IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

SANOFI and SANOFI-AVENTIS U.S. LLC, Plaintiffs, v. LUPIN ATLANTIC HOLDINGS S.A., LUPIN LTD. and LUPIN PHARMACEUTICALS INC., Defendants.	Civil Action No. 15-415-RGA (CONSOLIDATED)

TRIAL OPINION

Jack B. Blumenfeld, Derek J. Fahnestock, Stephen J. Kraftshik, MORRIS, NICHOLS, ARSHT & TUNNELL LLP, Wilmington, DE; William E. Solander, Daniel J. Minion, James R. Tyminski, Zachary L. Garrett, Anna E. Dwyer, FITZPATRICK, CELLA, HARPER & SCINTO, New York, NY.

Attorneys for Plaintiffs.

John M. Seaman, ABRAMS & BAYLISS LLP, Wilmington, DE; Maureen L. Rurka, Julia M. Johnson, Loren G. Rene, WINSTON & STRAWN LLP, Chicago, IL.

Attorneys for Defendant Sandoz Inc.

Dominick T. Gattuso, HEYMAN ENERIO GATTUSO & HIRZEL LLP, Wilmington, DE; Natalie C. Clayton, Christopher L. McArdle, Yi Wen Wu, ALSTON & BIRD LLP, New York, NY. Frank G. Smith, ALSTON & BIRD LLP, Atlanta, GA.

Attorneys for Defendants Watson Laboratories, Inc.

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ANDREWS, U.S. DISTRICT JUDGE:

Plaintiffs Sanofi and Sanofi-Aventis U.S. LLC (collectively, "Plaintiffs") bring this consolidated patent infringement case against Defendants Watson Laboratories, Inc. and Sandoz Inc. (collectively, "Defendants"). (C.A. No. 15-415-RGA, D.I. 188 at pp. 1, 3).[1] This opinion addresses allegations of infringement and invalidity with respect to U.S. Patent No. 9,107,900 (the "'900 patent").

I held a two-day bench trial relating to this patent. ("Tr."). The parties filed post-trial briefing with respect to infringement (D.I. 201; D.I. 203; D.I. 206) and invalidity. (D.I. 200; D.I. 204; D.I. 205). Having considered the documentary evidence and testimony, I make the following findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52(a).

I. BACKGROUND

Sanofi-Aventis U.S. LLC is the holder of approved New Drug Application No. 022425 for dronedarone tablets, 400 mg, which are prescribed under the trademark Multaq®. (D.I. 188, Exh. 1 at p. 2). The active ingredient in Multaq® tablets is N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-1-benzofuran-5-yl]methanesulfonamide hydrochloride, also known as dronedarone hydrochloride. (D.I. 188, Exh. 1 at p. 2). Plaintiffs make and sell Multaq® in the United States. (D.I. 188 at p. 1).

The '900 patent, entitled "Use of Dronedarone for the Preparation of a Medicament for Use in the Prevention of Cardiovascular Hospitalization or Mortality," issued on August 18, 2015. (D.I. 188, Exh. 1 at p. 2). The '900 patent is listed in the FDA's Approved Drug Products

[1] Citations to "D.I.___" are to the docket in C.A. No. 15-415 unless otherwise noted.

with Therapeutic Equivalence Evaluations (the "Orange Book") in connection with NDA No. 022425. (D.I. 188 at p. 1).

Plaintiffs are asserting claims 1, 6–9, and 14 of the '900 patent against Defendants. (D.I. 188, Exh. 2 at p. 1, Exh. 3 at p. 2). There are three independent claims: 1, 6, and 9. Claim 7 depends from claim 1. Claim 8 depends from claim 6. Claim 14 depends from claim 9. Defendants assert that claims 1, 7, 9, and 14 of the '900 patent are invalid as obvious.

The asserted claims read as follows.

Claim 1

> 1. A method of reducing a risk of cardiovascular hospitalization in a patient, said method comprising administering to said patient an effective amount of dronedarone or a pharmaceutically acceptable salt thereof, twice a day with a morning and an evening meal, wherein said patient does not have severe heart failure, (i) wherein severe heart failure is indicated by: a) NYHA Class IV heart failure or b) hospitalization for heart failure within the last month; and (ii) wherein said patient has a history of, or current, paroxysmal or persistent non-permanent atrial fibrillation or flutter, and (iii) wherein said patient has structural heart disease, wherein said structural heart disease is coronary heart disease; and (iv) wherein the patient has (a) an age greater than or equal to 75 or (b) an age greater than or equal to 70 and at least one cardiovascular risk factor selected from the group consisting of:
>
> i. hypertension;
> ii. diabetes;
> iii. a history of cerebral stroke or of systemic embolism;
> iv. a left atrial diameter greater than or equal to 50 mm; and
> v. a left ventricular ejection fraction less than 40%.

Claim 6

> 6. A method of reducing a risk of cardiovascular hospitalization in a patient, said method comprising administering to said patient an effective amount of dronedarone or a pharmaceutically acceptable salt thereof, twice a day with a morning and evening meal, (i) wherein said patient has a history of, or current, paroxysmal or persistent non-permanent atrial fibrillation or flutter; and (ii) wherein said patient has congestive heart failure defined as NYHA class III; and (iii) wherein said patient has not been hospitalized for heart failure within the last month.

Claim 7

7. The method according to claim 1, wherein the administration of said effective amount of dronedarone or pharmaceutically acceptable salt thereof is maintained for at least 12 months.

Claim 8

8. The method according to claim 6, wherein the administration of said effective amount of dronedarone or pharmaceutically acceptable salt thereof is maintained for at least 12 months.

Claim 9

9. A method of reducing a risk of cardiovascular hospitalization for atrial fibrillation in a patient, said method comprising administering dronedarone, or a pharmaceutically acceptable salt thereof, twice a day with a morning and an evening meal to a patient in need of reduction of said risk, wherein said patient does not have severe heart failure, (i) wherein severe heart failure is indicated by: a) NYHA Class IV heart failure or b) hospitalization for heart failure within the last month; and (ii) wherein said patient has a history of, or current, paroxysmal or persistent non-permanent atrial fibrillation, and (iii) wherein said patient has structural heart disease, wherein said structural heart disease is coronary heart disease; and (iv) wherein the patient has (a) an age greater than or equal to 75 or (b) an age greater than or equal to 70 and at least one cardiovascular risk factor selected from the group consisting of:

i. hypertension;
ii. diabetes;
iii. a history of cerebral stroke or of systemic embolism;
iv. a left atrial diameter greater than or equal to 50 mm; and
v. a left ventricular ejection fraction less than 40%.

Claim 14

14. The method according to claim 9, wherein the administration of said dronedarone or pharmaceutically acceptable salt thereof is maintained for at least 12 months.

(JTX-1).

II. LEGAL STANDARDS

A. Infringement

A patent is infringed when a person "without authority makes, uses, offers to sell, or sells any patented invention, within the United States . . . during the term of the patent . . . ." 35 U.S.C. § 271(a). A two-step analysis is employed in making an infringement determination. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). First, the court must construe the asserted claims to ascertain their meaning and scope. *See id.* The trier of fact must then compare the properly construed claims with the accused infringing product. *See id.* This second step is a question of fact. *Bai v. L & L Wings, Inc.*, 160 F.3d 1350, 1353 (Fed. Cir. 1998).

"Literal infringement of a claim exists when every limitation recited in the claim is found in the accused device." *Kahn v. Gen. Motors Corp.*, 135 F.3d 1472, 1477 (Fed. Cir. 1998). "If any claim limitation is absent from the accused device, there is no literal infringement as a matter of law." *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1247 (Fed. Cir. 2000). If an accused product does not infringe an independent claim, it also does not infringe any claim depending thereon. *See Wahpeton Canvas Co. v. Frontier, Inc.*, 870 F.2d 1546, 1553 (Fed. Cir. 1989). However, "[o]ne may infringe an independent claim and not infringe a claim dependent on that claim." *Monsanto Co. v. Syngenta Seeds, Inc.*, 503 F.3d 1352, 1359 (Fed. Cir. 2007). A product that does not literally infringe a patent claim may still infringe under the doctrine of equivalents if the differences between an individual limitation of the claimed invention and an element of the accused product are insubstantial. *See Warner–Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 39–40 (1997). The patent owner has the burden of proving

infringement by a preponderance of the evidence. *See SmithKline Diagnostics, Inc. v. Helena Labs. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988).

B. Obviousness

The presumption that all patents are valid is the starting point for any obviousness determination. 35 U.S.C. § 282. A patent claim is invalid as obvious under 35 U.S.C. § 103 "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." *Id.* § 103(a); *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406–07 (2007). Obviousness is a question of law that depends on the following factual inquiries: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the relevant art; and (4) any objective indicia of nonobviousness. *See KSR*, 550 U.S. at 406; *see also Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1347 (Fed. Cir. 2012). A court is required to consider secondary considerations, or objective indicia of nonobviousness, before reaching an obviousness determination, as a "check against hindsight bias." *See In re Cyclobenzaprine Hydrochloride Extended–Release Capsule Patent Litig.*, 676 F.3d 1063, 1078–79 (Fed. Cir. 2012). Relevant secondary considerations include commercial success, long felt but unsolved needs, failure of others, praise, unexpected results, and copying, among others. *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17–18 (1966); *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 662–63 (Fed. Cir. 2000); *Tex. Instruments, Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1178 (Fed. Cir. 1993).

"Generally, a party seeking to invalidate a patent as obvious must demonstrate . . . that a skilled artisan would have had reason to combine the teaching of the prior art references to

achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so." *In re Cyclobenzaprine Hydrochloride*, 676 F.3d at 1068–69. "The Supreme Court has warned, however, that, while an analysis of any teaching, suggestion, or motivation to combine known elements is useful to an obviousness analysis, the overall obviousness inquiry must be expansive and flexible." *Id.* at 1069. The improvement over prior art must be "more than the predictable use of prior art elements according to their established functions." *KSR*, 550 U.S. at 417. Evidence of obviousness, however, especially when that evidence is proffered in support of an "obvious-to-try" theory, is insufficient unless it indicates that the possible options skilled artisans would have encountered were "finite," "small," or "easily traversed," and "that skilled artisans would have had a reason to select the route that produced the claimed invention." *In re Cyclobenzaprine Hydrochloride*, 676 F.3d at 1072. Obviousness must be proven by clear and convincing evidence. *Id.* at 1078.

III. DISCUSSION

A. Infringement

1. Findings of Fact

1. The person of ordinary skill in the art ("POSA") with respect to the '900 patent is someone having a medical degree who is board certified in cardiology or electrophysiology with at least two years of clinical practice who also has knowledge of the design, implementation, and analysis of clinical studies.

2. The Indications and Usage section (section 1) of Defendants' labels indicates dronedarone tablets for reducing "the risk of hospitalization for atrial fibrillation in patients in sinus rhythm with a history of paroxysmal or persistent atrial fibrillation." This section directs a POSA to review, and a POSA would review, the Clinical Studies section (section 14) of the labels.

3. The Clinical Studies sections teach that dronedarone could be used for some patients with coronary heart disease.

4. The ATHENA study (section 14.1) discloses that "[d]ronedarone reduced the combined endpoint of cardiovascular hospitalization or death from any cause by 24.2%." A POSA would recognize that dronedarone's indicated benefit extended to the 60% of ATHENA

patients who had structural heart disease. A POSA would recognize that approximately half of the patients with structural heart disease would have coronary heart disease. A POSA would therefore understand that dronedarone's indicated benefit extended to some patients with coronary heart disease. In the context of Defendants' labels, a POSA would understand that "structural heart disease" is a term that includes coronary heart disease.

5. The EURIDIS/ADONIS study (section 14.2) provides further encouragement to a POSA that dronedarone's indicated benefit extended to some patients with coronary heart disease.

6. Defendants' labels encourage a POSA to administer dronedarone to some patients within the Age Criteria.[2]

7. Approximately 20–25% of the uses of dronedarone infringe claims 1, 7, 9 and 14 of the '900 patent.

8. Defendants' labels instruct a POSA to administer dronedarone to patients with coronary heart disease and who meet the Age Criteria. It is readily apparent from the Clinical Studies section that the use of dronedarone for these patients would reduce the risk of cardiovascular hospitalization. Defendants' labels induce infringement of claims 1, 7, 9 and 14 of the '900 patent.

9. The first page of Defendants' labels is a "Black Box" warning that discourages physicians from using dronedarone in patients with decompensated heart failure. Doctors would see this warning as a "flashing red light" in determining whether to prescribe dronedarone to NYHA ("New York Heart Association") Class III congestive heart failure ("CHF") patients, whether decompensated or not. The Black Box warning strongly teaches away from the use of dronedarone in Class III patients generally.

10. The Contraindications section (section 4), along with the Cardiovascular Death in NYHA Class IV or Decompensated Heart Failure section (section 5.1) and ANDROMEDA study (section 14.4), of Defendants' labels discourage a physician from prescribing dronedarone to Class III patients generally.

11. Many authoritative guidelines also discourage physicians from prescribing dronedarone to Class III patients generally.

12. The ATHENA study and Figure 4 of the Defendants' labels provide a POSA with very little encouragement to prescribe dronedarone to stable Class III patients. A POSA would remain skeptical, after combing through the Clinical Studies sections, of the safety

[2] "Age Criteria" refers to the portion of claims 1 and 9 of the '900 patent requiring that the patient have (a) an age greater than or equal to 75 or (b) an age greater than or equal to 70 and at least one cardiovascular Risk Factor. "Risk Factor" refers to the portion of claims 1 and 9 of the '900 patent that requires at least one cardiovascular risk factor selected from the group consisting of: (i) hypertension; (ii) diabetes; (iii) a history of cerebral stroke or of systemic embolism; (iv) a left atrial diameter greater than or equal to 50 mm; and (v) a left ventricular ejection fraction less than 40%.

of prescribing dronedarone to stable Class III patients because the label fails to make it clear that it is safe to do so.

13. Approximately 3% of the uses of dronedarone infringe claims 6 and 8 of the '900 patent.

14. Defendants' labels do not instruct a POSA to administer dronedarone to stable Class III patients. Defendants' labels do not induce infringement of claims 6 and 8 of the '900 patent.

2. Conclusions of Law

Plaintiffs argue that Defendants' product labels will induce infringement of the asserted claims.[3] 35 U.S.C. § 271(b) provides that "[w]hoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b). "In order to prevail on an inducement claim, the patentee must establish first that there has been direct infringement, and second that the alleged infringer knowingly induced infringement and possessed specific intent to encourage another's infringement." *ACCO Brands, Inc. v. ABA Locks Mfrs. Co.*, 501 F.3d 1307, 1312 (Fed. Cir. 2007). In other words, "inducement requires evidence of culpable conduct, directed to encouraging another's infringement, not merely that the inducer had knowledge of the direct infringer's activities." *DSU Med. Corp. v. JMS Co.*, 471 F.3d 1293, 1306 (Fed. Cir. 2006) (en banc). "[S]pecific intent may be inferred from circumstantial evidence where a defendant has both knowledge of the patent and specific intent to cause the acts constituting infringement." *Ricoh Co. v. Quanta Computer Inc.*, 550 F.3d 1325, 1342 (Fed. Cir. 2008). "[L]iability for induced infringement can only attach if the defendant knew of the patent and knew as well that 'the induced acts constitute patent infringement.'" *Commil USA, LLC v. Cisco Sys., Inc.*, 135 S. Ct. 1920, 1926 (2015) (quoting *Global–Tech Appliances, Inc. v. SEB S.A.*, 131 S. Ct. 2060, 2068 (2011)). The knowledge requirement may be satisfied by showing actual knowledge or willful blindness. *See Global–Tech*, 131 S. Ct. at 2068 (2011).

[3] Watson's current product label is found at JTX-54. Sandoz's product label can be found at JTX-42.

In Hatch-Waxman cases alleging that a proposed drug label will induce infringement by physicians, "The pertinent question is whether the proposed label instructs users to perform the patented method." *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010). "The label must encourage, recommend, or promote infringement." *Takeda Pharm. USA, Inc. v. West-Ward Pharm. Corp.*, 785 F.3d 625, 631 (Fed. Cir. 2015). "The mere existence of direct infringement by physicians, while necessary to find liability for induced infringement, is not sufficient for inducement." *Id.* Rather, "specific intent and action to induce infringement must be proven." *Id.*

a) Claims 1, 7, 9, 14

Defendants argue that they do not induce infringement of claims 1, 7, 9, and 14. Those four claims are directed to patients with coronary heart disease and who meet the Age Criteria.

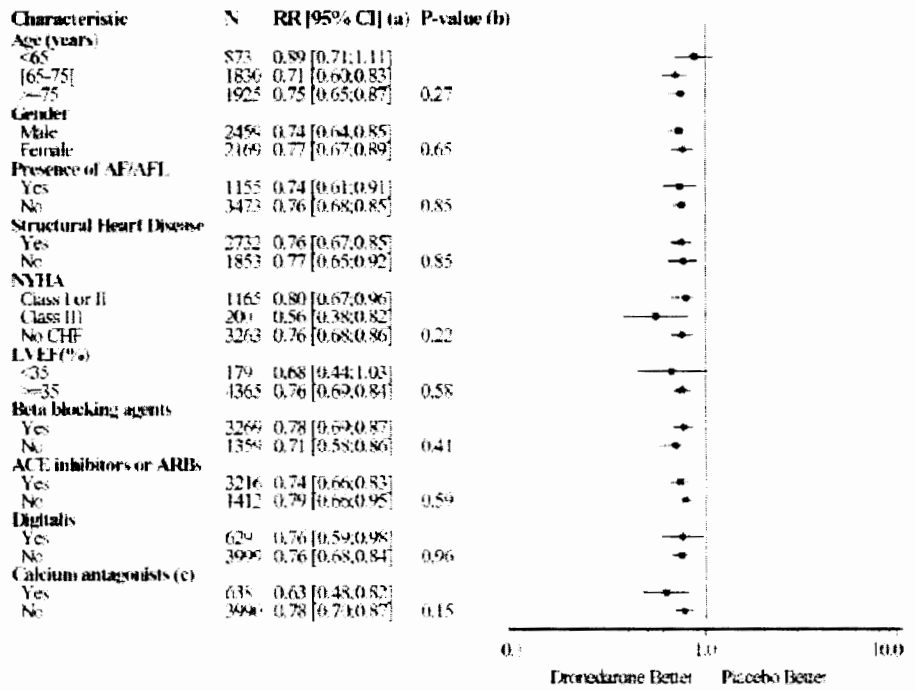
The person of ordinary skill in the art is someone having a medical degree who is board certified in cardiology or electrophysiology with at least two years of clinical practice who also has knowledge of the design, implementation, and analysis of clinical studies. (Tr. 58:18–59:3).

With respect to the label generally, Plaintiffs' expert, Dr. Kim, acknowledged that there is no express reference to a patient who has coronary heart disease and is over 70 years of age. (Tr. 144:10–14). The Indications and Usage section (section 1) of Defendants' labels indicates administering dronedarone tablets for reducing "the risk of hospitalization for atrial fibrillation in patients in sinus rhythm with a history of paroxysmal or persistent atrial fibrillation." (JTX-54 at 4).[4] This section does not expressly indicate the drug for patients with coronary heart disease. (Tr. 206:15–207:5). This section does direct a POSA to review, and a POSA would review, the Clinical Studies section (section 14). (Tr. 65:5–15).

[4] Citations are primarily to Watson's label. The parties do not suggest that Watson's label and Sandoz's label materially differ.

The Clinical Studies section of Defendants' labels supports the conclusion that the labels teach that dronedarone could be used for some patients with coronary heart disease. Section 14.1 discusses the ATHENA study. This study comprises the first four of the five pages in section 14. (JTX-54 at 18–21). The study looked at the effects of dronedarone in patients with a recent history of atrial fibrillation ("AF") "who were in sinus rhythm or who were to be converted to sinus rhythm." (JTX-54 at 18). "The objective of the study was to determine whether dronedarone could delay death from any cause or hospitalization for cardiovascular reasons." (JTX-54 at 18). The study found that "[d]ronedarone reduced the combined endpoint of cardiovascular hospitalization or death from any cause by 24.2%." (JTX-54 at 19). This was "generally consistent in all of the subgroups based on baseline characteristics or medications" as illustrated by Figure 4. (JTX-54 at 20–21). Figure 4 of the ATHENA study is located twenty pages after the first Black Box Warning. (JTX-54 at 21).

Figure 4: Relative Risk (Dronedarone tablets versus placebo) Estimates with 95% Confidence Intervals According to Selected Baseline Characteristics: First Cardiovascular Hospitalization or Death from any Cause.



(JTX-54 at 21).

A POSA would recognize from ATHENA that about 60% of the patients had structural heart disease. (Tr. 75:22–76:16). Structural heart disease patients exhibited a 24% reduction in the risk of cardiovascular hospitalization and death. (JTX-54 at 21). Dr. Kim estimates that half of those patients would have coronary heart disease. (Tr. 76:14–16). While the words "coronary heart disease" do not expressly appear anywhere in section 14.1 (Tr. 137:23–138:9), Dr. Zusman nevertheless concedes that a physician "might conclude" that the authors of the ATHENA study included patients with coronary heart disease. (Tr. 389:1–11). Dr. Kim stated that a POSA would infer that coronary heart disease patients are included within structural heart disease patients. (Tr. 138:21–139:1). Other evidence supports the finding that about 30% of ATHENA patients had coronary heart disease. (Tr. 78:11–14, 222:10–20, 250:13–22; JTX-23 at 4).

Section 14.2 discusses the EURIDIS and ADONIS study. This section weighs in Plaintiffs' favor. This study followed 1,237 patients treated with either dronedarone 400 mg twice daily or placebo. Section 14.2 states, "The most common co-morbidities were hypertension (56.8%) and structural heart disease (41.5%), including coronary heart disease (21.8%)." (JTX-54 at 21). This language suggests that coronary heart disease is a subset of structural heart disease.

I acknowledge that definitions of structural heart disease do not consistently include coronary heart disease as a subset. (Tr. 139:9–12). For example, the Medical School of Brown University's webpage defines structural heart disease as "congenital or acquired pathologies outside of atherosclerosis." (DTX-279). Dr. Kim stated that coronary heart disease is also called atherosclerosis. (Tr. 135:15–22). Dr. Kim used to work at Brown Medical. (Tr. 140:9–11). The University of Chicago Medicine's webpage describes structural heart disease as a "defect or

abnormality of the heart that is non-coronary." (DTX-280). The significance of these webpages is very low because these pages appear to be directed to a new surgical specialty in cardiology for valvular heart disease. (Tr. 73:6–75:21, 139:23–142:4). Overall, in the context of Defendants' labels, a POSA would understand "structural heart disease" to include coronary heart disease and that a person with coronary heart disease would be described as having structural heart disease.

There is encouragement to prescribe dronedarone to some patients within the Age Criteria. Defendants' labels suggest that dronedarone could be used in patients in the Age Criteria. The ATHENA patients ranged from 23–97 years old, where 42% were 75 years old or older. (JTX-54 at 19). All of the ATHENA patients met the "inclusion criteria." (Tr. 386:17–387:3). The inclusion criteria initially included patients greater than or equal to seventy years old, or less than seventy years old with at least one risk factor. (JTX-54 at 18). The inclusion criteria were revised to include patients greater than or equal to 75 years old, or greater than or equal to 70 years old with at least one risk factor.[5] (JTX-54 at 18). The EURIDIS and ADONIS patients ranged from 20–88 years old. (JTX-54 at 21). Dr. Zusman concedes that assuming the label discloses use in coronary heart disease patients, a physician "might have inferred" that dronedarone would provide a benefit in terms of reduction in cardiovascular hospitalization and death in patients consistent with the overall ATHENA population." (Tr. 387:17–388:12).

The evidence of noninfringing uses weigh in Defendant's favor. Dr. Zusman estimates that based on his experience, approximately 80% of dronedarone patients do not have both coronary heart disease and meet the Age Criteria. (Tr. 220:3–221:4). Dr. Kim estimates that this figure is approximately 75 to 80%. (Tr. 136:19–24). Plaintiffs concede that Defendants'

[5] The revised inclusion criteria directly match the Age Criteria. (Tr. 65:16–66:3).

products "may have substantial non-infringing uses." (D.I. 201 at p. 20). Defendants argue that because of *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348 (Fed. Cir. 2003), this fact is dispositive. I do not agree. There, the Federal Circuit upheld a summary judgment finding of no induced infringement in an ANDA case where only 2.1% of written prescriptions would be infringing, even when viewing the evidence in the light most favorable to the Plaintiff. *Warner-Lambert Co.*, 316 F.3d at 1363–66 ("Where there are many uses for a product, . . . and fewer than 1 in 46 sales of that product are for infringing uses, we are not in a position to infer or not infer intent on the part of [Defendants] without any direct evidence."). Here, 20–25% is not close to 2.1%.

In sum, while the Indications and Usage section does not expressly instruct the administration of dronedarone to patients with coronary heart disease who meet the Age Criteria, it directs a POSA to review, and a POSA would review, the Clinical Studies section. From the Clinical Studies section, it would be readily apparent to a POSA that the use of dronedarone for patients with coronary heart disease and who meet the Age Criteria would reduce the risk of cardiovascular hospitalization. (Tr. 84:7–14). A POSA would understand that a significant proportion of structural heart disease patients were coronary heart disease patients. The labels encourage a POSA to prescribe dronedarone to some patients within the Age Criteria. Although evidence of noninfringing uses weigh in favor of Defendants, that evidence is not dispositive. Considering all of this evidence as a whole, Plaintiffs have shown that Defendants' labels instruct a POSA to use dronedarone for patients within the Age Criteria and who have coronary heart disease.

Defendants argue that the patented uses described by the '900 patent do not correlate with the approved indication, making a finding of induced infringement improper. Defendants argue

that Multaq®'s indication is not directed to coronary heart disease patients meeting the Age Criteria. (D.I. 203 at pp. 24–25). Plaintiffs argue, and I agree, that the FDA did determine dronedarone to be safe and efficacious in coronary heart disease and stable Class III CHF patients on the basis of the ATHENA results. (D.I. 206 at pp. 3–4). Defendants proffer no evidence that the FDA did not determine dronedarone to be safe and efficacious in coronary heart disease patients within the Age Criteria. (D.I. 203 at 24–25). Thus, this argument is not persuasive. Defendants know about the '900 patent and know generic dronedarone will be administered in a manner that infringes the '900 patent. They intend that result. Again, Defendants' labels also instruct a POSA to use dronedarone for patients within the Age Criteria and who have coronary heart disease. Plaintiffs have met their burden of showing that Defendants' labels would induce infringement of claims 1, 7, 9, and 14 of the '900 patent.

b) Claims 6 and 8

Defendants argue that they do not induce infringement of claims 6 and 8, which is directed to patients with New York Heart Association Class III congestive heart failure. Defendants' labels contain a Black Box warning on the first page that discourages physicians from using dronedarone in patients with "decompensated heart failure." (JTX-54 at 1). The label is as follows:

WARNING:
INCREASED RISK OF DEATH, STROKE AND HEART FAILURE IN PATIENTS WITH DECOMPENSATED HEART FAILURE OR PERMANENT ATRIAL FIBRILLATION

Dronedarone tablets are contraindicated in patients with symptomatic heart failure with recent decompensation requiring hospitalization or NYHA Class IV heart failure. Dronedarone tablets double the risk of death in these patients (4, 5.1, 14.3).

Dronedarone tablets are contraindicated in patients in atrial fibrillation (AF) who will not or cannot be cardioverted into normal sinus rhythm. In patients with permanent AF, dronedarone tablets double the risk of death, stroke, and hospitalization for heart failure. (4, 5.2, 14.4)

(JTX-54 at 1). This warning is repeated on page 4. (JTX-54 at 4). "Decompensation" is when a patient goes from a lower NYHA classification to a higher classification. (Tr. 165:9–166:16; *see also* Tr. 63:9–12). The words, "Increased risk of death, stroke and heart failure in patients with decompensated heart failure or permanent atrial fibrillation," derive from the ANDROMEDA and PALLAS trials. (Tr. 122:20–123:3). Dr. Zusman, Defendants' expert, explained that a "symptomatic heart failure" patient population referred to in the Black Box's second paragraph is the Class III and IV patient groups. (Tr. 187:6–18). Doctors see this warning as a "flashing red light" in determining whether to prescribe to a patient. (Tr. 113:3–8). This warning serves to draw attention to patients who should not receive the drug because of the dangers. (Tr. 184:5–10). Some physicians seeing this warning will not use dronedarone in any heart failure patient. (Tr. 113:9–13). Dr. Kim, Plaintiffs' expert, avoids giving dronedarone to Class III patients in part due to the black box warning. (Tr. 110:4–8). Dr. Zusman believes that the warning applies "very definitely" to Class III patients. (Tr. 185:8–16). Dr. Zusman believes that the label "clearly teaches away" from the use of dronedarone in Class III patients. (Tr. 189:3–16).

Support for Defendants' position is found in other places of the label. Section 4 (Contraindications) states that dronedarone tables are contraindicated in patients with symptomatic heart failure with recent decompensation requiring hospitalization or Class IV symptoms. (JTX-54 at 5; Tr. 111:11–18). Section 5.1 provides a similar warning. (JTX-54 at 5; Tr. 111:19–112:5). Section 14.3 describes the ANDROMEDA study where 57% of patients had Class III CHF. (JTX-54 at 22). The ANDROMEDA patients were recently hospitalized with symptomatic heart failure and severe left ventricular systolic dysfunction. (JTX-54 at 22). This trial was "terminated because of excess mortality in the dronedarone group . . . . The main reason for death was worsening heart failure." (JTX-54 at 22). This trial also exhibited "excess

hospitalizations for cardiovascular reasons in the dronedarone group (71 percent versus 51 for placebo)." (JTX-54 at 22).

Other sources discourage a POSA from using dronedarone in Class III patients generally. Dr. Kim himself wrote in 2012 that, "According to the 2011 ACCF/AHA/HRS guideline update, dronedarone is not recommended in patients with heart failure, and the 2010 ESC guidelines do not recommend dronedarone in patients with NYHA III/IV or 'unstable or recently decompensated' NYHA II CHF." (PTX-5 at 9) (footnotes omitted). The 2014 AHA/ACC/HRS guideline reaffirms that dronedarone should not be used with treatment of AF in patients with NYHA Class III or IV heart failure. (Tr. 119:9–120:7). Dr. Kim testified that physicians utilize certain guidelines to try to understand how to use drugs for cardiology patients. (Tr. 113:14–17). These guidelines would discourage a POSA from using dronedarone in Class III patients, whether stable or unstable.

Weighing slightly in Plaintiffs' favor is the ATHENA study. (JTX-54 at 18–21). There is evidence that some physicians would understand that this study included "stable" Class III CHF patients, or patients who have not been hospitalized for heart failure within the last month, as distinguished from the recently decompensated Class III CHF patients of ANDROMEDA. (*See* Tr. 99:1–7, 122:10–19, 124:20–127:3). It is unclear whether a sample size of 200 Class III patients is sufficient to support the conclusion that dronedarone was safe or provided a benefit. (JTX-54 at 21; Tr. 130:23–131:9). Although Figure 4 of the label provides that the reduction in risk of cardiovascular hospitalization or death was 44% (JTX-54 at 21), there is doubt over whether this conclusion is meaningful. One reviewer for the Journal of the American College of Cardiology cast doubt on the ability to draw meaningful conclusions about the effect of dronedarone on Class III patients by stating that "[t]he [ATHENA] trial was not powered to

address outcomes in patients with Class III CHF . . . . In such underpowered analyses, it is arguably not appropriate to conduct significance testing." (DTX-251 at 3; Tr. 131:15–133:23, 135:1–14). The reviewer further wrote that "the sample size is insufficient to draw any meaningful differences." (DTX-251 at 3). JACC did not publish Dr. Stefan Hohnloser's submission on the ATHENA manuscript "most likely due to the very negative comments" of this reviewer. (DTX-251 at 2). On the other hand, the 95% confidence interval indicates an 18–62% reduction in risk. (Tr. 94:21–96:22; JTX-54 at 21). The p-value of 0.22 suggests that there is no difference in benefit between patients having CHF and those without CHF. (Tr. 94:21–96:22; JTX-54 at 21). Overall, Figure 4 would give a physician little encouragement to give dronedarone to a Class III patient. (Tr. 193:2–12).

Weighing strongly in Defendants' favor is evidence of noninfringing uses. Dr. Kim estimates that only 3% of patients treated with dronedarone have Class III CHF. (Tr. 97:23–98:3). This is despite the fact that more than 3% of AF patients have Class III CHF in the real world. (Tr. 105:9–12). Dr. Kim estimates that only five out of the hundreds of patients he has prescribed dronedarone had Class III CHF. (Tr. 104:23–105:4). Sanofi's documents suggest that 12% of all AF patients have Class III CHF. (DTX-217 at 5).

The evidence of noninfringing uses alone might be dispositive to this analysis. *See Warner-Lambert Co.*, 316 F.3d at 1363–66. Even if it were not, I would reach a conclusion of noninfringement. Considering all of the evidence as a whole, Plaintiffs have not shown that Defendants' labels instruct a POSA to use dronedarone for patients with stable NYHA Class III CHF. A POSA would not be encouraged by Defendants' labels to prescribe dronedarone to such patients. Although there is some evidence that a physician may interpret the label to prescribe

dronedarone for such patients, there is stronger evidence that a physician would be dissuaded from doing so.

Plaintiffs argue that a physician would read the Black Box warnings thoroughly, including the relevant Clinical Studies sections and understand that the unstable Class III CHF patients are significantly different from stable Class III CHF patients. I disagree. Even a thorough review of the entire label would leave a POSA with significant concerns after reading the Black Box warnings as to whether stable Class III CHF patients could safely take dronedarone. A POSA would remain skeptical about whether it was safe to prescribe dronedarone to stable Class III CHF patients. A POSA would not find adequate encouragement in ATHENA or Figure 4 of Defendants' labels because the labels fail to make it clear that it is safe to do so. Plaintiffs failed to meet their burden of showing that Defendants' labels would induce infringement of Claims 6 and 8.

B. Obviousness

1. Findings of Fact

1. The '900 patent is entitled to a priority date of February 11, 2009.
2. The POSA with respect to the '900 patent is someone having a medical degree who is board certified in cardiology or electrophysiology with at least two years of clinical practice who also has knowledge of the design, implementation, and analysis of clinical studies.
3. The CAST trials (late 1980s) taught that for patients who sustained a heart attack or myocardial infarction, all of whom had premature ventricular contractions or premature beats, certain antiarrhythmic drugs ("AADs") of Class I increased the risk of death.
4. DAFNE was a dose range study on dronedarone without statistical significance.
5. The rate vs. rhythm trials (2000) were six trials designed to investigate whether one should try to restore normal sinus rhythm in a patient or leave the patient in atrial fibrillation but simply control the patient's heart rate so that the patient was comfortable. These trials cast doubt on the safety of AADs.
6. SWORD showed that Sotalol was not safe and effective.

7. PROMISE showed that amiodarone did not decrease mortality.

8. The rate vs. rhythm trials, SWORD, and PROMISE suggest that AF may simply be a marker for underlying cardiovascular disease and that the risks of using AADs outweigh the benefits.

9. EURIDIS/ADONIS (2001) studied the effects of dronedarone on younger and healthier patients with non-permanent atrial fibrillation.

10. Singh (2007) published the results of EURIDIS/ADONIS. Singh found that dronedarone "was significantly more effective than placebo in maintaining sinus rhythm and in reducing the ventricular rate during recurrence of arrhythmia." Because it was a post-hoc analysis, a POSA would understand that it has inherent limitations in terms of reliability.

11. ANDROMEDA (2002) studied the safety of dronedarone on patients with highly unstable heart failure without consideration of the presence or absence of atrial fibrillation. This trial was terminated early because of excessive mortality in the treatment group, compared to placebo. ANDROMEDA cast significant doubt over the safety of dronedarone for such patients.

12. The FDA and EMEA initially rejected the approval of dronedarone even though both agencies considered post-hoc data from EURIDIS/ADONIS. ANDROMEDA gave both agencies concern and contributed to the finding of both agencies that dronedarone's risks outweighed its benefits.

13. ATHENA (2005) studied the effects of dronedarone on patients who had a history of non-permanent atrial fibrillation. The hypothesis to be tested in ATHENA was that dronedarone would have a favorable outcome on cardiovascular hospitalization in the ATHENA patient population. The ATHENA patients were different from the EURIDIS/ADONIS patients. The ATHENA patients were older and sicker. Among other difficulties, it is much more difficult to reverse the development of AF in older patients.

14. Hohnloser (January 2008) described in detail the design of the ATHENA trial, including why it was conducted and the "expected" outcome of the trial. Hohnloser states, "Since it was shown that dronedarone is not only capable of maintaining [sinus rhythm] in many patients, but also of controlling heart rate in case of [atrial fibrillation] relapses, it is expected that treatment with this compound will result in a significant reduction in the need of rehospitalizations for cardiovascular reasons." A POSA would view this statement as a hypothesis to be tested by the ATHENA trial. Because it is a hypothesis, it is not worth much weight because hypotheses are known to be disproven and rejected.

15. Dr. Radzik testified that the evidence leading up to the ATHENA trial did not show a reduction in the risk of cardiovascular hospitalization.

16. PALLAS sought to determine the impact of dronedarone on patients with permanent atrial fibrillation. It was prematurely terminated for safety reasons.

17. Internal Sanofi statements suggest that a POSA would be encouraged by the EURIDIS/ADONIS data and that the ATHENA trial proceeded because of the EURIDIS/ADONIS data. Some of these statements express concern over the safety of dronedarone. These statements do not constitute prior art. The emphasis given to some of the internal Sanofi statements may be the result of hindsight bias. These statements do not directly address the patient populations in claims 1, 7, 9, and 14.

18. DTX-104 is given limited weight in Defendants' favor because it is undated.

19. In DTX-78, an e-mail, Dr. Seiz simply communicates a statement made to him by Dr. Hohnloser and Dr. Torp-Pedersen, who both sat on the ATHENA Steering Committee. Dr. Hohnloser and Dr. Torp-Pedersen did not have the authority to speak on behalf of Sanofi with respect to the statements communicated to Dr. Seiz in DTX-78.

20. No weight is given to the secondary considerations of long felt but unmet need, unexpected results, skepticism, or commercial success.

21. Defendants have not shown by clear and convincing evidence that Claims 1, 7, 9, and 14 of the '900 patent are invalid as obvious.

2. Conclusions of Law

Defendants argue that claims 1, 7, 9, and 14 of the '900 patent are invalid as obvious. Again, the person of ordinary skill in the art is someone having a medical degree who is board certified in cardiology or electrophysiology with at least two years of clinical practice who also has knowledge of the design, implementation, and analysis of clinical studies. (Tr. 58:18–59:3).

a) Background

AF is a cardiac rhythm disorder characterized by an irregular rhythm, which is in contrast to the regular rhythm (normal sinus rhythm) associated with normal cardiac function. (Tr. 153:12–17). Dr. Zusman testified that a common cause of hospitalization for AF patients is the recurrence of AF resulting in problems such as fainting, chest pain, heart failure, palpitations, stroke or systemic embolization, and tachycardia (the rapid heart rate associated with AF). (Tr. 256:9–257:2). Dr. Zusman acknowledges that as of 2008, it was not known whether the maintenance of sinus rhythm actually prevents stroke in patients with AF. (Tr. 373:19–374:10).

Dr. Zusman acknowledges that as of 2008, it would be a significant finding if a company could demonstrate that dronedarone would reduce heart failure. (Tr. 336:2–10).

It is more difficult to reverse the development of AF in older patients. (Tr. 331:16–19). It is more difficult to maintain sinus rhythm in older patients. (Tr. 330:22–331:3). AF patients with additional cardiovascular risk factors are significantly more likely to experience adverse events in response to an antiarrhythmic drug. (Tr. 332:18–333:10). Older patients are also more likely to be on concomitant medications, increasing the chance of drug/drug interactions. (Tr. 331:20–332:3).

b) Scope and Content of the Prior Art

Plaintiffs do not dispute that the '900 patent is entitled to a priority date of February 11, 2009. (*See generally* D.I. 204; Tr. 234:1–5).

(1) CAST Trials

The CAST trials (late 1980s) taught that for patients who sustained a heart attack or myocardial infarction, all of whom had premature ventricular contractions or premature beats, certain AADs of Class I increased the risk of death. (Tr. 266:14–24). After the CAST trials, "safety is paramount." (Tr. 88:17–22).

(2) DAFNE

DAFNE (1999) was a trial that studied 400 mg of dronedarone, twice per day, given with the morning and evening meal in patients with non-permanent AF. (Tr. 229:20–230:12). It showed that dronedarone reduced the time to recurrence and the heart rate at the time of recurrence of AF patients. (Tr. 229:20–230:12). DAFNE was a dose range study, so it is without statistical significance. (Tr. 316:4–13).

(3) Rate vs. Rhythm Trials; SWORD; PROMISE

The rate vs. rhythm trials (2000) were six trials designed to investigate whether one should try to restore normal sinus rhythm in a patient or leave the patient in AF but simply control their heart rate so that the patient was comfortable. (Tr. 279:22–280:16, 85:3–16). One set of patients received AADs and rate control drugs (rhythm-control group). Another set received only rate control drugs (rate-control group). (Tr. 334:7–16, 85:3–16).

One of the trials, the AFFIRM trial, found an increase in hospitalization associated with AADs in the rhythm-control group. (Tr. 501:16–502:16; JTX-55 at 7). It also found an association with excessive mortality among older patients, those with heart failure, and those with coronary artery disease. (Tr. 333:11–18). Dr. Zusman admitted that there is no evidence to this day, that Sotalol, a drug used in AFFIRM, reduces the risk of cardiovascular hospitalization. (Tr. 318:7–10).

Another one of the trials, the AF-CHF trial, found that AADs had no benefit in mortality and a worsened rate of hospitalizations for AF. (Tr. 86:8–13). This led Dr. Rodney Falk (2005) to state, "The controlled trials have consistently demonstrated no benefit of attempts to maintain sinus rhythm over rate control in any primary or secondary end point evaluated." (PTX-40 at 16). Dr. Radzik, one of the inventors of the '900 patent, stated that "there was evidence that these drugs in general are rather deleterious for clinical outcomes, such as hospitalization, let alone death because there has always been a lot of concern about the possibility of increasing death with antiarr[h]ythmic drugs." (Tr. 502:11–16).

The SWORD study, done on Sotalol, tested the hypothesis that Sotalol would be safe and effective. It turned out that it was not. (Tr. 296:12–297:2, 298:2–7). The PROMISE study, done on positive inotropic drugs like amiodarone, another drug used in AFFIRM, showed that

they did not decrease mortality. (Tr. 376:15–377:8, PTX-40 at 16). A POSA would be aware that dronedarone was designed to be safer than amiodarone. (*See* JTX-46 at 1).

These trials suggest to a POSA in 2008 that AF is a marker of some underlying cardiovascular disease causing adverse outcomes such as stroke. (Tr. 86:14–22; PTX-40 at 16). These trials also suggest to a POSA that the adverse effects of AADs could outweigh the potential benefits. (Tr. 86:22–87:3).

(4) EURIDIS/ADONIS

EURIDIS/ADONIS (2001) were Phase III trials, studying the effects of dronedarone on patients "with at least one documented episode of AF during the previous 3 months and [sinus rhythm] for at least 1 hour." (JTX-23 at 2). It included patients with and without coronary heart disease. It included patients who meet and who do not meet the Age Criteria. (JTX-46 at 6). The patients were generally younger and healthier patients and had non-permanent AF. (JTX-23 at 2; Tr. 77:23–24). EURIDIS completed in August 2003. ADONIS completed in September 2003. (DTX-68 at 1; DTX-69 at 1).

Singh (2007) published the results of EURIDIS/ADONIS. Singh found that dronedarone "was significantly more effective than placebo in maintaining sinus rhythm and in reducing the ventricular rate during recurrence of arrhythmia." (JTX-46 at 1; Tr. 238:7–20). Singh further reported that "a post hoc analysis revealed that 21.2% of patients in the dronedarone group had been hospitalized or had died at 12 months, as compared with 32.0% of those in the placebo group (hazard ratio, 0.66; 95% CI, 0.47 to 0.93; P=0.02)." (JTX-46 at p. 993). Singh reported that for ADONIS, "24.5% of patients in the dronedarone group had been hospitalized or had died, as compared with 29.8% of those in the placebo group (hazard ratio, 0.80; 95% CI, 0.56 to

1.14; P=0.22)." (JTX-46 at p. 993).[6] Singh was published in The New England Journal of Medicine, which is generally considered "to be the most prestigious publication in the field of medicine or cardiology." (Tr. 235:20–236:2). It is peer-reviewed. (Tr. 236:2–3). A reviewer for the Singh article made the following comment:

> In the present study, virtually all of the primary endpoint impact from dronedarone was due to reduced cardiovascular hospitalization for AF recurrence. This outcome is predictable based on the well documented ability of dronedarone to prevent AF recurrence. Thus, the study essentially shows that a drug known to prevent AF will reduce hospitalization for AF recurrence in patients managed with a rhythm control strategy.

(DTX-191 at 5).

A post-hoc analysis in the context of a clinical trial is a retrospective analysis of clinical data that seeks to answer a question that was not a pre-specified endpoint in the original clinical trial. A POSA would know that post-hoc analyses have inherent limitations in terms of reliability and would therefore critically evaluate conclusions arising out of a post-hoc analysis in light of the known risks and benefits of a particular method of treatment. The data in Singh was not adjudicated. (Tr. 313:11–18). It is possible that its data is inaccurate. (Tr. 313:19–314:9). The conclusions of Singh could be based on "poor information." (Tr. 414:17–415:8).

(5) ANDROMEDA

ANDROMEDA (2002) studied the safety of dronedarone on patients with highly unstable heart failure without consideration of the presence or absence of AF. (Tr. 231:10–19, 88:10–20). Specifically, these patients had a "recent episode of decompensated heart failure and a left ventricular ejection fraction (LVEF) < 0.35." (JTX-23 at 2). ANDROMEDA was not an AF study. (JTX-23 at 4). This trial was terminated early because of excessive mortality in the

[6] A third post-hoc analysis, reported in a Sanofi document (with a version date of January 2007), indicated that "dronedarone decreased the risk of the combined endpoint of mortality or hospitalization for cardiovascular reasons by 20% (hazard ratio = 0.804, log rank p-value = 0.164." (JTX-64 at 15).

treatment group, compared to placebo. (JTX-23 at 2). At the time of the study, Dr. Zusman disagreed with the hypothesis of ANDROMEDA that dronedarone could reduce the risk of hospitalization due to heart failure in the ANDROMEDA population. (Tr. 309:14–22).

(6) Regulatory Consideration

Information contained in EURIDIS/ADONIS was submitted to the FDA for consideration with Sanofi's NDA for approval of dronedarone. (Tr. 319:17–20, 411:22–412:15). In initially rejecting dronedarone, the FDA considered the post-hoc data from EURIDIS/ADONIS. (Tr. 319:21–320:4). It appears the EMEA did the same. (JTX-17 at 19 ("A reduction in time to death and hospitalization was noted but this reflects an ancillary analysis and needs further confirmation, in particular in the context of the negative effects seen in [] ANDROMEDA . . . .")).[7] ANDROMEDA gave rise to the FDA's safety concern over approving dronedarone, and essentially led to the ATHENA study. (Tr. 329:24–330:8, 330:14–16, JTX-19 at 1). The FDA stated, "The data, however, do not indicate a favorable risk-benefit relationship for either rate control or prevention of AF recurrence." (JTX-19 at 1). The EMEA report stated that, pending the results of ATHENA, "At the moment, the ratio between efficacy and safety is considered negative." (JTX-17 at 24).[8] Dr. Zusman believes that had ANDROMEDA not been conducted, Sanofi would have secured regulatory approval. (Tr. 231:2–9). Had the FDA approved dronedarone, Sanofi would not have performed a safety trial such as ATHENA. (Tr. 478:8–22).

[7] I understand an "ancillary" analysis to mean a "post-hoc" analysis.

[8] This report also discloses that dronedarone should be taken twice a day with meals. (Tr. 251:21–252:5; JTX-17 at 5).

(7) ATHENA

ATHENA (2005) studied the effects of dronedarone on patients who had a history of non-permanent AF. (Tr. 233:2–9). ATHENA's results were published after the '900 Patent was filed. (Tr. 35:2-9). The hypothesis to be tested in ATHENA was that dronedarone would have a favorable outcome on cardiovascular hospitalization in the ATHENA patient population. (Tr. 301:8–302:6). The hospitalization endpoint was added because a study cannot show that a drug does not increase mortality without other endpoints. (Tr. 308:12–20). Dr. Zusman acknowledges that the investigators of ATHENA were entitled to assume anything they wanted in the design of ATHENA but believes they grounded it in a reasonable belief of the safety of dronedarone. (*See* Tr. 312:3–7).

The ATHENA trial had several differences from prior trials. With respect to the EURIDIS/ADONIS patient population, the patient population of ATHENA was older and sicker than that of EURIDIS/ADONIS, although the age ranges overlapped. (Tr. 71:1–3, 77:17–78:10; DTX-69 at 56 (reporting a median age of 66, mean age of 65, and range of 20–88 for ADONIS); DTX-68 at 57 (reporting a median age of 60, mean age of 60, and range of 15-93 for EURIDIS); DTX-67 at 57 (reporting a median age of 73, mean age of 72, and range of 23–97 years for ATHENA)). The patient population of ATHENA had 86% hypertension versus 56.8% in EURIDIS/ADONIS. (Tr. 788:2–4). The ATHENA population had more cardiovascular disease and more structural heart disease than the EURIDIS/ADONIS patient population. (Tr. 89:15–18). It should be noted that both trials had patients with non-permanent AF and similar rates of coronary heart disease. (JTX-46 at 2, 6; JTX-23 at 2, 4). Both trials excluded patients with permanent AF or who were NYHA Class IV. (JTX-46 at 2; JTX-23 at 3).

With respect to ANDROMEDA, ATHENA did not enroll patients hospitalized with new or worsening heart failure with severe left ventricular dysfunction. (Tr. 233:2–24). The ANDROMEDA patient population is sicker than the ATHENA patient population. (Tr. 481:10–21).

With respect to AFFIRM, Dr. Gaudin, another inventor of the '900 patent, explained that if amiodarone (an AAD used in AFFIRM) was used in an ATHENA-like study to evaluate cardiovascular hospitalization, it would be doubtful if it would have been as effective as dronedarone because amiodarone has not been observed to exhibit such a benefit. (Tr. 476:13–23). A POSA in 2008 would have been aware that drug/drug interactions could have a very significant effect on the outcome of ATHENA. (Tr. 332:4–7). Dr. Radzik believes that the evidence leading up to the ATHENA trial did not show a reduction in the risk of cardiovascular hospitalization. (*See* Tr. 501:16–502:16).

(8) Hohnloser

Hohnloser (January 2008) described in detail the design of the ongoing ATHENA trial, including why it was conducted and the expected outcome of the trial. (Tr. 243:12–20). While Hohnloser did not publish the results of ATHENA (Tr. 299:3–6), Hohnloser provides:

> Dronedarone reduced the risk of rehospitalization by approximately 20% in [EURIDIS/ADONIS]. Cardiovascular hospitalization is anticipated to precede the majority of cardiovascular deaths. The remaining deaths, by default deaths not preceded by cardiovascular hospitalization, are unlikely to be influenced by dronedarone. Thus, the overall decrease of risk for the primary endpoint in ATHENA is assumed to be 15% at 1 year.

(JTX-23 at 3). Hohnloser further stated that: "Since it was shown that dronedarone is not only capable of maintaining [sinus rhythm] in many patients, but also of controlling heart rate in case of AF relapses, it is expected that treatment with this compound will result in a significant reduction in the need of rehospitalizations for cardiovascular reasons." (JTX-23 at 4).

Dr. Zusman made statements suggesting that these quotations from Hohnloser reflect the hypothesis of the ATHENA trial. (*See, e.g.*, Tr. 300:11–17). Dr. Zusman also testified that Hohnloser knew "quite confidently" that dronedarone would reduce hospitalization because Hohnloser knew of the properties of dronedarone. (Tr. 257:3–6). Dr. Zusman testified that a POSA would understand that this expectation extends to patients with coronary heart disease. (Tr. 265:6–22).

c) Other Evidence

(1) PALLAS

PALLAS (2011) was a new indication seeking trial in which dronedarone was given to patients with permanent atrial fibrillation to see if it could impact outcomes. It enrolled an older and sicker population than ATHENA. It prematurely terminated for safety reasons. (Tr. 69:19–70:13, 293:7–16).

(2) Internal Sanofi Statements

Sanofi's Clinical Trial Protocol (March 2005), issued to ATHENA site investigators and to the FDA, provides:

> Given the trend for a beneficial effect of dronedarone in the AF/AFL population derived from EURIDIS/ADONIS data on the combined endpoint of hospitalization for cardiovascular reasons or any death it is expected that treatment with dronedarone can similarly decrease this combined endpoint in high risk patients with a history of AF/AFL.

(DTX-60 at 15). This statement in DTX-60 is found in the "Rationale" section.

A Sanofi document (April 2005) issued to institutions participating in ATHENA, provides:

> Dronedarone has been shown in two large international trials EURIDIS and ADONIS that it is able to reduce the frequency of recurrences of atrial fibrillation or atrial flutter in patients with a history of disturbed heart rhythm. It also appeared in these studies that patients treated with dronedarone were less

> frequently admitted to hospital. The frequency of adverse events was comparable in the dronedarone group and in the placebo group.
>
> Based on this knowledge it is expected that dronedarone improves the outcome in atrial fibrillation and atrial flutter patients by reducing the admissions to hospital and by prolonging the time in normal heart rhythm.

(DTX-117 at 1). DTX-117 further expresses that "there is no clear evidence" as to whether using dronedarone over placebo "will be a positive or negative difference." (DTX-117 at 4).

A Sanofi document (dated around 2006) that was an informed consent document for patients and was submitted to the FDA as part of Sanofi's NDA submission provides:

> Based on this knowledge it is expected, that dronedarone improves the outcome in atrial fibrillation and atrial flutter patients by reducing the admissions to hospital and by prolonging the time in normal heart rhythm.

(DTX-209 at 1; Tr. 257:24–258:21). This document may be a draft. (Tr. 479:3–15, 327:21–329:10).

A Sanofi document titled "Dronedarone Advisory Panel Meeting" (December 2005), states, "The panel considered the data showing reduction of CV hospitalization with dronedarone to be very reassuring, even though it was a post-hoc analysis." (DTX-77 at 4). This document further stated, "The panel voiced concern about excess mortality in the AF/AFL population." (DTX-77 at 3). It also stated, "The panel was concerned about the trend of sudden death in the AF/AFL population." (DTX-77 at 3).

Sanofi's ATHENA Clinical Study Report (May 2008), provided to the FDA, states:

> Given the trend for a beneficial effect of dronedarone in the AF/AFL population derived from the EURIDIS/ADONIS data on the combined endpoint of cardiovascular hospitalization or any death, the ATHENA study was designed to document the clinical benefit of dronedarone 400 mg BID in patients with AF/AFL or a history of AF/AFL and additional risk factors as evaluated by the composite endpoint of time to first cardiovascular hospitalization or death from any cause.

(DTX-67 at 22).

A May 2008 email from Dr. Radzik states:

> Availability of EURIDIS and ADONIS results that show the effectiveness and the good tolerance of dronedarone for the prevention of atrial fibrillation. These studies also show a benefit concerning the hospitalization of patients for cardiovascular reasons which would be the basis of the hypothesis of the ATHENA study.

(DTX-203).

Another May 2008 email from Dr. Radzik states, "[EURIDIS and ADONIS] show a benefit in hospitalization for cardiovascular reasons which will be . . . at the base for generating the hypothesis of ATHENA." (Tr. 488:8–490:4 (referencing DTX-198)).

In March 2009, Dr. Gerald Naccarelli, Chief of Cardiology at Penn State, told FDA, "Dronedarone has properties that can be expected to reduce the risk of death and cardiovascular hospitalization. A reduction in such risk was observed in the post-hoc analysis of EURIDIS and ADONIS." (DTX-97 at 31:1-3).

Although Defendants note that "the vast majority of its statements pre-date the ATHENA results," Defendants do not dispute that these internal Sanofi statements do not constitute prior art. (D.I. 205 at p. 3 n.4). Dr. Radzik further suggests that selection of some these statements could be the product of hindsight bias. (Tr. 490:16–18 ("[I]t's very easy once you have the results of something to say, well, this is the hypothesis that we had."). These statements do not directly address the patient populations in claims 1, 7, 9, and 14.

(3) DTX-104

DTX-104 is a document entitled, "Key data from dronedarone clinical development program." Defendants argue that it is an internal Sanofi obtained from the files of Dr. Radzik. It is marked "Confidential." (DTX-104). Defendant argues that it confirms that based on

EURIDIS/ADONIS, Sanofi believed that the reduction of cardiovascular and AF hospitalizations was an "expected benefit." The document provides:

> In an unadjusted analysis of time from randomization to first event within 12 months, dronedarone reduced the risk of all-cause hospitalization or death by 27% (p=0.01) compared with placebo and of cardiovascular hospitalization or death by 20% (p=0.164). Overall, 22.8% of dronedarone-treated patients were estimated to have a first all-cause hospitalization or death at 12 months, compared with 30.9% of placebo-treated patients.
>
> This finding is key and constituted the clinical basis for the expected benefit of dronedarone in the ongoing outcome study ATHENA.

(DTX-104 at 4). The document goes on to state:

> The results of ANDROMEDA triggered some skepticism among the cardiology community with regard to the safety of dronedarone in heart failure and potentially by extension in patients with all forms of signicant [sic] structural heart disease.

(DTX-104 at 8). Dr. Radzik could not identify this document and substantively rebutted its contents. (Tr. 490:23–491:9, 492:14–495:9). This document has no marks to suggest its origins, date, or whether it is a draft. (DTX-104). The document also contains typos, which might indicate it is a draft. (*See, e.g.*, DTX-104 at 8 ("dronedaroen")). Considering all of this, while this document suggests that Sanofi believed that the reduction of cardiovascular and AF hospitalizations was an "expected benefit," I attribute little weight to this document primarily because it is undated.

(4) DTX-78

The parties dispute whether DTX-78 is hearsay and whether a statement contained in DTX-78 is hearsay within hearsay. In this email, sent November 2006, Dr. Seiz communicates to individuals such as Sylvie Bozzi, Christophe Gaudin, and Dr. Radzik statements made to him by

Dr. Hohnloser and Dr. Torp-Pedersen, who both sit on the ATHENA Steering Committee.[9] He stated that Dr. Hohnloser and Dr. Torp-Pedersen were "convinced that dronedarone will be superior with regards to CV hospitalization." (DTX-78).

While DTX-78 is generally not hearsay because it is a statement by Dr. Seiz within the scope of his employment under Federal Rule of Evidence 801(d)(2)(D), the specific statement cited is hearsay within hearsay.

I do not think Dr. Seiz is making his own characterization of their views when he made the statement. While it is true that Dr. Seiz does not say "both said they are convinced," the context of the document suggests that Dr. Seiz is simply communicating Hohnloser and Torp-Pedersen's thoughts. For example, the email contains statements such as, "I got the request from Stefan Hohnloser and Christian Torp-Pedersen . . . about the need to . . . ," "They would like to know more about . . . ," and "Both are concerned that . . . ."

I do not think that Defendants have shown that Hohnloser or Torp-Pedersen had the authority to speak on behalf of Sanofi. Weighing in Defendants' favor, Hohnloser and Torp-Pedersen are members of the ATHENA steering committee. (DTX-78; Tr. 428:1–6). As members of the steering committee, they are responsible "for the execution and scientific reporting of the study." (JTX-64 at 18). The subject line of DTX-78 is "ATHENA – Steering Committee Meeting: Need for biostatistical support." (DTX-78). Weighing against, Hohnloser (2008) does not describe Drs. Hohnloser or Torp-Pedersen as "employees" of Sanofi, unlike Dr. Seiz's description, which clearly identifies him as an employee. (JTX-23 at 1). Hohnloser (2008) also associates Dr. Hohnloser with the J.W. Goethe University and Dr. Torp-Petersen with Bispebjerg University Hospital, again in contrast to Dr. Seiz, who is described as being with

[9] Sylvie Bozzi is a Sanofi employee and the project statistician on Multaq®. (Tr. 408:3–15).

Sanofi. (JTX-23 at 1). DTX-78 and JTX-23 do not expressly show that Sanofi authorized Hohnloser or Torp-Pedersen to speak on its behalf. It also appears that clinical trial investigators maintain a degree of independence from pharmaceutical companies. (DTX-60 at 46 (seeking to "preserv[e] the independence and accountability of the Investigator")). There is evidence that Hohnloser and Torp-Pedersen received "honoraria and/or consulting fees" and "[r]esearch support" from Sanofi, which indicates they are not Sanofi's employees. (JTX-23 at 1). Considering all of this as a whole, Defendants have not shown that speaking authority was bestowed expressly or implicitly upon Hohnloser or Torp-Pedersen. The evidence suggests that Hohnloser and Torp-Pedersen maintained a good amount of independence from Sanofi. Thus, the statements in DTX-78 are hearsay.

d) Comparing the Prior Art and the Claimed Subject Matter

The central dispute is whether a POSA would reasonably expect dronedarone to reduce the risk of cardiovascular hospitalization in AF patients with coronary heart disease and within the Age Criteria. I find that Defendants have failed to make this showing.

The CAST trials weigh in Plaintiffs' favor. They suggest that an increased emphasis on safety was placed on AADs. DAFNE does not weigh in either side's favor as it is without statistical significance.

AFFIRM found an increase in hospitalization associated with AADs. It suggested that the use of AADs are associated with excessive mortality in older patients, those with heart failure, and those with coronary artery disease. AF-CHF demonstrated that AADs resulted in a worsened rate of hospitalizations for AF. SWORD shows that Sotalol was not safe and effective. There is no evidence to this day that Sotalol reduces the risk of cardiovascular hospitalization. PROMISE showed that amiodarone did not decrease mortality. While weighing slightly in

Defendants' favor is the fact that a POSA would understand that dronedarone is designed to be an improvement from amiodarone, these trials overall weigh in Plaintiff's favor. These trials suggest that AF may simply be a marker for underlying cardiovascular disease and that the risks of using dronedarone would outweigh the benefits.

The post-hoc analysis of EURIDIS/ADONIS weighs in Defendants' favor. Singh is published in the well-regarded The New England Journal of Medicine. It suggests that dronedarone would decrease hospitalization or death. I note that this is corroborated by a third post-hoc analysis reported in a 2007 Sanofi document. The weight of Singh is limited by the fact that it is a post-hoc analysis with inherent limitations in terms of reliability and by the fact that the patient population is generally younger and healthier than that of ATHENA, as is further discussed below.

ANDROMEDA weighs strongly in Plaintiff's favor. It gave POSAs significant skepticism of the safety of dronedarone. Although the differences between the ANDROMEDA patient population and the ATHENA patient population weigh in Defendant's favor, it is also true that the ANDROMEDA trial was terminated early due to excessive mortality in the treatment group. As a result, ANDROMEDA casts a large cloud over the safety of dronedarone.

The lack of regulatory approval weighs in Plaintiff's favor. It suggests that a POSA would be skeptical of the safety of dronedarone. It suggests that a POSA would believe that the ratio between the efficacy and safety of dronedarone is negative. That the FDA and EMEA appear to have had access to the post-hoc data from EURIDIS/ADONIS, but nonetheless rejected the approval of dronedarone, confirms that significant weight should not be accorded to EURIDIS/ADONIS. Dr. Zusman's statement that, had ANDROMEDA not been conducted, Sanofi would have secured regulatory approval, is not persuasive because ANDROMEDA was

conducted, and as a result, POSAs at the time were very concerned about the safety of dronedarone.

Hohnloser is given slight weight in Defendants' favor. A POSA would have viewed Hohnloser's "expectation" statement about ATHENA that dronedarone would reduce hospitalization in the ATHENA patient population as simply a hypothesis like any other. When asked to identify the hypothesis of ATHENA, Dr. Zusman looked to Hohnloser. Hypotheses not guaranteed to be true. Dr. Zusman acknowledges that the investigators of ATHENA are entitled to assume anything they wanted. Dr. Zusman, himself, does not always accept hypotheses as he rejected the hypothesis of ANDROMEDA. The failures of the CAST trials, SWORD, and PALLAS corroborate Dr. Falk's statement that "the era of controlled clinical trials is littered with discarded common sense arguments." (PTX-40 at 16).

Thus, the fact that the FDA authorized the ATHENA trial does not weigh much in Defendant's favor. That the hospitalization endpoint was added because a study cannot be conducted with only the endpoint that a drug does not increase mortality, does not mean that the hospitalization endpoint was a given. I find Dr. Radzik's belief that the evidence leading up to the ATHENA trial did not show a reduction in the risk of cardiovascular hospitalization persuasive. Dr. Gaudin's belief that the failure of amiodarone to show a decrease in hospitalization suggests that dronedarone would not have exhibited such a benefit, which is also persuasive.

The differences between the ATHENA and EURIDIS/ADONIS patient populations further undermine the weight given to Hohnloser. The ATHENA population was older and sicker. The ATHENA population had a higher incidence of hypertension and cardiovascular disease. It is more difficult to reverse the development of AF in older patients. It is more

difficult to maintain sinus rhythm in older patients. AF patients with additional cardiovascular risk factors are significantly more likely to experience adverse events in response to an antiarrhythmic drug. Older patients are more likely to be on concomitant medications, increasing the chance of drug/drug interactions. A POSA in 2008 would have been aware that drug/drug interactions could have a very significant effect on the outcome of ATHENA.

Furthermore, given that no AAD has been shown to reduce stroke in patients with AF and that a POSA would not have expected dronedarone to reduce heart failure, limited weight is given to Dr. Zusman's statement that Hohnloser knew that dronedarone would reduce hospitalization based on the properties of dronedarone.

Internal Sanofi statements generally weigh in Defendant's favor. These statements confirm that a POSA would be encouraged by the EURIDIS/ADONIS data and that the ATHENA trial proceeded in light of EURIDIS/ADONIS. Additional weight is not attributed to these statements because (1) some of these statements also express concern over the safety of dronedarone, (2) these statements do not constitute prior art, (3) emphasizing some of the statements could be the result of hindsight bias, and (4) these citations do not directly address the patient populations in claims 1, 7, 9, and 14. DTX-104 is given limited weight in Defendant's favor because it is undated. No weight is attributed to DTX-78.

Considering all of the above, I do not think that Defendants have sufficiently shown that a POSA at the time of the priority date would have a reasonable expectation that dronedarone would reduce hospitalization for the sicker, older patients that make up claims 1, 7, 9, and 14 of the '900 patent. (Tr. 214:15–215:9, 71:1-9, 77:23–24). While the EURIDIS/ADONIS post-hoc analysis, Hohnloser, and some internal Sanofi statements form the bulk of evidence weighing in Defendants' favor, I think this evidence is significantly undermined by evidence such as the

CAST trials, the rate versus rhythm trials, SWORD, PROMISE, ANDROMEDA, the FDA/EMEA rejections, and also some internal Sanofi statements. I think there is substantial evidence teaching away from the conclusion that dronedarone would reduce hospitalizations in the claimed patient population. *See In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) ("In determining whether such a suggestion can fairly be gleaned from the prior art, the full field of the invention must be considered; for the person of ordinary skill is charged with knowledge of the entire body of technological literature, including that which might lead away from the claimed invention.").

e) Secondary Considerations

Defendants argue Sanofi would not have run ATHENA had the FDA approved dronedarone and Sanofi added the cardiovascular hospitalization endpoint because a study cannot without other endpoints show that a drug a does not increase mortality. They further argue that the ATHENA endpoint was based on EURIDIS/ADONIS. Defendants argue that these facts show that the claims are obvious. Because these points are duplicative of points made in the discussion of obviousness, they are attributed no additional weight in Defendants' favor.

As to long felt but unmet need, Defendants argue that because Sanofi markets Multaq® for uses that fall outside the scope of the '900 patent, this demonstrates that Sanofi does not consider the reduction in hospitalization risk to be a breakthrough in AF treatment. (D.I. 200 at p. 18 (citing to DTX-222; DTX-223; Tr. 145:12–147:1, 216:19–218:17)). Defendants argue that other drugs were available for AF treatment before dronedarone. (D.I. 200 at p. 19 (citing to Tr. 287:10–288:11)). They argue that physicians are still looking for a drug that reduces the rate of cardiovascular hospitalization by more than the 24% reduction from dronedarone. (D.I. 200 at p.

19 (citing to Tr. 288:12–24)). Having reviewed these citations, long felt but unmet need is not demonstrated.

Plaintiffs assert in summary fashion that "the evidence of record, as explained throughout this brief . . . demonstrates that the claimed inventions were not predictable, that there was skepticism, and that today dronedarone is one of two most commonly used AADs." (D.I. 204 at p. 24). Plaintiff only supports the proposition that dronedarone is one of two of the most commonly used AADs with a single citation. (D.I. 204 at p. 24 (citing to Tr. 384:15–385:14)). At Tr. 384:15–385:14, Dr. Zusman admits that dronedarone and amiodarone are the two most common rhythm control drugs used in his practice. (Tr. 384:15–385:14).

No additional weight is given to unexpected results or skepticism because Plaintiff's arguments are duplicative of the discussion above. No weight is given to the secondary consideration of commercial success because Dr. Zusman's statement that dronedarone is one of the two most common rhythm control drugs used in his practice does not show commercial success. Overall, on this record, the evidence of secondary considerations does not weigh in Plaintiffs' favor. Considering all of this evidence as a whole, Defendants have not shown by clear and convincing evidence that claims 1, 7, 9, and 14 of the '900 patent are invalid as obvious.

IV. CONCLUSION

For the foregoing reasons, Plaintiffs met their burden of showing that Defendants induce infringement of claims 1, 7, 9, and 14 of the '900 Patent. Plaintiffs failed to meet their burden of showing that Defendants induce infringement of claims 6 and 8 of the '900 patent. Defendants failed to meet their burden of showing that claims 1, 7, 9, and 14 of the '900 patent are invalid as obvious.

Plaintiffs are directed to submit an agreed-upon form of final judgment within two weeks.