UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF INDIANA
INDIANAPOLIS DIVISION

ELI LILLY AND COMPANY,	)	
	)	
Plaintiff,	)	
	)	
vs.	)	1:06-cv-1017-SEB-JMS
	)	
TEVA PHARMACEUTICALS USA, INC.,	)	
	)	
Defendant.	)	

ORDER GRANTING PLAINTIFF'S RENEWED MOTION FOR PRELIMINARY INJUNCTION

This cause is before the Court on the Renewed Motion for Preliminary Injunction [Docket No. 404], filed by Plaintiff, Eli Lilly and Company ("Lilly"), on February 9, 2009. Lilly holds an approved New Drug Application ("NDA") No. 20-815 relating to the use of raloxifene hydrochloride 60 mg tablets for the prevention or treatment of osteoporosis in postmenopausal women. Lilly markets the product disclosed in NDA No. 20-815 under the tradename EVISTA® ("Evista"). In connection with this NDA, Lilly listed twelve patents in the Orange Book, including: U.S. Patent Nos. 5,393,763 ("the '763 patent"); RE 39,049 ("the '049 patent"); 5,457,117 ("the '117 patent"); RE 38,968 ("the '968 patent"); 5,478,847 ("the '847 patent"); RE 39,050 ("the '050 patent"); 6,458,811 ("the '811 patent); 6,797,719 ("the '719 patent"); 6,894,064 ("the '064 patent"); 6,906,086 ("the '086 patent"); 5,811,120 ("the '120 patent"); and 5,972,383 ("the '383 patent") (collectively, "Lilly's raloxifene patents).

Defendant, Teva Pharmaceuticals USA, Inc. ("Teva"), has filed an Abbreviated New Drug Application ("ANDA") No. 78-193 with the FDA for raloxifene hydrochloride 60 mg tablets for the prevention of osteoporosis in postmenopausal women. Teva sought and has received FDA approval to market its generic raloxifene hydrochloride product before the expiration of the Lilly patents listed in the Orange Book. Pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), Teva's ANDA includes a "paragraph IV certification" to Lilly's raloxifene patents in which Teva certifies that each of Lilly's raloxifene patents is invalid, unenforceable, or would not be infringed by Teva's manufacture, use, or sale of its generic raloxifene product.

After receiving notice of the ANDA filing and paragraph IV certification, Lilly brought this suit against Teva for infringement of the '086 patent, the '968 patent, and the '049 patent (collectively, "the bone loss patents"); the '050 patent ("the low dose patent"); and the '811 patent, the '719 patent, and the '064 patent (collectively, "the particle size patents"). The bone loss and low dose patents cover the oral administration of raloxifene hydrochloride for prevention or treatment of post-menopausal osteoporosis. The particle size patents cover pharmaceutical compositions containing raloxifene particles having a certain size distribution. Teva concedes infringement of the bone loss patents and the low dose patent if they are found valid and enforceable, but challenges their validity and enforceability on the following grounds: obviousness, lack of enablement, and inequitable conduct. With regard to the particle size patents, Teva contends that its generic raloxifene product does not infringe and that, even if its product

did infringe, the particle size patents are invalid on the basis of obviousness and lack of enablement. On March 17, 2008, the Court held a *Markman* hearing at which the parties presented evidence, testimony, and oral argument as to the proper construction of disputed terms. On June 11, 2008, the Court issued a claim construction order construing claims of the particle size patents. Docket No. 181.

Lilly's suit triggered the 30-month statutory stay on the FDA's approval of Teva's generic raloxifene product, which was originally set to expire on November 16, 2008. However, on October 29, 2008, the Court granted Lilly's motion to extend the stay until the commencement of trial on March 9, 2009.[1] The hearing on Lilly's motions for a temporary restraining order and preliminary injunction was consolidated with the bench trial conducted from March 9, 2009, to March 24, 2009. On the opening day of trial, Teva notified the Court that it had received notice of final approval from the FDA of its generic raloxifene product. On that same day, the Court entered a TRO prohibiting Teva from launching its generic raloxifene product in the United States for ten days, subject to extension based on Lilly's proof in support of its motion for preliminary injunctive relief.

On the second day of trial, Teva informed the Court that it would voluntarily withhold launch of its generic raloxifene product until April 23, 2009, in order to allow the Court sufficient opportunity to rule on the preliminary injunction issues. Having considered the documentary evidence and testimony, the Court now enters its findings of

[1] On February 24, 2009, the Federal Circuit affirmed this ruling in Eli Lilly and Company v. Teva Pharmaceuticals USA, Inc., 557 F.3d 1346 (Fed. Cir. 2009).

fact and conclusions of law, pursuant to Federal Rules of Civil Procedure 52(a) and 65, and GRANTS Lilly's renewed motion for preliminary injunction.

Findings of Fact

The Patents at Issue

Lilly asserts infringement of the '086 bone loss patent, the '050 low dose patent, and the '811 particle size patent.[2] The claims of the '086 patent read as follows:

> 1. A method of inhibiting post-menopausal bone loss in a post-menopausal woman in need of treatment to prevent or treat post-menopausal osteoporosis comprising administering a single daily oral dose to said woman of an effective amount of . . . [raloxifene] hydrochloride.
>
> 2. The method of claim 1 wherein said woman has post-menopausal osteoporosis.
>
> 3. A method of inhibiting post-menopausal bone loss in a post-menopausal woman in need of treatment to prevent post-menopausal osteoporosis comprising administering a single daily oral dose to said woman of an effective amount of . . . [raloxifene] hydrochloride.

PTX 11 at col. 20, ln. 2-16. The '086 patent was issued to Larry Black which he assigned to, and is now owned by, Lilly. It reflects a priority application filing date of July 28, 1992.

[2] Teva has conceded infringement of the '086 patent. For the reasons detailed below, having determined that Teva has failed to raise a substantial question as to validity and enforceability of this patent, in light of the time exigency in connection with this ruling, we address only the '086 patent.

Postmenopausal Osteoporosis and Early Treatment of the Disease

The scientific evidence adduced at trial established that human bone is comprised of two types of bone – trabecular bone, which consists of a lattice work of interconnecting rods and plates, and cortical bone, which is a more solid structure. Docket No. 597 at 74:14-25. Approximately twenty percent (by weight or calcium content) of the adult skeleton is comprised of trabecular bone; cortical bone makes up the other eighty percent. Id. at 79:23-80:1. These two types of bone present different biologies: trabecular bone is more metabolically active and is also particularly responsive to estrogen. Id. at 80:6-9.

Over time, human bones go through a number of changes, primarily due to growth and remodeling. Bone growth occurs lengthwise. During this process, cartilage is present at the region of the growth plate, becomes calcified, and is replaced by trabecular bone. By adulthood, almost all bones in humans have stopped growing because the growth plates have closed and new bone is no longer produced. Id. at 82:3-11.[3] Bone remodeling is the process by which the trabecular portion of the bone is removed and then replaced, which changes both the shape and substance of the bone. Id. at 82:21-23. Approximately ten percent of the trabecular bone is replaced every year so that, over a ten-year period, the trabecular portion of the bone is entirely replaced. Id. at 80:21-24. The first stage of remodeling is bone absorption, whereby cells called "osteoclasts"

[3] In other species, such as rats, the growth plates remain open into adulthood, so the bones continue to grow to some extent even after the animal has reached adulthood. Docket No. 597 at 82:12-15.

essentially dig out part of the bone and remove it. The second stage of the remodeling process is bone formation, during which cells called "osteoblasts" replace the bone that was lost via absorption by laying down a protein substance like "collagen." Id. at 83:11-84:6. In healthy adults, the skeletal mass remains constant throughout the remodeling process because the amount of bone that is lost is replaced in similar amounts. Id. at 84:18-22.

However, when osteoporosis occurs, the replacement of bone during the remodeling process is incomplete, meaning that, at the completion of each remodeling cycle, more bone is removed than is replaced, causing a thinner bone. Id. at 86:25-87:2. Thus, the structure of the osteoporotic bone is not as strong as a normal, healthy bone, which makes it prone to fracture; that is the ultimate consequence of osteoporosis. Id. at 86:9-12. Osteoporosis is largely a consequence of a lack of sufficient estrogen in the system. Id. at 87:10-11. Before menopause, estrogen slows the process of resorption and remodeling, essentially acting as a "brake" on the process. Id. at 88:5-8. Following menopause, when women's bodies lose significant levels of systemic estrogen, the remodeling process becomes much more vigorous. Id. at 88:7-9. Osteoporosis is a relatively common condition: approximately one in two women beyond the age of fifty suffer an osteoporotic fracture at some point during the remainder of their lives. Id. at 86:15-18.

Because osteoporosis results mainly from a lack of estrogen in the system following menopause, the principal treatment, historically, for postmenopausal

osteoporosis has been estrogen replacement therapy ("EPT"). EPT successfully prevents bone loss as well as fractures. Id. at 93:15-22. However, there are significant problems associated with EPT, including increased risk of both breast and uterine cancer. Id. at 93:22-94:2. Therefore, researchers perceived a need and an opportunity to develop a drug to treat and prevent postmenopausal osteoporosis, which would act like estrogen in preventing bone loss but would not cause such damaging side effects in other tissues.

Early Development of Antiestrogens for Use in the Treatment of Breast Cancer

The class of compounds known as antiestrogens, which includes raloxifene, were originally developed to be used in the treatment of estrogen-dependent breast cancer. A large number of breast cancers are estrogen dependent, which means that estrogen stimulates their growth. Estrogen-dependent breast cancer cells contain so-called estrogen receptors. Endogenous estrogen, that is, estrogen found naturally within the body, binds to those receptors, stimulating the cancer cells and promoting growth of the cancer. Antiestrogens work to inhibit the growth of the cancer by binding to the estrogen receptors, thereby blocking the action of the estrogen. Id. at 95:4-96:4; 99:9-100:6. Some antiestrogens are very strong, allowing only a small amount to displace the natural estrogen. Others are weaker, requiring larger amounts to create the desired effect. Id. 97:13-15.

By the 1970's, two antiestrogen compounds, clomiphene and tamoxifen, were being investigated for their potential anti-cancer effects. Tamoxifen became one of the

first clinically successful antiestrogens used in the treatment of breast cancer. Id. 100:10-11. However, side effects developed from various antiestrogens, including tamoxifen, that were similar to the side effects of estrogen, itself. Id. at 102:10-12. Researchers discovered that, when certain antiestrogens were not competing with estrogen for the receptor (i.e., when there was little estrogen already in the system, such as in postmenopausal women), the antiestrogens, themselves, could interact with the estrogen receptors and display estrogenic properties of their own. Id. 102:10-103:2. For example, in the absence of estrogen, antiestrogens were found still to have a stimulatory estrogenic effect in the uterus, which was ultimately associated with an increased risk of endometrial cancer. Various antiestrogens mimic the effect of estrogen in varying degrees, and the degree to which a particular antiestrogen mimics estrogen is referred to as its intrinsic estrogenicity. Id. at 102:13-103:2. Tamoxifen, for example, has significant intrinsic estrogenicity; thus, despite its being an antiestrogen, at sufficiently high doses it can produce an effect roughly equivalent to forty percent of the effect of estrogen itself. Id. at 103:5-14; 103:23-104:2.

Early Development of Raloxifene for Use in the Treatment of Breast Cancer

Because of concerns associated with these estrogen-like side effects, researchers at Lilly, including Larry Black, set out to find a purer antiestrogen that would have positive effects in breast tissue, but lesser effects in the uterus. Larry Black, Lilly's inventor, received a Bachelor of Science degree in biological sciences from Indiana Central

College in 1966. He joined Lilly in 1966 where he remained employed until his retirement in December of 1993. Id. at 107:23-109:22. During the 1970's and 1980's, Mr. Black worked as a research scientist evaluating antiestrogen compounds, initially for use in the treatment of breast cancer. Id. at 110:13-111:1.

In the late 1970's, Mr. Black and another Lilly scientist, Dr. C. David Jones, began their research on the antiestrogenic properties of a family of molecules known as "benzothiophenes." One of the compounds within that family, known to the researchers only by its Lilly compound number "LY117018,"[4] displayed potential for development. Id. at 115:2-6. In November 1979, in the course of exploring the properties of molecules structurally related to LY117018, Dr. Jones first synthesized, and Mr. Black subsequently tested, the molecule now known as raloxifene; at that time, it was referred to only by its Lilly compound number "LY139481," which was an analog of LY117018.[5] Id. at 131:20-132:18. The chemical structures of LY117018 and raloxifene are virtually identical.

Unlike tamoxifen, both LY117018 and raloxifene contain free hydroxyl groups, the significance of which is discussed below. The chemical structure of raloxifene differs

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[4] Every compound synthesized by Lilly chemists is assigned an "LY" number for purposes of identification. If a certain molecule progresses through development to the point where it will be used in clinical studies, a name for the compound is then assigned. Docket No. 597 at 116:6-21.

[5] The compound LY139481, which eventually became "raloxifene," was first called "keoxifene." While the documentary evidence often uses the term "keoxifene," we have utilized the current name of the compound, "raloxifene," for sake of clarity and consistency throughout this opinion.

from LY118018 only in that the former has a six-membered nitrogen-containing ring, whereas the latter has a five-membered nitrogen-containing ring. Mr. Black determined that this difference gave raloxifene (LY139481) an improved activity profile, meaning that it had a higher affinity for the estrogen receptor, a lower intrinsic estrogenicity, and a greater ability to antagonize estrogen. Id. at 115:19-116:5; 117:13-17.

In 1980, a project team[6] was formed at Lilly to bring raloxifene through clinical trials for treatment of breast cancer. In the course of development, Lilly scientists discovered that the hydrochloride salt of raloxifene, identified as "LY156758," was easily prepared and had somewhat better water solubility. Thus, the decision was made by Lilly scientists to work with raloxifene hydrochloride, which ultimately became the active ingredient in Evista. In 1982, Mr. Black published his findings relating to raloxifene and its hydrochloride salt in an abstract of a presentation he delivered at the San Antonio Breast Cancer Symposium, entitled "LY156758: A Unique Antiestrogen Displaying High Affinity for Estrogen Receptors, Negligible Estrogenic Activity and Near-Total Estrogen Antagonism *In Vivo*." PTX 1625. In that abstract, Mr. Black reported that raloxifene produced a very minimal increase in uterine weight (one measure of a compound's intrinsic estrogenicity) in rats, while tamoxifen caused marked uterine growth. Additionally, he reported that raloxifene did not show any stimulatory effect on the

[6] At Lilly, "project team status" is acquired when the Project Team Approval Committee (PTAC) determines that sufficient information has been gathered to demonstrate a true potential for clinical activity for a particular compound. Docket No. 597 at 118:19-119:5.

luminal epithelial cells (another measure of a compound's intrinsic estrogenicity). Id.; Docket No. 597 at 134:22-136:1.

Bioavailability Issues Associated With Raloxifene

The pharmacokinetics of a compound, which term refers to the compound's absorption into the systemic circulation, its distribution throughout the body followed by its metabolism or conversion into other forms, and excretion out of the body ("ADME characteristics"), present significant considerations when determining whether and how to develop a drug for human clinical use. This is because a significant number of drug candidates fail in clinical trials due to ADME problems. Docket No. 599 at 328:3-11; 337:4-18. Thus, in order to optimize bioavailability in humans, researchers within Lilly looked for compounds with low metabolism rates that would be well absorbed. Id. at 337:13-18. Due in large part to the two free hydroxyl groups in its chemical structure, however, raloxifene proved to be highly metabolized in the liver, that is, the parent compound was converted into a glucuronide conjugate that was rapidly excreted from the body. Id. at 341:15-342:7; 342:16-21; 343:13-344:6. In the vast majority of compounds, this process of glucuronidation, or conjugation, serves to deactivate the drug. Docket No. 609 at 1186:2-5. It was known, in any event, prior to the issuance of the '086 patent that at least one compound, morphine-6, was active in conjugated form (id. at 1186:6-11) and that certain enzymes could in some cases reverse the effects of conjugation. Docket No. 597 at 139:24-140:7.

In preparation for developing raloxifene for the treatment of breast cancer, data relating to raloxifene's bioavailability was discovered in pre-clinical animal tests performed by Dr. Terry Lindstrom, a member of Lilly's raloxifene project team. In January 1983, in an abstract entitled "Disposition and Metabolism of a New Antiestrogen, LY156758, in Rats, Dogs, and Monkeys," and also in 1984, in a comprehensive journal article entitled "Disposition and Metabolism of a New Benzothiophene Antiestrogen in Rats, Dogs, and Monkeys," Dr. Lindstrom published the results of various animal studies he had conducted using raloxifene in which he found that the bioavailability of the parent raloxifene was approximately 39% in rats, 17% in dogs, and 5% in monkeys. Dr. Lindstrom further noted that in monkeys "the compound occurred primarily as the glucuronide conjugate of parent [raloxifene] with very little circulating free drug." PTX 684 at 841. However, Dr. Lindstrom's study did not test whether, despite the bioavailability problem, raloxifene had any effect on the animals. Docket No. 601 at 435:11-15.

In the drug development process generally, before clinical trials in patients can begin, a compound must first be tested for safety through so-called "Phase I" tests. Thus, before raloxifene could be developed for human use, it would have to undergo Phase I pharmacokinetic testing in humans. Id. at 472:8-473:18. In September and October 1982, in preparation for testing raloxifene for clinical purposes, Lilly completed a Phase I test of raloxifene using doses up to 200 mg in male human volunteers. The results of these tests, as reported in Lilly's internal documents, revealed that, although a

considerable amount of the glucuronide conjugate was present in the serum of the human volunteers, attempts to measure the parent raloxifene had been unsuccessful. PTX 594 at 17; PTX 816 at 2. Lilly conducted a second test in male human volunteers in which a 200 mg dose of raloxifene was administered once daily for fourteen days, but levels of parent raloxifene still could not be measured. PTX 597 at 17.

In 1985, raloxifene was given for the first time to humans for clinical purposes in a study conducted by Dr. Aman Buzdar. That study involved giving raloxifene to female breast cancer patients whose cancer had not responded to tamoxifen. In a 1988 article entitled "Phase II Evaluation of Ly156758 in Metastatic Breast Cancer," Dr. Buzdar published the results of his study, reporting that, with the exception of one minor response, there were no complete or partial responses to raloxifene.[7] From these results, Dr. Buzdar concluded that raloxifene "did not show any antitumor activity in this study and no further revaluation of this drug is recommended." PTX 437. Dr. Buzdar did note toxicity results that may have indicated drug effects, including the existence of hot flashes, fatigue, leg cramps, and mild nausea. Id. However, there was no placebo control group in Dr. Buzdar's study, so there was no way to ascertain the existence or frequency of these side effects in untreated women. Docket No. 607 at 1088:6-24. Although Dr.

[7] Trioxifene, an antiestrogen that, unlike raloxifene, does not contain the hydroxyl groups that make the compound subject to conjugation, had previously been administered by Dr. Buzdar to tamoxifen-resistent patients and had shown an objective response. PTX 437. Based on the knowledge that raloxifene had previously been shown to have a higher affinity for the estrogen receptor than either tamoxifen or trioxifene, Dr. Buzdar's Phase II study of raloxifene was initiated. Id.

Buzdar's reports do not attribute raloxifene's lack of efficacy to a bioavailability problem, some Lilly researchers, such as Dr. Lindstrom, believed that to be the cause. Docket No. 599 at 366:9-367:4.

In August 1987, Alan Schreiber and George Farnbach from the University of Pennsylvania visited Lilly to discuss developing raloxifene for the treatment of autoimmune diseases. A group of Lilly scientists who had been associated with the raloxifene clinical trial was convened to discuss Dr. Schreiber's proposal. In an internal memorandum, the group explained its reasons for rejecting the proposal, including their belief that, in light of the rapid glucuronide conjugation, it was "highly unlikely that sufficient raloxifene would be available in the serum to have any clinical effect." PTX 796 at 2. On October 5, 1987, Lilly's rejection of Dr. Schreiber's proposal was communicated by letter to Dr. Farnbach, which stated: "Not insignificant in our consideration of [raloxifene] are the disappointing bioavailability results observed during our Phase I clinical trial." PTX 1203.

Throughout this time period, a number of researchers outside of Lilly also published on raloxifene's rapid metabolic conversion. For example, in 1983, in an article entitled "Antioestrogenic and Antitumour Activities of a Series of Non-Steroidal Antioestrogens," A.E. Wakeling and B. Valcaccia address the decreased potency of several compounds, including raloxifene, when administered orally versus when administered subcutaneously. Wakeling stated that:

Metabolic differences may account for these discrepancies, since, in

> contrast to tamoxifen and trioxifene, both LY 117018 and LY 139481 [raloxifene] have free hydroxyl groups [citations omitted]. These compounds are likely to be susceptible to rapid conjugation and excretion, particularly when administered orally.

PTX 673 at EV 50 1039.

Dr. Craig Jordan also published on this issue. In 1983, in an article entitled "Differential Antiestrogen Action in the Immature Rat Uterus: A Comparison of Hydroxylated Antiestrogens with High Affinity for the Estrogen Receptor," Dr. Jordan and B. Gosden stated that:

> With regard to pharmacokinetics, LY117018 [the benzothiophene dihydroxyl analog of raloxifene] is a dihydroxylated antiestrogen and, as such, would be expected to be more rapidly conjugated and excreted than monohydroxytamoxifen. . . . This in fact seems to be the case as LY117018 is excreted from the immature rat five times more rapidly than monohydroxytamoxifen [citations omitted]. If monohydroxytamoxifen is considered to be a short-acting antistrogen compared with tamoxifen [citation omitted] then LY117018 should be classified as an ultra short-acting estrogen antagonist.

PTX 913 at 1257. In 1984, Dr. Jordan published a review article entitled "Biochemical Pharmacology of Antiestrogen Action" in which he discussed the hydroxylation of compounds such as raloxifene and states that "[c]learly this will facilitate the rapid metabolism and excretion of those compounds." PTX 843 at EV852112448.

The results discussed above from Lilly's Phase I testing, in which a significant amount of the glucuronide conjugate was present in the serum of the human volunteers, but no parent raloxifene was measured, were cited in a 1987 article entitled "Hormonal Modulation of Macrophage Clearance of IgG-Sensitized Cells," by M.C. Sanders, A.I.

Levinson, and A.D. Schreiber. In that article, the authors report that, while raloxifene was well-tolerated in the studies, the compound "appears to have a short serum half-life, which may be a result of rapid biotransformation." PTX 844 at 273.

Black's Studies on the Glucuronide Conjugate of Raloxifene

In an effort to address the widely discussed concerns regarding the bioavailability of raloxifene, Mr. Black began to conduct studies to attempt to determine whether, despite its rapid conjugation, the compound could still have efficacy. In 1983, Mr. Black conducted a study on ovariectomized rats in which he lowered the oral dose of raloxifene administered until no parent was detected, yet a large amount of the glucuronide was present, which duplicated the conditions observed in the human subjects in Lilly's Phase I testing. Despite there being no detectable parent in the serum, Mr. Black was able to measure an end-point response, to wit, an antiestrogenic effect in the uterus of the rat. Docket No. 597 at 140:20-141:18; PTX 715. Mr. Black believed that these results showed that the mere fact that the parent was not detectable in the serum did not necessarily indicate that it could produce no effect. Docket No. 597 at 141:18-20; see also PTX 715.

Later in 1983, Mr. Black obtained a sample of the raloxifene conjugate from the human subjects in the Phase I tests, which had been isolated from the urine collected from the subjects, which he administered intravenously into rats in an effort to reproduce the condition observed in the human subjects in which only the conjugate was present in the

bloodstream. Docket No. 597 at 142:25-143:19. Black's study included a control group and a second group that had been administered the parent raloxifene. The control group showed no effect, but the group administered the conjugate extract showed antiuterotropic activity similar to that caused by the parent compound. Id. at 143:10-144:8; PTX 817 at EV 7250 222. Thus, Mr. Black also concluded that these results supported the conclusion that the lack of detectable parent compound does not necessarily preclude efficacy. Docket No. 597 at 144:8-13. The results of this study were not published, but the study is discussed in the '086 patent. Id. at 145:1-4.

Mr. Black obtained a second sample of the human conjugate that had been extracted from the urine of the human subjects involved in the Phase I testing. Using that sample, Mr. Black conducted a study in which he evaluated the effect of the conjugate, the raloxifene parent, an estrogen control group, and a control extract on uterine tissue *in vitro*, that is to say, in a test tube assay, to determine their respective abilities to bind directly to the estrogen receptor. Id. at 148:5-12. Mr. Black tested the groups at two temperatures--four degrees and twenty-five degrees--and incubated them for one hour, four hours, and twenty-four hours. Id. at 148:14-20. At four degrees, the estrogen and the parent raloxifene bound normally to the receptor, but neither the blank control nor the conjugate interacted with the estrogen receptor. At twenty-five degrees, the blank control still did not show activity. However, as the conjugate was incubated, it displayed increasing levels of response, and, by twenty-four hours of incubation, its competition for the estrogen receptor was similar to that in the estrogen control and parent raloxifene. Id.

at 149-16-23; PTX 72 at EV 7243 1. From this series of experiments, Mr. Black concluded that, under physiological conditions, the conjugate observed in the human bloodstream could possibly be converted back to the parent compound. Docket No. 597 at 151:10-13. The results of these experiments were not published but also were referenced in the '086 patent. Id. at 151:14-18.

The Prior Art to the '086 Patent

a. The *Beall* Article

As various antiestrogens were being investigated and developed for clinical use in the treatment of breast cancer, researchers in the field began to hypothesize that, based on data sharing, that estrogen inhibits bone loss and that antiestrogens, in some cases, act like estrogen, antiestrogens might also be effective in the treatment of osteoporosis. For example, in 1984, Paula Beall, *et al.*, published an article entitled "Clomiphene Protects Against Osteoporosis in the Mature Overiectomized Rat" ("*Beall*"). PTX 1962. *Beall* disclosed that clomiphene, a mixed estrogen agonist-antagonist, prevents reductions in calcium content, cortical thickness, and trabecular bone in the femurs of ovariectomized rats, and concluded that these results "suggest a possible new line of investigation of the use of antiestrogenic drugs as therapeutic agents for hormone-dependent osteoporosis in animals and humans." Id. at 123.

b. The *Jordan* Reference

Because clomiphene is a partial estrogen, it was unclear whether those estrogen-like properties were responsible for *Beall*'s observed response on bone or whether other antiestrogens could also produce such an effect. PTX 218 at 31. In light of the concern that long-term tamoxifen treatment in breast cancer patients could lead to premature bone loss, following the publication of Dr. Beall's study, Dr. V. Craig Jordan conducted a similar study on intact and ovariectomized 9-month-old retired breeder rats to determine the effects of tamoxifen and raloxifene (then called "keoxifene") on bone density. In October 1987, the results of that study were published in an article authored by V. Craig Jordan, Erik Phelps, and J. Urban Lindgren entitled "Effects of anti-estrogens on bone in castrated and intact female rats" ("*Jordan*"). PTX 218.

Jordan reported that both tamoxifen and raloxifene inhibited bone loss in overiectomized rats and that raloxifene had a minimal estrogenic response in the uterus. *Jordan* concluded that these results "may have important implications for the clinical [human] applications of antiestrogens." Id. at 34. It further stated that "[i]t is possible . . . that in the future, tamoxifen could be considered to be used as a substitute for estrogen [for the prevention of osteoporosis in post-menopausal women]." Id. *Jordan* called for clinical work to be conducted with tamoxifen to determine whether the results obtained in the rat studies would be applicable to humans:

> These contrasting pharmacological actions of antiestrogens suggest that patients receiving long-term adjucant tamoxifen therapy for breast cancer should be evaluated to determine whether tamoxifen can retard the

development of osteoporosis.

Id. at 31. The *Jordan* article did not discuss further development of raloxifene for the purpose of treating or preventing postmenopausal osteoporosis. Docket No. 603:10-12. At the time, only tamoxifen had been approved for clinical use in humans. Docket No. 607 at 963:17-23.

c. The *Feldmann* Article

In 1989, in an article entitled "Antiestrogen and Antiandrogen Administration Reduce Bone Mass in the Rat" ("*Feldmann*"), S. Feldmann *et al.* reported, contrary to *Jordan*, that raloxifene did not inhibit bone loss in ovariectomized rats and that tamoxifen produced an effect only at the highest dose administered. PTX 181 at 251. *Feldmann* noted that the lack of an effect observed with raloxifene "might be a dosage problem," but concluded that "an antiestrogen which does not show an estrogenic effect on sex organs, will not with respect to bones." Id. at 250-51. As discussed above, by the time *Feldmann* was published, it was known in the field that raloxifene was a relatively pure antiestrogen that had a negligible estrogenic effect in the uterus.

d. The *Turken* and *Love* Articles

The 1987 article by Sheila Turken *et al.* entitled "Effects of Tamoxifen on Spinal Bone Density in Women With Breast Cancer" ("*Turken*") disclosed the results of a study examining the effect of tamoxifen on the bone mineral density of the spine over one year

of its administration to post-menopausal women with a history of breast cancer. PTX 1969. *Turken* disclosed that tamoxifen preserved the spinal bone mineral density in the postmenopausal breast cancer patients, whereas healthy bone mineral control subjects experienced a significant loss of spinal bone mineral over the same period of time. Id. at 1088.

In March 1992, in an article entitled "Effects of Tamoxifen on Bone Mineral Density in Postmenopausal Women With Breast Cancer" ("*Love*"), Richard Love *et al.* published results of a study on the effects of tamoxifen on spinal bone density in postmenopausal women with breast cancer. PTX 1917. Similar to *Turken*, *Love* disclosed that tamoxifen is associated with preservation of the bone mineral density of the lumbar spine in postmenopausal women. Id. at EV 8521 13098.

e. The *Moon* Article

In 1991, Lilly Moon *et al.* published an article entitled "Dose-Dependent Effects of Tamoxifen on Long Bones in Growing Rats: Influence of Ovarian Status" ("*Moon*"). PTX 349. *Moon* disclosed the results of a study testing the effects of tamoxifen on bone in intact and ovariectomized rats in which tamoxifen treatment prevented the decrease of trabecular bone volume in the ovariectomized rats, but resulted only in a small decrease in intact rats with the highest dose. Id. at 1568. *Moon* concludes that these results "are consistent with tamoxifen behaving as a partial estrogen agonist on rat bone." Id. The study in *Moon* did not test raloxifene, but with regard to tamoxifen, the authors conclude

that their "findings are consistent with the results of Jordan *et al.* [citation to *Jordan*], who reported that tamoxifen reduced the decrease in femur ash weight/volume in adult OVX [ovariectomized] rats, but did not alter this measurement in intact rats." Id. at 1573. Distinguishing the conflicting results of tamoxifen's effect on bone in ovariectomized rats reported in *Feldmann, Moon* criticized the measurement technique used in the study, the lack of a baseline control group, and the failure to include an estrogen-treated group in the study. Id. at 1573-74.

f. The '068 ("Jones") Patent

In 1981, Lilly filed an application that claimed the discovery of a class of compounds, including raloxifene. On November 29, 1983, the patent application issued to Charles Jones as U.S. Patent No. 4,418,068 ("the Jones patent"). The Jones patent teaches that the claimed compounds have less inherent estrogenicity and cause fewer estrogenic side effects than earlier compounds, such as tamoxifen. PTX 2029 at 37:28-46. It also discloses that raloxifene can be administered in a pharmaceutical composition such as a tablet "formulated to contain a daily dose" (id. at 39:7-11) and that it can be administered in dosages ranging from 0.05 mg/kg/day up to about 50 mg/kg/day. Id. at 38:55-58.

The Invention and the '086 Patent

In 1984, Mr. Black's raloxifene research shifted from the study of raloxifene's

possible use in the treatment of breast cancer to a new therapeutic target, the menopausal syndrome, a component of which is postmenopausal osteoporosis. Docket No. 597 at 154:23-155:7; 157:2-20. In February 1987, a proposal for Lilly's bone biology program targeted the investigation of the benzothiophene series of compounds in an effort to find an alternative to estrogen for the treatment of postmenopausal osteoporosis that would have advantages, such as reducing estrogenicity in the breast and uterus tissues, but that would also have an effect on bone and other menopausal problems. Id. at 160:15-18; PTX 1806.

In March 1988, Mr. Black began his experiments to study the effects of raloxifene on bone in various ovariectomized rat models. Initially, he experienced difficulty in finding a validated animal model that would consistently demonstrate bone loss from which it could then be shown to be prevented by estrogen.[8] Docket No. 597 at 173:19-22. In a series of experiments beginning in July 1988, Mr. Black used an older, retired breeder rat model, but found inconsistent results in his intact controls. In some of the experiments, he was unable to demonstrate bone loss upon ovariectomy with the retired rat model, but in other experiments, the retired breeder rats did show bone loss upon ovariectomy, which led him to conclude that the retired breeder rat was an unreliable

[8] To ensure that a particular animal model is a proper model for studying osteoporosis, it is necessary to determine that the animal model is losing bone, similar to occurring in the osteoporotic woman, and that it has an estrogen sensitivity, like the osteoporotic woman, so that estrogen is able to inhibit that bone loss. Docket No. 601 at 512:16-513:4.

model for bone loss.[9] Docket No. 597 at 174:12-18.

Mr. Black next undertook similar experiments using an approximately 3-month-old virgin rat model,[10] which he determined showed bone loss with ovariectomy and prevention of the bone loss with estrogen.[11] Docket No. 597 at 24-188:13. In March 1989, he studied the effects of raloxifene on the younger ovariectomized rat model, the results of which study revealed that the mean trabecular bone density observed for raloxifene was statistically significantly greater than the control. This finding led him to conclude that raloxifene prevented bone loss in that model. Id. at 191:1-23.

In November 1991, Lilly's PTAC approved a human clinical trial of raloxifene in postmenopausal women for the treatment of postmenopausal osteoporosis. Docket No. 597 at 192:12-22. However, significant concerns regarding bioavailability issues were

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[9] Lilly's expert, Scott Cannon Miller explained that when the animals go through reproductive cycles, they lose a significant amount of trabecular bone due to lactation. After lactation, there is a recovery phase during which they recover their lost bone mass. Therefore, when using retired breeders, it is important to take their reproductive history into consideration, because, if a particular retired breeder rat has too recently been lactating, its trabecular bone may be so depleted that the rat is unable to show bone loss upon ovariectomy. Docket No. 601 at 513:25-514:15. Teva's expert, Dr. John Kinney, agreed that variability in the retired breeder rat model can occur, but that it does not automatically lead to unreliable outcomes if a baseline control study is performed and the experiment on the rats continues a sufficient period of time so that the transient effects due to lactation become less material. Docket No. 607 at 1024:21-1025:14.

[10] The rats were received at 75 days old and were acclimated for one week before the experiments began. Docket No. 597 at 187:6-11.

[11] As with the retired breeder model, there are also problems that can be associated with the younger rat model. For example, the rat grows more rapidly when it is younger, so a baseline control study is necessary to determine whether the changes in bone are due to growth. Docket No. 7 at 970:3-8.

raised at the PTAC meeting relating to raloxifene. Many of the members were concerned about going forward with a compound that had known ADME issues. According to Dr. Thomas Bumol, a member of PTAC at the time, the committee gave its approval for the clinical test despite these concerns, at least in part because Lilly already had an open IND on raloxifene, which would allow the clinical tests to be conducted within six months, rather than the usual twelve to twenty-four months. Docket No. 601 at 491:13-492:7.

Before the results of the PTAC-approved clinical study approved by PTAC had been collected, Lilly filed its patent application for the bone loss patents. Thus, there is no clinical human data included in the '086 patent. However, the PTAC-approved clinical study is described as Example 5 of the '086 patent, using doses of 200 mg per day and 600 mg per day. PTX 11 at col. 18, ln. 15-col.19, ln. 20. Example 1 of the '086 patent explains Mr. Black's study on ovariectomized rats and provides the mean results of assays using raloxifene in four different doses on thirty rats per dose. Id. at col. 14, ln. 55-col. 16, ln. 10. The patent specification addresses the bioavailability issue and provides a rationale, derived from the results of the studies Mr. Black conducted in which he administered the glucuronide conjugate found in the bloodstream of the human subjects to rats, explaining the reason that the conjugation would not necessarily be detrimental to the efficacy of raloxifene in humans. Id. at col. 3, ln. 28-60.

In September 1992, the Phase II, GGGB "proof of concept" study to test raloxifene's efficacy in humans described in Example 5 of the '086 patent began. It was conducted by Dr. Michael Draper. The study ended in December 1992 and the results

came back at the beginning of January 1993. Docket No. 603 at 683:14-684:1. Both the 200 mg and the 600 mg doses of raloxifene showed statistically significant changes in one or more of the bone markers tested, unequivocally demonstrating activity in humans. Id. at 688:3-689:22.

The patent examiner twice rejected the original parent application to the '086 patent, based on *Jordan*. Following these rejections, Lilly scientist, Dr. Henry Bryant, submitted a declaration dated January 11, 1994, in which he asserted that, at the time of the invention, he would have had doubts about the conclusions set forth in *Jordan* because: (1) Dr. Jordan's statistical analysis was flawed; (2) the rats used in Dr. Jordan's research were an inappropriate model; (3) Dr. Jordan's measurement techniques were improper, (4) Dr. Jordan was an expert in cancer, not in bone, and his article was not published in a bone journal; and (5) *Jordan* and *Feldmann* reported conflicting results regarding raloxifene's inhibitory effect on bone loss. PTX 217. On June 16, 1994, following a third rejection by the patent examiner, James Sales, the Lilly patent attorney in charge of the prosecution of the bone loss patents at the time, submitted a response to the PTO's final rejection, reiterating the criticisms raised in Dr. Bryant's declaration. PTX 2-TA at 430-31. The parent application to the '086 patent was subsequently allowed by the examiner.

Lilly's Criticisms of the *Jordan* Study

Lilly based its appeals to the PTO rulings on its view that the Jordan study was

flawed in terms of making raloxifene obvious for the treatment of osteoporosis. Part of Lilly's criticism was based on the statistical methodology used by Dr. Jordan.

In *Jordan*, Lilly pointed out, the Student's t-test was used in the statistical analysis to compare five treatment groups. Student's t-test is an appropriate statistical method to evaluate differences between two groups and a properly conducted Student's t-test would demonstrate that two groups are statistically different at a ninety-five percent confidence level. Docket No. 601 at 542:4-8; 543:11-14. However, as more and more groups are compared against the control, the likelihood increases that the Student's t-test will show a difference simply by chance, which is called a Type I error. Docket No. 603 at 650:10-23. Therefore, Student's t-test can appropriately be used to compare multiple groups when a publication concludes that a compound has no effect at all, because when used on multiple groups Student's t-test is more likely to show a difference when there is not actually a difference than to inaccurately show no effect. Id. at 649:2-18. Nevertheless, in exploratory drug research, it can be preferable to have a Type I error (false positive) over a Type II error (false negative) because the cost of a false positive is merely that further testing will show that the drug actually does not work, while the cost of a false negative is that a potentially valuable drug is eliminated from further study. Buncher Rep. ¶¶ 37-41.

As discussed above, depending on their reproductive history, retired breeders rats, such as those used in the *Jordan* study, can have varying levels of trabecular bone based on how recently they went through the lactation process. As previously noted, when the

animals go through reproductive cycles, they lose a significant amount of trabecular bone due to lactation. Following lactation, there is a recovery phase during which the rats recover their lost bone mass. Thus, if a retired breeder rat has too recently been lactating, its trabecular bone may be so depleted that it is unable to show bone loss upon ovariectomy, which can affect the results of a bone loss prevention study. Docket No. 601 at 513:25-514:15. Although variability in the retired breeder rat model can occur, it does not necessarily lead to unreliable outcomes, if a baseline control study is performed and the experiment continues a sufficient period of time to allow the transient effects due to lactation to pass. Docket No. 607 at 1024:21-1025:14.

To be a proper model for osteoporosis, an animal model must, as is the case with the osteoporotic woman, lose bone upon ovariectomy but also have estrogen sensitivity, so that estrogen can be shown to inhibit that bone loss. Docket No. 601 at 512:16-513:4. A drug can then be compared against the estrogen control to determine its effect. Id. at 513:12-22. Although estrogen slowed the decrease in bone density produced by ovariectomy in *Jordan*, the decrease "was not statistically significant." PTX 218 at 34. However, *Jordan* explicitly provided that it is known that estrogen can reverse osteoporosis in rats and that a low dose of estradiol benzoate was purposefully selected to control the weight gain observed upon overiectomy. Id.

Conclusions of Law

I. Standard of Review for Preliminary Injunction:

The Court has discretion in deciding whether to grant preliminary relief to "prevent the violation of any right secured by patent." 35 U.S.C. § 283. The grant of injunctive relief is appropriate if the moving party is able to demonstrate: (1) a reasonable likelihood of succeeding on the merits; (2) irreparable harm if preliminary relief is denied; and (3) an inadequate remedy at law. Girl Scouts of Manitou Council, Inc. v. Girl Scouts of the United States of America, Inc., 549 F.3d 1079, 1086 (7th Cir. 2008). If the moving party fails to demonstrate any one of these three threshold requirements, the emergency relief must be denied. Id. However, if these threshold conditions are met, the Court must then assess the balance of harm – the harm to Lilly if the injunction is not issued against the harm to Teva if it is issued – and, where appropriate, also determine what effect the granting or denying of the injunction would have on nonparties (the public interest). Id.

In determining whether to grant injunctive relief, the district court must take into account all four of these factors and then "exercise its discretion 'to arrive at a decision based on the subjective evaluation of the import of the various factors and a personal, intuitive sense about the nature of the case." Id. (quoting Lawson Products, Inc. v. Avnet, Inc., 782 F.2d 1429, 1436 (7th Cir. 1986)). This process involves engaging in what is called the "sliding scale" approach, meaning that "the more likely it is the plaintiff will succeed on the merits, the less balance of irreparable harms need weigh toward its side; the less likely it is the plaintiff will succeed, the more the balance need weigh towards its

side." Abbott Laboratories v. Mead Johnson & Co., 971 F.2d 6, 12 (7th Cir. 1992). The sliding scale approach "is not mathematical in nature, rather 'it is more properly characterized as subjective and intuitive, one which permits district courts to weigh the competing considerations and mold appropriate relief.'" Ty, Inc. v. Jones Group, Inc., 237 F.3d 891, 895-96 (7th Cir. 2001) (quoting Abbott Laboratories, 971 F.2d at 12).

II. Discussion

A. Likelihood of Success on the Merits

To show a reasonable likelihood of success on the merits, Lilly must demonstrate "that it will likely prove infringement of one or more claims of the patents-in-suit, and that at least one of those same allegedly infringed claims will also likely withstand the validity challenges presented by the accused infringer." Amazon.com, Inc. v. Barnesandnoble.com, Inc., 239 F.3d 1343, 1351 (Fed. Cir. 2001). We need not (and will not) consider all of the proposed grounds set forth in Lilly's motion; for the sake of expediency as is required by a motion for preliminary injunctive relief, we shall base our decision here on the single claim that Teva's ANDA infringes Lilly's '086 patent. As discussed above, Teva has conceded infringement of the '086 patent, but challenges the patent's enforceability and its validity on grounds of obviousness and lack of enablement. Because Teva concedes infringement, we address only whether Lilly has demonstrated that the '086 patent is likely to withstand Teva's challenges to its validity and enforceability.

Validity and enforceability challenges during a preliminary injunction proceeding ordinarily can succeed on evidence that would not necessarily support a judgment of invalidity or unenforceability at trial. Id. at 1359. At the preliminary injunction stage, the challenger need only show a "substantial question" as to validity and enforceability. Id. The patentee is similarly held to a less stringent standard and need only present a "clear case" supporting the validity and enforceability of the patent in suit." Id. A patentee can make such a showing by demonstrating, for example, that the patent in suit has withstood previous validity challenges in other proceedings or benefitted from a long period of industry acquiescence in its validity. Id. In the case at bar, however, because the evidence presented on the entitlement to injunctive relief was merged with the trial on the merits, the Court is able to achieve greater certainty in its findings and conclusions, and hopefully greater clarity than would otherwise be possible.

1. Obviousness

Teva's first contention that the '086 patent is invalid is based on its view that the patent was obvious given the prior art. "A patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art."[12] 35 U.S.C. § 103(a). Obviousness is a

[12] Teva contends that a person having ordinary skill in the art to whom the '086 patent is (continued...)

question of law based on underlying findings of fact, which include: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art at the time the invention was made; and (4) objective evidence of nonobviousness, if any. In re Kublin, ___ F.3d ___, 2009 WL 877646, at *4 (Fed. Cir. Apr. 3, 2009) (citing Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966)).

Obviousness arises when a skilled individual "merely pursues 'known options' from a 'finite number of identified, predictable solutions.'" Id. at *8 (quoting KSR Intern. Co. v. Teleflex Inc., 550 U.S. 398, 421 (2007)). Section 103 also bars patentability unless "the improvement is more than the predictable use of prior art elements according to their established functions." 550 U.S. at 417. Obviousness does not require absolute predictability; all that is required is a reasonable expectation of success. Eli Lilly and Co. v. Zenith Goldline Pharmaceuticals, Inc., 471 F.3d 1369, 1377

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[12](...continued)
directed would be a person who has at least a bachelor's degree in a scientific discipline who has experience performing, or has knowledge about, animal studies and their usefulness in osteoporosis research. However, according to Teva, a person of ordinary skill in the art would not require extensive knowledge of pharmacokinetics or ADME characteristics, statistical analysis, or cellular biology. Docket No. 607 at 968:3-969:17. Lilly asserts that one of ordinary skill in the art would need to be at least conversant in pharmacokinetics and ADME and have a basic background knowledge of how those characteristics relate to the success of a drug. Docket No. 601 at 447:11-16.

Because the specification of '086 patent discusses the bioavailability problem associated with raloxifene and researchers in both the bone and cancer fields were publishing on the metabolism issues related to raloxifene and other compounds with free hydroxyl groups around the time of the invention, we conclude that a person of ordinary skill in the art at the time would necessarily have a general understanding of ADME characteristics in addition to the other qualifications described by Teva.

(Fed. Cir. 2006) (citing In re Longi, 759 F.2d 887, 896 (Fed. Cir. 1985)).

Teva's expert, Dr. Kinney, testified that in his view Claim 1[13] of the '086 patent was obvious because: (1) the need to inhibit postmenopausal bone loss was established in the prior art, since it was known at the time that bone loss led to increased incidence of fractures; (2) a single daily dose was disclosed in the '068 patent; (3) the Jordan reference discloses that raloxifene could be administered to inhibit bone loss in ovariectomized rats; and (4) the Turken reference demonstrated the predictive power of the rat model by finding a similar bone-inhibiting effect when tamoxifen was administered to humans. Docket No. 607 at 976:1-978:1.

However, whether in hindsight the path of the inventor looks obvious is irrelevant. As the Federal Circuit recently recognized in Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc., 520 F.3d 1358 (Fed. Cir. 2008), "In retrospect, [the inventor's] pathway to the invention, of course, seems to follow the logical steps to produce these properties, but at the time of invention, the inventor's insights, willingness to confront and overcome obstacles, and yes, even serendipity, cannot be discounted." Id. at 1364. So it appears here. The fact that, after testing both antiestrogen compounds, *Jordan* suggested that tamoxifen could possibly be considered for the prevention of osteoporosis in postmenopausal women, but made no specific suggestion that raloxifene could have such clinical use, coupled with the evidence regarding bioavailability concerns associated

[13] The parties' arguments as to Claim 1 apply equally to each of the disputed claims of the '086 patent.

with raloxifene in humans[14] and the fact that Dr. Jordan himself had published at the time regarding the rapid metabolism of compounds with free hydroxyl groups, such as raloxifene, a person of ordinary skill in the art would not have had a reasonable expectation of success in using raloxifene to treat human postmenopausal osteoporosis.[15] Although at the time of the invention it was known that the glucuronide conjugate of at least one compound, morphine-6, remained active and that certain enzymes could in some cases reverse the effects of conjugation, Teva's expert, Dr. Hayton, conceded that, in the "vast majority" of compounds, glucuronidation deactivates the drug. Docket No. 609 at 1186:2-5.

Further, neither *Turken* nor *Love* when considered in conjunction with *Jordan* would have rendered the clinical use of raloxifene to treat postmenopausal osteoporosis obvious because those prior art references disclosed only that *tamoxifen* inhibited bone

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[14] Teva contends that, the fact that Lilly received a large number of requests from researchers for raloxifene samples, despite knowledge of raloxifene's rapid metabolism, demonstrates that persons of ordinary skill in the art at the time believed that it nevertheless could still be active in the body. However, Dr. Russell explained that, as a purer antiestrogen, raloxifene was a useful research tool because of its low estrogenicity. Docket No. 603 at 664:7-21.

[15] At trial, both parties' experts battled over whether there were various shortcomings in *Jordan*, such as the use of the retired breeder rat model, the measurement technique employed, the statistical analysis applied, and the lack of an estrogen control, that would have led a person of ordinary skill in the art to question its teachings. Based on our review of the evidence and testimony presented at trial, we find that, while there were legitimate criticisms that could be leveled against *Jordan*, a person of ordinary skill in the art would have relied on the results in *Jordan* as reported. As detailed above, even though *Jordan* was clearly "inching up" on the science, in light of the known bioavailability problems associated with raloxifene at the time, even in light of the other prior art, *Jordan* would not have provided a person of ordinary skill in the art with a reasonable expectation of success in using raloxifene to treat postmenopausal osteoporosis in humans.

loss in clinical studies, not raloxifene. And, as discussed above, it was known at the time of the invention that tamoxifen's chemical structure differed from raloxifene in that tamoxifen does not have the free hydroxyl groups that make raloxifene susceptible to rapid metabolism and glucuronidation.

The fact that *Jordan*, as well as the Jones patent, *Beall*, *Moon*, and *Love*,[16] were all considered by the PTO during prosecution of the application further supports Lilly's likelihood of success in prevailing on this issue. See Impax Labs., Inc. v. Aventis Pharms., Inc., 468 F.3d 1366, 1378 (Fed. Cir. 2006) ("When the prior art was before the examiner during prosecution of the application, there is a particularly heavy burden in establishing invalidity.") (citations omitted). Thus, we conclude that Teva has failed to raise a "substantial question" of invalidity on the basis of obviousness and that Lilly is thus reasonably likely to prevail in demonstrating the nonobviousness of the '086 patent.

2. Enablement

The statutory basis for the enablement requirement is found in 35 U.S.C. § 112, which provides in relevant part:

> The specification shall contain a written description of the invention and of the manner and process of making and using it, in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the

[16] The Turken reference was not considered by the PTO, but because it discloses the same information as disclosed in *Love* (i.e., that tamoxifen inhibits bone loss in postmenopausal women), it is merely cumulative.

same.

Id. ¶ 1. The "enablement requirement is satisfied when one skilled in the art, after reading the specification, could practice the claimed invention without undue experimentation." Sitrick v. Dreamworks, LLC, 516 F.3d 993, 999 (Fed. Cir. 2008) (quoting AK Steel Corp. v. Sollac, 344 F.3d 1234, 1238-39 (Fed. Cir. 2003)). "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed . . . ." PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564 (Fed. Cir. 1996) (quoting Ex Parte Jackson, 217 U.S.P.Q. 804, 807 (1982)). Enablement is determined as of the filing date of the patent application. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384 (Fed. Cir. 1986).

The Federal Circuit has explained that "the how to use prong of section 112 incorporates as a matter of law that requirement of 35 U.S.C. § 101 that the specification disclose as a matter of fact a practical utility for the invention." In re Cortright, 165 F.3d 1353, 1356 (Fed. Cir. 1999) (quoting In re Ziegler, 992 F.2d 1197, 1200 (Fed. Cir. 1993)). There is a lack of utility under § 101 "when there is a complete absence of data supporting the statements which set forth the desired results of the claimed invention." In re Cortright, 165 F.3d at 1356 (quoting Envirotech Corp. v. Al George, Inc., 730 F.2d 753, 762 (Fed. Cir. 1984)).

"In the context of determining whether sufficient 'utility as a drug, medicant, and

the like in human therapy' has been alleged, 'it is proper for the examiner to ask for substantiating evidence unless one with ordinary skill in the art would accept the allegations as obviously correct." Rasmusson v. SmithKline Beecham Corp., 413 F.3d 1318, 1323 (Fed. Cir. 2005) (quoting In re Jolles, 628 F.2d 1322, 1325 (Cust. & Pat. App. 1980)). "Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person if the invention's asserted utility." In re Brana, 51 F.3d 1560, 1566 (Fed. Cir. 1995) (citing In re Bundy, 642 F.2d 430, 433 (CCPA 1981)).

There is no dispute that, after reading the '086 patent, a person of ordinary skill in the art would be able to administer raloxifene in a single daily dose of 200 mg or 600 mg to humans, as described in Example 5, without undue experimentation. E.g., Docket No. 607 at 1086:8-1088:1. However, Teva contends that, assuming the Court finds that the '086 patent is not obvious based on the known bioavailability issues associated with raloxifene, the '086 patent nevertheless fails to meet the enablement requirement because it discloses no more relevant information regarding human efficacy than that which was disclosed in *Jordan*. In other words, if the Jordan rat study could not predict that raloxifene would work to treat and prevent postmenopausal osteoporosis, then neither would the rat study described in the '086 patent. Thus, Teva's argument implicates the requirement set forth in § 101 (and incorporated into § 112) that the specification disclose as a matter of fact a practical utility for the invention, here, human efficacy.

Initially, we note that Teva's characterization of the '086 patent as including nothing more than that which was disclosed in *Jordan* is not entirely accurate. While there is no clinical data included in the '086 patent, the specification addresses the bioavailability issue and provides a rationale, derived from the unpublished results of the studies Mr. Black conducted in which he administered the glucuronide conjugate found in the bloodstream of the human subjects to rats, for why the conjugation would not necessarily be detrimental to the efficacy of raloxifene in humans. Id. at col. 3, ln. 28-60. Additionally, the clinical study approved by PTAC is described as Example 5 of the '086 patent, using doses of 200 mg per day and 600 mg per day. PTX 11 at col. 18, ln. 15-col.19, ln. 20.

Despite this additional information provided in the specification, in light of the significant concerns related to raloxifene's bioavailability and the fact that, even after reviewing the results of Mr. Black's human conjugate studies, many PTAC members were still not convinced that raloxifene would be active in humans (PTX 1102 at EV 7113 198-203), we shall assume for purposes of this ruling that a person of ordinary skill in the art at the time would reasonably doubt the asserted utility, to wit, that raloxifene could clinically be used to treat and prevent postmenopausal osteoporosis. However, such a finding does not end the inquiry. In cases where one of ordinary skill in the art would reasonably doubt the asserted utility, the law provides the patentee with the opportunity to present rebuttal evidence sufficient to convince such a person of the invention's asserted utility. See Rasmusson, 413 F.3d at 1323 (Fed. Cir. 2005); In re

Brana, 51 F.3d at 1566.

There is such evidence of record here. The results from the GGGB proof of concept study conducted by Dr. Draper demonstrate that raloxifene showed activity in humans at dosages of 200 mg and 600 mg in various bone markers, including serum osteocalcin, which correlates with metabolism in the bone. Docket No. 603 at 687:12-688:2. Enablement or utility is determined as of the application filing date, here, July 28, 1992. However, even though the results of the GGGB study were not available until early January 1993, slightly more than five months after the priority filing date of the '086 patent, those results are available to overcome the doubts as to the asserted utility since they pertain to the accuracy of a statement set out in the claim specification and goes to prove that the disclosure was in fact enabling (i.e., demonstrated utility) when filed. In re Brana, 51 F.3d at 1567 n.19 (citing In re Marzocchi, 439 F.2d 220, 224 n.4 (Cust. & Pat. App. 1971)).

In conclusion, as previously noted, there is no doubt that a person of ordinary skill, after reading the '086 patent, would be able to administer raloxifene in a single daily dose of 200 mg or 600 mg to humans as described in Example 5 of the specification without undue experimentation. Additionally, we find the results of the GGGB study showing raloxifene's activity in humans to be sufficient evidence to convince one of skill in the art of the asserted utility, to wit, that raloxifene would work in the treatment and prevention

of postmenopausal osteoporosis,[17] and thus, conclude that Teva's efforts to raise a substantial question as to enablement have fallen short.

3. Enforceability

Teva contends that the '086 patent is unenforceable because Lilly submitted a declaration to the PTO, dated January 11, 1994, from Dr. Bryant, that intentionally misrepresented *Jordan*. "A patent may be rendered unenforceable for inequitable conduct if an applicant, with intent to mislead or deceive the examiner, fails to disclose material information or submits materially false information to the PTO during prosecution." Digital Control, Inc. v. Charles Mach. Works, 437 F.3d 1309, 1313 (Fed. Cir. 2006). The party asserting inequitable conduct has the burden to prove "a threshold of materiality and intent by clear and convincing evidence." Id. Further, "materiality does not presume intent, which is a separate and essential component of inequitable conduct." GFI, Inc. v. Franklin Corp., 265 F.3d 1268, 1274 (Fed. Cir. 2001) (quoting Manville Sales Corp. v. Paramount Sys., Inc., 917 F.2d 544, 552 (Fed. Cir. 1990)). An intent to deceive "must generally be inferred from the facts and circumstances surrounding the applicant's overall conduct." Paragon Podiatry Lab., Inc. v. KLM Labs, Inc., 984 F.2d 1182, 1190 (Fed. Cir. 1993). However, "[w]hile intent to deceive the PTO may be found as a matter of

[17] Although the GGGB study was just the first in a number of tests conducted by Lilly to determine the efficacy of raloxifene in humans, it is sufficient to meet the utility requirement for enablement. See In re Brana, 51 F.3d 1560, 1568 (Fed. Cir. 1995) ("Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development.").

inference from circumstantial evidence, circumstantial evidence cannot indicate merely gross negligence." Molins PLC v. Textron, Inc., 48 F.3d 1172, 1181 (Fed. Cir. 1995).

In his declaration, Dr. Bryant asserted that, at the time of the invention, in his professional judgment he would have had doubts about the conclusions set forth in *Jordan* because: (1) Dr. Jordan's statistical analysis was flawed; (2) the rats used in Dr. Jordan's research were an inappropriate model; (3) Dr. Jordan's measurement techniques were improper, (4) Dr. Jordan was an expert in cancer, not in bone, and his article was not published in a bone journal; and (5) there was conflicting literature (*Feldmann*) regarding raloxifene's inhibitory bone loss effect. PTX 217. On June 9, 1994, after initial review of Dr. Bryant's declaration, the PTO again rejected the bone loss patents. On June 16, 1994, James Sales, the Lilly patent attorney in charge of the prosecution of the bone loss patents at the time, submitted a response to the PTO's final rejection, in which he stated that Dr. Bryant's declaration clearly indicates that, when analyzed, *Jordan* would have caused concern to one of ordinary skill in the art as to its actual teaching. PTX 2-TA at 430. The bone loss patents were subsequently allowed by the examiner.

The evidence in the record at best shows that others may have disagreed with Dr. Bryant's assertions to the PTO in which he explained his doubts as of the time of the invention about the findings reported in *Jordan*,[18] but it does not establish that the Bryant

[18] Two of Lilly's bone experts, Dr. Miller and Dr. Russell, both testified that they found nothing in Dr. Bryant's declaration that they regarded to be false or misleading. Docket No. 601 at 639:10-15; 572:15-24. Dr. Miller further testified that, "When I first read it, I thought it was amazingly similar to what I had written, without seeing it, criticisms of the Jordan paper." Id. at (continued...)

statements were knowingly false or that his dealings with the PTO evidenced an intent to deceive. Teva's own expert, Dr. Kinney, testified that he believed, not that Dr. Bryant had committed a fraud, only that Dr. Bryant was "mistaken" in his declaration. Docket No. 607 at 1076:20-23. The principal circumstantial evidence presented at trial regarding Dr. Bryant's dealings with the PTO consists of the following:

In his declaration, Dr. Bryant criticized Dr. Jordan's use of the retired breeder rat model, even though at trial he testified that the best animal model was still up for debate in the field at the time he filed his declaration with the PTO and that he had used retired breeder rats in some studies. Docket No. 605 at 900:22-902:5. In addition, on November 3, 1993, a few months before Dr. Bryant submitted his declaration, he had received an email from Dr. Janet Hock, another Lilly researcher, titled: "To clarify confusion re retired breeder rats." PTX 345 at EV 7093 289. In that email, Dr. Hock wrote that: "Re study using 9 month retired breeders and ralox; *some people* regard this age OXV [sic] as the best model for human E2 [estrogen] deficiency." Id. (emphasis added).[19] However, Dr. Bryant testified that, at the time he wrote his declaration, he had had conversations

[18](...continued)
572:25-573:4.

[19] We note that it is not entirely clear whether Dr. Hock was referring specifically to the 9 month-old retired breeder rat or simply to 9 month-old rats in general as the model that some in the field viewed as "the best." Docket No. 605 at 902:7-903:9; DTX 1303 (Janet Hock Video Deposition) at 117:22-119:23.

with other highly regarded scientists in the bone field, including Dr. Kimmel,[20] and, based on those discussions, his conclusion was that the retired breeder rat model was unreliable. Docket No. 605 at 879:4-882:7. The mere fact that there were certain people in the field who were using or advocating the retired breeder rat model does not establish, either directly or indirectly, that Dr. Bryant intended to deceive the PTO when he expressed his concerns about the model.

Dr. Bryant also criticized Dr. Jordan's use of Student's t-test to complete the statistical analysis published in the study. Admittedly, on a few occasions, a technician in Dr. Bryant's lab at Lilly also applied the Student's t-test inappropriately to analyze data that was never published. Docket No. 603 at 838:21-842:25. This fact, however, does not support the conclusion that Dr. Bryant's criticism of the method was disingenuous or offered in an effort to deceive the PTO when he opined that Dr. Jordan's use of Student's t-test to compare multiple groups and report a positive result in a published study was inappropriate.

Nor can we infer an intent to deceive from the fact that, shortly before he submitted his declaration to the PTO, an article that Dr. Bryant co-authored was published which represented that the result reached "is consistent with" the result reported in *Jordan* with regard to raloxifene's inhibitory effect on bone loss. One can reach

[20] In 1996, Dr. Kimmel published an article in which he stated, "However, when doing prevention experiments, the retired breeder female rat is generally unreliable because of both the (likely) already osteopenic condition of the skeleton from which little more bone could be lost, and the period of catch-up growth." PTX 403 at 678-79.

consistent results with another study without necessarily agreeing with the methodology utilized by the other researcher. Dr. Bryant testified that the citation to *Jordan* was included in his article because he felt it was important to "be clear about the previous data that is out there." Docket No. 603 at 818:10-11. It is true that Bryant did not always follow his own guideline in this regard as evidenced by the fact that, even though it was in the literature at the time, he did not also cite to *Feldmann* in his article. Nonetheless, in other publications and reports dated at approximately the same time he submitted his declaration to the PTO, Dr. Bryant pointed out *Feldmann*'s and *Jordan*'s conflicting reports regarding the effects of raloxifene in ovariectomized rat models, which is the same point that he made in his declaration. Docket No. 605 at 875:25-877:21; PTX 225; DTX 1159. In sum, the circumstantial evidence adduced at trial, even when considered as a whole, does not support an inference that Dr. Bryant acted with an intent to deceive in his submissions to or dealings with the PTO.

With regard to Attorney Sales, we find that, at most, the evidence indicates that Mr. Sales was negligent in failing to conduct a more thorough investigation to determine whether *Feldmann* was the only example of countervailing literature to *Jordan* before submitting his independent statement to the PTO in support of Dr. Bryant's declaration. However, in order to find an intent to deceive, "the alleged conduct must not amount merely to the improper performance of, or omission of, an act one ought to have performed." Molins, 48 F.3d at 1181. Mr. Sales testified that, at the time he filed his response, *Jordan* and *Feldmann* were the only references of which he was aware that

addressed raloxifene's effect on inhibiting bone loss and that he therefore believed the statements in Dr. Bryant's declaration to have been true. Because no evidence was presented at trial that would cause the Court to question these representations, we cannot find that, in filing his response, Mr. Sales acted with an intent to deceive the PTO.

For the foregoing reasons, based on the totality of the evidence adduced at trial, there is an insufficient basis to satisfy the threshold requirement for establishing the deceptive intent necessary for a finding of inequitable conduct. Accordingly, we find that Teva has failed to raise a substantial question as to the enforceability of the '086 patent.[21]

B. Irreparable Harm and Inadequate Remedy at Law

On March 24, 2009, Teva submitted a voluntary agreement to limit its raloxifene launch to no more than one million bottles of raloxifene hydrochloride tablets between April 23, 2009, and December 12, 2009, [Docket No. 592]. The one million bottles would be drawn from a supply of 950,625 thirty-count bottles, 73,597 one hundred-count bottles, and 4,742 one thousand-count bottles, or more than 40 million tablets. Docket No. 592. Teva contends that this limited launch will effectively eliminate the irreparable harms that Lilly has alleged. Lilly disagrees. So does the Court.

The Federal Circuit recognizes that the "essential attribute of a patent grant is that

[21] Because both materiality and intent are required to establish inequitable conduct, we need not address the materiality of the purported false statements attributed to Dr. Bryant and Mr. Sales.

it provides a right to exclude competitors from infringing the patent." Acumed LLC v. Stryker Corp., 551 F.3d 1323, 1328 (Fed. Cir. 2008). In light of that right, courts recognize that infringement may cause a patentee irreparable harm not completely remediable by a reasonable monetary payment. Id. That appears to be the situation here. Teva's promised limited launch will likely result in the same type of displacement of Evista in the marketplace as would a broader launch.[22] Lilly would no longer maintain marketing exclusivity with respect to Evista®, which, based on the experience of other drugs facing generic competition, would result in a rapid loss of market share and revenue[23] that will be difficult, if not impossible for Lilly to recover, even if the Court were to later rule in favor of Lilly and Teva's generic raloxifene product was removed entirely from the market. See Abbott Labs. v. Sandoz, Inc., 544 F.3d 1341, 1361-62 (Fed. Cir. 2008) (affirming the district court's finding of irreparable harm and citing precedent holding that loss of revenue and market position are evidence of irreparable harm).

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[22] Lilly's expert estimates that Teva's limited lunch represents approximately five to six months of the sales that Teva would realize in the absence of any limitation and expects that Teva would capture 80% of the Evista® market within two months of the launch. Lechanteur Supp. Decl. ¶ 2. Assuming that Teva's sales will take place throughout the full eight months of the limited launch period, Teva's expert estimates that the quantity of generic raloxifene supplied will amount to 20% to 23% of annual Evista® prescriptions. Bell Supp. Decl. (March 31, 2009) ¶ 5.

[23] For example, Pravachol® and Zoloft® faced generic entry in April and August 2006, respectively, and lost approximately 80% of their prescriptions to generics within three weeks of entry. Grabowski Decl. ¶ 18 (citing Richard Silver, "A Wall Street Perspective on Generics," 2007 GPhA Annual Meeting, March 1-3, 2007). Fosamax®, a competitor to Evista® in the osteoporosis category, lost approximately 89% of its prescriptions to generics within four months after generic entry. Id. ¶ 19.

Teva contends that, if it were later enjoined from distributing its generic raloxifene product, Lilly would be able to return to its prior market position. In support of this contention, Teva points to Plavix® as an example of a drug that regained and even surpassed its prior market share after a generic was on the market for a limited period. Supplemental Declaration of Gregory Bell ("Bell Supp. Decl. (February 19, 2009)") ¶ 2.2. However, in contrast to Plavix®, which held 91% of the market share of anti-platelet drugs, Evista® commands only 12% of the current osteoporosis market. Supplemental Declaration of Henry Grabowski ("Grabowski Supp. Decl.") ¶ 23. Lilly currently competes in the osteoporotic therapeutic category with seven competitors, including one generic (generic Fosamax®), and has nowhere near the dominant share of the market that Plavix® had at the time it faced a generic launch. Supplemental Declaration of Marcel Lechanteur ("Lechanteur Supp. Decl.") ¶ 6.

Additionally, even if, as Teva contends, Lilly were able to fully recover its position in the market, we find that there would nonetheless likely be irreparable damage to Lilly's relationship with physicians and customers in addition to causing a significant disruption or loss of research that otherwise would have been sponsored or completed by Lilly as well as a scaling back of investment in research and development which otherwise would not have occurred. None of these losses can be adequately compensated by a monetary payment from Teva. Lechanteur Supp. Decl. ¶ 8; see Abbott Labs., 544 F.3d at 1361-62. Thus, Lilly has demonstrated that Teva's limited launch of its generic product would result in its suffering substantial irreparable harm for which there is no adequate remedy

at law, if Lilly were to prevail in this litigation.

C. Balance of Harms

Teva contends that the balance of hardships weighs in its favor because it will be denied profits that it cannot recoup as a result of the indefinite delay to the launch of its generic product. However, Teva's harm is purely monetary, and will be protected by the corporate undertaking offered by Lilly. Therefore, we find that the monetary harm to Teva resulting from an additional period of delay in launching its generic raloxifene product is outweighed by the likelihood of substantial and irreparable harm to Lilly, as discussed above, if the preliminary injunction were not to issue.

D. Public Interest

It is well-established that the public has a substantial interest in the enforcement of patent rights, in light of the fact that the protection of those rights promotes investment by drug companies in research and development. Sanofi-Synthelabo v. Apotex, Inc., 470 F.3d 1368, 1383 (Fed. Cir. 2006) (recognizing the "public interest in encouraging investment in drug development and protecting the exclusionary rights conveyed in valid pharmaceutical patents"). Although we are mindful that the statutory framework under which Teva filed its ANDA seeks to make generic drugs available to the public, "it does not do so by entirely eliminating the exclusionary rights conveyed by pharmaceutical patents. Nor does the statutory framework encourage or excuse infringement of valid

pharmaceutical patents." Pfizer, Inc. v. Teva Pharms. USA, Inc., 429 F.3d 1364, 1382 (Fed. Cir. 2005). Having found that Lilly has demonstrated a likelihood that it will succeed in demonstrating at that the '086 patent is valid and enforceable, the public interest is clearly best served by permitting it to maintain the status quo during this period of time awaiting a final ruling on the merits.

III. Conclusion

As explained above, the Court GRANTS Plaintiff's, Eli Lilly and Company, Motion for Preliminary Injunction. Defendant, Teva Pharmaceuticals USA, Inc., is hereby PRELIMINARILY ENJOINED from launching in the United States its generic raloxifene product as described in ANDA No. 78-193. This PRELIMINARY INJUNCTION ORDER is effective immediately upon the entry of this ruling on the Court's docket and shall extend until further order of the Court or, in any event, no later than a final ruling on the merits.

IT IS SO ORDERED.

Date: 04/22/2009

SARAH EVANS BARKER, JUDGE
United States District Court
Southern District of Indiana

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