UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

ISIS PHARMACEUTICALS, INC., a Delaware Corporation, Plaintiff, v. SANTARIS PHARMA A/S CORP., a Delaware Corporation, and SANTARIS PHARMA A/S, a Danish Corporation, Defendants.	Case No. 11cv02214 BTM (KSC) **ORDER DENYING DEFENDANTS' MOTION FOR SUMMARY JUDGMENT WITHOUT PREJUDICE**

Plaintiff Isis Pharmaceuticals, Inc. ("Isis" or "Plaintiff") alleges that Defendants Santaris Pharma A/S Corp. and Santaris Pharma A/S (collectively, "Santaris" or "Defendants") have infringed upon two of Isis's patents. Pending before the Court is Defendants' motion for summary judgment, in which Defendants argue that their activities are protected by the "Safe Harbor" provision of 35 U.S.C. § 271(e)(1) (the "Safe Harbor").

I. BACKGROUND

The two patents at issue in this litigation provide for a form of biotechnology called antisense molecules. This background section provides an overview of antisense technology generally, the two relevant patents, and Plaintiff's specific infringement claims.

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a. Overview of antisense technology

Proteins, fundamental molecules found in all living cells, are primary actors within a cell. They perform a variety of essential functions such as catalyzing chemical reactions, communicating between cells, and providing structural support. The overproduction or abnormal production of proteins can cause disease. One method for treating a disease caused by the overproduction of a certain "target" protein is to create an "antisense" molecule that interrupts the cellular process of creating that protein.

The cellular process of creating proteins begins with genetic information ("genes") stored in DNA and proceeds in two stages: transcription and translation. During transcription, the gene for a particular protein is copied from a strand of DNA to a molecule called messenger RNA ("mRNA"). During translation, cellular machinery converts the information on the mRNA into proteins.

Antisense molecules—typically a type of a nucleic acid that is similar to DNA and mRNA molecules, but much shorter—are able to interrupt the genesis of the target protein at the translation stage by binding to the mRNA molecules containing the genetic information for that protein. Once bound to an mRNA molecule, the antisense molecule can obstruct the chemical process that translates the mRNA into a protein. The two biotechnology patents at issue in this litigation relate to antisense technology.

b. The '199 Patent

U.S. Patent No. 6,326,199, "Gapped 2' Modified Oligonucleotides" (the "'199 Patent"), claims, in independent claim 1, a method of enhancing an antisense molecule by creating structural features (a) enabling the antisense molecule to resist degradation before it reaches its target mRNA; (b) enhancing "binding affinity" (the strength of the chemical bond between the antisense molecule and the target mRNA); and (c) activating an enzyme called Rnase H that, once activated, severs the target mRNA, preventing translation into the target protein.

See Cplt. ¶¶ 19-21; '199 Patent Col. 31, ll. 39-49. Many of the dependent claims claim methods of modifying the molecule described in Claim 1 in additional ways.

Independent claim 11 claims a method of "modifying a sequence-specific ribo-nucleic acid" (i.e., a target mRNA or other type of RNA) using a molecule having the properties claimed in claim 1. ('199 Patent Col. 33, ll. 3-15.) In other words, claim 11 claims the method of using the antisense molecule described in claim 1 to affect the function of its target.

c. The '500 Patent

U.S. Patent No. 6,066,500, "Antisense Modulation of Beta Catenin Expression" (the '500 Patent"), is directed toward antisense technology that is designed specifically to inhibit the expression of a protein called Beta catenin. Beta catenin has been implicated in the development of several types of cancer, including cancer of the colon and of the skin. Independent claims 1 and 3 claim an antisense molecule of a particular size that hybridizes with the mRNA molecule responsible for generating Beta catenin, and thereby "inhibits the expression of Beta catenin." (Col. 65, ll. 53-54.) Many of the dependent claims claim a more specific type of molecule that meets the qualifications of the molecule described in claims 1 and 3.

Claims 11 and 20 claim a "method of inhibiting the expression of human Beta catenin in human cells or tissues comprising contacting said cells or tissues in vitro with the antisense compound of [claims 1 and 3] so that expression of Beta catenin is inhibited." (Col. 66, ll. 56-59; Col. 68, ll. 3-6.)

d. Isis's infringement claims

Plaintiff has alleged that Defendants have used molecules claimed by the '199 Patent, and the method of contacting cells with those molecules also claimed in the '199 Patent, to

"identify [gene] targets and/or to screen gapmer . . . antisense molecules for activity inhibiting a target. Santaris further sells and offers for sale in the United States the patented methods of the '199 Patent." (Cplt. ¶ 24.) Plaintiff further alleges that "Santaris has offered for sale and sold antisense compounds that inhibit Beta catenin production in violation of the '500 Patent." (Id. ¶ 26.)

Plaintiff alleges four specific agreements between Santaris and pharmaceutical companies based in the United States that form the basis of these infringement contentions:

January 4, 2011 announced agreement with Pfizer, Inc. Plaintiff alleges that Pfizer paid Santaris "$14 million for access to Santaris Pharma A/S Locked Nucleic Acid (LNA) Drug Platform to develop RNA-targeted drugs." (Id. ¶ 37 (quoting Cplt. Ex. 3, 4 Jan. 2011 Press Release).) Pfizer also allegedly "agreed to pay milestones to Santaris upon the identification of up to ten gene targets and the discovery of lead antisense LNA molecule candidates." (Id.) This agreement allegedly infringes the '199 Patent by "[o]ffering for sale and selling the process of using gapmers to reduce target RNA for target validation purposes; and/or [o]ffering for sale and selling the process of screening and identifying gapmer compounds to identify drug candidates for drug development." (Id. ¶ 39.)

July 27, 2006 announced agreement with Enzon Pharmaceuticals, Inc. Plaintiff alleges that Santaris "sold two antisense gapmer molecules and targets to Enzon for $6 million" (id. ¶ 41), and that, pursuant to the agreement, "Enzon nominated six additional targets for which Santaris agreed to identify LNA gapmer compounds that inhibit the nominated targets using Isis'[s] methods patented in the '199 Patent and compositions covered in the '500 Patent" (id. ¶ 42).

August 24, 2009 announced agreement with Shire PLC. Pursuant to this agreement, Santaris allegedly receives significant upfront payments, milestone payments and royalties for providing access to Santaris's LNA technology and exclusivity for three targets and an additional two targets to be nominated by Shire in the future. (Id. (citing Cplt. Ex. 6, 24 Aug. 2009 Press Release).) Plaintiff alleges that this agreement infringes on the '199 Patent by "[o]ffering for sale and selling the process of using gapmers to identify and reduce target

RNA for further drug discovery; and/or [o]ffering for sale and selling the process of screening and identifying gapmer candidates to identify drug candidates for drug development." (Id. ¶ 48.)

December 19, 2007 announced agreement with GlaxoSmithKline. Plaintiff alleges that, pursuant to this agreement, "Santaris would receive approximately $8 million as an upfront payment, milestone payments, and royalties for providing access to Santaris' LNA technology and exclusivity for four targets." (Id. ¶ 50.) Plaintiff alleges that this transaction infringed upon the '199 Patent in the exact same manner as the August 4, 2009 agreement with Shire PLC, described in the preceding paragraph. (Id. ¶ 52.)

II. STANDARD

Summary judgment is appropriate under Rule 56 of the Federal Rules of Civil Procedure if the moving party demonstrates the absence of a genuine issue of material fact and entitlement to judgment as a matter of law. Celotex Corp. v. Catrett, 477 U.S. 317, 322 (1986). A fact is material when, under the governing substantive law, it could affect the outcome of the case. Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 248 (1986); Freeman v. Arpaio, 125 F.3d 732, 735 (9th Cir. 1997). A dispute is genuine if a reasonable jury could return a verdict for the nonmoving party. Anderson, 477 U.S. at 248.

A party seeking summary judgment always bears the initial burden of establishing the absence of a genuine issue of material fact. Celotex, 477 U.S. at 323. Once the moving party establishes the absence of genuine issues of material fact, the burden shifts to the nonmoving party to set forth facts showing that a genuine issue of disputed fact remains. Celotex, 477 U.S. at 314. The nonmoving party cannot oppose a properly supported summary judgment motion by "rest[ing] on mere allegations or denials of his pleadings." Anderson, 477 U.S. at 256. When ruling on a summary judgment motion, the court must view all inferences drawn from the underlying facts in the light most favorable to the nonmoving party. Matsushita Elec. Indus. Co. v. Zenith Radio Corp., 475 U.S. 574, 587

(1986).

III. DISCUSSION

Section 271(e)(1)'s "Safe Harbor" provides:

> It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs[.]

35 U.S.C. § 271(e)(1). The Supreme Court has interpreted this statutory language to "provide[] a wide berth for the use of patented drugs in activities related to the federal regulatory process." Merck KGaA v. Integra Lifesciences I, Ltd, 545 U.S. 193, 202 (2005); see also Momenta Pharmaceuticals, Inc. v. Amphastar Pharmaceuticals, Inc., --- F.3d ---, 2012 WL 3140303, at *6 (Fed. Cir. 2012) ("Congress could not have been clearer in its choice of words: as long as the use of the patented invention is solely for uses 'reasonably related' to developing and submitting information pursuant to 'a Federal law' regulating the manufacture, use, or sale of drugs, it is not 'an act of infringement.').

In Merck, the Supreme Court clarified the scope of the Safe Harbor as it applies to patents for biological compounds:

> At least where a drugmaker has a *reasonable basis for believing that a patented compound may work, through a particular biological process, to produce a particular physiological effect*, and uses the compound in research that, if successful, would be appropriate to include in a submission to the FDA, the use is "reasonably related" to the "development and submission for information . . . under federal law."

Id. at 207 (citing 35 U.S.C. § 271(e)(1)) (alterations in original) (emphasis added).

The Safe Harbor does not apply, however, when a biological compound is used to perform "basic scientific research" or as a "research tool." "Basic scientific research" is performed when the researcher "lacks the intent to develop a particular drug or a reasonable belief that the compound will cause the sort of physiological effect the researcher intends to induce." Id. at 205-06.

"Research tools" are patented inventions that are "used in the development of . . .

regulatory submissions, but [are] not [themselves] subject to the [regulatory] approval process." Proveris Scientific Corp. v. Innovasystems, Inc., 536 F.3d 1256, 1265 (Fed. Cir. 2008). For example, in PSN Illinois, LLC v. Abbott Laboratories, No. 09 C 5879, 2011 WL 4442825, at *4-6 (N.D. Ill. Sept. 20, 2011), the Court found that the defendants' use of a patented protein receptor was a "research tool," where the receptor was used only to perform tests on other drug candidates *that did not themselves incorporate the patented invention*. "They were using a patented invention to develop their own patentable product. . . . 271(e)(1) offers no protection for such activity." Id. at *6.

Plaintiff has alleged in its complaint, and maintains in its opposition to Santaris's motion for summary judgment, that Santaris used and/or sold infringing compounds, methods, and processes both to conduct basic scientific research and as research tools. Against these allegations, and in support of its motion, Santaris presents only the declaration of one of its officers, Dr. Henrik Ørum, which states that Santaris does not begin using the antisense technology allegedly covered by the '199 and '500 Patents unless and until "a therapeutic target has been identified by someone else, and Santaris is sufficiently satisfied that it may achieve a therapeutic effect against a human disease by modulating the identified target with . . . antisense drugs." (Ørum Decl. ¶ 20.)

Dr. Ørum's declaration provides a broad overview of the process of generating a "library" of antisense drug candidates tailored to the "therapeutic target," performing *in vitro* and *in vivo* tests to "to identify the most effective drug candidates[,]" and transmitting the information gained during this process and/or samples of the antisense drug candidates themselves to Santaris's "partners." (Id. ¶ 22-35). The declaration concludes that if one of Santaris's pharmaceutical company partners "wish[es] to obtain FDA approval" for an antisense drug generated through this process, "[t]he data and results that Santaris has generated throughout the design and development process are used for purposes of submission to the FDA" (id. at ¶ 37). On the basis of these representations, Santaris argues that all of its activities fall within the Safe Harbor:

> [A]ll of Santaris's activities are undertaken with the express purpose and intent of developing a specific LNA antisense drug to treat an identified condition after

> a reasonable basis has been established and demonstrated that the activity of the RNA molecule of interest may be modulated to bring about the desired physiological effect.

(Def. Br. at 13.)

At the outset, the Court finds that the facts introduced by Santaris by way of the declaration of one of its officers falls short of the evidentiary burden placed on an accused infringer claiming exemption from infringement under § 271(e)(1). On remand from the Supreme Court's decision in Merck, the Federal Circuit noted that "the variety of experimental activity that may apply to any specific biologic or physiologic investigation reinforces the *fact-dependency of the inquiry*." Integra Lifesciences I, Ltd. v. Merck KgaA, 496 F.3d 1334, 1347 (Fed. Cir. 2007) (emphasis added). In that case, the Federal Circuit determined that the defendants' uses of the infringing biological compound were "reasonably related" to the development and submission of information to the FDA only after a detailed review of the purpose of *each of sixteen enumerated categories of accused experiments* in light of "extensive" trial testimony regarding "how and why all of these experiments were performed," the type of information generated by each experiment, and the type of information called for the by the specific FDA regulations at issue. Id. at 1343-44. The record before this Court stands in stark contrast to the record before the Federal Circuit in Integra. The Ørum declaration describes in general terms a process that *could* fall within the Safe Harbor. But even taking as true everything in the Ørum Declaration, the Court would decline to resolve Santaris's claim to the Safe Harbor exemption without a more specific analysis of Santaris's uses of the allegedly infringing compounds, methods, and processes. Moreover, the Court declines to grant summary judgment in favor of Santaris on all claims at this early stage in the litigation solely on the basis of the Ørum Declaration, without first providing an opportunity for Isis at least to conduct limited discovery and depose Dr. Ørum.

The Court also finds that Isis has called into question Santaris's claim that "Santaris does not perform any antisense technology work until a therapeutic target has been identified by someone else[.]" (Ørum Decl. ¶ 20.) First, Isis points to language in a press release covering one of the allegedly infringing sales between Santaris and a pharmaceutical

company suggesting that Santaris did not know, at the time it licensed antisense technology to the pharmaceutical company, which mRNA molecules the pharmaceutical company intended to target. See Gaede Decl. Ex. 11, 27 Jul. 2006 Press Release ("Enzon will make an initial up-front payment of $8 million to Santaris Pharma, followed by an additional $3 million *upon the successful identification of certain LNA targets.*") (emphasis added).

Second, Isis has introduced a sworn declaration of Dr. Ørum provided to the U.S. Patent and Trademark Office in December 2009 during the reexamination of one of Santaris's patents, in which Dr. Ørum states:

> The majority of our collaborators have taken *broad licenses* to our proprietary LNA ["locked nucleic acid"—a type of antisense molecule] platform in order to *discover*, develop, and commercialize new LNA-based drugs against RNA targets associated with disease.

(Gaede Decl. Ex. 23, 20 Dec. 2009 Second Declaration of Henrik Ørum Under 37 C.F.R. § 1.132, ¶ 3 (emphasis added).) This same declaration specifically references Santaris's agreements forming the basis of the alleged infringing acts in this lawsuit. To the extent Santaris is selling and/or licensing infringing "platform" technology so that another company can "discover and develop" drug candidates—rather than developing and/or licensing/selling specific drug candidates itself—Santaris could be using or selling patented technology to perform "basic scientific research." Merck, 545 U.S. at 207.

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IV. CONCLUSION

For all these reasons, the Court DENIES Santaris's motion for summary judgment without prejudice at this time. The parties shall be permitted 120 days following the entry of this Order to conduct limited discovery related to the issues raised by Santaris's Safe Harbor motion. The Court grants Santaris leave to re-file a motion for summary judgment pursuant to § 271(e)(1) within 30 days following the close of the limited discovery period.

IT IS SO ORDERED.

Dated: September 18, 2012

HONORABLE BARRY TED MOSKOWITZ
United States District Judge