United States Court of Appeals for the Federal Circuit

HOFFMANN-LA ROCHE INC. AND GENENTECH, INC.,
Plaintiffs-Appellants,

v.

APOTEX INC. AND APOTEX CORP.,
Defendants-Appellees.

2013-1128

- -

HOFFMANN-LA ROCHE INC. AND GENENTECH, INC.,
Plaintiffs-Appellants,

v.

DR. REDDY'S LABORATORIES, LTD. AND DR. REDDY'S LABORATORIES, INC.,
Defendants-Appellees.

2013-1161

- -

HOFFMANN-LA ROCHE INC. AND GENENTECH, INC.,
Plaintiffs-Appellants,

v.

WATSON LABORATORIES, INC., ACTAVIS, INC., WATSON PHARMA, INC., COBALT PHARMACEUTICALS INC., AND COBALT LABORATORIES, INC.,
Defendants-Appellees.

2013-1162

- -

HOFFMANN-LA ROCHE INC. AND GENENTECH, INC.,
Plaintiffs-Appellants,

v.

ORCHID CHEMICALS & PHARMACEUTICALS LTD., ORCHID HEALTHCARE, ORCHID PHARMACEUTICALS INC., AND ORGENUS PHARMA INC.,
Defendants-Appellees.

2013-1163

- -

HOFFMANN-LA ROCHE INC. AND

GENENTECH, INC.,
Plaintiffs-Appellants,

v.

MYLAN INC., MYLAN PHARMACEUTICALS INC., GENPHARM ULC (formerly known as Genpharm Inc.), AND **GENPHARM, L.P.,**
Defendants-Appellees.

2013-1164

Appeals from the United States District Court for the District of New Jersey in Nos. 07-CV-4417, 08-CV-3065, 08-CV-4053 and 10-CV-6241, Judge Stanley R. Chesler.

Decided: April 11, 2014

MARK E. WADDELL, Loeb & Loeb LLP, of New York, New York, argued for plaintiffs-appellants. With him on the brief were WARREN K. MACRAE, PAULA K. COLBATH, and KATHLEEN GERSH.

DEANNE M. MAZZOCHI, Rakoczy Molino Mazzochi Siwik, LLP, of Chicago, Illinois, argued for all defendants-appellees. With her on the brief were WILLIAM RAKOCZY, TARA M. RAGHAVAN, and ERIC R. HUNT, for Watson Laboratories, Inc., et al. On the brief were STEVEN E. FELDMAN, JAMES P. WHITE, LOUISE T. WALSH, PHILIP D. SEGREST, DANIEL R. CHERRY, and SHERRY L. ROLLO, Husch Blackwell LLP, of Chicago, Illinois, for Apotex Inc., et al; EDGAR H. HAUG, RICHARD E. PARKE, and RICHARD F. KURZ, Frommer Lawrence & Haug, LLP, of New York, New York, for Mylan Inc., et al.; STUART D. SENDER and

MICHAEL CHOI, Budd Larner, P.C., of Short Hills, New Jersey, for Dr. Reddy's Laboratories, Ltd., et al.; WILLIAM J. UTERMOHLEN, JAMES A. OLIFF, and JOHN W. O'MEARA, Oliff & Berridge, PLC, of Alexandria, Virginia, for Orchid Chemicals & Pharmaceuticals Ltd., et al. Of counsel were JAMES E. CECCHI, Carella, Byrne, Bain, Gilfillan, Cecchi, Stewart & Olstein, of Roseland, New Jersey, for Watson Laboratories, Inc., et al. ARNOLD B. CALMANN, Saiber, LLC, of Newark, New Jersey, for Mylan Inc., et al., BRUCE D. RADIN, Budd Larner, P.C., of Short Hills, New Jersey, for Dr. Reddy's Laboratories, Ltd., et al. and CHARLES N. QUINN, Fox Rothschild, LLP, of Exton, Pennsylvania, for Orchid Chemicals & Pharmaceuticals Ltd., et al.

Before NEWMAN, LOURIE, and BRYSON, Circuit *Judges*.

Opinion for the court filed by *Circuit Judge* BRYSON.
Dissenting opinion filed by *Circuit Judge* NEWMAN.

BRYSON, *Circuit Judge*.

Plaintiff Hoffmann-La Roche, Inc., ("Roche") appeals from the decision of the United States District Court for the District of New Jersey granting the defendant generic drug companies summary judgment of invalidity as to claims 1-8 of U.S. Patent No. 7,718,634 ("the '634 patent") and claims 1-10 of U.S. Patent No. 7,410,957 ("the '957 patent"). We affirm.

I

The patents at issue in this appeal are directed to methods of treating osteoporosis through the once monthly administration of ibandronate, one of a class of compounds known as bisphosphonates. Ibandronate, a salt of ibandronic acid, is commercially available as Roche's once monthly Boniva®, which was approved by the United States Food and Drug Administration ("FDA") in 2005 for

the treatment of osteoporosis. Once monthly Boniva® provides a 150 milligram ("mg") dose of ibandronate.

Osteoporosis is a disease characterized by abnormal bone resorption. Resorption, the biological process by which bone is broken down, causes decreased bone strength and an increased risk of fractures. Bisphosphonates are "potent inhibitors of bone resorption." '957 patent, col. 1, ll. 39-40. They inhibit abnormal bone destruction and enable the gradual restoration of lost bone mineral density ("BMD").

Bisphosphonates are generally known to have a low bioavailability when administered orally, i.e., only a small fraction of a given dose is absorbed into the blood. Additionally, oral administration of bisphosphonates can result in adverse esophageal and gastrointestinal side effects. As a result of the side effects and to improve the bioavailability of the drug, patients taking bisphosphonates must adhere to a dosing regimen that requires a bisphosphonate tablet to be taken in a fasting state at least 30 minutes before eating or drinking. In the past, the inconvenience of that regimen created problems of patient compliance. Researchers in the field believed that less-frequent dosing would result in patients continuing the treatment for the long term, which is required for bisphosphonate treatments to be successful.

Roche owns the '634 patent and the '957 patent, which is the parent of the '634 patent. Claims 1-8 of the '634 patent and claims 1-10 of the '957 patent are at issue in this case and describe a method of treating osteoporosis consisting of orally administering about 150 mg of ibandronic acid once monthly on a single day. Claim 1 of the '634 patent is representative of the claims on appeal:

> 1. A method for treating or inhibiting postmenopausal osteoporosis in a postmenopausal woman in need of treatment or inhibition of postmenopausal osteoporosis by administration of a phar-

maceutically acceptable salt of ibandronic acid, comprising:

(a) commencing the administration of the pharmaceutically acceptable salt of ibandronic acid by orally administering to the postmenopausal woman, on a single day, a first dose in the form of a tablet, wherein the tablet comprises an amount of the pharmaceutically acceptable salt of ibandronic acid that is equivalent to about 150 mg of ibandronic acid; and

(b) continuing the administration by orally administering, once monthly on a single day, a tablet comprising an amount of the pharmaceutically acceptable salt of ibandronic acid that is equivalent to about 150 mg of ibandronic acid.

II

The defendants in this case are generic drug manufacturers who submitted Abbreviated New Drug Applications ("ANDAs") to the FDA for approval to engage in the manufacture and sale of generic versions of Boniva® prior to the expiration of Roche's patents. Roche sued the defendants in the United States District Court for the District of New Jersey alleging infringement under 35 U.S.C. § 271(e)(2) based on the defendants' ANDA filings.

Roche moved for a preliminary injunction. The district court denied the motion, holding that Roche had failed to prove it was likely to succeed in defeating the defendants' obviousness challenge. This court affirmed the district court's denial of the preliminary injunction. *See Hoffmann-La Roche Inc. v. Apotex Inc.*, 496 F. App'x 46 (Fed. Cir. 2012).

While the appeal of the preliminary injunction decision was pending, the district court granted the defend-

ants' motion for summary judgment of invalidity of claims 1-8 of the '634 patent due to obviousness under 35 U.S.C. § 103(a). As to the frequency of dosing, the court found that once monthly oral dosing of ibandronate was established in the prior art. As to the amount of the monthly dose, the court found that the combination of several prior art references suggested a dosage level of about 150 mg per month, or at least indicated that a monthly dose of 150 mg was obvious to try.

The district court considered Roche's evidence of objective considerations of nonobviousness but concluded that "Roche's objective considerations evidence does not rise to the level of a mere scintilla, and it is not sufficient to defeat the motion for summary judgment." In response to Roche's argument that the 150 mg once monthly dose gave results that were superior to a 2.5 mg daily dose, the court found that Roche had "pointed to no evidence in support of [its] claim that the skilled artisan would have been surprised that the 150 mg once-monthly dose was superior to the 2.5 mg daily dose." The court refused to consider contentions, raised at oral argument, that the 150 mg dose had a superior and unexpected level of bioavailability, because Roche had not raised that argument in its opposition brief.

Pursuant to Federal Rule of Civil Procedure 56(f) the court then raised, on its own motion, the issue of summary judgment of invalidity of claims 1-10 of the '957 patent. After considering the parties' submissions, the court held those claims invalid for the same reasons that applied to the claims of the '634 patent. Roche argued that it was unexpected that an intermittent ibandronate regimen would be effective in reducing fractures. But the court concluded that the evidence on which Roche relied failed to show that a person of skill in the art would not have had a reasonable expectation that the patented method would succeed in reducing fractures. The court explained that "empirical confirmation that a method for

increasing bone mineral density helps increase bone strength enough that bones break less easily would not appear to be all that surprising."

In its motion for reconsideration, Roche argued that the district court had improperly failed to consider evidence that the 150 mg dose of ibandronate showed an unexpected level of bioavailability as compared with lower doses. On the merits of that argument, the district court found that the "evidence that the 150mg dosage was absorbed better by the body simply has no relevance to the core finding that the difference between the 150mg dose and the prior art was small" and that there was a reasonable expectation of success with the 150 mg dose.

Roche timely appealed the grants of summary judgment of obviousness.

III

The issue in this case is whether it would have been obvious at the time of invention to select a once monthly oral dosing regimen of ibandronate to treat osteoporosis and to set that dose at 150 mg.

A. Monthly Dosing

1. A relatively infrequent dosing schedule has long been viewed as a potential solution to the problem of patient compliance stemming from the inconvenience of oral bisphosphonate regimens. Fosamax®, a prior art bisphosphonate product sold by Merck & Co., was administered weekly, and several prior art references taught once monthly oral dosing of ibandronate or other bisphosphonates.

First, an article in the trade journal Lunar News entitled *Update: Bisphosphonates* ("Lunar News") stated that "[r]esearchers are seeking solutions for better compliance," including approaches that "use bisphosphonates with high potency yet low irritability, such as . . . iband-

ronate (Roche). Oral agents could be given intermittently (once/month, for example) and still be quite potent." Second, a 2001 article by Carey Krause in Chemical Market Reporter ("Krause") disclosed that Roche would likely seek FDA approval of an "oral once-monthly" formulation of ibandronate in 2003. Finally, United States Patent No. 6,468,559 ("Chen") disclosed coated-dosage forms of bisphosphonic acids and methods for orally administering those dosage forms. Ibandronic acid was identified as one of many known bisphosphonic acids. Chen disclosed a preferred embodiment in which "a dosage form of the invention is administered to a patient . . . preferably once a month." Lunar News, Krause, and Chen therefore specifically taught the monthly administration of ibandronate.

Similarly, the prior art contained references to the monthly oral administration of bisphosphonates in general. United States Patent Application No. 2003/0118634 ("Schofield") taught dosing of "bone-active phosponate[s]" and referred to equivalent doses that "can be given every other day, twice a week, weekly, biweekly or monthly." United States Patent No. 5,616,560 ("Geddes") disclosed a bisphosphonate administration regimen in which "said bisphosphonate is administered at least 1 day of every said thirty(30)-day treatment period."

2. Roche argues that the art taught away from once monthly dosing because, according to Roche, it was widely believed as of the date of invention that a bisphosphonate regimen with a dose-free interval longer than one or two weeks would not be effective. To support that contention, Roche primarily relies on the alleged failure of its intravenous ibandronate study ("Recker") to demonstrate antifracture efficacy with quarterly dosing. Secondarily, Roche relies on a prior art article by Thomas Schnitzer ("Schnitzer") speculating that the failure of the Recker study was due to the long dose-free interval.

The Recker study, however, showed a 26% reduction in vertebral fractures with intravenous ibandronate administered once every three months. The study was a "failure" only in the sense that the 26% reduction was statistically insignificant given the large number of patients that would have been required to reach a statistically significant conclusion about the relative rates of fractures in the control and subject groups. With respect to the reduction of hip fractures, for example, Recker concluded that "a meaningful conclusion with regard to efficacy could not be made owing to the low absolute number of hip fractures." Recker's failure to generate statistically significant results points to a fault in the study; it does not teach that infrequent ibandronate dosing is ineffective in treating osteoporosis.

The prior art references that interpreted Recker's results demonstrate only that it was unknown why Recker was unsuccessful in demonstrating statistically significant antifracture efficacy. Schnitzer speculated that the long drug-free interval was to blame for the inconclusive results and that dosing intervals longer than one or two weeks would be ineffective. On the other hand, an article by Dr. Dennis Black ("Black") described speculation that the doses used in Recker were too low. In fact, Roche itself subsequently acknowledged that the Recker study was underdosed. Thus, Schnitzer's speculation did not amount to an affirmative teaching away from monthly oral dosing of ibandronate, especially in the face of Black's competing explanation of the Recker results.

Any doubt about the efficacy of oral ibandronate dosing that may have been created by Schnitzer's speculation was put to rest by an article published in 2001 by Riis et al. entitled *Ibandronate: A Comparison of Oral Daily Dosing Versus Intermittent Dosing in Postmenopausal Osteoporosis* ("Riis"). Riis demonstrated that "intermittent ibandronate is as effective as the continuous treatment in terms of significantly increasing BMD at the

spine and hip and suppressing markers of bone turnover." Riis showed that increases in BMD equivalent to those obtained with a 2.5 mg per day treatment regimen were obtained with a regimen of 20 mg of ibandronate every other day for the first 24 days of every three-month period. Those results, Riis concluded, "confirm[ed] preclinical data showing that it is the total dose over a predefined period and not the dosing regimens that is the determining factor for effect on bone mass and architecture after ibandronate treatment." Riis's teaching that a dose-free interval of more than two months did not impact the BMD efficacy of ibandronate was directly contrary to Schnitzer's speculation that such a dosing regimen would not be effective. Therefore, even if Schnitzer's interpretation of the Recker study were viewed as teaching away from monthly dosing, Riis's contrary findings substantially undermined that interpretation.

Roche argues that Riis did not overcome Schnitzer's interpretation because Riis was not an antifracture trial. Roche argues that prior art focusing only on BMD and bone-turnover improvements, instead of on antifracture efficacy, does not bear on the obviousness analysis in this case because such prior art does not establish a reasonable expectation of success in reducing fracture risk.

While it is true that BMD improvements do not perfectly correlate with antifracture efficacy, it was well established in the art that BMD is a powerful surrogate for measuring fracture risk. For example, Roche's own expert explained:

> Bone mineral density is directly related to fracture risk. It is one of the most powerful surrogate markers in the field of medicine. It is as powerful an indicator of osteoporosis as blood pressure is a predictor of stroke. For every standard deviation reduction in bone mineral density, fracture risk is doubled.

Roche's patents do not themselves present data demonstrating antifracture efficacy for a once monthly 150 mg dose. In fact, antifracture efficacy for Boniva® was demonstrated to the FDA through a "bridging study" that used BMD and bone turnover results—not antifracture testing—to establish the therapeutic noninferiority of the 150 mg monthly dose relative to the previously approved 2.5 mg daily dose, for which antifracture efficacy had been demonstrated.

Conclusive proof of efficacy is not necessary to show obviousness. All that is required is a reasonable expectation of success. *See PharmaStem Therapeutics, Inc. v. ViaCell, Inc.,* 491 F.3d 1342, 1363-64 (Fed. Cir. 2007); *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). Riis—along with other prior art that used BMD improvement as the primary efficacy marker for treating osteoporosis—established at least a reasonable expectation that once monthly dosing of ibandronate could successfully treat osteoporosis and reduce fracture risk.

B. Selecting the 150 mg Dose

1. Riis confirmed the total-dose concept whereby "the efficacy of ibandronate depends on the total oral dose given rather than on the dosing schedule." Riis therefore teaches that in setting the dosage level for an intermittent ibandronate regimen, one need only scale up a known-effective dose from a short-interval regimen—e.g., daily dosing—to achieve approximately the same BMD and bone-loss efficacy with a long-interval regimen.

The prior art provided substantial guidance as to the total dose, within a given time period, that would produce effective results. A 1996 article by Ravn et al. ("Ravn") reported the results of a study that measured BMD improvements and bone-turnover markers for daily ibandronate doses of 0.25 mg, 0.5 mg, 1.0 mg, 2.5 mg, and 5 mg. The authors concluded that the "average change in bone mass showed positive outcome in all regions in the groups

receiving ibandronate 2.5 and 5.0 mg." The 2.5 mg dose exhibited a response that was "virtually equal" to the 5 mg dose, even though it contained only half the amount of ibandronate. The 2.5 mg dose was thereby deemed the "most effective dose."

A person skilled in the art looking to scale to a monthly dose of oral ibandronate from a known-effective daily dose was thus faced with a very limited set of possibilities: Of the five daily doses tested in Ravn, only the 2.5 and 5 mg doses "showed positive outcome in all regions." Even though the 5 mg dose did not demonstrate greater efficacy than the 2.5 mg dose, it was still deemed an equivalently effective dose so that someone scaling it to a single monthly dose of 150 mg (5 mg/day x 30 days/month) would have anticipated equivalent success in raising BMD and limiting bone turnover, based on Riis.

Additionally, United States Patent No. 6,432,932 ("Daifotis") disclosed weekly doses of ibandronate "from the group consisting of 35 mg, 40 mg, 45 mg, or 50 mg." The 35 mg weekly dose corresponds to the same total dose as a 5 mg daily dose. The total-dose equivalent to 5 mg of ibandronate per day is thus the only dose that appears in both Ravn and Daifotis—suggesting that there was a reasonable expectation of success with the total-dose equivalents of the 5 mg daily dose, i.e., 150 mg per month.

Accordingly, the prior art pointed to a monthly treatment of 150 mg of ibandronate. At the very least, the 150 mg dose was obvious to try: There was a need to solve the problem of patient compliance by looking to less-frequent dosing regimens. And, based on Ravn and Daifotis, in light of Riis's total-dose concept, there were only a "finite number of identified, predictable solutions." *KSR Int'l Co. v. Teleflex*, 550 U.S. 398, 421 (2007).

2. Roche contends that findings by the FDA taught away from further development of the 5 mg daily dose (and its total-dose equivalents) because the FDA approved

a 2.5 mg daily dose of ibandronate instead of a 5 mg daily dose. But the FDA never made any findings contrary to the 5 mg daily dose, because it was never asked to approve that dose. Instead, in approving the 2.5 mg daily dose, the FDA merely restated the results of Ravn and concluded that "the 2.5 mg daily dose of ibandronate has the most favorable benefit – risk ratio and is the most appropriate dose for the prevention and treatment of postmenopausal osteoporosis."

Roche next contends that Schofield taught away from using anything other than the lowest effective dose of a bisphosphonate, which, according to Roche, was established by Ravn to be 2.5 mg for ibandronate. Schofield, however, does not teach that the lowest effective dose is the only dose that should be used when treating osteoporosis with a bisphosphonate. Instead, Schofield merely defined the lowest effective dose as a measure of a drug's potency relative to its therapeutic effects. Schofield then described a preferred embodiment of a method for treating bone disorders in which the maintenance dose of a "bone-active phosphonate" ranged from 2.5 to 15 mg per day. That range clearly encompasses more than just a lowest effective dose. Moreover, Ravn never purported to establish a lowest effective dose. Instead, it sought to establish a "most effective [daily] dose."

Roche argues that the district court misinterpreted and misapplied the total-dose concept from Riis. According to Roche, the district court "took a technical leap" in finding that Riis's total-dose concept implied only simple multiplication to scale from an efficacious daily dose to a monthly dose. The evidence before the district court, however, showed that the total-dose concept can be used as an effective rule of thumb by a person skilled in the art deciding how to scale to an efficacious intermittent dose of ibandronate. The Riis study, in particular, established that the total dose concept can reliably predict that the efficacy of an ibandronate treatment depends on the total

dose administered to a patient over a given period, not on the amount administered at any single point in time. In light of that evidence, it was reasonable to expect that a once monthly dose of 150 mg would have roughly the same efficacy as a daily dose of 5 mg.

C. Safety of the 150 mg Dose

Roche next contends that there are disputed issues of fact as to whether it would have been obvious to administer once monthly doses of 150 mg in light of alleged safety concerns about the adverse gastrointestinal effects of ibandronate and other bisphosphonates.

First, Roche argues that Ravn taught away from further development of the 5 mg daily dose, and thereby its total-dose equivalents, because Ravn taught that the 2.5 mg daily dose was more effective than the 5 mg daily dose and had fewer side effects. Ravn, however, concluded that "the responses in the groups receiving 2.5 and 5 mg ibandronate were virtually equal," not that the 2.5 mg dose was more effective. And although patients on the 5 mg daily dose dropped out of the study at a higher rate than patients on lower doses, Ravn did not conclude that the higher drop-out rate was statistically significant. Instead, the authors merely noted that a higher frequency of diarrhea was experienced with the 5 mg dose. A higher frequency of diarrhea does not necessarily teach away from the 5 mg daily dose or its equivalents, however, as the prior art indicated that modest gastrointestinal side effects must be weighed in light of the benefits of the drug. Indeed, Ravn itself concluded that "[i]n the present study, the side effect profile of ibandronate seemed to be safe" and that "[i]n general, the safety evaluation did not reveal any differences between ibandronate and placebo treated groups."

Moreover, even if the higher incidence of diarrhea and the larger number of dropouts in the Ravn study were initially enough to teach away from further development

of the 5 mg daily dose and its total dose equivalents, any such teaching away would have been overcome by Riis's finding that an oral administration of 20 mg of ibandronate every other day for 24 days, followed by a nine-week rest phase, resulted in the same rate of side effects as a 2.5 mg daily regimen.

Aside from Ravn, Roche does not point to any references suggesting that there were safety concerns associated with the 150 mg dose. Nor was Roche's expert, Dr. Harris, aware of anything that taught that a once monthly, 150 mg dose of ibandronate would be unsafe.

To the contrary, the prior art establishes that doses even higher than 150 mg were considered safe. United States Patent No. 6,143,326 ("Möckel") stated that rapid-release ibandronate formulations showed "no significant side effects . . . in clinical studies using ibandronate even at high dosages" and disclosed single-dose units up to 250 mg. Defendants' expert, Dr. Yates, testified that the disclosures in Möckel would have led a person of ordinary skill in the art to understand that ibandronate doses up to 250 mg would be well tolerated. Likewise, Daifotis disclosed that "[f]or human oral compositions comprising ibandronate . . . a unit dosage typically comprises from about 3.5 mg to about 200 mg of the ibandronate compound."

There is thus no genuine issue of fact concerning whether the prior art taught away from the 150 mg dose based on safety concerns.

D. Unexpected Results

Roche argues that the district court erred by granting summary judgment of obviousness because the evidence of record showed that the 150 mg monthly dose was more effective than the 2.5 mg daily dose and that the superior effectiveness of the 150 mg monthly dose was unexpected. Roche also contends that ibandronate's nonlinear bioa-

vailability at the 150 mg dosage level was an unexpected result.

Roche's MOBILE study, published in 2005, demonstrated that a 150 mg monthly dose is more effective than a 2.5 mg daily dose with respect to BMD improvement in the lumbar spine and most hip sites. The MOBILE study demonstrated, for example, a mean BMD improvement in the lumbar spine of 4.9% after one year for patients taking the 150 mg monthly dose and 3.9% after one year for patients taking the 2.5 mg daily dose. Another study published in 2005 showed that the extent of ibandronate's bioavailability is nonlinear with increasing dosages: Increasing the oral dose by 50 percent, from 100 mg to 150 mg, resulted in a nearly 150 percent increase in the amount of the drug absorbed by the blood.

While the evidence would support a finding of superior efficacy of the 150 mg monthly dose in raising BMD levels, as compared to a 2.5 mg daily dose, that improved efficacy does not rebut the strong showing that the prior art disclosed monthly dosing and that there was a reason to set that dose at 150 mg. *See In re Merck & Co.*, 800 F.2d 1091, 1099 (Fed. Cir. 1986). The evidence of superior efficacy does nothing to undercut the showing that there was a reasonable expectation of success with the 150 mg monthly dose, even if the level of success may have turned out to be somewhat greater than would have been expected.

For the same reasons, the nonlinear bioavailability of ibandronate does not rebut the *prima facie* showing of obviousness of a once monthly dose of 150 mg. The increased level of bioavailability has not been shown to be responsible for the improved osteoporosis treatment efficacy of the 150 mg dose. A study by Ravn et al. in 2002 showed, for example, that a near doubling of the blood-serum concentration of ibandronate with a 5 mg daily dose, compared to a 2.5 mg daily dose, produced no

further BMD increase and no further reduction in bone turnover. Other record evidence confirms that "[d]ue to strong binding to the bone surface, the effects of the systemically available amount of a bisphosphonate are almost exclusively related to its concentration in bone rather than [blood] serum level." The evidence regarding bioavailability is therefore of little relevance to the obviousness inquiry.

Accordingly, we uphold the judgment of the district court that claims 1-8 of the '634 patent and claims 1-10 of the '957 patent would have been obvious in light of the prior art and are therefore invalid.

AFFIRMED

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NEWMAN, *Circuit Judge*, dissenting.

Hoffmann-LaRoche's once-a-month Boniva® ibandronate medication for osteoporosis required twelve years of research and clinical testing and evaluation to demonstrate its efficacy when dosed once a month and its safety at this high monthly dosage. The prior investigations of intermittent dosing, and the publications describing protocols of lesser success, missed the protocol that produced this successful method. Indeed, this prior art weighs heavily against obviousness, for despite extensive exploration, this successful protocol was not discovered.

Invalidation of this patent is not supported by clear and convincing evidence. The court's ruling of obviousness violates the principles of *Graham v. John Deere Co.*, 383 U.S. 1 (1966) (all factors must be considered, including commercial success, failure of others, and long-felt need). The court's reasoning violates the guidance of *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007) (the

standard of obvious-to-try requires a limited number of specified alternatives offering a likelihood of success in light of the prior art and common sense), this court instead invoking judicial hindsight to reconstruct the patented subject matter.

Nowhere amid the many studies of bisphosphonate osteoporosis treatments over a wide range of dosages and conditions, did any reference show or suggest the Boniva® combination of a single 150 mg dose and once-a-month administration. No reference suggested the effectiveness and safety of this combination. Nonetheless, my colleagues declare this treatment obvious to them. My colleagues' primary reason, that 150 mg is thirty times the daily dose of 5 mg, does not mention that the FDA refused to approve the 5 mg dose due to its toxic side effects. Surely this leads away from the obviousness of a single dose thirty times larger.

I respectfully dissent.

DISCUSSION

The unexpected results of the patented method are conceded by the panel majority. The evidence on summary judgment was that many others sought and failed to find an efficacious intermittent treatment schedule. The prior art relied on by my colleagues surrounded but missed the Roche method. The prior art shows that safety is likely to be compromised at high doses, and that efficacy is likely to be compromised at extended dosing intervals. Nonetheless, this court now holds that it was obvious to do what no one did or even suggested; my colleagues simply disregard the preferences and toxicity warnings and discard the procedures of the prior art.

The prior art shows intermittent therapies ranging from every other day to once a week to twice a week to twice a month to every three months plus varying initial loading periods, in a wide range of dosages. The prior art

is replete with warnings of toxicity and patient non-compliance. The panel majority acknowledges that Roche's MOBILE study and the nonlinear bioavailability data (discussed *infra*) demonstrate that the 150 mg monthly treatment produced unexpected results, but deems this irrelevant; the court now, with knowledge of Roche's success, deems Roche's successful method to have been obvious all along.

The Supreme Court recognized in *KSR* that a patent challenger must "identify a reason that would have prompted a person of ordinary skill in the relevant field" to arrive at the patented invention. 550 U.S. at 418. My colleagues, unable to find any suggestion of the Roche protocol in the prior art, accept the argument that a monthly single dose of 150 mg was obvious because a monthly dose of 150 mg is thirty times a daily dose of 5 mg. The FDA had refused to approve a daily dose of 5 mg due to its demonstrated heightened toxicity. The success of a dose thirty times larger than the prohibited 5 mg dose cannot reasonably be predicted. Neither the prior art, nor common sense, provides the expectation that a once-a-month treatment at a dosage of 150 mg would be safe and effective.

A. The Prior Art

1. The Möckel Patent

My colleagues combine many references to support their ruling of obviousness. They cite the Möckel patent[1] for the proposition that single doses of more than 150 mg were "known." Möckel is directed to coated tablet formulations, not the concentration of active ingredients. Möckel provides specific examples of ibandronate tablets containing a maximum dose of 50 mg, states that the preferred upper limit is 100 mg, and that the formula-

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[1] U.S. Patent No. 6,143,326 (filed Apr. 1, 1997).

tions could contain up to about 250 mg. Möckel shows no formulated dose larger than 50 mg, although the reference contains the usual expansive statements of the patent scrivener.

Möckel states that "no significant side effects were observed in clinical studies using ibandronate at high dosages," but does not state that "high" exceeds his preferred upper limit, for at that time the FDA had determined that "[a] single oral dose of 100 mg is the maximum tolerable dose of ibandronate." J.A. 8558. Yet my colleagues rely on this reference as rendering obvious Roche's specific once-a-month dosage of 150 mg.

2. Lunar News

Other references also show that the field was seeking a better bisphosphonate protocol, and that the problems were not solved. The Lunar News article,[2] on which the panel majority places heavy reliance, broadly states that some osteoporosis agents can be given intermittently. However it never directly associates ibandronate with oral therapy. Instead, the Lunar News article states the then-current wisdom that "[t]he projected mode for ibandronate is injection once every three months." J.A. 24321. Contrary to the panel majority, this article supports unobviousness of the Roche therapy, not obviousness.

3. The Chen Patent

The Chen patent[3] is similarly inapt. Chen sought to minimize the adverse effects associated with bisphosphonic acids by combining the bisphosphonic acid with a carrier that acts as a dispersing medium for the active agent. Chen lists all of the known bisphosphonic acids,

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[2] *Update: Bisphosphonates*, LUNAR NEWS, Spring, 27–29 (1999).

[3] U.S. Patent No. 6,468,559 (filed Apr. 28, 2000).

and states that oral dosages may be administered anywhere between once every two weeks and once every twelve weeks, with the optimal frequency of once every twelve weeks. Chen does not provide any example using ibandronate, and does not suggest a specific dosage or dosage interval for any ibandronate-containing product. Nor does Chen state what parameters may lead to a successful regimen.

4. The Geddes Patent

The other references on which my colleagues rely are no more helpful to their conclusion. The Geddes patent[4] is directed to a combination therapy of a bisphosphonate compound and a hormone, and states that the bisphosphonate may be dosed from every day to once a month. Geddes does not mention ibandronate or the dosage or suggest that it may be effective at 150 mg once a month.

5. The Schofield Patent Application

The Schofield application,[5] on which the court also relies, describes a treatment regimen featuring a front-end "loading period" of 7 to 180 days, followed by a maintenance dose. The loading dose of bisphosphonate may be given daily or every other day, while the maintenance dose may be given anywhere from daily to monthly. Schofield further states that the loading dose is about two to twenty times greater than the maintenance dose. Schofield mentions ibandronate as a possible active agent appropriate for use in its methods, but provides no dosages or specified periods for ibandronate.

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[4] U.S. Patent No. 5,616,560 (filed Mar. 20, 1996).

[5] U.S. Patent Application Pub. No. 2003/0118634 (filed Dec. 17, 2002).

6. The Riis Article

Several references address intermittent treatment, but none suggests once-monthly administration of 150 mg of oral ibandronate. The court relies on the Riis article,[6] which shows dosing patients with 20 mg of ibandronate every other day for twenty-four days, followed by a 9-week period of no treatment, then returning to 20 mg every other day for twenty-four days, and a 9-week period of no treatment, etc. The court characterizes this as definitive proof of the "total dosing concept." However, Riis makes no suggestion that the once-a-month dosing at the high dosage used by Roche could replace Riis' elaborate procedure.

Riis illustrates the general belief that some sort of complex dosing is needed if daily doses are supplanted. The simplicity of the Boniva® regimen is nowhere to be found, although the need for a better regimen was well recognized. *See Graham*, 383 U.S. at 18 (objective evidence of nonobviousness includes long-felt need and failure of others). Riis contains no suggestion that a once-monthly dosage of 150 mg would be both safe and effective–this became known only after Roche discovered it.

7. The Recker Study

By comparison, the Recker article,[7] which sets forth in its introduction the state of the art in 2004, states that "oral bisphosphonates must be administered frequently

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[6] BJ Riis et al., *Ibandronate: A Comparison of Oral Daily Dosing Versus Intermittent Dosing in Postmenopausal Osteoporosis*, 16 J. BONE MIN. RES., 10, 1871–78 (1997).

[7] R. Recker et al., *Insufficiently Dosed Intravenous Ibandronate Injections are Associated with Suboptimal Antifracture Efficacy in Postmenopausal Osteoporosis*, 34 BONE 890 (2004).

(e.g., daily or weekly)" and in accordance with "stringent dosing recommendations."

Only this court reads the prior art to suggest and render obvious that which eluded the art at the time.

8. The Ravn Study

The court attempts to overcome the shortcomings of the prior art by applying the total dose concept of Riis to the dosage ranges in the Ravn[8] reference. Ravn tested daily treatment using a range of dosages and concluded that 2.5 mg per day is the most effective dose. Yet the court selects Ravn's 5.0 mg dose, despite its increased toxicity and Ravn's preference for the lower dose, to scale up to Roche's 150 mg dose. Ravn does not suggest a once-monthly dose of 150 mg.

It is also noteworthy that the Riis publication, which is later in time than Ravn, selected the 2.5 mg dosage, not the 5.0 mg dosage, as a framework for intermittent dosing.

9. The Daifotis Patent

The panel majority also cites a patent issued to Roche's expert Dr. Daifotis[9] as evidence of obviousness of monthly oral dosing. Dr. Daifotis described dosing schedules ranging from twice a week to twice a month, and recommended once-a-week dosing of 7 mg to 100 mg, with a preferred range of 35 mg to 50 mg per week. Daifotis does not show or suggest any monthly dosage, or that

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[8] P. Ravn et al., *The Effect of Bone Mass and Bone Markers of Different Doses of Ibandronate: A New Bisphosphonate for Prevention and Treatment of Postmenopausal Osteoporosis: A 1-Year Randomized, Double-Blind, Placebo-Controlled Dose-Finding Study*, 15 BONE 527–33 (1996).

[9] U.S. Patent No. 6,432,932 (filed Sep. 2, 1999).

monthly dosing might be effective. Nonetheless the panel majority selects the Daifotis 35 mg per week dosage, calculates that 35 mg times 4 weeks is about 150 mg per month, and combines this calculation with Riis and Ravn to find obvious the Roche combination of dosage and schedule.

B. The Bioavailability Explanation

My colleagues agree that the results achieved with the Boniva® product were not suggested or predicted. In her expert report Dr. Daifotis discussed the scientific basis that had later been found to explain the successful treatment obtained with this protocol. Dr. Daifotis presented a published scientific article by Reginster[10] et al. showing the disproportionate uptake of ibandronate into the blood stream, an unpredicted and unusual result. Dr. Daifotis testified that this explains the unexpected efficacy of Roche's 150 mg dose. The record contains the following graphical portrayal, where the mean area under the curve (AUC) indicates the average concentration of ibandronate in the blood:

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[10] Jean-Yves Reginster et al., *Monthly Oral Ibandronate is Well-Tolerated and Efficacious in Postmenopausal Women: Results From the Monthly Oral Pilot Study*, 90 J. OF CLIN. ENDOCRIN. & METAB. 5018–24 (2005).

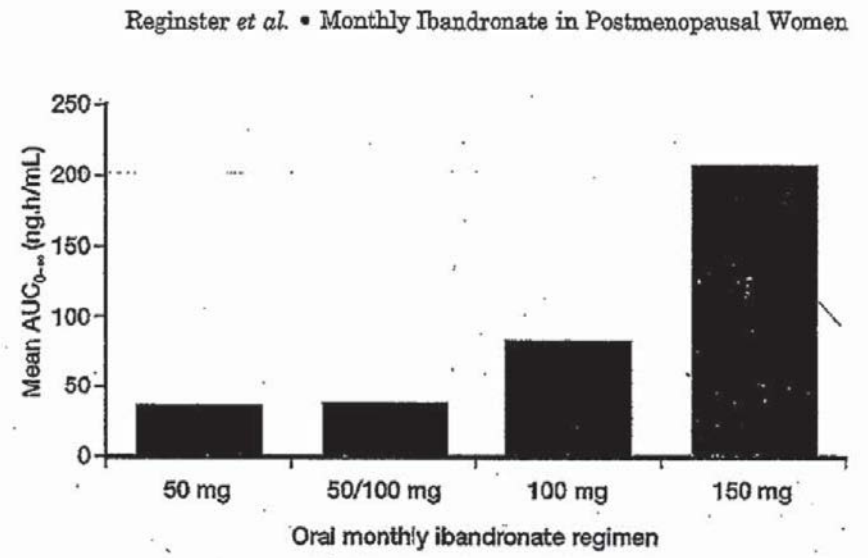

FIG. 3. Mean $AUC_{0-\infty}$ for monthly oral ibandronate in serum (initial dose only).

Dr. Daifotis explained that "[t]his was a surprising finding concerning the disproportionate amount of ibandronate that becomes available from oral administration of amounts above about 50 mg, and it was unknown as of May 2002." J.A. 20726–27 ¶108. Dr. Daifotis explained that "[t]he benefit of this surprising result was that a patient could receive higher than thought possible amounts of active drug to be available to inhibit osteoclasts, while at the time not adversely affecting the safety profile of a 150 mg dose of ibandronate." J.A. 20732 ¶115.

Dr. Daifotis also cited clinical trial data showing that a 150 mg monthly dose of ibandronate is superior at increasing bone density in the lumbar spine of postmenopausal women, as compared to 100 mg given once a month, 50 mg given on two consecutive days in a single month (50/50) and a 2.5 mg daily dose.

The record contains other scientific articles, *e.g.*, Paul D. Miller et al., *Monthly Oral Ibandronate Therapy in*

Postmenopausal Osteoporosis: 1-Year from the Mobile Study, 20 J. BONE MINER. RES. 1315–22 (2005). Nothing in the prior art renders the result expected, predicted, or obvious.

C. Expert Testimony

Also of record were the reports of Roche's experts Dr. Bilezikian and Dr. Harris. Roche explained that each opines that, at the time of the inventions, a person skilled in the art would not have had any reasonable expectation of succeeding with a safe, effective, and well-tolerated once-monthly oral dosage of ibandronate in an amount as large as 150 mg.

The trier of fact is "require[ed to] consider all evidence relating to obviousness before finding a patent invalid on those grounds." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1075 (Fed. Cir. 2012). It is noteworthy that although the generic producers who are defendants herein also presented expert reports, no expert provided anything other than a personal opinion that the Roche discovery was obvious.

The evidence of long-felt need, failure of others, and commercial success was unrebutted, and no adverse expert provided any evidence from which the success of the Boniva® product could be confidently predicted. Their only argument was that it would have been "obvious to try" the Roche method. Of course, it is possible to speculate about all sorts of treatment schedules, as in the Krause newsletter,[11] but speculation without specificity and a plan for achieving a reasonable likelihood of success does not provide clear and convincing evidence of obviousness on the ground of "obvious to try."

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[11] Carey Krause, *Roche, GlaxoSmithKline in Drug Pact*, Chem. Market Reporter, December 17, 2001.

D. Obvious to Try

For an invention to be obvious to try, there must be a finite number of known choices in the prior art, and a reasonable expectation of success for the choice that is tried. *KSR,* 550 U.S. at 421. Obvious to try cannot be found when the prior art gives no hint that a specific trial might achieve the desired result. *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009) (quoting *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)). Dr. Daifotis testified, "monthly oral dosing of alendronate was not seen as a feasible or desirable endeavor for investigation; if it had been, we would have explored it." J.A. 20717.

The law of "obvious to try" requires that there be a limited number of defined alternatives and a suggestion that the desired result is likely to be achieved through the proposed trial. The Court stated:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

KSR, 550 U.S. at 421. Here, however, even my colleagues agree that the result was unpredicted, and that there was no suggestion in the prior art, or in common sense, that this procedure might produce the sought-after result. Nonetheless, my colleagues invalidate the successful treatment as "obvious to try."

The extensive experimentation with other regimens and dosages demonstrates that this selection was not obvious to try. The failure to meet this long-felt need weighs heavily against my colleagues' finding that the Roche protocol, although not obvious to investigators in

the field, is obvious to this court. As stated in *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995), "[t]he basic principle behind this rule is straightforward—that which would have been surprising to a person of ordinary skill in the particular art would not have been obvious." As established in *KSR*, absent limited alternatives and some direction toward the successful path, "obvious to try" is not applicable.

The prior art does not suggest the Roche protocol, or that it might have a reasonable expectation of success. Only with knowledge of Roche's success, can one reconstruct that which is not suggested in the prior art. If anything, the large amount of study and publication adds to the uncertainty, for it provides no direction for potential success. The court's holding today will simply discourage improvements in crowded fields, by holding that even if such investigation should succeed, a patent is not available.

From my colleagues' invalidation of the patent on this significant medical advance, I respectfully dissent.