No. 17-290

IN THE

Supreme Court of the United States

MERCK SHARP & DOHME CORP.,
Petitioner,

v.

DORIS ALBRECHT, ET AL.,
Respondents.

On Writ of Certiorari to
the United States Court of Appeals
for the Third Circuit

BRIEF OF *AMICI CURIAE* JOSEPH LANE, M.D., AND VINCENT VIGORITA, M.D., IN SUPPORT OF RESPONDENTS

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INTEREST OF *AMICI CURIAE* AND SUMMARY OF ARGUMENT[1]

An improper understanding of osteology frames Petitioner's bid for legal immunity. Petitioner claims that the language it proposed to warn of stress fractures would also have warned of atypical femur fractures associated with long-term use of the osteoporosis drug Fosamax (a bisphosphonate). Petitioner thus argues that it is clear FDA would have rejected a label change that would have warned of atypical femur fractures because FDA declined to approve a proposed label change concerning stress factures.

That legal argument misconceives medical science. Stress fractures are radiographically and symptomatically different from atypical femur fractures associated with long-term use of Fosamax. The particular language Petitioner proposed in a Prior Approval Supplement (PAS) to warn of "stress fractures"—an incomplete fracture that generally presents in non-bisphosphonate patients and typically heals on its own—cannot reasonably be read to warn of atypical femur fractures—a complete break in the bone that is associated with long-term use of Fosamax, and that requires surgery.

Amici curiae are physicians with expertise in metabolic bone disorders, other bone diseases, and the pathology of bone diseases. *Amici* have a strong interest in this case because legal immunity from failure-to-

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[1] No counsel for a party authored this brief in whole or in part and no person other than *amicus* and its counsel made a monetary contribution to its preparation or submission. The parties' letters consenting to the filing of *amicus* briefs are on file with the Clerk.

warn liability may turn on a proper understanding of osteology.

Joseph Lane, M.D., received his undergraduate degree from Columbia College, his medical degree from Harvard Medical School, and undertook his surgical internship and residency at the Hospital of the University of Pennsylvania. Dr. Lane performed bone collagen research at the National Institutes of Health (NIH) from 1967 to 1969. In 1975, Dr. Lane was appointed Assistant Professor and Chief of the Metabolic Bone Disease Service at the Hospital for Special Surgery of Cornell Medical School (HSS). HSS is nationally ranked as the number one center for orthopedics by U.S News & World Report.[2] Dr. Lane ultimately attained a full professorship and currently serves as the Medical Director of the Metabolic Bone Disease Service and Osteoporosis Prevention at HSS. Dr. Lane has authored or co-authored over three hundred peer-reviewed articles in areas such as bone biology, tissue injury and repair, trauma, and metabolic bone disease.

Dr. Lane has served on numerous committees for the American Academy of Orthopaedic Surgeons (AAOS), including its Board of Directors and as Chairman of the Council on Musculoskeletal Specialty Societies. Dr. Lane previously served as the President of the Orthopaedic Research Society and as the Chairman of the NIH Orthopaedic Study Section. In 2008, Dr. Lane co-authored the retrospective study from

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[2] https://www.usnews.com/info/blogs/press-room/articles/2018-08-14/us-news-announces-2018-19-best-hospitals

HSS which found that long-term alendronate[3] use resulted in an atypical femur fracture odds ratio of 139.33; more simply, patients taking long-term alendronate had an odds ratio for this unusual fracture pattern which was 139 times higher (13,900%) than those studied patients not taking alendronate. Neviaser, *Low-Energy Femoral Shaft Fractures Associated with Alendronate Use.* 22 J ORTHOP. TRAUMA 346-50 (May-June 2008).[4] In addition to presenting the study's preliminary findings, Dr. Lane and his co-authors published their research in the New England Journal of Medicine in March 2008. Lenart, *Atypical Fractures of the Femoral Diaphysis in Post-Menopausal Women Taking Alendronate*, 358 NEJM 1304-06 (March 2008).[5]

In 2005, three years before that publication, Dr. Lane reported to Petitioner that no fewer than twenty-five HSS patients had suffered from low-energy *atypical* femur fractures. Dr. Lane also told Petitioner that physicians at this hospital call this type of fracture the "Fosamax fracture."[6] In 2008, Dr. Lane served as a consultant to Petitioner during the time when Petitioner was determining how it would prepare the requested drug label change pertaining to reports of fractures in patients taking Petitioner's medication,

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[3] Petitioner's Fosamax is the trade name for the drug alendronate.

[4] JA385-399.

[5] JA661-663.

[6] JA445-449, at 448.

Fosamax.[7] Dr. Lane's reports to Petitioner contributed to the need for Petitioner to provide a warning or precaution to prescribers of Fosamax.

In the spring of 2009, the American Society for Bone and Mineral Research (ASBMR) commissioned a Task Force on Subtrochanteric Fractures. JA97-98 (Burr Decl.¶4); JA283-384 (Shane, *Atypical Subtrochanteric and Diaphyseal Femoral Fractures: Report of a Task Force of the American Society of Bone and Mineral Research*, 25 J BONE MINER RES. 2267-2294 (2010)). Dr. Lane served as a member of the task force. JA283. Its first report was published in September 2010.[8] JA285.

In 2011, HSS presented Dr. Lane with its Lifetime Achievement Award for his innovative research on bone disease and the use of bisphosphonates in treating osteoporosis and, more specifically, his research which helped identify the association between long-term use of bisphosphonates and the increased risk for certain bone fractures.[9]

Vincent Vigorita, M.D., received his undergraduate degree from Williams College and his Medical Degree from New York Medical College. He performed his internship and residency at The Johns Hopkins Hospital, and his fellowship at the Memorial Sloan Kettering Cancer Center. Dr. Vigorita is Professor Pathology

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[7] JA467-468.

[8] A follow-up report was published in 2014. Dr. Lane was also a co-author of this second report. Shane, *Atypical Subtrochanteric and Diaphyseal Femoral Fractures: Second Report of a Task Force of the American Society of Bone and Mineral Research*. 29 J BONE MINER RES. 1-23 (2014).

[9] https://www.hss.edu/newsroom_joseph-m-lane-lifetime-achievement-award.asp

& Orthopedic Surgery at the State University of New York Health Science Center, Downstate, in Brooklyn, New York. Since 1980, Dr. Vigorita has been a Diplomat of the American Board of Pathology. From 1983 to 1992, Dr. Vigorita was visiting scientist in the division of research at HSS. He has authored or co-authored more than eighty peer-reviewed medical articles pertaining to various aspects of bone disorders and pathology, including articles he co-authored with Dr. Lane on metabolic bone disease (osteoporosis). Dr. Vigorita is the author of the medical textbook *Orthopaedic Pathology*, which is in its Third Edition. In 2010, he was invited to present to the International Skeletal Society on the topic of dysfunctional osteoclast activity and bisphosphonate treatment. In 2012, Dr. Vigorita was the lead author of a peer-reviewed case report pertaining to pathologic features of fractured bone during bisphosphonate therapy. Vigorita, *Osteoclast Abnormalities in Fractured Bone During Bisphosphonate Treatment for Osteoporosis: a Case Report*, 41 SKELETAL RADIOL. 861-65 (2012).

ARGUMENT

I. Petitioner's Proposed Warning of Stress Fractures Did Not Warn of Atypical Femur Fractures.

Dr. Lane's reports to Petitioner, as well as his and others' publications in peer-reviewed medical literature, contributed to the need for Petitioner to provide a precaution to prescribers of Fosamax about atypical femur fractures. In 2005, Dr. Lane told Petitioner that no fewer than twenty-five HSS patients had suffered from low-energy *atypical* femur fractures. Later, in the summer of 2008, Dr. Lane served as a consultant to Petitioner when it was considering adding a warning to address reports of these unusual fractures. JA464-476. Petitioner's own meeting minutes leave little doubt that the fractures reported by Dr. Lane's group were atypical femur fractures, not mere stress fractures. *See* JA468.

In September 2008, Petitioner submitted a PAS proposing to add language to the *Warnings and Precautions* section of Fosamax's label. The proposal emphasized "stress fracture(s)" six times, including in a statement that "stress fractures with similar clinical features also have occurred in patients not treated with bisphosphonate." JA707.

On May 22, 2009, FDA informed Petitioner in writing that it had rejected Petitioner's proposal. JA510-514. Specifically, FDA told Petitioner that "[i]dentification of 'stress fractures' may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature." JA511.

Petitioner's focus on "stress fractures" in proposed labeling would not have conveyed to physicians and patients what Dr. Lane had reported to Petitioner: Fosamax patients were experiencing serious fractures that orthopedic physicians had not previously seen.

A. The femur and fractures: a medical overview.

1. The femur is the thigh bone in the human body. If you have seen a "skull and cross-bones," such as on pirate flag, you have seen a depiction of two thigh bones.

The end of the femur closest to the torso is called "proximal"; and the opposite end most distant from the torso is called "distal." The portion closest to the torso resembles a ball on a neck; we call this the "femoral head." The femoral head joins the pelvis at the socket, or "acetabulum." Together, the femoral head and acetabulum comprise the hip joint.

The portion of the proximal femur which resembles a neck for the head is called the "femoral neck." The neck connects the femoral head to what appears as a hump on the top of the long shaft of the femur. This hump is called the "greater trochanter" on the top end, and the "lesser trochanter" on the bottom end of the hump where it connects to the straight portion of the bone. The term "subtrochanteric" refers to the portions below, which together form the "trochanter."

Viewing the femur a step removed, you see that the head connects to the neck, which connects to the trochanter, which connects to a straight, long shaft of bone. That portion of the bone is called the "diaphysis." It connects to the bulb-looking distal end of the femur through the end of the shaft (the "metaphysis"),

and flares out and connects to the bulbous portions of the end of the bone, the "lateral and medial epicondyles," terminating at the "lateral and medial condyle."

Like most bones, the femur is comprised of the "cortex," or "cortical bone," which is the outer, hard-candy shell of the bone surrounding another type of bone called the "cancellous" or "trabecular" bone. Cancellous bone is a spongy type of bone situated in the interior of the bone; it is the portion of our bones responsible for producing bone marrow. The portion of the bone where the cancellous bone is found is often referred to as the "medullary canal," and surgical approaches which ream out that canal and place hardware are referred to as "intramedullary reaming."

2. Fractures follow different patterns. A "transverse" fracture refers to a fracture that goes across the shaft of the bone; in other words, from one side of the cortical bone, across the medullary canal containing the cancellous bone, and then to the other side of the cortical bone. An "oblique" fracture proceeds across the bone in an angled fashion. A "stress fracture" refers to a hairline crack in which portions of the bone on either side of the crack are not displaced from each other. A "displaced" or "completed" fracture refers to a fracture where two or more fragments of bone are no longer joined to the other fragment.

"Stress fractures" can progress to a displaced or completed fracture. A "traumatic fracture" is one which results from trauma or an exertion of significant force on the bone, and it typically results in a completed or displaced fracture. A "low-energy" fracture,

in contrast, is a fracture that occurs without significant trauma.

B. Petitioner's proposed warning about stress fractures did not accurately convey what it knew about atypical femur fractures.

The FDA was concerned about Petitioner's repeated focus on the term "stress fracture," and rightfully so. The medical literature addressed *atypical* femur fractures that may have started as a simple stress fracture but progressed to something far more serious than a garden-variety stress fracture. But Petitioner chose to craft a warning emphasizing stress fractures and risks associated with stress fractures, even though that language did not reflect the unusual clinical outcomes Fosamax patients were experiencing.

"'Stress fractures,' in the medical community, commonly refers to an *incomplete* fracture of a long bone which is clinically diagnosed by pain in the affected region, an x-ray or MRI showing a periosteal or endosteal reaction, and/or a bone scan showing increased local metabolic activity in the painful region. JA144 (Burr Decl. ¶83) (emphasis added).[10] Because "the vast majority of stress fractures never progress to a full and complete fracture," *id*., a stress fracture is distinguishable from an atypical femur fracture, which results in a *completed* femoral fracture. *See* JA101-02 (Burr Decl. ¶12).[11]

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[10] Dr. David Burr was the Co-Chair of the ASBMR Task Force and served as to the co-editor of the medical textbook entitled Musculoskeletal Fatigue and Stress Fractures (2001). JA144.

[11] The only mention of "stress fracture" in either of Dr. Lane's publications predating Petitioner's PAS noted an atypical femur fracture that was "propagated" from a stress fracture which had

X-rays of stress fractures and atypical femur fractures illustrate these differences. Look first at an image of a stress fracture in a femur:[12]

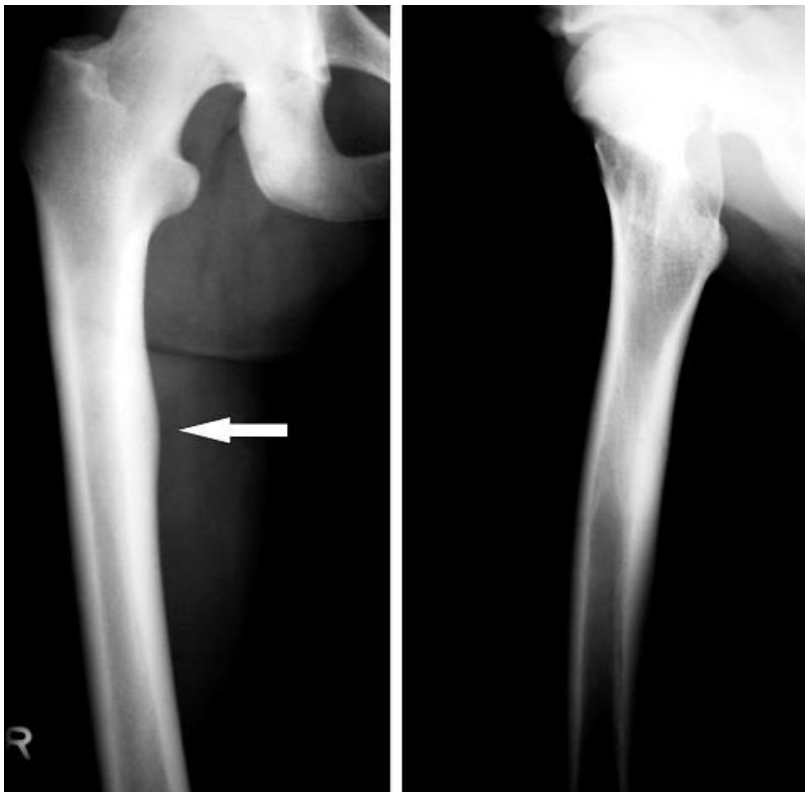

Figure 1 Anteroposterior and lateral roentgenograms showing stress fractures in the proximal third of the right femoral shaft (white arrow).

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failed to heal due to Fosamax. (JA385, 396 (Neviaser, *Low-Energy Femoral Shaft Fractures Associated with Alendronate Use*).

[12] Ivkovic, *Stress Fractures of the Femoral Shaft in Athletes: a New Treatment Algorithm*, 40 BR J SPORTS MED 518-520 (2006), at fig. 1.

Look next at radiographs of atypical femur fractures in three patients:[13]

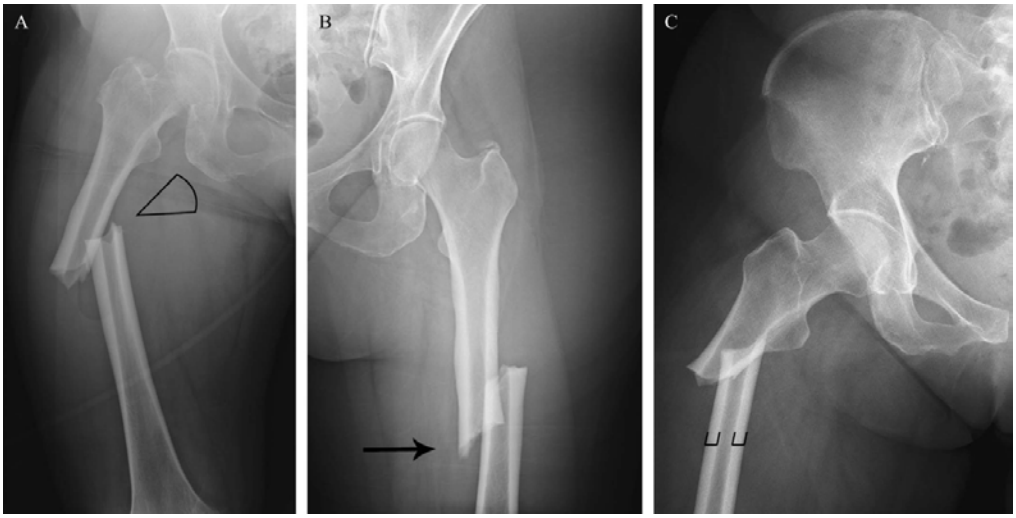

FIGURE 1. Representative radiographs of femoral shaft fractures sustained from minimal trauma in patients taking alendronate. Although each radiograph demonstrates the pattern in its entirety, we have highlighted the following features. A, Fracture pattern pictured with an arch measuring 30 degrees to highlight transverse nature. B, The arrow pointing out the unicortical beak C, Hypertrophied cortices outlined.

In this second set of images, a fracture pattern runs across the bone, and—atypically—involves a thickening (hypertrophy) rather than a thinning of the cortical bone by the fracture sites. JA661-663 (Neviaser, *Low-Energy Femoral Shaft Fractures Associated with Alendronate Use*); JA385, 387-89 396 (Lenart, *Atypical*

[13] Neviaser, *Low-Energy Femoral Shaft Fractures Associated with Alendronate Use,* 22 J ORTHOP TRAUMA 346-50, at fig. 1 (May/June 2008).

Fractures of the Femoral Diaphysis in Post-Menopausal Women Taking Alendronate).

FDA was aware of the Neviaser and Lane article. In June 2008 (*see* JA666-67), FDA emailed Petitioner to say "we are aware of reports" regarding "[t]he subtrochanteric type of hip or femoral fracture" that "is reportedly rare in patients with osteoporosis not on bisphosphonates. We are concerned about this developing safety signal." That email listed five studies, with the Neviaser and Lane study listed first.

Although *amici* and colleagues "identif[ied] a fracture that is specific to patients being treated with alendronate and tends to occur after use of more than 4 years," JA393 (Neviaser, *Low-Energy Femoral Shaft Fractures Associated with Alendronate Use*), Petitioner failed to present FDA with language that warned of such atypical fractures.

FDA acted appropriately when it rejected the language on stress fractures and invited Petitioner to "resubmit" its application after "fully address[ing] all the deficiencies listed." JA512. The term "stress fracture" conveys to the prescriber a fracture which typically can be treated conservatively, meaning, without surgery. Generally, doctors treat stress fractures in patients by prescribing rest or inactivity in the affected bone. Most stress fractures heal without any further intervention and do not progress to a complete fracture. JA144 (Burr Decl. ¶83).

But that is not what the medical community observed in certain Fosamax patients. An atypical femur fracture may start as a stress fracture, but it will not heal on its own (as a stress fracture might). And it progresses to a fully displaced fracture of the femur

(unlike a stress fracture which typically is incomplete).[14]

Once these complete fractures occur, the clinical outcome far exceeds what a patient with just a stress fracture experiences. "Because of the propensity for delayed healing, the morbidity [or medical problems] of these [atypical subtrochanteric and femoral shaft] fractures is particularly high." JA349.

Complete fractures require invasive surgery. An open reduction, internal fixation surgery of an atypical femur fracture involves the physician cutting through the patient's skin, fat, and muscle, and reaming out much of the cancellous bone in the medullary canal. A long rod is then hammered into place in order to reduce the fracture (or bring the bone fragments back into relative alignment). The rod is secured with bone screws. JA350.

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[14] "Low-energy fractures of the femoral shaft with a simple, transverse pattern and hypertrophy of the diaphyseal cortex are associated with alendronate use. This may result from propagation of a stress fracture whose repair is retarded by diminished osteoclast activity and impaired microdamage repair resulting from its prolonged use." JA386 (Neviaser, *Low-Energy Femoral Shaft Fractures Associated with Alendronate Use*).

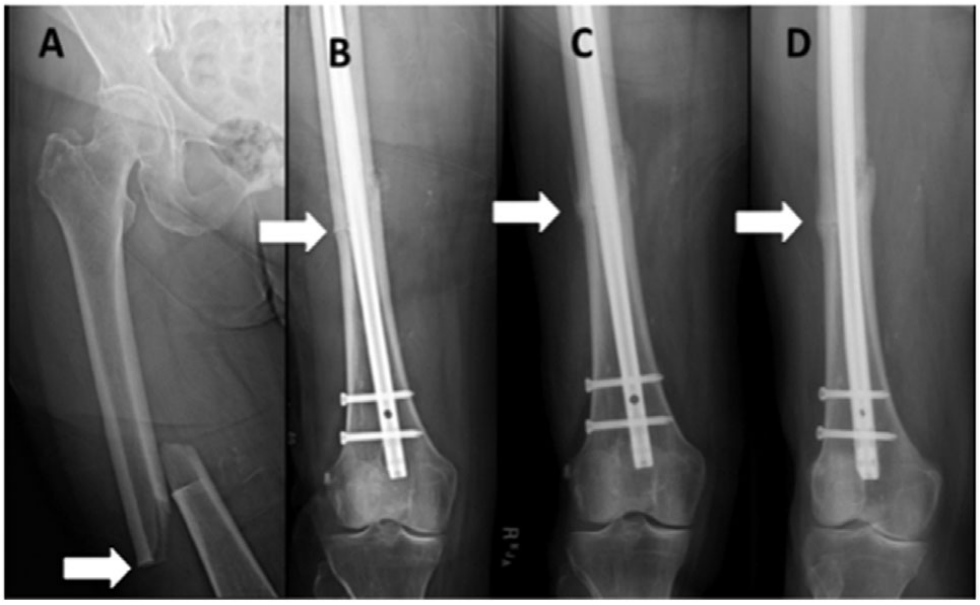

FIGURE 1. Representative radiographs of femoral shaft fractures sustained from minimal trauma in patients taking alendronate. Although each radiograph demonstrates the pattern in its entirety, we have highlighted the following features. A, Fracture pattern pictured with an arch measuring 30 degrees to highlight transverse nature. B, The arrow pointing out the unicortical beak C, Hypertrophied cortices outlined.

The patient typically has this hardware in place for the rest of her life.[15]

This type of clinical result in a patient who has undergone no or minimal initiating trauma is in part what makes these fractures atypical. JA661. *Amici* thus wholeheartedly agree with Dr. Burr: "By choosing to characterize [atypical femur fractures] as 'stress

[15] Shane, *Atypical Subtrochanteric and Diaphyseal Femoral Fractures: Second Report of a Task Force of the American Society of Bone and Mineral Research.* 29 J BONE MINER RES. 1-23, at fig. 1 (2014).

fractures' in its submission to the FDA, Merck improperly conflated the underlying fracture mechanism that leads to [atypical femur fractures] with the ultimate outcome." JA144 (Burr Decl. ¶84).

C. Petitioner's proposed warning failed to identify the association between Fosamax and atypical femoral fractures.

These femoral fractures are also atypical in the sense that orthopedic physicians had not seen these fractures before Fosamax or other bisphosphonate drugs were marketed. JA101-02 (Burr Decl. ¶12).

The incidence of such unique fractures came to the medical community's attention "principally in the setting of [bisphosphonate] use"; by comparison, the "incidence in the general population not exposed to [bisphosphonates] is unknown." JA291 (ASBMR Task Force Report). Atypical femur fractures are observed in Fosamax patients because Fosamax, by design, interferes with the removal of old bone and the replacement of that bone with new bone. The goal of this drug regimen is to preserve bone mineral density. But when the drug is administered to patients for lengthy periods, the bone can become more dense and, at the same time, less resilient to fracture. JA103-109 (Burr Decl., ¶¶15-23). By interfering with the bone turnover process, bisphosphonates can interfere with the healing of non-displaced stress fractures. JA136 (Burr Decl. ¶ 68) ("Fosamax and other BPs reduce the body's ability to repair a stress fracture once it has begun, but prior to complete fracture.").

As early as 2002, Dr. Lane and his colleagues began describing these atypical femoral breaks as "Fosamax fractures;" and they informed Petitioner of this in 2005.

In 2005 and 2007, two published case series "suggested a link between prolonged bisphosphonate therapy and atypical fractures." JA661.[16] And, beginning in 2005, Dr. Lane and his colleagues shared, with Petitioner, their preliminary findings on atypical fractures in Fosamax patients. Their research was ultimately published in 2008 in the New England Journal of Medicine.

"[A]lthough different studies and authors have used slightly different variations on how they describe [atypical femur fractures]," Dr. Burr has concluded (and we agree), "there is, and was before September of 2008, remarkable consistency in the overall description of this unique fracture and its high association in the literature with Fosamax and other bisphosphonates. JA139-140 (Burr Decl. ¶74).

Despite this, Petitioner proposed a warning that these fractures had "similar clinical features" to fractures suffered by non-bisphosphonate patients. *See* JA138. This proposal failed to convey the unique features of these fractures. FDA was thus right to reject Petitioner's proposed warning.

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[16] Goh, *Subtrochanteric Insufficiency Fractures in Patients on Alendronate Therapy: A Caution*, 89-B J BONE AND JOINT SURG 349-53 (2007) (JA400-14); Odvina, *Severely Suppressed Bone Turnover: A Potential Complication of Alendronate Therapy*, 90 J CLIN ENDOCRINOL METAB 1294-1301 (2005) (JA415-444).

D. There is compelling evidence that FDA would have approved a label change that warned of atypical femur fractures associated with Fosamax.

1. Petitioner's description of stress fractures in its July 2008 labeling submission was medically inconsistent with the atypical femur fractures that *amici* and other physicians around the world had observed. In fact, FDA recognized this distinction in rejecting Petitioner's proposal.

FDA indicated that it was aware of the potential for Fosamax to cause atypical femur fractures. On June 13, 2008, an FDA staff member notified Petitioner that FDA was "aware of reports regarding the occurrence of subtrochanteric hip fractures in patients using bisphosphonates." JA666. FDA was referring to five published articles in the medical literature; Dr. Lane's was the first listed. JA667. None of these articles focused on ordinary stress fractures; rather, all described atypical femur fractures associated with Fosamax.

Also on June 13, FDA asked Petitioner to submit "all hip and femoral fracture" reports it had received to date. JA666. Notably, FDA did not seek any information focused specifically on the atypical features seen prominently in patients in the published medical literature. FDA's request did not draw attention to the unique transverse fracture pattern, the absence of trauma associated with the fractures, or the suppressed bone remodeling seen in many atypical femur fracture patients. These omissions suggest FDA did not yet fully understand the nature of atypical femur fractures and was in need of a medically accurate education on the subject.

In late June 2008, Petitioner asked Dr. Lane and other medical experts to discuss the state of knowledge on atypical femur fractures. By that time, Petitioner had amassed a growing number of atypical femur fracture adverse event reports. Indeed, as early as 2005, Dr. Lane had reported "25 patients with long bone fractures that have taken Fosamax … for a long time. He also reported that 100% of patients in his practice who have experienced femoral fractures (without being hit by a taxicab) were taking Fosamax … for over 5 years. At [his] hospital they call it the 'Fosamax Fracture.'" JA126. This June 2008 meeting was held soon after Dr. Lane and his colleagues publicized that long-term Fosamax use resulted in an odds ratio of 139.33 for suffering an atypical femur fracture when compared to patients that had never taken Fosamax. JA385-386 (Neviaser, *Low-Energy Femoral Shaft Fractures Associated with Alendronate Use.* 22 J ORTHOP TRAUMA 346-50 (May/June 2008)).

Petitioner's medical consultants confirmed that the fractures Dr. Lane and others had observed should not have been be characterized as stress fractures, and that instead the observed fractures presented more consistently as insufficiency fractures. JA467-468. The consultants also explained the distinction between, on the one hand, the insufficiency fractures seen in Fosamax patients; and on the other, stress fractures. The consultants advised Petitioner that "insufficiency fractures occur *with normal activity in abnormal bone*." JA467 (emphasis in original). Conversely, "stress fractures may be caused by *increased activity in normal quality bone*." JA467 (emphasis in original). Nevertheless, Petitioner's proposal focused on stress fractures, with the phrase repeated six times. JA707.

2. Petitioner's proposed warning language improperly focused solely on the originating element of the fracture (the stress injury), rather than ultimate outcome (the atypical femur fracture). As such, the proposed language elided critical distinctions between incomplete and complete factures, and the corresponding injury and medical treatment.

Another problem with Petitioner's proposal: It omitted any discussion of the pathogenesis of atypical femur fractures. Language advising of the severity of the break would have distinguished a Fosamax associated fracture from typical osteoporotic fracture.

By September 2008, there was a robust body of medical literature demonstrating that Fosamax significantly suppresses bone remodeling, which severely decreases bone toughness and reduces the body's ability to recover from a stress injury. Rather than provide this information about the pathogenesis of this atypical fracture, Petitioner cautioned the reader of its proposed warning to conduct an "evaluation for known causes and risk factors (*e.g.*, vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse)." JA707. But these risk factors are associated with stress fractures—not atypical femur fractures. *See* JA142 (Burr Decl. ¶ 79)

Further, Petitioner's language failed to document the association of atypical femur fractures with long-term Fosamax use. Reports of atypical femur fractures both before and after September 2008 have generally been seen in patients using the drug for five years or more. This information would have distinguished an atypical femur fracture from a minor stress

fracture, and would have prompted due consideration of the risks and benefits of long-term use of Fosamax.

Still more, Petitioner's proposed language improperly suggested there was an established background rate for atypical femur fractures in patients not exposed to Fosamax. This suggestion was not supported by medical evidence, and it erroneously conflated typical fractures seen in the osteoporotic population with so-called Fosamax fractures.

Lastly, Petitioner made no effort in its proposed language to define atypical features of these fractures. By September 2008, many publications had adequately described atypical femur fractures as being low energy fractures occurring along the femoral shaft or subtrochanteric regions of the femur, with a transverse fracture line, a periosteal reaction, associated with cortical thickening, prodromal pain, and frequently seen bilaterally. But these valuable insights were not reflected in Petitioner's proposed language.

3. There is little doubt Petitioner understood the deficiencies in its proposals. Upon receiving FDA's Complete Response letter, Petitioner's employee James Adams acknowledged that FDA "believed that our justification to support the proposed Precaution text was inadequate. *It believes that 'stress fractures' may not be clearly related to atypical subtrochanteric fractures.*" JA515 (emphasis added). Petitioner's most senior scientist responsible for Fosamax, Dr. Arthur Santora, reacted similarly: "FDA wouldn't let us mention stress fractures." JA517.

Following these exchanges, a task force consisting of 28 individuals formed by the American Society for Bone and Mineral Research met to synthesize the known evidence concerning atypical femur fractures.

JA287. FDA noted, in March 10, 2010, that it was working with this task force to "gather additional information that may provide more insight into this issue." JA519-520. The task force acted quickly to evaluate the existing evidence and ultimately created a list of major and minor features associated with atypical femur fractures. JA292. Importantly, nearly all of the evidence the task force reviewed was equally available to Petitioner when it proposed its labeling update in September 2008. In the end, the task force's report referenced 177 medical journal articles—172 more than had been previously made available to FDA. JA359-384; JA667.

On the same day that the task force published its findings, FDA publicly acknowledged that the case definition for atypical femur fractures created by the task force would "help greatly in identifying cases and reporting on them." JA523. The FDA also indicated it was "considering labeling revisions." JA525.

Less than one month later, FDA issued another public statement on atypical femur fractures. In this statement, FDA announced that information on atypical femur fractures would be added to the *Warnings and Precautions* section of labeling for bisphosphonates, including Fosamax. JA246. FDA's description of atypical femur fractures included detail lacking in Petitioner's earlier proposal.

On October 13, 2010, FDA asked Petitioner to update labeling for Fosamax to include a warning about atypical femur fractures. JA527. In response, Petitioner again proposed warning language that focused heavily on stress fractures and attendant risk factors associated with stress fractures. JA606-607.

FDA rejected aspects of Petitioner's proposal shortly thereafter, on December 16. Critically, the agency deleted *all* references to stress fractures, and *all* references to risk factors associated with stress fractures but not seen with atypical femur fractures. JA606-607. Current labeling for Fosamax makes no reference to stress fractures or risk factors associated with stress fractures.

The agency took this action because, "for most practitioners, the term 'stress fracture' represents a minor fracture and this would contradict the seriousness of the atypical femoral fractures associated with bisphosphonate use. In addition, the risk factors listed in the proposed changes have not been sufficiently validated to include in labeling at this time." JA566.

This would hardly have come as a surprise to Petitioner. After all, FDA had rejected Petitioner's stress-fracture warning of 2008 because its "[i]dentification of 'stress fractures'" and "[d]iscussion of the risk factors for stress fractures" was not supported by the state of medical knowledge at that time (JA511-12)—including as reported in the Neviaser and Lane article. *See* JA666-67.

CONCLUSION

The judgment of the court of appeals should be affirmed.

Respectfully submitted,

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