effects are accompanied by similar cardiac tissue DEA levels, i.e. the bioavailability of DEA is also superior. Therefore more importantly, administration of DEA lead to reduced pathological alterations in the lungs and the liver, i.e. similar antiarrhythmic effects are accompanied with milder toxic and adverse effects. In my opinion, such results of the present invention would not have been expected without performing the experiments described in our patent application based on the view of the references cited in the aforementioned Office action [of November 21, 2016].

Varro Decl. ¶ 3.

While Appellant asserts that Example 1 in the Specification shows unexpected results, neither Appellant's briefs nor the Varro Declaration include any specific analysis of Example 1, or any specific discussion why Example 1 is evidence of unexpected results. In any event, Appellant's Example 1 involves analysis of excised rabbit hearts in which atrial fibrillation was induced by electrical stimulation. *See* Spec. 8–9. The Specification states that the results of the experiments in Example 1 "suggest that DEA may be a promising drug candidate for treatment and/or prevention of atrial fibrillation." *Id.* at 9.

As discussed above, however, Tieleman, Varro 1, and Varro 2 all disclose that DEA has antiarrhythmic properties similar to AMIO, a drug known in the art to treat atrial fibrillation. Thus, even putting aside the speculative nature of the Specification's conclusion as to the results of Example 1, we are not persuaded that the results in Example 1 would have been unexpected.

While Appellant asserts that Example 2 in the Specification shows unexpected results, neither Appellant's briefs nor the Varro Declaration include any specific analysis of Example 2, or any specific discussion why Example 2 is evidence of unexpected results. In any event, Appellant's Example 2 analyzes the effect in conscious rats of one month pretreatment with either DEA or AMIO, followed by a surgically induced myocardial infarction. *See* Spec. 10–11. As to the results of the experiments in Example 2, the Specification states as follows:

> Long-term oral AMIO or DEA pretreatment provided significant protection against life threatening arrhythmias and improved the chance to survive the acute phase of experimental myocardial infarction. This protective effect was produced by similar plasma or myocardial DEA concentrations. ***However, this effective concentration could be achieved by applying smaller doses of DEA***.

Spec. 11 (emphasis added).

We first note that Example 2 makes no specific mention of atrial fibrillation, the disorder treated in Appellant's representative claim 5. We note, moreover, that the effect seen in Example 2 came from chronic administration of DEA, whereas representative claim 5 is not limited to chronic administration. We are not persuaded, therefore, the results shown in Example 2 are commensurate in scope with claim 5.

As to the fact that DEA was shown to be more potent than AMIO in Appellant's Example 2, we note Nattel's disclosure that DEA was seen to be more potent than AMIO in similar experiments performed on dogs. *See* Nattel 200 (disclosing that DEA "was more potent with a 50% effective concentration" as compared to AMIO); *see also id.* at 207 ("In our experiments, the antiarrhythmic potency of [DEA] was about three times that of [AMIO] based on plasma concentration."). Given these disclosures in Nattel, we are not persuaded that Appellant has explained sufficiently why the results of Appellant's Example 2 would have been considered unexpected.

Appellant's Example 3 analyzes the effects of four weeks of chronic oral treatments with either DEA or AMIO on pacemaker-induced atrial fibrillation in dogs. *See* Spec. 11–16.

As to the results of the experiments in Example 3, the Specification states that "chronic oral [AMIO] (50 mg/kg/day) and [DEA] (25 mg/kg/day) treatment effectively and similarly decreased the incidence of atrial fibrillation, the duration of atrial fibrillation episodes and increased atrial effective refractory periods in conscious, chronically instrumented Beagle dogs." *Id.* at 14. As to Example 3, the Specification also notes that "liver and lung tissue DEA levels were significantly and markedly higher following AMIO treatment than following DEA treatment." *Id.*

Example 3 thus shows that in a dog model of atrial fibrillation, orally administered DEA exerts similar therapeutic effects at half the dosage of AMIO, consistent with Appellant's arguments. *See* Appeal Br. 10–12; Varro Decl. ¶ 3. As noted above, however, Nattel discloses that DEA was seen to have significantly more potent antiarrhythmic properties than AMIO

in dog experiments. *See* Nattel 200, 207. Although Nattel did not disclose that its experiments involved atrial fibrillation, Nattel's results nonetheless suggest that the superior potency of DEA seen in Appellant's Example 3 was not unexpected. Given Nattel's disclosure, we are not persuaded that Appellant has explained sufficiently why the results of Appellant's Example 3 would have been considered unexpected.

The results seen in Example 3, moreover, came from chronic administration of DEA, whereas representative claim 5 is not limited to chronic administration. We note, moreover, that claim 5 does not include any limitations as to dosage, and therefore encompasses dosages that would be expected to be effective for AMIO. We are not persuaded, therefore, that the results shown in Example 3 are commensurate in scope with claim 5, or that claim 5 reflects the asserted unexpected improvement in DEA dosage as compared to AMIO.

While Appellant asserts that Example 4 in the Specification shows unexpected results, neither Appellant's briefs nor the Varro Declaration include any specific analysis of Example 4, or any specific discussion why Example 4 is evidence of unexpected results. In any event, Appellant's Example 4 is a 28-day toxicology study in rats that received either 200 mg/kg/day of AMIO or 100 mg/kg/day of DEA. *See* Spec. 16–17. As to liver toxicity, the Specification states that the results of the experiments in Example 4 "may suggest that treatment with the metabolite (DEA) leads to reduced hepatotoxic side effects compared to treatment with amiodarone (AMIO)." *Id.* at 17. As to lung toxicity, the Specification states that the results of the experiments in Example 4 "may suggest that DEA treatment

might be more beneficial considering one of the most serious adverse effects of chronic AMIO treatment, the development of pulmonary fibrosis." *Id.*

The results seen in Example 4, however, came from chronic administration of DEA, whereas representative claim 5 is not limited to chronic administration. We note again, moreover, that claim 5 does not include any limitations as to dosage, and therefore encompasses higher DEA dosages than tested in Example 4. We are not persuaded, therefore, that the results shown in Example 4 are commensurate in scope with claim 5, or that claim 5 reflects the asserted unexpected improvement in DEA dosage as compared to AMIO. Moreover, given that the DEA dosage was half the AMIO dosage, we are not persuaded that Appellant has explained sufficiently why the results of Appellant's Example 4 would have been considered unexpected.

In sum, for the reasons discussed, Appellant does not persuade us that the Examiner erred in determining that the process recited in Appellant's representative claim 5 would have prima facie obvious to a skilled artisan. For the reasons discussed, Appellant also does not persuade us that it has advanced objective evidence of nonobviousness sufficient to outweigh the prior art evidence of prima facie obviousness advanced by the Examiner. We note in particular that where, as here, the prior art presents a strong case of obviousness, secondary considerations "do not necessarily control the obviousness conclusion." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007) (citation omitted).

In sum, for the reasons discussed, based on the totality of the record, we find that the preponderance of the evidence supports the Examiner's conclusion that the process of representative claim 5 would have been

obvious in view of Varro 1, Varro 2, Tieleman, and Letelier. We therefore affirm the Examiner's rejection of claim 5 over those references. Claims 6–11 fall with claim 5. *See* 37 C.F.R. 41.37(c)(1)(iv).

OBVIOUSNESS—
TIELEMAN, LETELIER, AND VARRO 2

In rejecting Appellant's claims 5–9 over Tieleman, Letelier, and Varro 2, the Examiner relied on substantially the same teachings in each of the references discussed above, except for Varro 1. *See* Ans. 8–10.

As discussed above, given Varro 2's teaching that chronic oral administration of DEA exerts therapeutic antiarrhythmic effects similar to those of AMIO, as well as its teaching that DEA treatment would possibly be an effective and less dangerous antiarrhythmic treatment than AMIO, we agree with the Examiner that a skilled artisan, viewing Varro 2 alongside the teachings discussed above in Tieleman and Letelier, had a good reason for, and a reasonable expectation of success in, chronic oral administration of DEA, instead of AMIO, as a treatment for atrial fibrillation (the most commonly encountered arrhythmia).

In traversing this rejection, Appellant states only that it "hereby fully incorporates by reference the above comments regarding the rejection of Claims 5–11 under 35 U.S.C. 103(a) as being unpatentable over Varro I and Varro 2 in view of Tieleman et al. and Letelier et al., which comments are believed to fully address this rejection." Appeal Br. 12.

As discussed above, we do not find those arguments persuasive. We therefore affirm the Examiner's rejection of claims 5–9 over Tieleman, Letelier, and Varro 2.

OBVIOUSNESS—
TIELEMAN, LETELIER, NATTEL, AND VARRO 2

In rejecting Appellant's claims 5–9 over Tieleman, Letelier, Nattel, and Varro 2, the Examiner relied on substantially the same teachings in Tieleman, Letelier, and Varro 2, discussed above, and cited Nattel as additional evidence that the claimed process of treating atrial fibrillation with DEA would have been obvious. *See* Ans. 10–13.

Appellant's arguments do not persuade us of error in the Examiner's rejection. *See* Appeal Br. 13. As discussed above, Nattel teaches that DEA accumulation is important to the therapeutic antiarrhythmic effect of chronic AMIO treatment, and that DEA can exert a more potent effect than AMIO. Accordingly, for the reasons discussed above, we find that Nattel bolsters the suggestion from the collective teachings of Tieleman, Letelier, and Varro 2 that chronic oral administration of DEA would be a suitable treatment for atrial fibrillation. For the reasons discussed above, we are also unpersuaded that the passage on page 207 of Nattel teaches away from Appellant's claimed invention.

Accordingly, because Appellant's arguments do not persuade us of error in the Examiner's rejection of claims 5–9 over Tieleman, Letelier, Nattel, and Varro 2, we affirm that rejection.

CONCLUSION

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
5–11	103(a)	Varro 1, Varro 2, Tieleman, Letelier	5–11	
5–9	103(a)	Tieleman, Letelier, Varro 2	5–9	
5–9	103(a)	Tieleman, Letelier, Nattel, Varro 2	5–9	
Overall Outcome			5–11	

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