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

JOINT APPENDIX (VOLUME I OF II)
(Pages 1–399)

DAVID C. FREDERICK
Counsel of Record
KELLOGG, HANSEN, TODD,
FIGEL & FREDERICK, PLLC
1615 M Street, N.W.,
Suite 400
Washington, D.C. 20036
(202) 326-7951
dfrederick@kellogghansen.com

Counsel for Respondents

SHAY DVORETZKY
Counsel of Record
JONES DAY
51 Louisiana Avenue, N.W.
Washington, D.C. 20001
(202) 879-3939
sdvoretzky@jonesday.com

Counsel for Petitioner

SEPTEMBER 13, 2018

PETITION FOR CERTIORARI FILED AUGUST 22, 2017
CERTIORARI GRANTED JUNE 28, 2018

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General Docket
Third Circuit Court of Appeals

Court of Appeals Docket #: 14-1900
Nature of Suit: 4365 Personal Injury-Product Liability In Re: Fosamax
Appeal From: United States District Court for the District of New Jersey
Fee Status: Paid
Docketed: 04/17/2014
Termed: 03/22/2017

* * *

Date Filed	Docket Text
	* * *
08/13/2015	ECF FILER: REDACTED CONSOLIDATED ELECTRONIC PROOF BRIEF with Volume I of Appendix attached on behalf of Appellant Doris Albrecht, filed. Certificate of Service dated 08/13/2015 by ECF.--[Edited 08/13/2015 by SLC]--[Edited 08/13/2015 by MS] (DCF) [Entered: 08/13/2015 10:52 AM]
10/28/2015	ECF FILER: ELECTRONIC PROOF BRIEF on behalf of Appellee Merck & Co Inc, filed. Certificate of Service dated 10/28/2015 by ECF. (JHB) [Entered: 10/28/2015 05:24 PM]
	* * *

11/04/2015	ECF FILER: ELECTRONIC AMICUS/INTERVENOR BRIEF on behalf of Pharmaceutical Research and Manufacturers of America in support of Appellee/Respondent, filed. Certificate of Service dated 11/04/2015 by ECF. F.R.A.P. 29(a) Permission: YES. [Entry was mistakenly spread and has been removed from all other fosamax cases; modifier added]--[Edited 11/05/2015 by EMA]--[Edited 05/04/2016 by GPK removing PROOF from docket text.] (AWP) [Entered: 11/04/2015 04:32 PM]
	* * *
12/21/2015	ECF FILER: ELECTRONIC PROOF REPLY BRIEF on behalf of Appellant Doris Albrecht, filed. Certificate of Service dated 12/21/2015 by ECF. --[Edited 01/06/2016 by EAF - Text edited to reflect Proof"] (DCF) [Entered: 12/21/2015 01:44 PM]
	* * *
12/28/2015	ECF FILER: ELECTRONIC APPENDIX on behalf of Appellant Doris Albrecht, filed. Certificate of service dated 12/28/2015 by ECF. (DCF) [Entered: 12/28/2015 12:11 PM]

12/28/2015	ECF FILER: ELECTRONIC APPENDIX on behalf of Appellant Doris Albrecht, filed. Certificate of service dated 12/28/2015 by ECF. (DCF) [Entered: 12/28/2015 12:14 PM]
12/28/2015	ECF FILER: ELECTRONIC APPENDIX on behalf of Appellant Doris Albrecht, filed. Certificate of service dated 12/28/2015 by ECF. (DCF) [Entered: 12/28/2015 12:16 PM]
12/28/2015	ECF FILER: REDACTED ELECTRONIC APPENDIX on behalf of Appellant Doris Albrecht, filed. Certificate of service dated 12/28/2015 by ECF. (DCF) [Entered: 12/28/2015 12:18 PM]
12/29/2015	HARD COPY RECEIVED from Appellant Doris Albrecht - Appendix. Copies: 4. Volumes: 2 - 5 (Volume 5 received - REDACTED and UNDER SEAL) (EAF) [Entered: 12/31/2015 03:05 PM]
	* * *
01/11/2016	ECF FILER: REDACTED ELECTRONIC BRIEF with Volume I of Appendix attached on behalf of Appellant Doris Albrecht, filed. Certificate of Service dated

	01/11/2016 by ECF. (DCF) [Entered: 01/11/2016 10:15 AM]
	* * *
01/12/2016	HARD COPY RECEIVED from Appellant Doris Albrecht - Reply Brief. Copies: 7. (SJB) [Entered: 01/12/2016 11:05 AM]
01/12/2016	HARD COPY RECEIVED from Appellee Merck & Co Inc - Brief. Copies: 7. (NON-COMPLIANT)-- [Edited 01/21/2016 by EMA] (SJB) [Entered: 01/12/2016 11:07 AM]
01/12/2016	HARD COPY RECEIVED from Appellant Doris Albrecht - Brief with Volume I of Appendix attached. Copies: (FILED UNDER SEAL) (SJB) [Entered: 01/12/2016 11:25 AM]
01/12/2016	HARD COPY RECEIVED from Appellant Doris Albrecht - REDACTED Brief with Volume I of Appendix attached. Copies: 7. (SJB) [Entered: 01/12/2016 11:27 AM]
	* * *
01/27/2016	HARD COPY RECEIVED from Appellee Merck & Co Inc - Brief. Copies: 7. (KEL) [Entered: 01/27/2016 11:27 AM]
	* * *

03/22/2017	PRECEDENTIAL OPINION Coram: FUENTES, CHAGARES and RESTREPO, Circuit Judges. Total Pages: 89. Judge: FUENTES Authoring. (SLC) [Entered: 03/22/2017 07:37 AM]
03/22/2017	JUDGMENT, Reversed and Remanded. Costs shall not be taxed. (SLC) [Entered: 03/22/2017 07:39 AM]
	* * *
04/24/2017	ORDER (SMITH, Chief Judge, AMBRO, CHAGARES, JORDAN, HARDIMAN, VANASKIE, SHWARTZ, KRAUSE, RESTREPO and *FUENTES, Circuit Judges) denying Petition for En Banc and for Panel Rehearing filed by Appellee Merck & Co Inc, filed. FUENTES, Authoring Judge. (*Judge Fuentes vote is limited to panel rehearing only.) (CJG) [Entered: 04/24/2017 01:38 PM]
05/01/2017	MANDATE ISSUED, filed. (Resent with correct appendix)--[Edited 05/01/2017 by SLC] (SLC) [Entered: 05/01/2017 07:18 AM]
	* * *

U.S. District Court

District of New Jersey [LIVE] (Trenton)

CIVIL DOCKET FOR CASE #: 3:12-cv-05485-FLW-LHG

KNOPICK et al v. MERCK & CO. et al
Assigned to: Judge Freda L. Wolfson
Referred to: Magistrate Judge Lois H. Goodman
Lead case: 3:08-cv-00008-FLW-LHG
Member case: (View Member Case)
Cause: 28:1332 Diversity-Product Liability
Date Filed: 08/31/2012
Date Terminated: 06/13/2018
Jury Demand: Plaintiff
Nature of Suit: 365 Personal Inj. Prod. Liability
Jurisdiction: Diversity

In Re

FOSAMAX (ALENDRONATE SODIUM) PRODUCTS LIABILITY LITIGATION (NO. II)

* * *

Date Filed	#	Docket Text
08/31/2012	1	COMPLAINT against MERCK & CO., MERCK SHARPE & DOHME CORP. (Filing fee $ 350 receipt number 4549895) with JURY DEMAND, filed by CAROL KNOPICK. (Attachments: # 1 Civil Cover Sheet)(jjc) (Entered: 08/31/2012)
		* * *

U.S. District Court

District of New Jersey [LIVE] (Trenton)

CIVIL DOCKET FOR CASE #: 3:12-cv-01275-JAP-LHG

STEVES et al v. MERCK SHARPE & DOHME et al
Assigned to: Judge Joel A. Pisano
Referred to: Magistrate Judge Lois H. Goodman
Lead case: 3:08-cv-00008-FLW-LHG
Member case: (View Member Case)
Cause: 28:1332 Diversity-Product Liability
Date Filed: 03/01/2012
Date Terminated: 12/17/2014
Jury Demand: Plaintiff
Nature of Suit: 365 Personal Inj. Prod. Liability
Jurisdiction: Diversity

In Re

FOSAMAX (ALENDRONATE SODIUM) PRODUCTS LIABILITY LITIGATION (NO. II)

* * *

Date Filed	#	Docket Text
03/01/2012	1	COMPLAINT against MERCK SHARPE & DOHME, NORTHSTAR RX, LLC, PHARMACEUTICALS, INC., SANOFI-AVENTIS, U.S., INC., SANOFI-AVENTIS, U.S., LLC, TEVA PHARMACEUTICALS USA, INC., WARNER CHILCOTT (US), LLC (Filing fee $ 350 receipt number 4212913.) JURY DEMAND., filed by JAMES

STEVES, SUSAN STEVES.(jjc)
(Entered: 03/02/2012)

* * *

U.S. District Court

District of New Jersey [LIVE] (Trenton)

CIVIL DOCKET FOR CASE #: 3:11-cv-05304-JAP-LHG

GLYNN et al v. MERCK SHARP & DOHME CORP.
Assigned to: Judge Joel A. Pisano
Referred to: Magistrate Judge Lois H. Goodman
Lead case: 3:08-cv-00008-FLW-LHG
Member case: (View Member Case)
Cause: 28:1332 Diversity-Product Liability
Date Filed: 09/15/2011
Date Terminated: 06/27/2013
Jury Demand: Plaintiff
Nature of Suit: 365 Personal Inj. Prod. Liability
Jurisdiction: Diversity

In Re

FOSAMAX (ALENDRONATE SODIUM) PRODUCTS LIABILITY LITIGATION (NO. II)

* * *

Date Filed	#	Docket Text
		* * *
01/15/2013	26	DECLARATION of Karen A. Confoy in Support of Merck's Motion for Summary Judgment and Motion for Summary Judgment Based Upon Federal Preemption re 25MOTION for Summary Judgment *Based Upon Federal Preemption*, 24 MOTION for Summary Judgment by

		MERCK SHARP & DOHME CORP.. (Attachments: # 1 Ex. 1, # 2 Ex. 2, # 3 Ex. 5, # 4 Ex. 7, # 5 Ex. 9, # 6 Ex. 13, # 7 Ex. 14, # 8 Ex. 15, # 9 Ex. 16, # 10 Ex. 17, # 11 Ex. 19, # 12 Ex. 20, # 13 Ex. 22, # 14 Ex. 23, # 15 Ex. 25, # 16Ex. 26, # 17 Ex. 31, # 18 Ex. 32, # 19 Ex. 33, # 20 Ex. 36, # 21 Ex. 41)(CONFOY, KAREN) (Entered: 01/15/2013)
		* * *
04/29/2013	213	JURY VERDICT FORM. (dm) (Entered: 04/30/2013)
		* * *

U.S. District Court

District of New Jersey [LIVE] (Trenton)

CIVIL DOCKET FOR CASE #: 3:08-cv-00008-FLW-LHG

MOLNAR et al v. MERCK & CO., INC.
Assigned to: Judge Freda L. Wolfson
Referred to: Magistrate Judge Lois H. Goodman
Cause: 28:1332 Diversity-Product Liability
Date Filed: 01/02/2008
Date Terminated: 06/27/2013
Jury Demand: Plaintiff
Nature of Suit: 367 Personal Injury: Health Care/Pharmaceutical Personal Injury Product Liability
Jurisdiction: Diversity

In Re

FOSAMAX (ALENDRONATE SODIUM) PRODUCTS LIABILITY LITIGATION (NO. II)

* * *

Date Filed	#	Docket Text
		* * *
07/14/2011	113	CASE MANAGEMENT ORDER NO. 4. Signed by Chief Judge Garrett E. Brown, Jr on 7/14/2011. (eaj) (Main Document 113 replaced on 7/15/2011) (mmh). (Entered: 07/14/2011)
		* * *

08/05/2013	2870	Letter from James E. Cecchi to the Honorable Joel A. Pisano, U.S.D.J. re 2857 Application/Petition,. (Attachments: # 1 Exhibits A and B)(CECCHI, JAMES) (Entered: 08/05/2013)
		* * *
08/12/2013	2881	Letter from Karen A. Confoy re 2857 Application/Petition, 2870 Letter. (CONFOY, KAREN) (Entered: 08/12/2013)
		* * *
08/15/2013	2895	ORDER that the plaintiffs identified in Appendix A SHOW CAUSE why their pre-September 14, 2010 injury claims should not be dismissed and any briefs and supporting papers shall be filed within 45 days of entry of this Order; that Merck shall have 30 days to file a reply to plaintiffs' response to this Order; that plaintiffs' liaison counsel shall ensure all plaintiffs receive a copy of this Order. Signed by Judge Joel A. Pisano on 8/13/2013. (mmh) (Entered: 08/15/2013)
		* * *

09/30/2013	2946	DECLARATION of James E. Cecchi re 2895 Order to Show Cause, by PHYLLIS MOLNAR. (CECCHI, JAMES) (Entered: 09/30/2013)
		* * *
10/01/2013	2996	DECLARATION of Donald A. Ecklund re 2895 Order to Show Cause, by PHYLLIS MOLNAR. (Attachments: # 1 Exhibits to the Ecklund Declaration, # 2 Exhibits to the Ecklund Declaration, # 3 Exhibits to the Ecklund Declaration, # 4 Exhibits to the Ecklund Declaration, # 5 Exhibits to the Ecklund Declaration, # 6 Exhibits to the Ecklund Declaration, # 7 Exhibits to the Ecklund Declaration, # 8 Exhibits to the Ecklund Declaration, # 9 Exhibits to the Ecklund Declaration, # 10 Exhibits to the Ecklund Declaration, # 11 Exhibits to the Ecklund Declaration, # 12 Exhibits to the Ecklund Declaration, # 13 Exhibits to the Ecklund Declaration, # 14 Exhibits to the Ecklund Declaration, # 15 Exhibits to the Ecklund Declaration, # 16 Exhibits to the Ecklund

		Declaration, # 17 Exhibits to the Ecklund Declaration, # 18 Exhibits to the Ecklund Declaration, # 19 Exhibits to the Ecklund Declaration, # 20 Exhibits to the Ecklund Declaration, # 21 Exhibits to the Ecklund Declaration, # 22 Exhibits to the Ecklund Declaration, # 23 Exhibits to the Ecklund Declaration, # 24 Exhibits to the Ecklund Declaration, # 25 Exhibits to the Ecklund Declaration, # 26 Exhibits to the Ecklund Declaration, # 27 Exhibits to the Ecklund Declaration, # 28 Exhibits to the Ecklund Declaration, # 29 Exhibits to the Ecklund Declaration, # 30 Exhibits to the Ecklund Declaration, # 31 Exhibits to the Ecklund Declaration, # 32 Exhibits to the Ecklund Declaration)(CECCHI, JAMES) (Entered: 10/01/2013)
		* * *
10/30/2013	3035	DECLARATION of Karen A. Confoy in Support of Merck's Replies to Plaintiffs' Briefs in Response to Court's Order to Show Cause re 3032 Statement, 3031 Brief,,

		by MERCK SHARP & DOHME CORP.. (Attachments: # 1 Exhibits 2 & 3, # 2 Exhibit 4, 1 of 2, # 3 Exhibit 4, 2 of 2, # 4 Exhibits 5 & 6, # 5 Exhibit 7, 1 of 2, # 6 Exhibit 7, 2 of 2, # 7 Exhibit 8, 1 of 4, # 8 Exhibit 8, 2 of 4, # 9 Exhibit 8, 3 of 4, # 10 Exhibit 8, 4 of 4, # 11 Exhibits 9 - 11, # 12 Exhibits 13 - 17, # 13 Exhibits 19 & 20, # 14Exhibit 30, # 15 Exhibits 32 – 34, # 16 Exhibit 36, # 17 Exhibits 41 & 42, # 18 Exhibit 43, # 19 Exhibits 45 & 46, # 20 Exhibit 48, # 21 Exhibits 50 - 52, # 22 Exhibit 56, # 23 Exhibit 61, # 24 Exhibits 63 & 64, # 25 Exhibits 67 & 68, # 26 Exhibits 72 - 78, # 27 Exhibits 80 - 83)(CONFOY, KAREN) (Entered: 10/30/2013)
10/30/2013	3036	Exhibit to 3035 Declaration,,, by MERCK SHARP & DOHME CORP.. (Attachments: # 1 Exhibit 84, 2 of 3, # 2 Exhibit 84, 3 of 3, # 3 Exhibit 85, 1 of 7, # 4 Exhibit 85, 2 of 7, # 5 Exhibit 85, 3 of 7, # 6 Exhibit 85, 4 of 7,

		# 7 Exhibit 85, 5 of 7, # 8 Exhibit 85, 6 of 7, # 9 Exhibit 85, 7 of 7, # 10 Exhibits 86 - 88, # 11 Exhibit 89, 1 of 8, # 12 Exhibit 89, 2 of 8, # 13 Exhibit 89, 3 of 8, # 14 Exhibit 89, 4 of 8, # 15 Exhibit 89, 5 of 8, # 16 Exhibit 89, 6 of 8, # 17 Exhibit 89, 7 of 8, # 18 Exhibit 89, 8 of 8, # 19Exhibit 90, 1 of 8, # 20 Exhibit 90, 2 of 8, # 21 Exhibit 90, 3 of 8, # 22 Exhibit 90, 4 of 8, # 23 Exhibit 90, 5 of 8, # 24 Exhibit 90, 6 of 8, # 25 Exhibit 90, 7 of 8, # 26Exhibit 90, 8 of 8, # 27 Exhibits 91 - 93)(CONFOY, KAREN) (Entered: 10/30/2013)
10/30/2013	3037	Exhibit to 3035 Declaration,,, by MERCK SHARP & DOHME CORP.. (Attachments: # 1 Exhibit 12, # 2 Exhibit 18, # 3 Exhibits 21 - 29, # 4 Exhibit 31, # 5 Exhibit 35, # 6 Exhibits 37 - 40, # 7 Exhibit 44, # 8 Exhibit 47, 1 of 2, # 9 Exhibit 47, 2 of 2, # 10 Exhibit 49, # 11 Exhibits 53 - 55, # 12 Exhibits 57 & 58,

		# 13 Exhibit 59, 1 of 5, # 14 Exhibit 59, 2 of 5, # 15 Exhibit 59, 3 of 5, # 16 Exhibit 59, 4 of 5, # 17 Exhibit 59, 5 of 5, # 18 Exhibit 60, # 19 Exhibit 62, # 20 Exhibits 65 & 66, # 21 Exhibits 69 - 71, # 22 Exhibit 79)(CONFOY, KAREN) (Entered: 10/30/2013)
		* * *
10/02/2015	4065	Letter from Karen A. Confoy re 4056 Order on Motion to Seal. (Attachments: # 1 Exhibit A Documents (Part 1 of 18), # 2Exhibit A Documents (Part 2 of 18, # 3 Exhibit A Documents (Part 3 of 18, # 4 Exhibit A Documents (Part 4 of 18, # 5 Exhibit A Documents (Part 5 of 18, # 6 Exhibit A Documents (Part 6 of 18, # 7 Exhibit A Documents (Part 7 of 18, # 8 Exhibit A Documents (Part 8 of 18, # 9 Exhibit A Documents (Part 9 of 18, # 10 Exhibit A Documents (Part 10 of 18, # 11 Exhibit A Documents (Part 11 of 18, # 12 Exhibit A Documents (Part 12 of 18, # 13 Exhibit A Documents (Part 13 of 18, # 14 Exhibit A

Documents (Part 14 of 18, # 15 Exhibit A Documents (Part 15 of 18, # 16 Exhibit A Documents (Part 16 of 18, # 17 Exhibit A Documents (Part 17 of 18, # 18 Exhibit A Documents (Part 18 of 18, # 19 Exhibit B Documents (Part 1 of 5), # 20 Exhibit B Documents (Part 2 of 5), # 21 Exhibit B Documents (Part 3 of 5), # 22 Exhibit B Documents (Part 4 of 5), # 23 Exhibit B Documents (Part 5 of 5))(CONFOY, KAREN) (Entered: 10/02/2015)

* * *

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: FOSAMAX (ALENDRONATE SODIUM) PRODUCTS LIABILITY LITIGATION (No. II) *This Document Relates To All Cases*	MDL No. 2243 Civ. No. 08-08 (GEB) (LHG)

~~[PROPOSED]~~ CASE MANAGEMENT ORDER NO. 4
(Pretrial Schedule)

It appearing that the civil actions listed on Schedule A, attached hereto, which were transferred to this Court by order of the Judicial Panel on Multidistrict Litigation pursuant to its order of May 23, 2011, merit special attention as complex litigation, it is therefore ORDERED that:

1. APPLICABILITY OF ORDER

The provisions of this Order shall govern the practice and procedure in actions: (1) transferred to this Court by the Judicial Panel on Multidistrict Litigation pursuant to its order of May 23, 2011 listed on Schedule A; (2) all related actions alleging that the prescription medicine FOSAMAX® and/or alendronate sodium caused patients prescribed it to suffer femur fractures or similar bone injuries that were filed in the District of New Jersey and were previously before this Court; and (3) any "tag-along" actions later filed in, removed to, or transferred to this Court. The Clerk will send a copy of this Order to

counsel for any plaintiffs or newly named defendants in any case newly filed in or transferred to this Court. Moreover, all pending motions and outstanding discovery requests in the transferor courts are vacated and superseded by this Order and subsequent orders issued by this Court.

The civil actions listed on Schedule A are coordinated for pretrial purposes. Any "tag-

* * *

8. REMAND STIPULATIONS

In the event that a case is remanded to the transferor court, the parties shall furnish to the Clerk of the transferee court a stipulation or designation of the contents of the record and furnish all necessary copies of any pleadings filed so as to enable the Clerk of the transferee court to comply with the order of remand.

9. EARLY DISCOVERY AND TRIAL CASES

9.1 Selection of Early Discovery Cases

All cases in which Merck is the only defendant that have been filed in, transferred to, or subject to transfer to this Court by September 14, 2011 are available for selection. Plaintiffs' counsel will make their best efforts to file any additional cases of which they are presently aware that will be part of this MDL by September 14, 2011. The parties will meet and confer regarding a process for the selection of 40 cases, a list of which shall be filed with the Court by September 23, 2011. Should the parties be unable to reach agreement on a process for selecting the 40 cases, the parties are to submit their respective proposals to the Court by August 22, 2011. In addition, the parties

shall further meet and confer to address *Lexecon*-related issues with respect to the 40 cases selected for early discovery; should the parties be unable to agree with respect to the issue, the parties shall submit their respective proposals to the Court by August 22, 2011. Fact discovery in these 40 cases will be completed by July 31, 2012.

9.2 Process for Selection of Trial Candidates

The Court intends to try bellwether cases in this litigation. The parties are to meet and confer on a process for selection of three or four cases for early trial ("Early Trial Cases") from those cases identified pursuant to Section 9.1 above; the trial case selection process used by the parties shall be structured such that the Early Trial Cases are identified by April 30, 2012.

9.3 Expert and Pre-Trial Motions

A. Expert Discovery Expert discovery on general causation (i.e., whether Fosamax or alendronate can be a cause of femur fractures), as well as all expert discovery in the Early Trial Cases, should be completed by ~~December 14~~ **November 28**, 2012, in accordance with the following schedule:

~~September 10~~ **August 31**, 2012 – Plaintiffs' Rule 26(a)(2) disclosures shall be served.

~~October 15~~ **October**, 2012 – Merck's Rule 26(a)(2) disclosures shall be served.

~~November 12~~ **October 26**, 2012 – Depositions of Plaintiffs' experts shall be completed.

~~December 14~~ **November 28**, 2012 – Depositions of Merck's experts shall be completed.

B. *Daubert* Motions

Any *Daubert* motions on general causation or in the Early Trial Cases shall be filed by ~~January 4, 2013~~ **December 3, 2012**. Opposition briefs shall be filed by January 3~~0~~, 2013, and reply briefs shall be filed by ~~February 13~~ **January 17**, 2013. A *Daubert* hearing ~~will be held in February 2013~~ **may be scheduled at the Court's discretion.**

C. Dispositive Motions in the Early Trial Cases

Dispositive motions in the Early Trial Cases shall be filed on ~~January 4, 2013~~ **December 3, 2012**. Opposition briefs shall be filed by January 3~~0~~, 2013, and any reply briefs shall be filed by ~~February 13~~ **January 17**, 2013. Oral argument on any dispositive motions filed in the Early Trial Case with the earliest trial date ~~will be held in February 2013~~ **may be scheduled at the Court's discretion**. A separate schedule will be issued for ~~oral argument on any dispositive motions filed in the remaining Early Trial Cases, as well as for~~ the timing of motions in limine to be filed in each of the Early Trial Cases.

9.4 Trial

The first trial shall begin on the first available date after March 1, 2013. While it is premature to make predictions regarding the anticipated length of trials, the parties have informed the Court that the four bellwether trials in the Fosamax ONJ MDL have each lasted approximately 3 weeks.

Next scheduling and case management conference September 21, 2011 @ 1pm in Trenton.

SO ORDERED.

Dated: Trenton New Jersey
July 14, 2011

/s/ Garrett E. Brown, JR.
GARRETT E. BROWN, JR.
UNITED STATES DISTRICT JUDGE

Attachments

ANAPOL, SCHWARTZ, WEISS, COHAN FELDMAN & SMALLEY, P.C.
BY: TRACY A. FINKEN, ESQUIRE
GREGORY S. SPIZER, ESQUIRE
AMBER RACINE, ESQUIRE
1040 KINGS HIGHWAY NORTH
CHERRY HILL, NJ 08034
(856) 482-1600; FAX (856) 482-1911

ATTORNEY FOR PLAINTIFFS

IN THE UNITED STATES DISTRICT COURT OF NEW JERSEY

SUSAN STEVES and	:	**CIVIL ACTION**
JAMES STEVES, wife/husband	:	**NO.**
10111 State Highway 37	:	
Ogdensburg, NY 13669,	:	
Plaintiffs	:	
	:	
vs.	:	
MERCK SHARPE & DOHME	:	**JURY TRIAL**
One Merck Drive	:	**DEMANDED**
White House Station, NJ, 08889	:	
	:	
TEVA PHARMACEUTICALS	:	
USA, INC.	:	
1090 Horsham Road	:	
North Wales, PA	:	
	:	
NORTHSTAR RX, LLC	:	
PHARMACEUTICALS, INC.	:	
4971 Southridge Blvd. Suite 101	:	
Memphis, TN 38141	:	
	:	
SANOFI-AVENTIS, U.S., INC	:	
55 Corporate Drive	:	
Bridgewater, New Jersey 08807	:	
	:	
SANOFI-AVENTIS, U.S., LLC	:	
55 Corporate Drive	:	
Bridgewater, New Jersey 08807	:	

and	:
WARNER CHILCOTT (US), LLC	:
100 Enterprise Drive	:
Rockaway, New Jersey 07866	:
	:
Defendants	:
	:

COMPLAINT

Plaintiffs, Susan Steves and James Steves, wife and husband, by way of Complaint against Defendants, Merck Sharpe & Dohme Corporation, f/k/a Merck & Co., Inc. ("Merck"), TEVA Pharmaceutical USA, Inc., ("TEVA"), NorthStar Pharmaceuticals, Inc. ("NorthStar") (Merck, TEVA and NorthStar referred to collectively as "Fosamax Defendants"); Sanofi-Aventis U.S. Inc., Sanofi-Aventis U.S. LLC, and Warner Chilcott (US), LLC, As Successor to Procter & Gamble Pharmaceuticals, Inc. (collectively referred to herein as "Actonel Defendants"), upon information and belief, allege as follows:

PARTIES

1. Plaintiffs, Susan Steves and James Steves, are wife and husband and are citizens of the State of New York, residing at 10111 State Highway 37, Ogdensburg, New York, 13669.

2. Defendant, Merck Sharpe & Dohme, f/k/a Merck & Co., Inc. (hereinafter "Merck"), is a corporation organized and existing under the laws of the State of New Jersey, with its principal place of business at One Merck Drive, White House Station, NJ, 08889.

* * *

62. Defendants knew of the significant risk of severely suppressed bone turnover, brittle bones, multiple stress fractures and low energy femoral fractures that could result from long-term bisphosphonate use, but Defendants did not adequately and sufficiently warn or instruct consumers, including Plaintiff Susan Steves, her physician or the medical community, of such risks.

63. As a direct result, Plaintiff, Susan Steves, was prescribed ACTONEL for approximately six (6) years and FOSAMAX/ALENDRONATE SODIUM for approximately seven (7) years and has been permanently and severely injured, having suffered serious consequences from long-term FOSAMAX use. Plaintiff, Susan Steves, requires and will in the future require ongoing medical care and treatment.

64. Plaintiff, Susan Steves, has suffered from mental anguish from the knowledge that she will have life-long complications as a result of the injuries she sustained from the use of FOSAMAX/ALENDRONATE SODIUM and ACTONEL.

65. Plaintiff, Susan Steves, was prescribed and began taking ACTONEL in approximately 1998.

66. Plaintiff, Susan Steves, was prescribed and began taking brand name FOSAMAX in approximately September 2004.

67. Plaintiff, Susan Steves, began to use ALENDRONATE SODIUM, generic FOSAMAX, manufactured by Defendant, TEVA, in approximately May 2008.

68. Plaintiff, Susan Steves, began to use ALENDRONATE SODIUM, generic FOSAMAX,

manufactured by Defendant, NorthStar, in approximately September 2010.

69. Plaintiff, Susan Steves, used ACTONEL as prescribed and in a foreseeable manner consistently from approximately 1998 through approximately 2004.

70. Plaintiff, Susan Steves, used FOSAMAX as prescribed and in a foreseeable manner consistently from approximately 2004 through approximately May 2008.

71. Plaintiff, Susan Steves, used generic ALENDRONATE SODIUM, manufactured by Defendant, TEVA, as prescribed and in a foreseeable manner consistently from approximately May 2008 through approximately September 2009.

72. Plaintiff, Susan Steves, used generic ALENDRONATE SODIUM, manufactured by Defendant, NorthStar, as prescribed and in a foreseeable manner consistently from approximately September 2009 through approximately July 2011.

73. As a direct and proximate result of her long-term FOSAMAX/ALENDRONATE SODIUM and ACTONEL use, Plaintiff, Susan Steves, suffered severely suppressed bone turnover and severe femur fractures.

74. Plaintiff, Susan Steves, used FOSAMAX, as prescribed and in a foreseeable manner consistently in brand-name form from approximately 2004 though May 2008 and, subsequently, in generic form, known as ALENDRONATE SODIUM, from approximately May 2008 through June 2011

75. As a direct and proximate result of her long-term FOSAMAX/ALENDRONATE SODIUM use, Plaintiff, Susan Steves, suffered severely suppressed bone turnover and femur fractures.

76. On or about March 25, 2008, Plaintiff suffered a severe femur fracture of her left leg.

77. On or about July 16, 2011, Plaintiff suffered a severe femur fracture of her right leg.

78. It is believed and therefore averred that Susan Steves' low energy femur fractures were suffered due to the harmful long-term effects of FOSAMAX/ALENDRONATE SODIUM and ACTONEL use, a consequence that was never made known to Plaintiff, Susan Steves, or her physicians by Defendants.

79. Plaintiff, Susan Steves, as a direct and proximate result of long-term FOSAMAX/ALENDRONATE SODIUM and ACTONEL use, suffered severe mental and physical pain and suffering and has sustained permanent injuries and emotional distress.

80. Plaintiff, Susan Steves, used ACTONEL which had been provided to her in a condition that was substantially the same as the condition in which it was manufactured and sold.

81. Plaintiff, Susan Steves, used FOSAMAX/ALENDRONATE SODIUM which had been provided to her in a condition that was substantially the same as the condition in which it was manufactured and sold.

82. Plaintiff, Susan Steves, would not have used ACTONEL for so many years had Defendants properly disclosed the risks associated with its long-term use.

83. Plaintiff, Susan Steves, would not have used FOSAMAX/ALENDRONATE SODIUM for so many years had Defendants properly disclosed the risks associated with its long- term use.

84. Defendants, through their affirmative misrepresentations and omissions, actively concealed from Plaintiff, Susan Steves, and her physicians the true and significant risks associated with long-term FOSAMAX/ALENDRONATE SODIUM and ACTONEL use. The running of any applicable statute of limitations has been tolled by reason of Defendants' fraudulent concealment.

85. As a result of Defendants' actions, Plaintiff, Susan Steves, and her prescribing physicians were unaware, and could not have reasonably known or have learned through reasonable diligence, that Plaintiff had been exposed to the risks identified in this complaint, and that those risks were the direct and proximate result of Defendants' acts, omissions, and misrepresentations.

86. It is believed and therefore averred that Defendants knew or should have known and failed to warn that long term use of FOSAMAX/ALENDRONATE SODIUM and ACTONEL was unsafe because it could cause low energy femur fractures of the type that plaintiff, Susan Steves, suffered.

87. Defendants with their heightened knowledge and experience, knew or should have known that long term use of bisphosphonates, including

FOSAMAX/ALENDRONATE SODIUM and ACTONEL, could inhibit the production of new bone cells (osteoblasts) and therefore would prevent repair of naturally occurring micro fractures in the femur which could lead to serious low energy femur fractures, and/or that prolonged suppression of bone remodeling with FOSAMAX/ALENDRONATE SODIUM could lead to serious low energy femur fractures; and that femur fractures caused by long term FOSAMAX/ALENDRONATE SODIUM use could occur despite the apparent absence of sufficient trauma.

88. While FOSAMAX/ALENDRONATE SODIUM has been marketed, it is believed and therefore averred, that prior to plaintiff's suffering femur fractures, Defendants received adverse reaction reports from different FOSAMAX/ALENDRONATE SODIUM users throughout the country that these patients were experiencing bone brittleness, susceptibility to fractures, femoral stress fractures, and/or low energy femoral shaft fractures after long-term use of FOSAMAX/ALENDRONATE SODIUM.

89. While ACTONEL has been marketed, it is believed and therefore averred, that prior to plaintiff's suffering femur fractures, Defendants received adverse reaction reports from different ACTONEL users throughout the country that these patients were experiencing bone brittleness, susceptibility to fractures, femoral stress fractures, and/or low energy femoral shaft fractures after long-term use of ACTONEL.

90. It is believed and therefore averred that Defendants disregarded and has refused to follow up

on the reports of patients, who after using FOSAMAX/ALENDRONATE SODIUM and ACTONEL, have experienced and reported bone brittleness, susceptibility to fractures, femoral stress fractures, and/or low energy femoral shaft fractures.

91. It is believed and therefore averred that Defendants failed to submit these reported adverse consequences to the FDA and has failed to advise physicians and the public.

* * *

COUNT III

PRODUCTS LIABILITY-FAILURE TO WARN (N.J. Products Liability Act-N.J.S.A. 2A58C-1) AS TO FOSAMAX DEFENDANTS

119. Plaintiffs repeat and incorporate by reference all other paragraphs of this Complaint as if fully set forth herein.

120. Defendant Merck researched, developed, designed, tested, manufactured, inspected, labeled, distributed, marketed, promoted, sold, and otherwise released into the stream of commerce the pharmaceutical, FOSAMAX, and in the course of same, directly advertised or marketed the product to consumers or persons responsible for consumers, and therefore had a duty to warn of the risks associated with the use of FOSAMAX.

121. Defendant, NorthStar, manufactured, inspected, labeled, distributed, marketed, promoted, sold, and otherwise released into the stream of commerce the pharmaceutical, ALENDRONATE SODIUM, and in the course of same, directly

advertised or marketed the product to consumers or persons responsible for consumers, and therefore had a duty to warn of the risks associated with the use of ALENDRONATE SODIUM.

122. Defendant TEVA manufactured, inspected, labeled, distributed, marketed, promoted, sold, and otherwise released into the stream of commerce the pharmaceutical, ALENDRONATE SODIUM, and in the course of same, directly advertised or marketed the product to consumers or persons responsible for consumers, and therefore had a duty to warn of the risks associated with the use of ALENDRONATE SODIUM.

123. FOSAMAX/ALENDRONATE SODIUM was under the exclusive control of Defendants and was unaccompanied by appropriate warnings regarding the risk of severely suppressed bone turnover, resulting stress fractures, femur fractures and other severe and permanent injuries associated with its use. The warnings given did not accurately reflect the risk, incidence, symptoms, scope or severity of such injuries to the consumer. The promotional activities of Defendants further diluted or minimized the warnings given with the product.

124. Defendants downplayed the serious and dangerous side effects of FOSAMAX/ALENDRONATE SODIUM to encourage sales of the product; consequently, Defendants placed its profits above its customers' safety.

125. FOSAMAX/ALENDRONATE SODIUM was defective and unreasonably dangerous when it left the possession of the Defendants in that they contained warnings insufficient to alert Plaintiff, Susan Steves,

to the dangerous risks and reactions associated with them, including, but not limited to severely suppressed bone turnover and femur fractures. Even though Defendants knew or should have known of the risks and reactions associated with FOSAMAX/ALENDRONATE SODIUM, they still failed to provide warnings that accurately reflected the signs, symptoms, incident, scope, or severity of the risks associated with the product.

126. Plaintiff, Susan Steves, used FOSAMAX/ALENDRONATE SODIUM as intended or in a reasonably foreseeable manner.

127. Plaintiff, Susan Steves, could not have discovered any defect in FOSAMAX/ALENDRONATE SODIUM through the exercise of reasonable care.

128. Fosamax Defendants, as manufacturers of pharmaceutical drugs, are held to the level of knowledge of an expert in the field and, further, Defendants had knowledge of the dangerous risks and side effects of FOSAMAX/ALENDRONATE SODIUM.

129. Plaintiff, Susan Steves, did not have the same knowledge as Defendants and no adequate warning was communicated to her physicians.

130. Defendants had a continuing duty to warn consumers, including Plaintiff and her physicians, and the medical community of the dangers associated with FOSAMAX/ALENDRONATE SODIUM, and by negligently and/or wantonly failing to adequately warn of the dangers associated with its use, Defendants breached their duty.

131. Although Defendants knew, or were reckless in not knowing, of the defective nature of FOSAMAX/ALENDRONATE SODIUM, they

continued to design, manufacture, market, and sell FOSAMAX/ALENDRONATE SODIUM without providing adequate warnings and instructions concerning the use of FOSAMAX/ALENDRONATE SODIUM so as to maximize sales and profits at the expense of the public health and safety, in knowing, conscious, and deliberate disregard of the foreseeable harm caused by FOSAMAX/ALENDRONATE SODIUM.

132. As a direct and proximate result of Defendants' failure to adequately warn or other acts and omissions of Defendants described herein, Plaintiff, Susan Steves, developed severely suppressed bone turnover, causing her to suffer severe and permanent injuries, including severe femur fractures, pain and mental anguish, including diminished enjoyment of life, and fear of developing other harmful conditions.

133. In addition, Defendants' conduct in the packaging, warning, marketing, advertising, promotion, distribution, and sale of FOSAMAX/ALENDRONATE SODIUM was committed with knowing, conscious, willful, wanton, and deliberate disregard for the value of human life, and the rights and safety of consumers such as Plaintiff, Susan Steves, thereby entitling Plaintiff to punitive damages so as to punish Defendants and deter it from similar conduct in the future.

WHEREFORE, Plaintiffs demand judgment against Fosamax Defendants for any and all damages, (including, but not limited to severe physical pain and suffering; mental anguish; severe anxiety; loss of life's pleasures; loss of enjoyment of life; and loss of future earning capacity, future earnings and income), as well

as punitive damages, cognizable in accordance with the laws of the State of New Jersey, together with interest, cost of suit and counsel fees.

* * *

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

	Docket No.
IN RE: FOSOMAX (ALENDRONATE SODIUM) PRODUCTS LIABILITY LITIGATION (No. II) *This Document Relates to: Carol Knopick v. Merck & Co. and Merck Sharpe & Dohme Corp.*	MDL Docket No. 2243 Civ. No. 08-08(GEB) (LHG) **COMPLAINT AND DEMAND FOR JURY TRIAL** **JUDGE JOEL A. PISANO**

COMPLAINT

1. This is an action for personal injury, statutory, compensatory, and punitive damages due to Plaintiff as a result of Defendants' concealment of risks associated with their drug Fosamax as well as their gross exaggeration of the purported fracture reduction benefits conferred by the drug Fosamax, and their over promotion of the drug for non-approved, or "off- label" indications.

PARTIES

2. Plaintiff Carol Knopick ("Plaintiff") currently resides at 8511 Barstow, Lenexa, Kansas 66219. Plaintiff used the medication Fosamax for the

treatment and/or prevention of osteopenia and/or osteoporosis.

3. Defendant Merck & Co., Inc. ("Merck & Co.") is a corporation organized and existing under the laws of the State of New Jersey, with its principal place of business located at One Merck Drive, Whitehouse Station, New Jersey. Merck & Co., a global pharmaceutical company, directly and through its agents, advertises, solicits, promotes, and distributes prescription drugs, including Fosamax.

4. Defendant Merck Sharpe & Dohme Corp. is a subsidiary of Merck & Co. and is a corporation incorporated under the laws of the State of New Jersey with its principal place of business located at One Merck Drive, Whitehouse Station, New Jersey.

5. At all times relevant to this Complaint, (collectively, "Defendants") designed, manufactured, marketed, distributed, and sold for profit the prescription drug product known as Fosamax through interstate commerce, including in New Jersey.

* * *

B. Fosamax Causes Femur Fractures and Other Serious Injuries

30. Over the last few years, there have been an increasing number of reports of patients suffering multiple fractures and low energy femoral fractures as a result of severely suppressed bone turnover caused by Fosamax use. Severely suppressed bone turnover from Fosamax use has been well recognized in the medical literature.

31. There is also evidence from at least one animal study that the severe suppression of bone turnover

and bone remodeling that occurs with alendronate therapy, can result in the accumulation of microdamage in bone as well as a reduction in some of the biomechanical properties of bone. Mashiba et al., *Suppressed Bone Turnover by Biphosphonates Increases Microdamage Accumulation and Reduces Some Biomechanical Properties in Dog Rib*, 15J, Bone and Mineral 613 (2000). These findings were further reflected in human studies: "Our findings raise the possibility that severe suppression of bone turnover may develop during long-term alendronate therapy, resulting in increased susceptibility to, and delayed healing of, nonspinal fractures." Odvina, Clarita V., et al., *Severely Suppressed Bone Turnover: A Potential Complication of Alendronate Therapy*, 90 J. Clin. Endocrinal. Metab. 1294–1301 (2005).

32. On January 7, 2008, the FDA issued a medical advisory warning doctors and Fosamax patients of the "possibility of severe and sometimes incapacitating bone, joint, and/or muscle pain," and advising physicians to discontinue prescribing Fosamax if such complaints occurred during therapy. One week later, the January 15, 2008 issue of the Journal of Rheumatology contained an article that concluded that Fosamax patients have a 287% higher chance of developing osteonecrosis (of the jaw, hip, and knee) than those not taking the drug.

33. On February 23, 2011, the journal of the American Medical Association contained an article entitled *Bisphosphonate Use and the Risk of Subtrochanteric or Femoral Shaft Fractures in Older Women*. The study concluded that "bisphosphonate use, treatment for 5 years or longer was associated with an increased risk of subtrochanteric or femoral

shaft fracture (adjusted odds ratio 2.74; 95% confidence interval, 1.25–6.02)."

C. Defendants' Failure to Warn of the Dangers of Fosamax

34. Despite its knowledge of this dangerous side effect that can result from Fosamax use, Defendants refuse to warn patients, physicians and the medical community about the risk of severely suppressed bone turnover. Defendants continue to defend Fosamax, mislead physicians and the public, and minimize unfavorable findings.

35. Defendants failed to change any of their prescribing information, package inserts or drug manuals supplied to the medical and pharmaceutical professions and the general public in order to warn of the potential for femur fractures after long-tern Fosamax use, until finally ordered to do so by the FDA on October 13, 2010.

36. Consumers, including Plaintiff, who have used Fosamax for treatment of osteoporosis/osteopenia, have several alternative available safer products to treat the conditions but have not been adequately warned about the significant risks and lack of benefits associated with Fosamax therapy.

37. Defendants knew of the significant risk of severely suppressed bone turnover, brittle bones, multiple fractures and low energy femoral fractures that could result from Fosamax use, but did not adequately and sufficiently warn consumers, including Plaintiff, «Phisher» physicians or the medical community, of such risks.

D. Plaintiff's Use of Fosamax

38. Plaintiff was prescribed and began taking Fosamax in approximately 2003 through 2008. Fosamax was provided to Plaintiff in a condition that was substantially the same as the condition in which it was manufactured and sold.

39. Plaintiff used Fosamax as prescribed and in a foreseeable manner.

40. After 2008, Plaintiff was prescribed and took a generic bisphosphonate medication from approximately 2008 through 2010.

41. As a direct and proximate result of her Fosamax use, Plaintiff suffered from stress fractures of her right and left femurs, which was diagnosed on approximately May 9, 2009. Plaintiff also suffered from a severe fracture of her right femur, which was diagnosed on approximately September 2, 2010.

42. Plaintiff, as a direct and proximate result of Fosamax use, suffered severe mental and physical pain and suffering and has sustained permanent injuries and emotional distress.

43. Plaintiff would not have used and her physicians would never have been prescribed Fosamax for so many years had Defendants properly disclosed the risks associated with its use.

* * *

COUNT II

PRODUCTS LIABILITY – FAILURE TO WARN

(N.J. Products Liability Act – N.J.S.A. 2A:58C-2 *et seq*.)

55. Plaintiff repeats, reiterates, and realleges each and every allegation contained in this Complaint with the same force and effect as if fully set forth herein.

56. Defendants researched, developed, designed, tested, manufactured, inspected, labeled, distributed, marketed, promoted, sold, and otherwise released into the stream of commerce Fosamax, and directly advertised or marketed the product to consumers or persons responsible for consumers, and therefore had a duty to warn of the risks associated with the use of Fosamax.

57. Fosamax was under the exclusive control of Defendants and was unaccompanied by appropriate warnings regarding the risk of severely suppressed bone turnover, resulting fractures, or low energy femoral fractures and other severe and permanent injuries associated with its use. The warnings given did not accurately reflect the risk, incidence, symptoms, scope or severity of such injuries to the consumer or physicians. The promotional activities of Defendants further diluted or minimized the warnings given with the product.

58. Defendants downplayed the serious and dangerous side effects of Fosamax to encourage sales of the product; consequently, Defendants placed their profits above its consumers' safety.

59. Fosamax was defective and unreasonably dangerous when it left the possession of Defendants in

that it contained warnings insufficient to alert Plaintiff to the dangerous risks and reactions associated with it, including, but limited to severely suppressed bone turnover, multiple fractures, and low energy femoral fractures. Even though Defendants knew or should have known of the risks and reactions associated with Fosamax, it still failed to provide warnings that accurately reflected the signs, symptoms, incident, scope, or severity of the risks associated with the product.

60. Plaintiff used Fosamax as intended or in a reasonably foreseeable manner.

61. Plaintiff could not have discovered any defect in Fosamax through the exercise of reasonable care.

62. Defendants, as manufacturers of pharmaceutical drugs, are held to the level of knowledge of an expert in the field and, further, had knowledge of the dangerous risks and side effects of Fosamax.

63. Plaintiff did not have the same knowledge as Defendants and no adequate warning was communicated to her physicians.

64. Defendants had a continuing duty to warn consumers, including Plaintiff and «Phisher» physicians, and the medical community of the dangers associated with Fosamax, and by negligently and/or wantonly failing to adequately warn of the dangers associated with its use, Defendants breached their duty.

65. Although Defendants knew, or were reckless in not knowing, of the defective nature of Fosamax, they continued to design, manufacture, market, and sell Fosamax without providing adequate warnings and

instructions concerning the use of Fosamax so as to maximize sales and profits at the expense of the public health and safety, in knowing, conscious, and deliberate disregard of the foreseeable harm caused by Fosamax.

66. As a direct and proximate consequence of Defendants' actions, omissions, and misrepresentations, Plaintiff suffered severely suppressed bone turnover, bilateral stress fractures and a severe fracture of her right femur. In addition, Plaintiff required and will continue to require healthcare and services and Plaintiff has incurred and will continue to incur medical and related expenses as a result of her injuries. Plaintiff also has suffered and will continue to suffer mental and physical pain and suffering, diminished capacity for the enjoyment of life, a diminished quality of life, increased risk of premature death, aggravation of preexisting conditions and activation of latent conditions, and other losses and damages.

67. In addition, Defendants' conduct in the packaging, warning, marketing, advertising, promotion, distribution, and sale of Fosamax was committed with knowing, conscious, willful, wanton, and deliberate disregard for the value of human life, and the rights and safety of consumers such as Plaintiff, thereby entitling Plaintiff to punitive damages so as to punish Defendants and deter them from similar conduct in the future.

WHEREFORE, Plaintiff demands judgment against Defendants individually, jointly and/or severally and demands compensatory, statutory and punitive damages available under New Jersey law, together

with interest, costs of suit, attorneys' fees and all such other relief as the Court deems just and proper.

* * *

1. Did Bernadette Glynn prove by the preponderance of the evidence that she experienced an atypical femur fracture in April 2009?

   YES _____ NO _____X_____

   (If you answered "NO" to Question #1, please skip to the end, date and sign the verdict form, and inform the court officer that you have reached a verdict. If you answered "YES" to Question #1, please proceed to Question #2.)

2. Did Bernadette Glynn prove by the preponderance of the evidence that her use of Fosamax was a substantial contributing factor to her atypical femur fracture?

   YES _____ NO _____

   (If you answered "NO" to Question #2, please skip to the end, date and sign the verdict form, and inform the court officer that you have reached a verdict. If you answered "YES" to Question #2, please proceed to Question #3.)

3. Did Bernadette Glynn prove by the preponderance of the evidence that Merck should have warned her Fosamax prescribers of a risk of atypical femur fracture prior to her injury and that Ms. Glynn's prescribers would not have prescribed Fosamax to her had they been warned about atypical femur fracture?

   YES _____ NO _____

(If you answered "NO" to Question #3, please skip to the end, date and sign the verdict form, and inform the court officer that you have reached a verdict. If you answered "YES" to Question #3, please proceed to Question #4.)

4. What amount, if any, will fairly and adequately compensate Plaintiff for her pain and suffering related to her injury?

$_____

DATED: TRENTON, NEW JERSEY
APRIL 29, 2013

CARELLA, BYRNE, CECCHI, OLSTEIN, BRODY & AGNELLO, P.C.

COUNSELLORS AT LAW

CHARLES C. CARELLA
BRENDAN T. BYRNE
PETER G. STEWART
ELLIOT M. OLSTEIN
JAN ALAN BRODY
JOHN M. AGNELLO
CHARLES M. CARELLA
JAMES E. CECCHI

JAMES T. BYERS
DONALD F. MICELI
A. RICHARD ROSS
CARL R. WOODWARD, III
MELISSA E. FLAX
DAVID G. GILFILLAN
G. GLENNON TROUBLEFIELD
BRIAN H. FENLON
LINDSEY H. TAYLOR
CAROLINE F. BARTLETT

JAMES D. CECCHI (1933-1995)
JOHN G. GILFILLAN III (1936-2008)

5 BECKER FARM ROAD
ROSELAND, N.J. 07068-1739
PHONE (973) 994-1700
FAX (973) 994-1744
www.carellabyrne.com

RICHARD K. MATANLE, II
FRANCIS C. HAND
AVRAM S. EULE
RAYMOND W. FISHER

OF COUNSEL

RAYMOND J. LILLIE
WILLIAM SQUIRE
ALAN J. GRANT*
STEPHEN R. DANEK
DONALD A. ECKLUND
MEGAN A. NATALE
AMANDA J. BARISICH
ZACHARY S. BOWER+
MICHAEL CROSS

*MEMBER NY BAR ONLY
+MEMBER FL BAR ONLY

August 5, 2013

Via ECF

Hon. Joel A. Pisano
United States District Judge
Clarkson S. Fisher Bldg.
& U.S. Courthouse
402 E. State Street
Trenton, New Jersey 08608

Re: *In re: Fosamax (Alendronate Sodium) Products Liability Litigation*
Master Docket 3:08-08 (JAP)(LHG)

Dear Judge Pisano:

This firm, together with Seeger Weiss LLP, is co-liaison counsel for the plaintiffs in the above-referenced matter. Please accept this letter brief in lieu of a more formal opposition to defendant Merck Sharp & Dohme Corp.'s ("Merck") application for the entry of a show-cause order. (Dkt. No. 2857) Plaintiffs respectfully request that the Court deny Merck's application.

A. Merck's Request for Entry of an Order to Show Cause is Procedurally Improper and Must be Denied.

Plaintiffs oppose the entry of Merck's proposed order because it is an inappropriate procedural mechanism for the adjudication of Plaintiffs' claims. Merck selected this mechanism without any guidance from the Court that Plaintiffs are aware of. Prior to filing, Merck engaged in no pre-motion conference or meet and confer with the Plaintiffs to discuss appropriate scheduling, or whether an order to show cause would be the appropriate means for seeking dismissal in this case. Merck has provided no indication why the use of an order to show cause, as opposed to a standard notice of motion, is warranted here. Clearly, Merck took this posture to avoid the requirements of a Rule 56 Motion for Summary Judgment, which would require Merck to set forth the facts and evidence on which it relied in seeking to preempt the claims of all Plaintiffs subject to the proposed order.

Issuing Merck's proposed order to show cause would be highly prejudicial to Plaintiffs, especially considering that the order concerns a case dispositive issue, such a procedure was never discussed by the Court or Merck in the presence of the Plaintiffs, and the preposterous 30-day timeframe Merck wishes to impose on hundreds of separate Plaintiffs.

At the July 18, 2013 status conference held to discuss how to address the preemption issue in this litigation after the *Glynn* preemption ruling, there was no mention of Merck requesting an order to show cause. Ex. A, Transcript of July 18, 2013 Status

Conference ("Status Conference"). Rather, at the July 18, 2013 conference, the Court indicated that if Plaintiffs did not file a notice of appeal in the *Glynn* case, Merck would be required to file a motion to dismiss all of the pre-label change cases on the basis of preemption. *Id.* at 14:13–15.

An order to show cause is not an appropriate means to resolve the preemption issue in this litigation. As noted in Charles Wright and Arthur R. Miller's treatise on federal procedure, orders to show cause are not provided for in the Federal Rules of Civil Procedure, and parties' use of notices of motions is preferable. Orders to Show Cause and Rules Nisi, 5 Fed. Prac. & Proc. Civ. § 1195 (3d ed.). Generally, such orders are invoked when there is some compelling issue that requires expedited resolution to prevent an imminent harm. The Local Civil and Criminal Rules of the District of New Jersey ("Local Rules") only mention use of orders to show cause in the context of preliminary injunctions, disciplinary proceedings, and arbitration. Local Rules 65.1, 104.1, 201.1. The Local Rules do not contemplate the use of an order to show cause outside of these contexts. And even within the context of issuing a preliminary injunction, the Local Rules specify that:

> No order to show cause to bring on a matter for hearing will be granted except on a clear and specific showing by affidavit or verified pleading of good and sufficient reasons why a procedure other than by notice of motion is necessary.

Local Civil Rule 65.1(a). Without even an attempt to justify the basis for the order to show cause, the Court should deny Merck's request for relief.

B. Entry of Merck's Proposed Order Would Eviscerate Plaintiffs' Due Process Entitlement to be Heard on the Preemption Issue.

Entry of Merck's proposed order to show cause would constitute an egregious violation of due process and accepted standards for the management of complex litigation. The Due Process Clause requires that everyone shall have the protection of their day in court, which "hears before it condemns and proceeds not arbitrarily, but upon inquiry, and renders judgment only [after a full and fair presentation of the evidence] after trial." *Truax v. Corrigan*, 257 U.S. 312, 332 (1921). While aggregation of cases does not per se violate the requirements of due process, any form of aggregation must honor a party's right to due process so as not to run afoul of the U.S. Constitution. Thus, at a minimum, the judicial process must provide a meaningful opportunity for all parties to be heard.

Were the Court to adopt Merck's request to aggregate and dispose of Plaintiffs' suits in the inappropriate manner proposed, the Court would deprive Plaintiffs of their fundamental right to be heard. Following the *Glynn* trial, the Court informed the parties that it would not apply its forthcoming preemption decision in *Glynn* to the remaining Fosamax femur cases pending in the federal litigation. The Court stated on the record that "[t]he point is I'm not going to enter any order which terminates 3300 cases in an MDL. I'm going to enter an order that does or does not terminate Mrs. Glynn's case." Ex. B, Transcript of April 30, 2013 Post-Trial Status Conference, at 25:17-20. The Court further noted that if evidence bearing on preemption was proffered in the

next trial case, *Zessin v. Merck*, the Court would consider such evidence at that time. *Id.* at 20:10-11. Though the time to disclose experts in Zessin had closed, that is not so for any of the other cases in the MDL.

Plaintiffs strongly urge the Court to reconsider its position that the *Glynn* trial record may be used to adjudicate preemption in other cases. As counsel for Plaintiffs informed the Court at the July 18 Status Conference, experts have yet to be designated in any case aside from *Glynn* and *Zessin*, and Merck has turned over many documents to Plaintiffs after it was too late to review them and incorporate them into the *Glynn* trial. Ex. A, Status Conf. Tr. 8:9-9:16; 10:21-11:5. Merck proposes that the unfavorable evidentiary rulings from the *Glynn* trial record, which excluded much of the relevant preemption evidence, be applied to their claims. Merck's attempt to substitute the *Glynn* record, in place of Plaintiffs' constitutionally-entitled day in court, is patently unjust and violates their fundamental rights.

The Court should not allow Merck to fast-track an omnibus decision on a case dispositive issue that concerns the rights of hundreds of injured Plaintiffs. The preemption issue is not ripe for determination on a global basis in the manner proposed. MDL Plaintiffs have not been afforded the opportunity to submit expert reports different from those disclosed in *Glynn*. Merck seeks to deprive hundreds of Plaintiffs from coming forward with their own experts on what was known, knowable, and appropriate to warn of at the different points in time. These hundreds of litigants have not been afforded an evidentiary hearing where they could make their preemption case, present

evidence, and cross-examine Merck's regulatory expert's testimony on the labeling issues. Plaintiffs should be afforded a hearing on preemption that enables them to create a full record, which would incorporate pertinent expert testimony and all relevant materials obtained in discovery, including those provided by Merck during and after the *Glynn* trial.

Plaintiffs also object to the entry of Merck's proposed order because, though preemption is decided as a matter of law by the court, underlying factual issues concerning the state of scientific knowledge over time and the likely regulatory response at distinct points prevent the Court from adjudicating hundreds of Plaintiffs' cases under a single preemption analysis. As the Supreme Court aptly explained, "*consolidation is permitted as a matter of convenience and economy in administration, but does not merge the suits into a single cause, or change the rights of the parties*…." *Johnson v. Manhattan Ry. Co.*, 289 U.S. 479, 496-497 (1993). On this motion, Merck indiscriminately groups Plaintiffs who have not meaningful connection to each other in an attempt to terminate the Fosamax femur litigation. These Plaintiffs did not file their complaints together, they are not represented by joint counsel, and their respective injury dates range over more than a decade. Merck's brief in support of its proposed order acknowledges that the state of the scientific evidence at the time of Plaintiff's injury is centrally relevant to the issue of preemption.[1] The developing science

[1] *See* Def. Br. at 2 n. 1 (acknowledging that "claims that accrued after the release of the American Society of Bone and Mineral Research ("ASMBR") study on September 14, 2010,

related to Fosamax and femur fractures was not stagnant during the broad time period at issue on this motion (1999 through September 10, 2010). Accordingly, there are different arguments as to why preemption is inappropriate for different Plaintiffs subject to this motion, based on the evolving science at the time of different Plaintiffs' injuries.

C. Even If the Court Enters Merck's Procedurally - Undefined and Constitutionally - Violative Order, Plaintiffs Must be Afforded Sufficient Time to Oppose so That They May Clearly Define the Relevant Plaintiff Groups.

At the very least, if the Court enters Merck's proposed order, Plaintiffs should be permitted sufficient time to respond to Merck's sweeping application, as it cannot be done in the 30 day period that Merck has asked for. The grant of appropriate time to respond does not prejudice Merck. By positioning their motion to dismiss as an order to show cause, Merck has sought to shift the burden to Plaintiffs to come forth with evidence, and Plaintiffs' rights and ability to do so should not be constrained to 30 days. The massive coordination effort contemplated in Merck's proposed order tasks Plaintiffs' liaison counsel with coordinating a unified response amongst the hundreds of separate Plaintiffs and the many different law firms (including referring firms) who represent them. It is virtually impossible to responsibly coordinate such an effort within the 30-day time limit Merck proposes.

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might be subject to a different analysis from that undertaken in *Glynn*.")

In order to respond, Plaintiffs must identify the appropriate plaintiff groups, inform their clients of Merck's application, and prepare coordinated responses based on the different injury groups. Merck does not intend to make the necessary evidentiary showing to support its request to dismiss on an individual basis for each Plaintiff. Failure of the Court to allow sufficient time for Plaintiffs to identify the appropriate groupings with which to respond will result in a grave injustice to Plaintiffs. There is a particularly high risk that, if Plaintiffs are not afforded a fair and reasonable time to respond, the Court will overlook the nuanced differences between the timing of Plaintiffs' claims that are necessary to consider on the preemption issue.

Precisely defining and identifying the commonalties among the Plaintiffs is central to the proper adjudication of their legal claims, particularly in a mass tort litigation. "The [Supreme] Courts emerging view is that the Constitution limits common law tort adjudication to those cases between individual parties or well-defined and carefully-circumscribed groups. Under this new model, it is constitutionally inappropriate for a common law court to adjudicate the rights, liabilities, and interests of persons […] who cannot be identified or described with a reasonable degree of specificity at the time of the adjudication." Gifford, *The Constitutional Bounding of Adjudication: A Fuller(ian) Explanation for the Supreme Court's Mass Tort Jurisprudence*, 44 Ariz. St. L. J. 1109 (2012).

In determining what issues are proper for an aggregate ruling, courts have a duty to ensure that cases are properly identified and that the germane

evidence on the issue has been fully developed and vetted, so that the ruling affects only those Plaintiffs whose cases are truly related. According to the Manual for Complex Litigation, the ability of the court to identify the common case features and properly issue aggregate decisions depends on the "maturity" of the litigation.

> Litigations are generally considered mature if through previous cases, (1) discovery has been thorough, producing a consensus that the available important information has been provided, (2) a number of verdicts have been received indicating the value of claims, and (3) Plaintiffs claims have been shown to have merit. […] A "mature" mass tort is one that rests on clearly established law and tested and accepted evidence. […] In a less mature mass tort, [the Manual warns that] aggregation decisions may be more difficult and may require the judge to obtain additional information. […] If there are few prior verdicts, judgments, or settlements, additional information may be needed to determine whether aggregation is appropriate. The need for such information may lead a judge to require a number of single-plaintiff, single-defendant, or other smaller trials. […] As another technique, the judge may stay or defer decisions in the cases before it until more advanced cases or dispositive motions pending in other cases are concluded.

Manual for Complex Litigation, Fourth (2013) § 22.316, Obtaining Information About Common Issues and Case Values.

The Fosamax femur litigation is hardly "mature." Rather, there is new evidence being produced that bears on the preemption issue. Much of evidence on preemption that the Court considered in *Glynn* is heavily contested. Other Plaintiffs have not had an opportunity to challenge Merck's interpretation of the evidence. On a matter of such great magnitude, which potentially affects hundreds of cases in the federal litigation, has broader implications for the larger Fosamax femur litigation, and is of great interest beyond the Fosamax litigation, the Court should proceed with great care, by allowing Plaintiffs a full and fair opportunity to be heard on the issue of preemption.

Conclusion

For all of the foregoing reasons, Plaintiffs respectfully request that the Court deny Merck's application.

Respectfully submitted,

CARELLA, BYRNE, CECCHI,
OLSTEIN, BRODY & AGNELLO

/s/ James E. Cecchi

JAMES E. CECCHI

cc: All Counsel of Record

FOX ROTHSCHILD LLP
ATTORNEYS AT LAW

Mail: P.O. Box 5231,
Princeton, NJ 08543-5231
Princeton Pike Corporate Center
997 Lenox Drive, Building 3
Lawrenceville, NJ 08648-2311
Tel 609.896.3600
Fax 609.896.1469
www.foxrothschild.com

Karen A. Confoy
Direct Dial: (609) 844-3033
Email Address:
kconfoy@foxrothschild.com

August 12, 2013

Via ECF

The Honorable Joel A. Pisano, U.S.D.J.
United States District Court
Court House and Post Office Building
402 East State Street
Trenton, New Jersey 08608

Re: *In re Fosamax (Alendronate Sodium) Products Liability Litigation*
Master Docket 3:08-08 (JAP) (LHG)

Dear Judge Pisano:

Defendant Merck Sharp & Dohme Corp. ("Merck") submits this reply to Plaintiffs' August 5, 2013 letter opposing Merck's request for an Order to Show Cause Why the Claims of Plaintiffs Alleging Injury Prior to September 14, 2010 Should Not Be Dismissed (cited herein as "Pls.' Opp'n").

Plaintiffs argue in their letter that a "show cause" order is procedurally improper and would compromise their due process rights. In effect, Plaintiffs suggest

that the Court and the parties should separately visit the preemption question one case at a time over the next several decades. Plaintiffs' approach would turn the efficiency goals of this MDL proceeding on their head.

The reality is that show-cause orders were designed for precisely the purpose proposed here and that such an order has already been used in this very litigation to accomplish the same result. Plaintiffs' claims of procedural impropriety are therefore frivolous. So too are their invocations of due process. By design, the show-cause approach preserves due process because it affords every affected plaintiff the opportunity to present a basis to distinguish his or her case from the one previously decided (if any such basis exists).

Plaintiffs' objections are particularly improper because they were the ones who selected *Glynn* as the first bellwether trial and promoted the case as being "representative" of the other cases in the litigation. (*See* attached Exhibit A, ECF No. 839,839–1, Plaintiffs' Submission Regarding Bellwether Trial Sections at 4–5.) In fact, in their bellwether trial proposal, Plaintiffs specifically argued that their bellwether trial candidates – including *Glynn* – did "not have case-specific dispositive legal issues and/or [ ] unique factual issues specific to" the particular plaintiffs. (*Id*. at 2.) Thus, Plaintiffs cannot be heard to argue that the preemption ruling in *Glynn* has no relevance to other MDL cases.

Nor is there any reason to heed Plaintiffs' call for more time. As the Court has already recognized, more than enough time has been afforded to all parties to develop a record on preemption. If, for some reason,

any part of this record was omitted from the *Glynn* case (a highly dubious proposition), 30 days provides more than enough time for Plaintiffs to present that evidence to the Court.

A. Entry Of A Show-Cause Order Is Procedurally Proper.

Plaintiffs' contention that a show-cause order "is an inappropriate procedural mechanism for the adjudication of Plaintiffs' claims" (Pls.' Opp'n at 1–2) is precisely backwards. Plaintiffs essentially posit that the same preemption issue should be relitigated in every case, relying largely on the apparent lack of any local rule of procedure expressly authorizing the use of show-cause orders to resolve dispositive issues. (*See generally id*.) This argument makes no sense.

For one thing, it ignores ample on-point case law – including precedent from this very multidistrict proceeding. As Merck's opening brief pointed out, MDL courts routinely use show-cause orders to evaluate whether a ruling in one case is determinative of other member cases. *See*, *e.g.*, *Schadle v. Qualitest Pharm., Inc.* (*In re Darvocet, Darvon & Propoxyphene Prods. Liab. Litig.*), No. 2:12-159-DCR, 2012 WL 3290145, at *1 (E.D. Ky. Aug. 10, 2012); *In re Allstate Ins. Co. Fair Labor Standards Act Litig.*, No. 2:03md1541, 2009 WL 3011042, at *1 (D. Ariz. Sept. 16, 2009) (Def.'s Br. at 8–9); *see also*, *e.g.*, *In re Deep Vein Thrombosis Litig.*, No. 04-106 VRW, 2005 WL 1422349, at *1 (N.D. Cal. June 17, 2005) (recounting how court issued order directing plaintiff to show cause why his case should not be dismissed under reasoning in prior preemption order); *In re Sulzer Hip Prosthesis & Knee Prosthesis Liab. Litig.*, 455 F. Supp.

2d 709, 713 (N.D. Ohio 2006) (observing that court entered order directing plaintiffs to show cause why their claims should not be dismissed in light of opinion that dismissed a member case on preemption grounds). Where plaintiffs fail to distinguish their claims from those rejected in such a ruling, courts routinely resolve legal issues and dismiss those claims based on simple application of the prior decision. *See*, *e.g.*, *Naydeck v. Merck Sharp & Dohme Corp.* (*In re Fosamax Prods. Liab. Litig.*), Nos. 10 Civ. 4831(JFK), 06 MD 1789(JFK), 2013 WL 271741, at *3 (S.D.N.Y. Jan. 24, 2013); *Darvocet*, 2012 WL 3290145, at *1; *Allstate*, 2009 WL 3011042, at *1. And even though local rules do not address show-cause orders in this context (Pls.' Opp'n at 2), the Court has already made clear that it believes such procedures are appropriate by using a show-cause order to apply a dispositive ruling in prior cases – on a preemption issue, no less. (*See* Def.'s Br. at 9 (summarizing this Court's entry of order directing Plaintiffs to show cause why their claims against Generic Defendants should not be dismissed based on prior preemption ruling); *cf.* Pls.' Opp'n at 2 (arguing without relevant citation that an "order to show cause is not an appropriate means to resolve the preemption issue in this litigation").) Plaintiffs do not even attempt to address this on-point precedent.[1]

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[1] Plaintiffs also contend that the Wright & Miller treatise advises against the use of motions to show cause (*see* Pls.' Opp'n at 2), but the same section of the treatise acknowledges that "a request for a show cause order usually will be entertained and treated as a motion, if doing so will not prejudice the opposing parties." 5 Charles Alan Wright et al., *Federal Practice & Procedure* § 1195 (3d ed.).

Plaintiffs' position not only ignores ample case law adopting the show-cause approach but would also destroy the efficiency that is the promise of coordinated MDL proceedings. "The goal of the [MDL] process is to 'promote the just and efficient conduct' of 'civil actions involving one or more common questions of fact' that are pending in different districts." *In re Asbestos Prods Liab. Litig. (No. VI)*, 718 F.3d 236, 243 (3d Cir. 2013) (citation omitted). The aim of efficiency is secured by ensuring that "hundreds or . . . thousands . . . of cases, coordinated, will proceed toward resolution on the merits with less burden and expense overall than were each litigated . . . individually." *In re Phenylpropanolamine (PPA) Prods. Liab. Litig.*, 460 F.3d 1217, 1229 (9th Cir. 2006). Here, a show cause order would achieve that goal. As this Court recognized in *Glynn*, the critical question for preemption purposes is whether "there is 'clear evidence that the FDA would not have approved a change' to the prescription drug's label" prior to a plaintiff's injury. *Glynn v. Merck Sharp & Dohme Corp.* (*In re Fosamax Prods. Liab. Litig.*), Nos. 11-5304, 08-08, --- F. Supp. 2d ---, 2013 WL 3270387, at *7 (D.N.J. June 27, 2013) (quoting *Wyeth v. Levine*, 555 U.S. 555, 571 (2009)) (footnote omitted). The Court held that Merck had produced "clear evidence" to demonstrate that the FDA would not have approved a Warning or Precaution regarding low-energy femoral shaft fractures prior to her injury, and it consequently deemed the plaintiffs' claims preempted. *Id.* The Court's holding in *Glynn* is squarely applicable to other similar cases, and it is far more efficient to resolve that issue in a coordinated manner

than to do so case by case over the course of several years or decades.[2]

In truth, providing each of the "hundreds of litigants . . . an evidentiary hearing" (Pls.' Opp'n at 3), as Plaintiffs propose, would subvert the MDL process. The preemption question is common across the group of plaintiffs identified in Merck's motion and turns on legal questions – not individualized factual ones. Moreover, it has already been resolved after exhaustive deliberation in *Glynn*. Accordingly, the most efficient course is to enter an order to show cause that could potentially dispose of a significant number of cases in this MDL proceeding.[3]

B. Entry Of A Show-Cause Order Fully Comports With Due Process.

Plaintiffs next maintain that "[e]ntry of Merck's proposed order to show cause would constitute an egregious violation of due process and accepted standards for the management of complex litigation"

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[2] Plaintiffs' allusion to the "developing science related to Fosamax and femur factures . . . during the broad time period at issue on this motion" (Pls.' Opp'n at 4), misunderstands the issue. The critical question for purposes of the preemption issue is whether the *FDA* would have approved a Fosamax label that addressed the alleged risks of femoral fracture. Thus the only relevant scientific development was the release of the ASBMR study on September 14, 2010, which prompted the FDA to reconsider label revisions. Plaintiffs have not identified any further evidence suggesting that the FDA would have approved a Warning or Precaution regarding atypical low-energy femoral factures prior to September 14, 2010.

[3] Plaintiffs also complain that Merck did not consult with them prior to filing its motion (Pls.' Opp'n at 1), but Merck knows of no requirement for such consultation, and Plaintiffs cite none.

because it would "deprive Plaintiffs of their fundamental right to be heard." (Pls.' Opp'n at 2–3.) The apparent premise of this argument is that a show-cause order would operate to adjudicate thousands of cases on an aggregate basis without affording individualized consideration to each case. (*See id*. at 3–4.) Not so.

"'[T]he essential requirements of due process . . . [are] notice and an opportunity to respond.'" *Ross v. Duggan*, 402 F.3d 575, 584 (6th Cir. 2004) (quoting *Cleveland Bd. of Educ. v. Loudermill*, 470 U.S. 532, 546 (1985)). Thus, dismissal of a plaintiffs claims does not offend due process as long as the plaintiff is given the opportunity to brief the legal issues and oppose dismissal. *See*, *e.g.*, *Molosky v. Wash. Mut., Inc.*, 664 F.3d 109, 119–20 (6th Cir. 2011); *In re Bartle*, 560 F.3d 724, 730 (7th Cir. 2009).

For these reasons, MDL courts have rejected due process challenges to show-cause orders intended to facilitate expeditious resolution of constituent cases. In the *Diet Drugs* litigation, for example, the MDL court upheld the use of a show-cause procedure that determined one plaintiff to be ineligible for settlement under a class settlement agreement. *In re Diet Drugs (Phentermine/Fenfluramine/Dexfenfluramine) Prods. Liab. Litig.*, No. 99-20593, 2006 WL 3791338 (E.D. Pa. Dec. 20, 2006). To prove eligibility for settlement, claimants had to submit (among other things) proof of left atrial enlargement. *Id*. at *1. The settlement also provided for an audit of such claims, and in one such audit, the claimant's assertion of left atrial enlargement was rejected, which triggered a show-cause process in which the claimant had to provide evidence proving eligibility for settlement. *Id*. After

the claimant failed to produce credible countervailing evidence and her claim was rejected, she argued that the show-cause process violated her due process rights. *Id*. at *2. The MDL court rejected this claim as "meritless." *Id*. at *3. As the court explained, "[t]he audit and show cause process, as approved by this court, compl[ies] with due process requirements, as claimant has had notice and an opportunity to present her evidence in support of her claim." *Id*.

The show-cause procedure proposed by Merck affords Plaintiffs the same sort of "notice and an opportunity to present [their] evidence." Responding to the show-cause order would give each Plaintiff a meaningful opportunity to fully brief every issue, present any supposed evidence that was not presented in *Glynn* or its aftermath, and identify any ostensible case-specific issues.

C. Thirty Days Is Sufficient Time For Plaintiffs To Respond.

Plaintiffs finally complain that they need more than 30 days to respond because: (1) the tasks of "identify[ing] the appropriate plaintiff groups," informing clients, and "coordinat[ing] responses based on the different injury groups" will be too burdensome in light of the number of parties and law firms involved; and (2) the relevant evidence has yet to be "fully developed and vetted." (Pls.' Opp'n at 5–6.) These arguments lack merit.

First, there are no "different injury groups" (*id*. at 5) or any other material differences among the remaining Plaintiffs with respect to the preemption issue. Notably, while Plaintiffs repeatedly suggest that subsequent cases will present different facts that

will materially alter the preemption analysis, they do not offer any examples of these supposedly different facts. The central preemption question in each case is whether the FDA would have allowed a label revision prior to September 14, 2010. Thus, Plaintiffs' insistence that they must be afforded time to summon "pertinent expert testimony" or other "relevant materials" specific to individual cases (*id*. at 4) is nonsensical.

Second, the notion that the record on preemption is not yet "fully developed and vetted" (*id*. at 5) is preposterous, as evidenced by the fact that it was never suggested prior to the bellwether *Glynn* trial.[4] The issue of federal preemption – and its application to Fosamax Plaintiffs' claims – has been front and center in this litigation since its inception. Plaintiffs have had years to gather evidence related to preemption arguments in the MDL proceeding and in fact did just that. For example, the Plaintiffs' Steering Committee deposed a number of key Merck witnesses whose testimony is relevant to the issue of preemption well in advance of the first bellwether trial in *Glynn*, including: (1) James Adams, a former member of global regulatory affairs for Fosamax at Merck; (2) Dr. Elinor Chen, a Merck regulatory liaison; (3) Dr. Anastasia Daifotis, a former vice president of global medical affairs at Merck with overall responsibility for Fosamax; and (4) Dr. Arthur Santora, Executive Director for the Clinical Development of Fosamax.

Based on this and other evidence identified by the parties, the Court carried out a thorough and

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[4] Indeed, general fact discovery of Merck concluded on December 31, 2012. CMO No. 10, ¶ 1.2.

deliberate analysis of the preemption question in *Glynn*, hearing arguments and evidence at a month-long trial and through three separate rounds of briefing. *See Glynn*, 2013 WL 3270387, at *5. Shortly before its preemption ruling, reflecting on the months of work by all parties and the Court on the preemption issue, the Court expressed disbelief that any further discovery or development of the record could be required. In the Court's words, the notion that more discovery is required is "'not an argument [Plaintiffs" should be making'" at this point, and "'I don't know what more you want to put in the record.'" (*See* Def.'s Br. at 6–7 (quoting trial transcripts).) Nevertheless, Plaintiffs submitted a nearly 60-page post-trial brief, featuring 62 exhibits, consisting largely of new evidence not presented at trial. *See* 2013 WL 3270387, at *9. Stressing the "several opportunities" given to Plaintiffs "to introduce evidence in opposition to preemption," the Court concluded that Plaintiffs had "not refuted the fact that clear evidence exists" to support a finding of preemption — and that even Plaintiffs' new evidence could not undermine that conclusion. *Id.* Thus, contrary to Plaintiffs' assertion (Pls.' Opp'n at 6), the record on preemption is very "mature" at this stage, and 30 days is ***more*** than enough time to respond to a show-cause order.

In short, there is no good reason to deny or delay the relief Merck seeks. Accordingly, Merck respectfully requests that the Court grant its request for an order to show cause.

Respectfully submitted,

s/ Karen A. Confoy
Karen A. Confoy

Enclosure

cc: Counsel of Record (via ECF)

EXHIBIT A

W E I T Z
&
L U X E N B E R G
A PROFESSIONAL CORPORATION
LAW OFFICES
700 BROADWAY NEW YORK, NY 10003-9536
TEL. 212-558-5500 FAX 212-344-5461
WWW.WEITZLUX.COM

April 30, 2012

Via Electronic Mail and ECF
The Honorable Joel A. Pisano, USDJ
United States District Court
Court House and Post Office Building
402 East State Street
Trenton, New Jersey 08608

Re: Fosamax MDL 2243; Bellwether Trial Selections

Dear Judge Pisano,

I am writing on behalf of the Plaintiffs to submit the following as the factual summaries of the six (6) selected Fosamax femur fracture cases and to set forth our position regarding which cases are appropriate and representative bellwether trial selections pursuant to Case Management Order 9. Attached is the final submission in this regard.

Very truly yours,

WEITZ & LUXENBERG, P.C.

By: /s/ *Edward Braniff*
Edward Braniff

Enclosures (1)

cc: David J. Heubeck, Esq. (w/encl.)
(via ECF and email)

Karen A. Confoy, Esq. (w/encl.)
(via ECF and email)

Christopher Seeger, Esq. (w/encl.)
(via ECF and email)

David R. Buchanan, Esq. (w/encl.)
(via ECF and email)

Paul J. Pennock, Esq. (w/encl.)
(via ECF and email)

James E. Cecchi, Esq. (w/encl.)
(via ECF and email)

Chris Midura, Esq. (w/encl.)
(via ECF and email)

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: FOSAMAX (ALENDRONATE SODIUM) PRODUCTS LIABILITY LITIGATION (No. II) *This Document Relates To All Actions*	MDL No. 2243 Civ. No. 08-08(JAP) (LHG) **Plaintiffs' Submission regarding Bellwether Trial Selections**

Background on Atypical Subtrochanteric and Diaphyseal Femur Fractures

Fosamax (alendronate sodium) is a medication that belongs to a class of drugs known as bisphosphonates. Bisphosphonates are approved for the treatment of certain metabolic bone diseases such as osteoporosis, but have been under serious scrutiny from the pharmacological and clinical communities for some time over the long-term effects they have in bone. In particular, studies have found and it is generally accepted that Fosamax will cause highly irregular, patterned, and thus atypical subtrochanteric and diaphyseal femoral fractures. Before the advent of Fosamax, subtrochanteric and diaphyseal femur fractures were always accompanied by high trauma (*e.g.*, car crashes, accidents, etc.) and were essentially nonexistent in the medical literature because there was nothing unique about such a fracture in the context of such severe trauma. Now, however, they are recognized as fractures that can be and are regularly induced by Fosamax.

Case Selection Factors

The Plaintiffs submit that in selecting appropriate and representative bellwether trial cases there are certain factors that should weigh heavily. It is important that these factors inform the Court, Merck and the Plaintiffs on the fundamental issues of liability and causation across the majority of cases, not a minority of unusual cases. The cases selected should not have case-specific dispositive legal issues and/or a unique factual issues specific to that plaintiff. Cases without unique case specific facts will serve the bellwether purpose by being instructive on a macro level, and not subject the individual case to a potential dismissal or defense verdict because of a unique fact or series of facts. Similarly, if a unique case-specific dispositive legal argument/issue exists, that too should prevent that case from being selected as final bellwether trial case. In the event Merck prevails on such an issue, there would be a nullification of the entire bellwether process as there will be no clearer general understanding of liability and causation. The massive amount of time, personnel, and financial resources expended by the Court and parties will not move the litigation forward, if a case littered with unusual facts and issues of law is selected. All three of the defendants' selections have unusual complications.

In contrast, all three of the proposed Plaintiff cases involve the atypical, subtrochanteric or diaphyseal femoral fractures that plaintiffs' experts opine are the most highly associated with prolonged use of Fosamax. In their review of the aggregated scientific and medical data, plaintiffs' experts are of the view that bisphosphonate-associated femoral fractures most

typically exhibit several features that Plaintiffs believe should also be present in this litigation's bellwether selections. These fractures are usually caused by "low-energy," moderate to no trauma (e.g., fall from standing height or less), are subtrochanteric (below the femoral neck) or diaphyseal (in the femoral shaft), are generally transverse (perpendicular to the femoral shaft), or short oblique (diagonally oriented) in their fracture configuration, are not noncomminuted or if comminution is present, it is minimal (the bone is not "shattered"), and the break usually extends cleanly through both cortices of the bone in a "complete" break (when it does not, incomplete fractures involve only the lateral cortex). Other characteristics that often present with these Fosamax-related injuries include the potential for "beaking" or "flaring" of the lateral cortex (a periosteal reaction to the stress fracture), generalized increase in cortical thickness of the femoral shaft, prodromal dull or aching pain in the groin or thigh appearing weeks to months prior to fracture, bilaterality of the fracture (both legs are often affected), and delayed healing. Plaintiffs would encourage the bellwether selections' fractures to conform with and display as many of these abovementioned criteria as possible.

Also, to be truly representative of the larger pool of cases in this mass tort, the bellwethers should not have unusual and unique co-morbid conditions that defendants can use to either complicate questions of Merck's tort liability or the degree of damages the plaintiff suffered. Plaintiffs urge that atypical medical and social history be avoided in the bellwether selections. Therefore, we respectfully submit that the Court should exclude current smokers and alcoholics,

those currently undergoing chemotherapy or radiation treatment, have metabolic disorders or diseases such as diabetes or have significant genetic, metabolic or endocrine-related bone disorders, are significant users of other complicating medications (glucocorticoids, heparin, or methotrexate, selective serotonin reuptake inhibitors (SSRIs) and proton pump inhibitors (PPIs)). All of defendants' selections have one or more of these unnecessary and inappropriate complicating factors. While such cases can and do present meritorious claims, they are so different from the mass of filings that they should not lead this litigation.

Bellwether Summaries

Below please find the Plaintiffs' factual summary of each of the six (6) bellwether cases, including the facts that render some of these cases more appropriate and representative bellwether trial selections, and the facts of others that make them less instructive to serve as bellwether cases.

***Bernadette Glynn v. Merck Sharp and Dohme Corporation*, MDI, Docket No. 3:11-cv-05304-GEB-LHG**[1]

I. Personal Background

Bernadette Glynn was a 54-year-old married mother of two adult children who had been taking Fosamax for six years at the time of her left femoral fracture on April 17, 2009. Mrs. Glynn is a Caucasian women living in upstate New York, perennially traveling to Florida during the winter months with her husband, Richard Glynn. She is a part-time librarian

[1] Plaintiff's counsel in this case is Perry Weitz of Weitz & Luxenberg, PC.

at a local elementary school and enjoys exercise[2] and the outdoors with her friends and husband.

II. Fosamax Use and Injury

Mrs. Glynn began Fosamax use on March 6, 2003 and testified that she used it continuously until April of 2009. The available records indicate consistent use for weekly dosages from June 28, 2005 to February 22, 2008 whereupon she began generic alendronate use through April of 2009. On April 17, 2009, Mrs. Glynn was carrying items from her garage to the front yard. She testified that she felt a pinch in her left femur, she massaged the area and began to move forward and felt the pinch again. Mrs. Glynn massaged the area again and when she tried to move, she felt pain. She screamed and crumbled to the ground, experiencing what felt like the 'bones rubbing against each other.' She called 911 from her cell phone as no one was home.

Mrs. Glynn was transported to the hospital via ambulance where she underwent open reduction-internal fixation surgery to repair the fractured femur. Following surgery, Mrs. Glynn had extensive physical and occupational therapy during a 4-day hospital stay, 9-day nursing home stay and later at her own residence upon discharge from the nursing home. She still has had residual femur pain and experiences pain in her opposite femur. She has sought the consultation of other physicians for these conditions.

Mrs. Glynn's has a previous history as a smoker of a 1/2 pack per day for 40 years (she quit in the early 2000s) and potentially suffered from

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[2] Plaintiff Glynn regularly engaged in 20 mile or longer bicycle trips prior to femur fracture.

hyperparathyroidism, a condition masked by her Fosamax use.

Mrs. Glynn's case is a very representative case and would be an excellent selection as an initial bellwether trial. Her case involves a low-trauma injury following extensive Fosamax use in which there are no concomitant conditions or medications that compromise her bone quality nor has she sustained previous fractures. She is a young woman with an active lifestyle. This case would help inform the Court, Merck and the Plaintiffs on the very fundamental issues of liability and causation.

***Eleanor On aka v. Merck Sharp and Dohme Corporation*, MDL Docket No. 3:11-cv-05302-GEB-LHG**[3]

I. <u>Personal Background</u>

Eleanor Onaka was a 78-year-old married mother of two adult children who had been using Fosamax for six years prior to her left femoral fracture on June 30, 2009. Mrs. Onaka is a Japanese-American woman living in a single family home in Honolulu, HI with her husband, Harry Onaka. They live near both her son and daughter's families and enjoy spending time together. Mrs. Onaka was previously part-owner and worker in her family-owned grocery in Honolulu. She has additionally traveled and lived in several parts of Asia with her husband, a federal government employee and veteran of American military service during WWII and the Korean War. Both are now

[3] Plaintiff's counsel in this case is Perry Weitz of Weitz & Luxenberg, PC.

retired and Mrs. Onaka enjoys their family, church volunteer work and her lifelong passion for gardening.

II. Fosamax Use and Injury

Mrs. Onaka filled her first Fosamax prescription for 10 mg daily tablets on February 2, 2003 and switched to 70 mg weekly Fosamax tablets on June 28, 2004. She then began using Fosamax Plus D beginning on November 15, 2006 and continued until she was switched to generic alendronate sodium on August 4, 2009. Mrs. Onaka, at the age of 78, suffered an "atypical fracture of her left femur on alendronate therapy" per her surgical records dated June 30, 2010.

On the day of her fracture, Mrs. Onaka was gardening outside her home. She had been sitting on a gardening stool and picking it up at intervals to move to different locations. When her husband called her to lunch, Mrs. Onaka began standing up from her stool. She heard a loud crack in her left femur and crumbled to the ground, yelling for her husband to help her. She remained in the yard until the ambulance arrived.

After being transported to the hospital by emergency medical staff, Mrs. Onaka underwent open reduction-internal fixation surgery to repair the femur. The femur was reamed from the trochanter extending distally. A titanium rod was then inserted into the femur and attached at the trochanter with a pin to hold it in place. She had an initial 8-day stay in the hospital, and then received physical and occupational therapy during a 12-day stay in a rehabilitation facility. Prior to her discharge from rehabilitation, her family members had to make several alterations to her home due to her injury

including a ramp from ground level to the garage door to facilitate a more fluid transition to her post-surgery life. Today, she ambulates without aid, but is constantly monitored for signs of fracture in her opposite femur.

Eleanor Onaka's case is a very representative case and is a good bellwether trial selection. Her case involves an atypical, non-traumatic femoral fracture following an extended 7½ years of alendronate sodium use, without previous fracture or bone-compromising conditions or concomitant medications. She lives a healthy active lifestyle. This case would help inform the Court, Merck and the Plaintiffs on the very fundamental issues of liability and causation.

***Marilyn Young v. Merck Sharp and Dohme Corporation*, MDL Docket No. 3:11-cv-03225-GEB-LHG**[4]

I. <u>Personal Background</u>

Marilyn Young is a 74-year-old widowed mother of two adult children and grandmother to four grandchildren from San Jose, California. Mrs. Young was prescribed Fosamax for approximately three years prior to experiencing a right femoral fracture. She continued with Fosamax use for another three years and then experienced a second femoral fracture, this time on the left side. Mrs. Young enjoys spending time with her family, gardening and shopping. Each of these passions has been affected by her bilateral femoral fractures.

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[4] Plaintiff's counsel in this case is Dave Buchannan of Seeger Weiss LLF.

II. Fosamax Use and Injury

Mrs. Young was diagnosed with osteoporosis in 2001 and began taking Actonel, another type of the bisphophonate class of drug. She was switched to Fosamax on August, 23, 2003. In February 2006, she switched to Fosamax Plus D which she continued taking until October 9, 2009.

While moving to sit on her couch she sustained a right mid-femur fracture in June 2006. She underwent surgical intervention, received rehabilitation in the hospital for seven days and endured physical therapy upon release. Starting in October of 2006 she began suffering from residual pain in her right leg, which was diagnosed as non-union of her femur fracture. Due to the non-union of her femur fracture, she had to undergo a second surgery in December, 2007, in which the screws of her previous implant were removed. Although she has some pain and limitations that have persisted, her condition has been improving.

However, in June 2009, while walking into her daughter's house, she sustained a second femur fracture. This break occurred in her opposite (left) femur. Treatment included a 3-day hospital stay, surgical repair, and extensive physical therapy.

Although Marilyn Young suffered two Fosamax related fractures, there are other cases among the thousands of Fosamax cases across the country that also suffered two fractures. Despite the dual fractures, it is a representative case and is a good bellwether trial selection. Her case involves an atypical, non-traumatic femoral fracture following just under 5 years of bisphosphonate use, without previous

fracture, followed by another fracture after continued alendronate sodium use. While Ms. Young has been previously diagnosed with Grave's Disease and did take thyroid medication for an extended period prior to and concurrent with her Fosamax use, she has otherwise lived a healthy and active lifestyle.

Defense Selections:

***Ruth Berlin v. Merck Sharp and Dohme Corporation*, MDL Docket No. 3:11-cv-05720-GEB-LHG[5]**

I. <u>Personal Background</u>

Ruth Berlin is 4'9", 135 lbs and recently celebrated her 72nd birthday. She lives in Silver Spring, MD with her husband Arthur. She has three children, each in their 40's. She is a retired elementary school teacher for Montgomery County public schools. She enjoys playing mahjong, traveling, being active, and until suffering her femur fracture, was a member of her church's choir.

II. <u>Fosamax Use and Injury</u>

Ms. Berlin claims Fosamax use beginning in October, 1999, continuing through May, 2011. She began using generic Fosamax in January of 2009. After 2 1/2 years of generic sodium alendronate use, Ms. Berlin suffered a femoral fracture in June of 2011.

Ms. Berlin is not a suitable selection for bellwether trial due to several factors. There are several conditions from which Ms. Berlin suffers. Plaintiff has suffered from endometrial cancer, chemotherapy,

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[5] Plaintiff's Counsel in this case is Dylan Nelson Esq., of the law firm Aaron Levine & Associates.

radiation, and corticosteroid use. These conditions render Ms. Berlin's case an unrepresentative of the currently pending cases.

Additionally, after she was selected as part of the Early Discovery Cases, Plaintiff's counsel discovered that Ms. Berlin had suffered a spinal fracture just prior to her initial Fosamax prescription. Such a significant fracture unrelated to her medication use, would potentially result in the jury deciding this case on unique case-specific issues that do not generally inform on the fundamental issues liability and causation.

***Judith Hoholik v. Merck Sharp and Dohme Corporation*, MDL Docket No. 3:11-cv-05305-GEB-LHG[6]**

I. Personal Background

Judith Hoholik is a retired 73-year-old resident of Perry, Michigan. Mrs. Hoholik is married for 53 years and has four adult children and nine grandchildren. She enjoys spending time with her grandchildren, reading, and crafts.

II. Fosamax Use and Injury

Mrs. Hoholik used Fosamax between March of 2005 and March of 2009. During this period, she sustained left femoral neck fracture on February 2, 2009. Due to the location of the fracture in the femoral neck, not the subtrochanteric area as are the majority of cases, Mr. Hoholik's fracture is not an appropriate bellwether trial case.

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[6] Plaintiff's Counsel in this case is Jonathan Mencel Esq., of the Charles Johnson Law Firm.

More importantly, Mrs. Hoholik claims she only received Fosamax by way of samples from her primary care doctor, and thus there are no pharmacy records available to the parties to confirm her usage, its dosage or duration. Most of the supporting documentation of Mrs. Hoholik's Fosamax use is contained within her personal diary and calendars, and was not fully confirmed by her pharmacy records, doctors' records and doctors' testimony. Although such evidence is more than sufficient for plaintiff to meet her prima facie burdens, there will be "a trial with a trial" on the issue of usage and most cases will not suffer from that deficiency. There will be yet another "trial with in a trial" issue with regard to usage, as to whether she took brand-name Fosamax or generic alendronate during the period the drug was available in generic form, to the date of Plaintiff's injury. The open questions of duration, dosage and use of brand-name Fosamax in Mrs. Hoholik's case renders it a poor representative for bellwether selection.

Beyond the issues of duration, dosage, and use, Mrs. Hoholik is a Michigan resident. Her Fosamax use and injury both occurred in Michigan. The choice of law analysis regarding the application of Michigan's Tort Reform Act might require the Court to engage in a public policy analysis of applying that claim-barring law and perhaps even a Constitutional analysis. Therefore, the choice of law analysis will be far more complicated than in 90% of the pending cases because of the stringent Michigan law purporting to bar personal injury claims for prescription drug injuries.

***Deloris Zessin v. Merck Sharp and Dohme Corporation*, MDL Docket No. 3:11-cv-03918-GEB-LHG; 3:11-cv-03919-GEB-LHG**[7]

I. Personal Background

Deloris Zessin was a 74-year-old, married mother of three who had been taking Fosamax for approximately 10 years before she suffered a left distal femur fracture on April 23rd, 2007. Deloris is an avid golfer. She is a non-smoker who lived with her husband until he passed away in September, 2011. Deloris has a history of lumbar spinal stenosis and osteoarthritis affecting her lower extremities. She has a family history positive for heart disease, cancer and arthritis.

II. Fosamax Use and Injury

Mrs. Zessin claims that she has used Fosamax consistently from October 1997, through December of 2007. Mrs. Zessin testified that her family physician, Dr. Larry Birch, provided her with samples of Fosamax during this time. In late December, 2006, Mrs. Zessin began experiencing leg and muscle pain that increased when walking up stairs. She sought the medical advice of her family physician, who recommended that she see a specialist and was given epidural injections for the pain. On April 23, 2007 Mrs. Zessin fell to the ground while pushing a self propelled lawnmower on her level driveway. She was taken to Faith Regional Hospital, in Norfolk, Nebraska by emergency medical staff. Upon admission, she was diagnosed with a fracture of the

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[7] Plaintiff's counsel in this case is Edward Braniff of Weitz & Luxenberg PC.

femoral diaphysis between the middle and distal third of the femur.

Mrs. Zessin spent four days in the hospital and was discharged on April 27, 2007. She was told to discontinue Fosamax in December of that year, due to concerns relating to osteonecrosis of the jaw. Her pharmacy records indicate that she started taking Evista 60mg tablets on December 12, 2007 afterwards switching to generic alendronate sodium on February 23, 2008.

Mrs. Zessin's medical history complications include: previous hip stress fracture, osteoarthritis, bilateral total knee arthroplasty, calcium and vitamin D deficiencies and a diagnosis of degenerative joint disease concurrent with spinal stenosis. As such, Mrs. Zessin's case is not a representative case and will not inform the Court, Merck or the Plaintiffs in a meaningful way nor will her trial move the litigation forward. The jury will be mired in resolving very unique case-specific issues that do not inform on the fundamental issues of failure to warn, liability and causation.

Conclusion:

The ultimate trial selections should be representative of other cases so that the parties and the Court can achieve the desired results of a bellwether trial. The Plaintiffs strongly urge the Court to select cases that address the fundamental issues of liability and causation, and not those that present issues that are case-specific and/or unique to the given bellwether case.

For the reasons set forth above, the Plaintiffs respectfully request that the Court select the following

three, above-described cases for the trial pool: Bernadette Glynn, Eleanor Onaka and Marilyn Young.

Respectfully submitted,

/s/ Edward Braniff
Edward Braniff

Karen A. Confoy
FOX ROTHSCHILD, LLP
Princeton Pike Corporate Center
997 Lenox Drive, Building 3
Lawrenceville, NJ 08648
Telephone: (609) 896-3600
Facsimile: (609) 896-1469
Attorneys for Defendant Merck Sharp & Dohme Corp.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

IN RE: FOSAMAX (ALENDRONATE SODIUM): PRODUCTS LIABILITY LITIGATION **THIS DOCUMENT RELATES TO:** All Actions	**MDL No. 2243** Master Docket No. 08-08 (JAP)(LHG)

ORDER TO SHOW CAUSE WHY THE CLAIMS OF PLAINTIFFS ALLEGING INJURY PRIOR TO SEPTEMBER 14, 2010 SHOULD NOT BE DISMISSED

This MDL consists of products liability suits concerning Fosamax, a prescription bisphosphonate medicine indicated for, *inter alia*, the treatment and prevention of osteoporosis. Plaintiffs in these cases assert state law claims against Merck Sharp & Dohme Corp. ("Merck") – the manufacturer of Fosamax – alleging that Fosamax caused plaintiffs to suffer atypical femur fractures. Plaintiffs' claims all emanate

from a general theory that Merck failed to provide an adequate warning about the risk of such fractures.

On June 27, 2013, after affording the Plaintiffs' Steering Committee ("PSC") and Glynn's counsel repeated opportunities to present their evidence, this Court entered judgment as a matter of law for Merck in the bellwether *Glynn* case on the ground that federal law preempts claims like the *Glynn* plaintiffs' claims against Merck. *See Glynn v. Merck Sharp & Dohme, Corp.*, Case Nos. 11-503, 08-08, --- F. Supp. 2d ---, 2013 WL 3270387 (D.N. Jun. 27, 2013). The Court reached this decision because Merck had presented clear evidence that the FDA would not have approved a Warning or Precaution about low-energy subtrochanteric or femoral shaft fractures in the Fosamax label prior to Mrs. Glynn's injury. *Id.* at *7.

IT APPEARING TO THE COURT, based on all of the evidence presented by the parties in *Glynn*, including the evidence presented at trial, that there is clear evidence that the FDA would not have approved a Warning or Precaution about low-energy subtrochanteric or femoral shaft fractures in the Fosamax label before the American Society for Bone and Mineral Research ("ASBMR") released its first report on bisphosphonates and atypical femur fractures on September 14, 2010; and

IT APPEARING TO THE COURT that the plaintiffs listed in Appendix A to this Order allege they incurred injuries before September 14, 2010; and

IT APPEARING TO THE COURT that the plaintiffs listed in Appendix A assert claims all emanating from a general theory of failure to warn and that the claims

are therefore preempted under this Court's ruling in *Glynn*; and

IT APPEARING TO THE COURT that there is a need to ensure consistency in connection with all complaints that are pending in this MDL,

IT IS on this 13th day of August 2013,

ORDERED that the plaintiffs identified in Appendix A, through their liaison counsel, SHOW CAUSE why their pre- September 14, 2010 injury claims should not be dismissed on preemption grounds pursuant to this Court's ruling in *Glynn* and any briefs and supporting papers shall be filed within ~~thirty (30)~~ **45** days of entry of this order; it is further

ORDERED that Merck shall have thirty (30) days to file a reply to plaintiffs' response to this Order; it is further

ORDERED that the Court may schedule oral argument at its discretion; it is further

ORDERED that plaintiffs' liaison counsel shall ensure that all plaintiffs receive a copy of this Order.

s/ Joel A. Pisano
Hon. Joel A. Pisano
United States District Judge

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: FOSAMAX (ALENDRONATE SODIUM) PRODUCTS LIABILITY LITIGATION (No. II)	MDL No. 2243 Civil Action No. 3:08-cv-08(JAP)(LGH) **DECLARATION OF JAMES E. CECCHI**
THIS DOCUMENT APPLIES TO: ALL ACTIONS REFERENCED IN EXHIBIT A TO THE COURT'S ORDER TO SHOW CAUSE	

JAMES E. CECCHI declares as follows:

1. I am a member of the law firm of Carella, Byrne, Cecchi, Olstein, Brody & Agnello, P.C. ("Carella, Byrne"), and am an attorney admitted to practice before this Court. I have personal knowledge of the matters set forth herein. If called as a witness, I could competently testify to the matters set forth herein.

2. I respectfully submit this Declaration in response to the Order to Show Cause.

3. Carella, Byrne and Seeger Weiss LLP are the Court-appointed Co-Liaison Counsel for the Plaintiffs in the above-captioned litigation.

4. Pursuant to the Order to Show Cause, Co-Liaison Counsel and members of the PSC endeavored to reach counsel for all Plaintiffs identified on Exhibit A to ensure that all Plaintiffs received a copy of this Order.

5. Our efforts included, among other tasks, reviewing the master docket and conducting on-line investigations to ascertain counsel email addresses. In addition, my firm placed telephone calls to more than 20 law firms for whom we could not identify an email address and advised them to call my firm and speak with Donald Ecklund if they were not aware of the entry of the Order to Show Cause or needed a copy of this Order. No law firm called in response to our voicemail messages or telephone conversations.

6. Several counsel for Plaintiffs had a clear understanding of the import of the Order and called my office, Seeger Weiss LLP, and Weitz & Luxenberg concerning the practical limitations confronting them and their clients. In this respect, several attorneys expressed concerns that the Order precluded them from filing individual briefs on behalf of their clients despite the fact that Co-Liaison Counsel are not representative counsel for their clients.

7. In addition to contacting counsel to notify them of the entry of the Order to Show Cause, multiple emails were sent and several conference calls were held in an attempt to keep counsel for the Plaintiffs identified on Exhibit A apprised of the comprehensive response that the PSC was preparing and, to the extent practicable, to include them in the response through the inclusion of declarations.

8. The PSC believed that declarations from the affected Plaintiffs, their counsel, and, to the extent available within a 45-day window, treating doctors were necessary, particularly given the absence of any opportunity for the overwhelming majority of these Plaintiffs to pursue any case specific discovery or for their counsel to file responsive briefs on their behalf.

9. I believe that the number of declarations from clients, counsel, and treating doctors would have been greater if additional time had been provided.

10. Attached as Exhibit A is a true and correct copy of the Declaration of Edward Braniff.

11. Attached as Exhibit B is a true and correct copy of Declaration of Carmen S. Scott.

12. Attached as Exhibit C is a true and correct copy of Declaration of Bradley D. Honnold.

13. Attached as Exhibit D is a true and correct copy of Declaration of Troy F. Tatting.

14. Attached as Exhibit E is a true and correct copy of Declaration of Nancy A. Mismash.

15. Attached as Exhibit F is a true and correct copy of Declaration of David P. Dearing.

16. Attached as Exhibit G is a true and correct copy of Declaration of Frank E. Piscitelli, Jr.

17. Attached as Exhibit H is a true and correct copy of Declaration of Tracy A. Finken.

18. Attached as Exhibit I is a true and correct copy of Declaration of Bryan F. Aylstock.

19. Attached as Exhibit J is a true and correct copy of Declaration of Brian A. Goldstein.

20. Attached as Exhibit K is a true and correct copy of Declaration of Evan D. Buxner.

21. Attached as Exhibit L is a true and correct copy of Declaration of Brandon L. Bogle.

22. Attached as Exhibit M is a true and correct copy of Declaration of Calvin S. Tregre, Jr.

23. Attached as Exhibit N is a true and correct copy of Declaration of Sarah J. Showard.

24. Attached as Exhibit O is a true and correct copy of Declaration of Brenda S. Fulmer.

25. Attached as Exhibit P is a true and correct copy of Declaration of Bernard Daskal.

26. Attached as Exhibit Q is a true and correct copy of Declaration of Robert G. Germany.

27. Attached as Exhibit R is a true and correct copy of Declaration of Aaron M. Levine.

28. Attached as Exhibit S is a true and correct copy of Declaration of Charles H. Johnson.

29. Attached as Exhibit T is a true and correct copy of Declaration of Mark A. Tate.

30. Attached as Exhibit U is a true and correct copy of Declaration of Marilyn T. McGoldrick.

31. Attached as Exhibit V is a true and correct copy of Declaration of N. Kirkland Pope.

32. Attached as Exhibit W is a true and correct copy of Declaration of Brian J. Malloy.

33. Attached as Exhibit X is a true and correct copy of Declaration of Roy E. Barnes.

34. Attached as Exhibit Y is a true and correct copy of Declaration of Stuart L. Goldberg.

35. Attached as Exhibit Z is a true and correct copy of Declaration of William B. Curtis.

36. Attached as Exhibit AA is a true and correct copy of Declaration of John D. Sileo.

37. Attached as Exhibit AB is a true and correct copy of Declaration of Richard A. Gurfein.

38. Attached as Exhibit AC is a true and correct copy of Declaration of Peter E. Goss.

39. Attached as Exhibit AD is a true and correct copy of Declaration of Keith Halpern.

40. Attached as Exhibit AE is a true and correct copy of Declaration of David B. Satisky.

41. Attached as Exhibit AF is a true and correct copy of Declaration of John S. Simmons.

42. Attached as Exhibit AG is a true and correct copy of Declaration of Dennis F. O'Brien.

43. Attached as Exhibit AH is a true and correct copy of Declaration of Bobby J. Bell, Jr.

44. Attached as Exhibit AI is a true and correct copy of Declaration of James Zonas.

45. Attached as Exhibit AJ is a true and correct copy of Declaration of James P. Ginzkey.

46. Attached as Exhibit AK is a true and correct copy of Declaration of David P. Matthews.

47. Attached as Exhibit AL is a true and correct copy of Declaration of Brian Cummings.

48. Attached as Exhibit AM is a true and correct copy of Declaration of John David Hart.

49. Attached as Exhibit AN is a true and correct copy of Declaration of Michael S. Pemberton.

50. Attached as Exhibit AO is a true and correct copy of Declaration of Randall E. Smith.

51. Attached as Exhibit AP is a true and correct copy of Declaration of Janet Brooks Holmes.

52. Attached as Exhibit AQ is a true and correct copy of Declaration of Timothy S. Peck.

53. Attached as Exhibit AR is a true and correct copy of Declaration of Jessica E. Vertullo.

54. Attached as Exhibit AS is a true and correct copy of Declaration of Douglas R. Plymale.

55. Attached as Exhibit AT is a true and correct copy of Declaration of Ronald R. Benjamin.

56. Attached as Exhibit AU is a true and correct copy of Declaration of James V. Doyle, Jr.

57. Attached as Exhibit AV is a true and correct copy of Declaration of James J. Rosemergy.

58. Attached as Exhibit AW is a true and correct copy of Declaration of Sarah F. Jubinville.

59. Attached as Exhibit AX is a true and correct copy of Declaration of Moshe Horn.

I declare, under penalty of perjury, that the foregoing facts are true and correct.

Executed on September 30, 2013

/s/ James E. Cecchi
JAMES E. CECCHI

[Exhibit 1 to Ecklund Declaration]

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE:FOSAMAX (ALENDRONATE SODIUM) PRODUCTS LIABILITY LITIGATION (No. II)	MDL No. 2243 Civil Action No. 3:08-cv-08 (JAP)(LGH)
THIS DOCUMENT APPLIES TO: ALL ACTIONS REFERENCED IN EXHIBIT A TO THE COURT'S ORDER TO SHOW CAUSE	

EXPERT DECLARATION OF DAVID B. BURR, PH.D., F.A.A.A.

* * *

1. I, David B. Burr, hereby submit the declaration in support of the Plaintiffs' Opposition to The Order to Show Cause Regarding Federal Preemption. I have personal knowledge of the matter contained in the declaration. If called, I could, and would, testify competently thereto.

BACKGROUND AND QUALIFICATIONS

2. I received a Bachelor of Arts from Beloit College in 1973, and a Master of Arts (1974) and Ph.D. (1977) from the University of Colorado, all in Anthropology.

I was Instructor and Assistant Professor of Anatomy at the University of Kansas before joining West Virginia University in 1980 as Assistant Professor of Anatomy and Orthopedic Surgery. I joined the Indiana University School of Medicine in 1990 as Chair of the Department of Anatomy, a position I held until the end of 2010. I also held a joint appointment in Orthopedic Surgery from 1990–2010, and hold appointments in Biomedical Engineering at Purdue University (courtesy, 2000- present) and Indiana University-Purdue University at Indianapolis (IUPUI, 2002–present). In 2012, I was appointed an Indiana University Distinguished Professor, and I currently serve as the Associate Vice Chancellor for Research at IUPUI.

3. My research activities have included study of the biological and mechanical aspects of age-related bone and cartilage change, bone remodeling physiology using animal models, and human clinical biopsies, and more specifically the causes of skeletal fragility in osteoporosis and in Type 2 diabetes. I have 30 years of experience in studies involving histological and histomorphometric endpoints in both bone and cartilage. I have for many years been a leader in studying the role of skeletal fatigue and microcrack-mediated remodeling in bone biomechanical and physiological adaptation. I am widely considered to be an expert in skeletal biomechanics and remodeling physiology. My laboratory is equipped to characterize histological and dynamic histomorphometric features of different tissues, and to utilize bone density (BMD) and imaging techniques (μCT, pQCT) to analyze tissues in animal models. I was funded by the NIH for over 20 years to do research in these areas, and am

frequently asked to write review articles or book chapters on these topics. I am the author of more than 230 research articles in the peer- reviewed literature, more than 50 book chapters and reviews, and five books on the structure, function and mechanics of bone. Two of these books are highly relevant to this report: RB Martin, DB Burr and NA Sharkey, *Skeletal Tissue Mechanics* (1998) (currently undergoing revision for the 2nd edition), and DB Burr and C Milgrom, eds., *Musculoskeletal Fatigue and Stress Fractures* (2001). I was also a co-Guest Editor with Dr. Graham G. Russell of a special issue of the Journal *BONE* on Bisphosphonates (vol. 49(1), 2011).

4. At the request of the American Society for Bone and Mineral Research (ASBMR) leadership, Dr. Elizabeth Shane contacted me on May 11, 2009 to ask whether I would co-chair the ASBMR Task Force on Subtrochanteric Fractures. I agreed, and Dr. Shane and I proceeded to identify participants for the Task Force, with the approval of the ASBMR. The ASBMR asked us to address several important questions related to these atypical femoral fractures, including to "review carefully the currently available information in order to assess what is actually known and what is not known about atypical femoral fractures and their potential relationship with BP [bisphosphonate] usage." As part of this report, I was one of four members of the Task Force to conduct teleconferences with representatives of companies that market drugs to treat osteoporosis in the U.S. This included Amgen, Eli Lilly, Genentech, Merck, Novartis, and Warner-Chilcott. Our report was subsequently published in the Journal of Bone and Mineral Research in November 2010 (Shane et al.,

2010). I drafted much of the portion of this report that reviewed current knowledge and the potential relationship of atypical femoral fractures (AFFs) to BP usage (pp. 2269–2272 in the final report). This draft was reviewed by all members of the Task Force, and approved. Subsequently, after conferring with several other members of the original Task Force and with ASBMR leadership, it was decided that a review of the original definition of AFFs and an update on the epidemiology and potential pathogenesis of AFFs was warranted. The original Task Force was reconvened, and an update of what is known about AFFs is currently online with the *Journal of Bone and Mineral Research* (*JBMR*, to be published in print early next year, Shane et al., 2014)

5. I was President of the Association of Anatomy, Cell Biology and Neurobiology Chairpersons between 2001–2002. I served on the Executive Board of the American Association of Anatomists (1998–2011), and as its President (2007–2009). I served as Program Chair (2005–2006) and as President (2008–2009) of the Orthopaedic Research Society. In 2004, I became the Director of the Sun Valley International Workshop on Skeletal Tissue Biology, which is now sponsored by the International Bone and Mineral Society ("IBMS"). I remain the Director of the IBMS Sun Valley International Workshop on Musculoskeletal Biology today. The Sun Valley Workshop began in 1965, and is widely recognized to have had a major impact on scientific thinking in the field of skeletal biology particularly in areas related to histomorphometry, in vivo animal models, and biomechanics (www.ibmsonline.org), and receives support from the National Institutes of Health, the pharmaceutical

industry, equipment manufacturers, and other professional societies.

6. I am an Associate Editor for the Journal *BONE* and the *Journal of Musculoskeletal and Neuronal Interactions*, Editor-in-Chief for *Current Osteoporosis Reports*, and serve on the editorial boards for four other scientific journals: *Journal of Biomechanics*, *Calcified Tissue International*, *Osteoporosis International*, and *Journal of Bone and Mineral Metabolism*. I have reviewed manuscripts for 40 different Journals and I typically review approximately 50 submitted articles per year in my field.

7. I am a Fellow of the American Association of Anatomists. I won the Borelli Award, the highest award offered from the American Society of Biomechanics, in 2008; the Glenn W. Irwin Award for Distinguished Faculty Service from Indiana University in 2010; and the Gideon A. Rodan Excellence in Mentorship Award from the American Society for Bone and Mineral Research, also in 2010.

8. A true and correct copy of my curriculum vitae is attached hereto as Exhibit A.

9. I have never testified as an expert witness in any litigation. I am being compensated for my time spent on this matter at the rate of $600 per hour.

10. The opinions expressed herein are stated to a reasonable degree of scientific certainty, based on my education, research, and experience as a researcher in the causes of skeletal fragility in osteoporosis and in Type 2 diabetes. My opinions in this document are further based on my review of the medical literature, various documents provided to me by counsel, and

generally accepted principles of science. The materials I relied upon or reviewed in forming the opinions I express in this declaration are set forth in Exhibit B. I reserve my right to supplement this declaration at a later date based upon receipt of additional information received during the course of the litigation.

II. SUMMARY OF OPINIONS

9. I have been asked by the Plaintiffs' attorneys to consider what Merck knew or should have known at various points in time about the potential for serious insufficiency stress fractures[1] as a result of continuous use of Fosamax. It is my opinion that by the early 1990's, Merck knew or should have known that suppression of bone remodeling could be associated with an increased burden of unrepaired microcracks in bone tissue, and that this could negatively impact bone's mechanical properties.

10. I have also been asked by the Plaintiffs' attorneys to consider the evidence available to Merck at various points in time about Fosamax's association with low energy femoral fractures, including the potential for long-term Fosamax treatment to result in serious insufficiency stress fractures. It is my opinion that the reports received by Merck as well as the

[1] Herein, I use the term "insufficiency stress fracture" to mean an insufficiency fracture, which the ASBMR Task Force defines as a fracture which is the result of "normal loading of an abnormal or deficient bone," which has as its mechanism of action a fatigue or stress process. A stress fracture results from repetitive loading that overwhelms the body's capacity for repair In using the term "insufficiency stress fracture," I am specifically excluding other types of insufficiency fractures, such as those which may be caused by low bone mass.

scientific data that was being generated by myself and other researchers should have caused Merck to study the association between Fosamax and low energy femoral fractures, including serious insufficiency stress fractures, many years before 2008.

11. I have also been asked by the Plaintiffs' attorneys to consider Merck's efforts to study the potential for insufficiency stress fractures as a result of long-term continuous use of Fosamax. It is my opinion that my studies and those of some of my colleagues between 2000–2006 clearly suggest that suppression of bone remodeling by alendronate was associated with increased microcrack burdens, and moreover that this was associated with significantly reduced bone toughness, and increased bone brittleness that would be consistent with the development of a stress fracture-like lesion. I am not aware of any efforts made by Merck to study this association.

12. I have also been asked by the Plaintiffs' Attorneys to review the material Merck submitted to the FDA on September 15, 2008 to determine whether Merck adequately described the nature of the Atypical Femoral Fracture ("AFF") problem to the FDA. It is my opinion that in several areas Merck improperly characterized the nature of the AFF problem to the FDA, including a failure to describe the potential underlying pathogenesis to the FDA, a failure to inform the FDA that femoral insufficiency stress fractures were rarely seen before Fosamax and other bisphosphonates were available, improperly suggesting various risk factors to the fracture that were not supported by data, and conflating the underlying mechanism of the fracture (stress fracture,

which often doesn't result in a complete break of the bone) with the ultimate outcome (a completed subtrochanteric femoral fracture).

III. THE RELATIONSHIP BETWEEN FOSAMAX, BONE TURNOVER, MICROCRACK, AND STRESS FRACTURE

A. Fosamax, As It Is Designed, Causes a Significant Reduction In Bone Turnover That Has Negative Effects On Bone Tissue Properties

13. Bone is constantly being remodeled in part to maintain calcium balance in the body, and in part to repair and remove microcracks, which are linear cracks that accumulate in the bone matrix as a function of normal activities. Remodeling is a process in which bone is resorbed at a location, and subsequently new bone is deposited at that same location. Usually, the processes of resorption and formation are in balance, but in postmenopausal women, resorption exceeds formation. Over time, this causes bone loss. Therefore, one approach to reducing bone loss is to reduce the overall amount of bone remodeling. .

14. Fosamax, as it is designed, causes a significant reduction in bone turnover, and reduced erosion depth [Boyce et al., 1995; Allen et al., 2010]. Evidence from both human clinical studies and from pre-clinical studies with animals, suggests that treatment with Fosamax suppresses bone remodeling by 70–95% [Chavassieux et al., 1997; Bonnick et al., 2006; Rosen et al., 2005; Mashiba et al., 2000; Allen et al., 2006]. However, the effect of Fosamax and other bisphosphonates (BPs) on bone turnover is highly

location specific and when assessed histologically can differ by an order of magnitude across skeletal sites [see Burr and Allen, 2013 for review of some of these studies]. BPs also exert a time-dependent effect on bone remodeling. For instance, in animal studies, clinical doses of alendronate did not reduce remodeling rate significantly following one year of treatment, but reduced remodeling rates by 85% following three years of treatment [Allen et al., 2006, 2008]. The nitrogen-containing bisphosphonates, such as Fosamax, act both physicochemically and through inhibition of metabolic pathways. The physicochemical action allows bisphosphonates to bind to bone, stabilizing the matrix and preventing its resorption. It has now been shown that BPs not only bind to bone in areas undergoing active resorption, but can enter the bone through canaliculi and can be found on many internal surfaces [Rogers 2009, Turek 2012]. Metabolically, BPs disrupt the cholesterol synthetic pathway from which the prenylated proteins required for osteoclast function and survival are derived. The loss of the resorptive function occurs via inhibition of a key enzyme in this pathway, farnesyl pyrophosphate synthase (FPS), and by prenylation of GTP-ases. Bisphosphonates may not kill all the osteoclasts, but they prevent the remaining osteoclasts from functioning properly.

15. Suppression of remodeling has been shown to increase bone mass, but numerous studies demonstrate that it also creates older bone and negatively affects bone tissue quality. BP treatment is associated with increases in bone mineralization, microcrack accumulation, and alterations in the cross-linking of collagen. Any of these changes, either alone

or in combination, could compromise the mechanical properties of the bone as I will discuss in more detail below.

16. Both pre-clinical and clinical studies show that by reducing the turnover of bone and thereby increasing mean tissue age, BP treatments lead to a significantly higher average tissue mineralization [Boivin et al., 2000; Burr et al., 2003] and lower heterogeneity of mineralization across the bone matrix [Roschger et al., 2001]. Under normal conditions, bone remodeling preferentially renews the more highly mineralized bone matrix. By suppressing remodeling, however, BPs allow more highly mineralized regions to persist for a longer time. Moreover, suppression of remodeling allows more of the newly formed bone to become fully mineralized without replacement. Thus, Fosamax increases the overall mineralization of the tissue by suppressing remodeling and allowing more sites to achieve full mineralization. Increased mineralization will increase both the strength and the stiffness of bone, but increased stiffness is usually associated with reduced toughness [Zioupos et al. 1994, Currey, 2004]. The effect of increased mineralization on reduced toughness has been known for many years [Currey, 1969; Currey et al., 1996; Zioupos, 1998].

17. By reducing bone turnover, and not allowing renewal of the organic bone matrix, BPs permit increased collagen cross-linking. Bone collagen contains both enzymatic and non-enzymatic collagen crosslinks that stabilize the matrix and have significant impact on the bone's mechanical properties. The organic matrix constitutes the principal toughening mechanism in bone and

therefore plays a substantial role in determining properties of energy absorption/toughness [Wang et al., 2002]. Cross-links that are formed through non-enzymatic processes generate advanced glycation endproducts (AGEs) that are associated with tissue that is less tough [Allen et al. 2008], more brittle [Vashishth, 2009] and can sustain less energy before fracture [Viguet-Carrin et al., 2006; Tang et al., 2009].

18. The increased brittleness caused by changes to bone's organic matrix and mineralization allow for greater initiation of microcracks [Allen and Burr, 2007]. In the majority of studies that have documented increased microcracks with BP-treatment, a concomitant decrease in bone toughness has also been quantified [Komatsubara et al., 2003; Mashiba et al., 2000, 2001; Allen et al., 2006; Allen and Burr, 2007]. Microcrack accumulation with BPs is likely the consequence of the increased brittleness and reduced toughness, and not the cause of it. AGEs naturally accumulate in bone as it ages, but under normal rates of bone turnover, they are prevented from accumulating to high levels. However, when bone turnover is suppressed, they can accumulate and make it more likely for cracks to propagate. BPs may exacerbate this effect, particularly in older people who naturally, because of aging, have higher AGEs than younger individuals. The effect is compounded because the BPs impair targeted remodeling more than stochastic remodeling [Li et al., 2001], thereby allowing microcracks to persist for a longer period of time.

B. The Accumulation Of Older Bone Caused By Remodeling Suppression Results In Bone That Is Less Tough And More Susceptible To Microcrack Propagation

19. Studies using animal models have shown repeatedly that the mechanical properties of the tissue, specifically material toughness[2] are reduced with BP-treatment. Following 1–3 years of treatment at doses at or above those used in postmenopausal women, bone toughness in vertebrae and ribs of dogs is 14–33% lower compared to control animals [Mashiba et al., 2000, 2001; Allen et al., 2006; Allen and Burr, 2007]. More recent data show that toughness in BP-treated animals continues to decline with long-term treatment without a significant change in microcrack accumulation or a further increase in mineralization [Allen and Burr, 2007]. This suggests that neither microcracks nor mineralization is completely responsible for the progressive deterioration in the bone's material properties leaving progressive changes to collagen, or the interaction among all these properties, as the cause of this progressive toughness decline.

20. BP treatment is associated with changes in both the initiation and repair of microcracks. This has been demonstrated repeatedly in animal models using various different oral bisphosphonates at doses

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[2] Toughness is a measure of the ease with which cracks in a material can be initiated and can grow. The probability of fracturing from repeated loads is increased with decreased toughness. Stress fractures occur as a result of repeated cyclical loading, as I will explain in more detail below.

ranging from ½ to 6x the dose used for treatment of post-menopausal osteoporosis, and with treatment durations lasting from 1 to 3 years. Significantly more microcracks are consistently noted in the trabecular bone of the lumbar vertebrae and usually in the cortical bone of the rib with BP treatment [Mashiba et al., 2000, 2001; Allen et al., 2006; Allen and Burr, 2007]. Although increased numbers of microcracks also have been noted in the ilium, thoracic spinous process, and femoral neck of dogs treated with bisphosphonates, these sites appear less prone to significant microcrack accumulation (< 2-fold relative to untreated) [Mashiba et al., 2001; Allen and Burr, 2007]. This site-specificity may be important in evaluating damage accumulation in bone from human patients, as such evaluations can only occur from iliac crest biopsies which may underestimate the amount of damage accumulating in the spine or ribs. Recent data from iliac crest biopsies of treatment naïve women and women treated for five years with Fosamax show increased microcrack accumulation with bisphosphonate treatment [Stepan et al., 2007]. Both low femoral neck BMD and increasing age were associated with greater microcrack formation, suggesting that older patients with especially low BMD might be more at risk for damage accumulation. A separate study in which iliac crest biopsies of women treated with alendronate were compared to cadaveric bone showed no significant difference in microcrack levels, although in this study the cadavers used as "untreated controls' were almost 10 years older than the treated patients, and previous drug treatment history was unknown [Chapurlat et al., 2007]. The well-known age-related increase in microcracks [Diab

et al., 2006; Norman and Wang, 1997; Schaffler et al., 1995] and unknown treatment history, therefore, make this an unsuitable control population. The role that bone turnover plays in this accumulation is demonstrated by evaluations in iliac crest biopsies from patients who were pre-treated with alendronate, and then subsequently treated with a course of teriparatide [Stepan et al 2010]. In this case, the microcrack accumulation caused by remodeling suppression was reversed by subsequent administration of teriparatide, and those patients with the lowest BMD had the greatest removal of microcracks. Although this study was not able to conclude that a change in bone turnover rate was associated with this reduction in microcracks, such a conclusion seems eminently plausible.

21. The propensity to initiate microcracks following BP treatment has been shown [Iwata et al., 2006]. Vertebrae from dogs treated for one year with either risedronate or alendronate at doses equivalent to those used to treat postmenopausal osteoporosis in women were subjected to a cyclic loading protocol in compression (5 Hz for 100,000 cycles at loads ranging from 100–300% of the dogs' body weights). Using a double *en bloc* staining protocol with different fluorochromes, this test demonstrated that cracks were significantly more likely to initiate in bone from dogs that had been treated for one year with alendronate, than in those treated either with risedronate or with saline vehicle. This may account in part for the significant and nonlinear inverse relationship between microcrack accumulation and remodeling suppression [Allen et al. 2007]. Cracks are

both more likely to begin following treatment, and their repair is reduced [Li et al. 2001].

C. Less Tough Bone Is More Susceptible To Serious Insufficiency And/Or Stress Fractures

22. Stress fractures are nontraumatic, low energy fractures caused by repeated applications of loads below the fracture threshold. They occur in a variety of skeletal locations commonly in physically active people. They are generally the result of the gradual accumulation of microcracks in bone until the cracks coalesce and can be visualized radiographically or scintigraphically [Burr, 1997; Burr and Milgrom, 2001]. The term "stress fracture" often applies to fractures resulting from excessive loading of a normal bone. An insufficiency stress fracture, on the other hand, is used to connote a fracture caused by normal loading of a bone that has poor quality and material properties.

23. Bone that is less tough can either initiate more microcracks, or allow them to grow and coalesce more quickly. Although the formation of a microcrack will dissipate energy and delay fracture, once the crack is formed, the residual mechanical properties of the tissue are reduced. It has been shown that the presence of microcracks in bone reduces strength [Burr et al., 1997; Burr et al. 1993], reduces the elastic modulus of the tissue (by definition, a reduction in elastic modulus is the criterion used by engineers to define damage in many materials) [Burr et al., 1998], and reduces toughness [Mashiba et al., 2000, 2001].

D. Toughness, Not Strength, Is The Critical Material Property When Assessing Propensity For Stress Fracture

24. Strength and stiffness are often used to define the health of a bone, but they are not so clearly, or physiologically, related to risk of fracture as the amount of energy required to cause fracture. A bone that is strong and stiff may require much less energy to fracture than a bone that is weaker and more compliant. Bone mineral density is highly correlated with strength and stiffness [Currey, 2002], but there is a more complex relationship between BMD and the energy required to cause fracture. For instance, highly mineralized osteopetrotic bone is very stiff and very strong, but also very brittle, resulting in failure with lower energy, and increased risk of fracture. The modulus of toughness of a bone is a measure of how much energy is required to cause the bone tissue to crack. Lower modulus of toughness, therefore, indicates that the bone can fail at lower energy, and is often associated with a brittle-type fracture. The probability of fracturing from repeated loads is increased with decreased toughness. It has been shown [Currey, 2004] that stiffness and toughness are usually inversely related in bone, so that increased material stiffness (modulus) may signal reduced energy to fracture (toughness).

IV. MERCK KNEW AS EARLY AS 1990 THAT CONTINUOUS USE OF FOSAMAX COULD MAKE BONES SUSCEPTIBLE TO SERIOUS INSUFFICIENCY AND/OR STRESS FRACTURES

25. In 1990 in an Operational Plan related to Phase I and IIa studies, Merck posed the question "What would be the undesirable consequences of excessive suppression of bone resorption by MK-217?"[3] They contended: "Microscopic fractures occur in normal bone due to the mechanical stress of normal activity. The bone remodeling process eliminates these fractures through local bone resorption and formation of new bone. If MK-217 inhibits the remodeling process too greatly, inadequate repair may take place. Both nonclinical and clinical studies will address this question by assessing bone strength in treated animals, and bone histology and histomorphometry in MK-217-treated humans and animals." [MRK-FOSNJ-SAN-00557997]

26. In April 1990, in a memo to the MK-217 Product Team, Dr. BJ Gertz stated: "The consultants . . . did question whether chronic reductions in bone turnover would increase the risk of stress fractures, i.e., an effect on bone quality. The two year dog study will address that question." [MRK-FOSMDL-00897340] After searching the available literature, I have been unable to locate a published 2 year dog study that evaluated the change in mechanical properties in dogs treated with Fosamax. One study in ovariectomized nonhuman primates [Balena et al., 1993] was

[3] MK-217 is the internal identification used by Merck for the compound that was later named Fosamax.

conducted by Merck, but only measured femoral strength and stiffness. This is an incomplete characterization of the mechanical integrity of bone. As indicated before, the more relevant parameters for assessing the potential risk for fracture, in my opinion, are energy to fracture and toughness, neither of which were measured by Merck in the Balena study.

27. In a separate memo in May 1990 from CP Peter, the consultants recommended that bone quality in chronically treated dogs, rats, baboons and pigs be assessed, and that such an assessment address the concerns about stress fractures adequately. They also recommended that bone scintigrams be made to evaluate the possible occurrence of stress fractures. [MRK-FOSNJ-SAN-00541807] I am unable to find a published study from Merck in which bone quality was assessed in dogs chronically treated with alendronate. From other documents (March 1991), it appears that the canine study was a fracture healing study and was only 25 weeks long, inconsistent with "chronic" exposure. In any event, it is surprising in light of this recommendation made by several experts in the field (Drs. Kaplan, Kleerkoper, and Einhorn) that in the nonhuman primate study reported by Balena et al. [1993], which could have begun to address this question, only bone strength, not mechanical measures of bone quality, were measured. Reasonable scientists at this time should have known that mechanical measures of bone intrinsic (material) properties were necessary measurements in assessing the risk of fracture.

28. In April of 1991, Dr. Henry Bone expressed his concern that MK-217 could produce a "profound suppression of bone resorption so that micro-fractures

would not heal." [MRK-FOSMDL-00897472] He suggested a dose response study in patients older than 70 years.

29. In July of 1991, in response to a letter from Dr. Gideon Rodan posing questions about the risk/benefit ratio of decreased bone turnover by a "resorption inhibitor," and the level of turnover suppression that could be considered "safe," Dr. Michael Parfitt stated: "The main risk of reducing turnover would be an increase in bone age. The expected consequences of this would be increased osteocyte death, hyper-mineralization, increased brittleness and accumulation of fatigue damage because of increased production and decreased repair." [MRK-FOSNJ-SAN-00541788] Although stressing that these were purely theoretical considerations, it is my contention that this should have sensitized Merck to the possibility of the negative mechanical effects of increased bone age at least beginning with the first reports by Mashiba et al. in 2000, 2001.

30. The Project Team minutes from August 13, 1991 conclude from Dr. Parfitt's statements that "there should be no concern regarding the possibility of 'freezing' bone while receiving alendronate therapy at the therapeutic doses." [MRK-FOSMDL-00897641] Although Dr. Parfitt stated that reducing turnover to the lower end of the reference range for healthy premenopausal women would leave a comfortable margin for safety, most reasonable scientists would conclude that a significant reduction in bone turnover rate would increase bone age, with the consequent negative effects stated by Dr. Parfitt.

31. In August of 1991, the potential negative effects on bone mechanical properties caused by suppression of remodeling specifically with bisphosphonates, was a topic of discussion at the International Sun Valley Hard Tissue Workshop. On the final day, during a summary and synthesis of the meeting, this was discussed in detail, and the general consensus was that this could be a problem. I recall this because it was at this meeting that I realized that experiments needed to be performed to address this potential negative effect of remodeling suppression. It was key to my future work. Dr. G. Seedor and Dr. Gideon Rodan from Merck, as well as Dr. Donald Kimmel, who was then at Creighton University but was eventually employed by Merck, attended this meeting, as did other Merck advisors such as Dr. Robert Recker.

32. Early in 1995, I wrote the following in Project 3 of Dr. Conrad Johnston's Program Project Grant ("Some Determinants of Bone Mass in the Elderly"):

> "The **primary goal** of this proposal is to determine whether treatment with an agent that reduces bone turnover significantly (e.g. bisphosphonates) will increase bone fragility. A **second goal** is to determine how much bone remodeling can be inhibited before bone strength is compromised. A **third goal** is to determine whether bisphosphonate treatment reduces bone strength by allowing microcrack accumulation, inhibiting mineralization of new bone, or through a combination of these. Whether spontaneous fractures occur or not, the effects of bisphosphonate treatment on microcrack and osteoid accumulation, and by extension their effects on strength, need to be documented

> because of questions raised by earlier animal studies (Flora et al., 1980, 1981; and human clinical trials (Storm et al., 1990; Watts et al., 1990).
>
> "Questions have been raised regarding the effects of reducing bone turnover on the mechanical integrity of bone. These discussions have influenced the FDA decisions about guidelines for drugs for the treatment of osteoporosis. In most cases a reduction in bone turnover is associated with increased bone mass and decreased fracture risk (e.g. the effects of estrogen therapy). It has been reasoned that marked reduction in turnover may be damaging, but this is only supported by animal experiments with etidronate (Flora et al., 1980, 1981). These experiments have not been repeated. It is important to know the influence of bone turnover on mechanical integrity and such data are not currently available."

One of the reviewers on the NIH review panel for this project was Dr. David Dumpster. The proposal was deemed important, and subsequently funded. This is the work that eventually was published by Mashiba et al. [2000, 2001]. Therefore, by early 1995, it is clear that investigators in the scientific community were aware of the possibility that remodeling suppression could negatively affect bone mechanical properties and it was deemed important enough that an independent review panel convened by the NIH felt it was worthy of funding.

33. At a Merck consultants' meeting in 1997, a consensus was achieved that "change in bone density

is not an adequate surrogate for fracture risk and therefore none of the currently available surrogates can substitute for fractures as measures of efficacy." [Exh. 1.1876 (P000001876)] Given this statement, it is my contention that Merck should have sought data on mechanical properties of bone following alendronate treatment from animal studies (as these are not possible to perform in humans).

34. In December 1997, it was affirmed that the then-proposed FLEX trial could not answer "one important question: Longer-term alendronate could be more detrimental than placebo." [Exh. 1.1879 (P000001879)] It is surprising that at least seven years after the question of the potential detrimental effects of alendronate was raised, this important question had not been answered by any studies performed by Merck.

V. ALTHOUGH AWARE OF THE POTENTIAL FOR SERIOUS INSUFFICIENCY STRESS FRACTURES WITH FOSAMAX TREATMENT, MERCK IGNORED A GROWING BODY OF DATA ESTABLISHING THE CONNECTION

A. Numerous Animal Studies Showed The Connection Between Fosamax Use and Microcracks

35. In 2000, Mashiba et al. published a paper showing that treatment with high doses of alendronate for only one year resulted in a significant increase in bone microcracks, and a significant reduction in bone toughness, in the *cortical bone* of the rib.

36. The following year, Mashiba et al. [2001], showed that treatment with high doses of alendronate for only one year resulted in a significant increase in bone microcracks, and a significant reduction in bone toughness in the lumbar vertebrae, a primary site for osteoporotic fractures.

37. In 2003, Komatsubara et al. published a paper in which dogs were treated with a different bisphosphonate, incadronate, for three years. This work showed that BP treatment for a prolonged time was associated with a significant increase in microcracks, and a 40% reduction in intrinsic modulus of toughness in lumbar vertebrae. This toughness reduction was about twice what Mashiba et al. [2001] found following one year of treatment with alendronate. Subsequently, Komatsubara et al. [2004] reported a significant increase in microcracks in cortical bone from the rib of dogs treated with incadronate, but this was not accompanied by reduced toughness. This was confusing, and I discussed this work with one of the senior authors (Dr. Satoshi Mori) to determine how they had calculated modulus of toughness. They could not explain how the calculation was performed, as the value had been generated by system software. It was unclear to me at the time that they had corrected accurately for the increased bone volume that was associated with bisphosphonate treatment. As I could not verify the method of calculation for modulus of toughness, I have continued to view this work with skepticism.

38. Following publication of the Mashiba papers, there remained a question about whether bisphosphonates suppressed both stochastic (i.e. random) remodeling generally associated with calcium

metabolism, and remodeling targeted specifically to repair microcracks. This was highly relevant to the question about whether bisphosphonates prevented crack repair. Some scientists at the time believed that bisphosphonates might suppress overall turnover, but allow the repair of microcracks. We designed a study and consulted with Dr. Michael Parfitt about our experimental design. We reported the results of this study in a paper by Li et al. [2001], in which dogs were assigned to control, risedronate-treated, or alendronate-treated groups. In the control group, we found three times more associations between cracks and resorption spaces than expected, indicating that remodeling normally targets cracks for repair, validating our earlier studies [Burr and Martin, 1993]. By contrast, although there was an increased damage accumulation in the bisphosphonate-treated groups, fewer cracks than expected were associated with resorption spaces, indicating that suppression of remodeling significantly suppressed the targeted repair of microcracks. The number of observed associations of cracks and the maximum number of potential associations was not different than 1.0. This means that the bisphosphonates eliminated targeted remodeling (ie, the repair of damage), and that any remodeling apparent in the bone was incidental to the repair of damage. We concluded: "Although the accumulation of cracks in bisphosphonate-treated dogs could also be a function of increased tissue mineralization and increased mean tissue age associated with global remodeling suppression, these data further suggest that the complete suppression of targeted remodeling could account for this increased microcrack burden."

39. It is clear that Merck investigators discounted this data in a deprecating way. In internal memos, Dr. Rodan referred to "this whole turnover microcrack imaginary monster" (March 21, 2001) and later characterized our results as "the so-called microcrack, defined by the fuchsin stain . . ." (March 31, 2001) [MRK-FOSMDL-DAI-00032511]. In another email, Merck employee John Orloff stated that "bone 'toughness', which was found to be significant in the Burr paper, is a convoluted and derived biomechanical parameter that depends on the directly measured biomechanical parameters which were not found to be significant." (March 20, 2001) [MRK-FOSMDL-SAN-00064649].. Merck ignored our data and, instead, sought to downplay it by stating that "so far there is absolutely no evidence that treatment up to 7 years has any deleterious effect . . . ." Mr. Orloff concludes his email by stating that "some of these people really irritate me."

40. Subsequently (August 21, 2001), Merck scientist Dr. Santhanagopal, stated "Based on what we know theoretically, [Burr's] contention is correct." He also cites work in 1994 by Peter Zioupos that "conclusively [shows] that the phenomenon of yield and damage in bone is due to 'microcracking' of the bone material." [MRK-FOSMDL-PEV-00025671]

41. In late 2001, I wrote the following statement in a grant proposal that was subsequently funded and formed the basis for papers showing that clinical doses of alendronate also will cause increased accumulation of microcracks and, over a three year treatment period, a 27% decline in vertebral toughness:

"Bisphosphonates increase bone mass and decrease vertebral and non-vertebral fracture incidence in postmenopausal osteoporotic women [Black et al., 1996; Ensrud et al. 1997; Karpf et al., 1997; Cummings et al. 1998; Eastell et al., 1999; Watts et al., 1999] by reducing the activation frequency of new bone remodeling and by reducing resorption depth [Steiniche et al., 1991; Storm et al., 1993; Balena et al. 1993; Chavassieux et al., 1997; Balena et al., 1996; Motoie et al., 1995]. They are effective because they inhibit bone remodeling, preventing the loss of bone that occurs through resorption and allowing refilling of the remodeling space. However, in doing so they also may prevent the repair of microdamage [Mashiba et al. 2000, 2001; Hirano et al., 2000]. Animal and post-mortem human studies show that microdamage accumulation in bone will reduce the elastic modulus of the tissue [Schaffler et al., 1989; Keaveny et al., 1994; Jepsen and Davy, 1997; Burr et al., 1998; Pidaparti et al., 2000], will decrease bone strength [Burr et al., 1997], and can increase energy dissipation [Pattin et al., 1996] when bone is loaded.

"We recently showed that an 85–95% decrease in activation frequency (Ac.F) in trabecular bone of the lumbar vertebrae, or a 53–68% decrease in Ac.F. in the cortical bone of the rib, is associated with a 2–3 fold increase in damage accumulation [Mashiba et al., 2000, 2001]. In both cases, damage accumulation to these levels was associated with a 20% decrease in tissue toughness (the amount of energy required to

> cause the bone tissue to fail). It is not known whether the rate of microdamage accumulation will accelerate with continued suppression of remodeling, or whether it will reach an asymptote that signals a new balance between remodeling and damage. Nor is the appropriate balance between remodeling suppression and effective repair of damage known."

42. These funded studies resulted in the paper by Allen et al., [2006] which showed that microcrack accumulation in the vertebrae of dogs treated with alendronate or risedronate at clinical doses for one year was significantly increased compared to vehicle-treated dogs. This work showed a 14% reduced toughness in the vertebrae of these animals, which was not statistically significant probably because of low statistical power. This work also showed that damage accumulation in the lumbar vertebrae was negatively and nonlinearly associated with reduced bone turnover, measured by activation frequency. In other words, the greater the suppression of bone turnover, the more damage accumulated in the tissue.

43. This was followed in 2007 [Allen and Burr, 2007] by a paper showing an increase in microcrack density in dogs treated at clinical doses for three years which was not statistically significant. However, this paper also showed a statistically significant 27% decline in bone toughness in dogs treated with clinical doses of alendronate compared to controls, and a statistically significant reduction in bone toughness in dogs treated at higher doses.

44. In 2004, we embarked on a trial to determine whether short-term suppression of bone turnover

using bisphosphonates (in this case, risedronate) could prevent or delay the onset of stress fractures in Israeli soldiers undergoing basic training [Milgrom et al., 2004]. Our expectation was that a short period of treatment would suppress the initial loss of bone during remodeling targeted to repair microcracks in a group known to have high rates of stress fractures, and that it would prevent or delay the onset of stress fractures. Because of a high dropout rate, statistical significance could not be demonstrated, but the results showed that the soldiers treated with bisphosphonate had a higher incidence of stress fractures of the femur, tibia and metatarsus.

B. Beginning in 1998, Merck Began to Receive Reports of Unusual Femur Fractures Which Should Have Triggered Merck To Study The Connection Between Fosamax and Insufficiency-Type Femur Fractures

45. As early as 1999, Merck began to receive Suspect Reaction Reports from the medical community indicating that physicians were seeing patients who had been taking Fosamax present with long bone fractures.

46. In 1999, Merck received a report of a female patient who had been taking Fosamax and who had developed "insufficiency fracture[s] in both of her thigh bones, which were not caused by trauma, and which were associated with thigh pain." [MRK-FOSMDL-01337515]. This report illustrates a classic example of what was likely bilateral incomplete atypical femoral fractures ("AFF") in this patient. Indeed, in this report, the patient had prodromal pain

in her "thigh bones" (this is the same as the femur). Prodromal pain is associated with stress fractures and is one of the minor features of an atypical femoral fracture. The fractures were also bilateral, and associated with no trauma, both additional features of AFFs. Furthermore, the bilaterality of the fractures strongly suggests a pathologic process occurring in the bones, as opposed to a traumatic event. A report like this is fully consistent with the potential adverse consequence of continuous treatment with Fosamax that Merck had been alerted to years earlier.

47. In 1999, Merck received a report of a 53-year old female patient who "developed bilateral femoral fractures in the absence of trauma." The reporter indicated that the patient "had normal spine bone mineral density and slight osteopenia at her hip." [MRK-FOSMDL-01337513]. This report is further evidence of non-traumatic bilateral femoral fractures in a patient taking Fosamax. Importantly, this patient did not have osteoporosis. As with the previous case, the bilaterality in this case is suggestive of a pathologic process. Although the warnings Merck received years earlier about the possibility for insufficiency stress fractures after Fosamax treatment were not site-specific, these reports should have provided a clue to Merck that further study of unusual femoral fractures in people and bone mechanical properties in animals models were needed in light of its preexisting knowledge of, and warnings from advisors about, the potential for stress fractures with Fosamax treatment.

48. In 2000, Merck received another report regarding a 77-year old female who developed "a spontaneous femoral fracture." This woman's fracture

had been preceded by complaints of pain while walking (i.e. prodromal pain). [MRK-FOSMDL-01337511]. A "spontaneous" fracture also suggests that this was a low energy fracture without trauma. Again, the absence of trauma, the involvement of the femur, and the prodromal pain prior to fracture, all characteristics of AFFs, should have alerted Merck that Fosamax use may have been involved in predisposing to these femoral fractures. These clues should have caused Merck to further study this potential, particularly in light of its prior knowledge and advice from consultants.

49. In 2002, Merck received a report of two female patients who had "stress fractures on tension surfaces . . . of their femurs that have not healed." The physician who made this report asked Merck the correct questions: "Is decreased osteoclastic resorption also contributing to decreased coupled osteoblastic formation? Would this limit healing potential of stress fractures?" [MRK-FOSMDL-01337516]. This report was generated by a physician who was treating more than one patient who had developed femoral stress fractures subsequent to Fosamax use. Merck had been alerted to the possibility of such fractures over a decade before. By 2002, Merck had received multiple reports of this type of fracture *in the femur*. Merck should have designed a study to investigate the potential for long-term Fosamax use to cause insufficiency stress fractures in the femoral shaft.

50. In 2003, Merck received a very detailed report of a 59-year old woman who had developed bilateral stress fractures after at least five years of Fosamax treatment. The woman had normal bone mineral density at her hip, although she had a previous spinal

compression fracture. In 2002, the physician noted that an MRI showed a "diffuse/poorly defined focus of intense edema within the intramedullary cavity of the proximal left femoral shaft and thickening of cortical margin of the outer left proximal femoral shaft." This finding is consistent with a stress fracture on the left femur in a patient with cortical thickening. Because cortical thickening should normally be associated with increased bone strength and stiffness, this should have caused Merck to question whether the intrinsic material properties of the bone tissue were negatively affected by Fosamax. Later in 2002, a bone scan revealed "increased . . . uptake in the proximal left femur which may have represented a fracture or a tumor." By 2003, a bone scan showed that the stress fractures were now bilateral in both femurs. In 2006, the physician concluded that the fractures "may be due to hypermineralization due to long term use of alendronate sodium." [MRK-FOSMDL-01337531]. This report provided Merck with the most clues to date about Fosamax's potential to cause insufficiency stress fractures in the femoral shaft. The reporter noted many of the classic signs of an AFF: prodromal pain, bilaterality, and radiographic evidence of a stress fracture based on a positive bone scan. A reasonable scientist who was aware of Fosamax's potential for causing insufficiency stress fractures would consider these reports important and take steps to develop more scientific evidence to further examine Fosamax's role in causing serious femoral shaft insufficiency stress fractures that could progress to a complete fracture.

51. In 2004, Merck received information regarding an abstract presented by Dr. Clarita Odvina and

colleagues of several patients with unusual fractures who had suppressed bone turnover. [MRK-FOSMDL-01337552]. Several of these patients had low trauma fractures of their femur, including two patients with bilateral femoral fractures after 5 and 8 years of treatment with Fosamax, respectively. As noted in the adverse experience report submitted by Merck to the FDA, "[t]he authors commented that femoral shaft fractures were rare even in patients with osteoporosis. Therefore, the occurrence of femoral shaft fractures in the four patients on long term bisphosphonate therapy raised the possibility that such treatment might be associated with spontaneous unusual fractures." At this point in time, Merck had a large amount of data which suggested that Fosamax was associated with unusual femoral shaft fractures, including insufficiency stress fractures of the femur.

52. In 2005, Merck received a report from Dr. Joseph Lane, a respected doctor and scientist who is a member of the ASBMR Task Force on atypical femoral fractures, of "25 patients with long bone fractures that [*sic*] 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.'" Later in that report, Dr. Lane reported to Merck that bone biopsies of these patients show that the "bone is asleep and there is a subset of people who are over-suppressed . . . ." Dr. Lane also reported to Merck that his hospital (the Hospital for Special Surgery in New York City) was planning a study "to look at long bone fractures in patients who were treated with Fosamax . . . versus a control group who

was not." [MRK-FOSMDL-GOL-00012457-00012460]. In that same email, Merck identified another report by Dr. Lane in which he identified a woman in her 70's who had been experiencing thigh pain and later broke her femur after taking Fosamax for 7 years. I am not aware of any efforts Merck made to obtain more information on the 25 fractures reported by Dr. Lane. Certainly by this point in time (if not much earlier), Merck had ample data to suggest that Fosamax was associated with or contributing to a particular kind of femoral shaft fracture.

53. These reports, combined with Merck's prior knowledge of the potential for insufficiency stress fractures associated with long-term Fosamax use, should have caused Merck to study this serious problem.

C. Merck's Internal Data Apparently Provided Clues To This Developing Safety Signal

54. I reviewed the expert report prepared by David Madigan, Ph.D. Dr. Madigan purported to "examine whether a signal of problematic oversuppression of bone turnover and associated atypical femur fracture syndromes existed for Fosamax . . . ." I am not an expert in pharmacovigilence or bio-statistics and, as such, I have no opinion on whether the methods and techniques Dr. Madigan used are sound or valid. However, in the context of my prior opinions regarding what Merck knew about Fosamax's potential for causing serious insufficiency stress fractures, certainly a data signal for "femur fracture" and "stress fracture" should have alerted Merck to more fully study the question that was first raised by outside and

inside scientists in the early 1990's. The search terms used by Dr. Madigan for adverse events were those "selected by Merck to internally evaluate the same." Dr. Madigan's report shows that the signal for a stress fracture in those taking Fosamax first emerged in 2003, and the signal for "femur fracture" first emerged in 2005. Furthermore, the signals Dr. Madigan detected for delayed union, malunion, and nonunion, while not directly attributable to Fosamax treatment, are indicative of a kind of fracture that is difficult to heal such as an atypical femoral fracture, and first emerged as a signal in 2002.

D. Merck Failed To Adequately Study The Potential For Long Term Fosamax Use To Cause Serious Insufficiency Stress Fractures

i. Bone Material Property Testing

55. There are a number of biomechanical parameters that can be used to characterize the mechanical integrity of bone. The key relationship is that between load applied to a structure and displacement in response to the load. The slope of the elastic region of the load-displacement curve represents the extrinsic stiffness of the structure. Besides stiffness, strength can be derived by measuring the maximum force at failure, and work or energy to failure can be calculated by measuring the area under the load-displacement curve. Each of these measured parameters reflects a different property of the bone: maximum force reflects the general integrity of the bone structure, stiffness is closely related to mineralization, and energy to failure is the amount of energy necessary to break the bone. The

biomechanical status of bone is poorly described by any single one of these parameters. For instance, a very stiff bone can also be very brittle and break easily. When load and deformation are normalized for the amount and distribution of bone by engineering formulae, a stress-strain curve is generated which allows the calculation of intrinsic, or tissue-level, strength (ultimate stress or strain), stiffness (elastic modulus) and the modulus of toughness (energy to failure). These concepts are described in more detail in Turner and Burr [1993, 2001].

ii. How Does One "Properly" Test Bone Toughness?

56. It is also possible to test bone toughness in a different way using techniques associated with true fracture mechanics. The goal with these techniques is to describe the fracture process in a material, without regard to its geometry. It allows one to test the probability that a crack may be initiated in a material, and the probability of it growing to a critical size. A fracture mechanics test produces two key parameters: the critical stress intensity factor, K_c, and the critical strain energy release rate, G_c. K_c is also known as fracture toughness, but is different than the modulus of toughness. Both toughness and modulus of toughness are acceptable mechanical tests to evaluate the properties of a material, including bone tissue, but they provide different information. Fracture mechanics tests are better for defining the relationship between the local stress field near a crack tip and the subsequent growth of the crack. Modulus of toughness provides a measure of the amount of energy that is required to cause tissue failure, irrespective of geometry or bone mass.

iii. Merck Failed To Do Mechanical Testing Of Bone After Long Term Use Of Fosamax

57. Merck investigators measured bone strength of both cortical (from the radius) and lumbar vertebral bone in several studies using large animal models [Peter et al., 1996; Balena et al., 1993]. However, they calculated only strength in the Balena study, and only strength and stiffness in the Peter study. A single mechanical measure is insufficient to fully characterize the mechanical integrity of a bone, for reasons stated above. It would have been relatively easy to also calculate energy to fracture and to convert the load-deformation curve to a stress-strain curve to calculate ultimate stress, modulus of elasticity and modulus of toughness, but this was not done. Therefore, it is my opinion that Merck investigators did a poor job of characterizing bone mechanical quality, particularly after recognizing that suppression of remodeling could have significant deleterious effects. Moreover, the Peter study was only a 25 week study in which the primary outcome was related to fracture healing. This is an insufficient amount of time to see significant changes with treatment in a dog (about 2 remodeling cycles, which would be equivalent to about 8 months of treatment in a human).

E. Summary

58. Therefore, it is my contention that:

a. By 1990, Merck knew that fractures, including stress fractures, due to inadequate microcrack repair could be a cause for concern.

b. By 1991, many scientists recognized the potential problem that suppression of bone turnover could impair mechanical properties of bone.

c. By 2000, it had been proven with statistical confidence that suppression of bone turnover by alendronate impaired the mechanical properties of bone, including bone modulus of toughness, a critical property in assessing a bone's susceptibility to stress fracture.

d. By 2004, there was evidence to suggest that bisphosphonates might increase the incidence of stress fractures in a physically fit, highly active, metabolically normal population of Israeli soldiers.

e. Certainly by 2005, after having access to all of the animal data described above, the numerous adverse event reports describing low energy femoral fractures, and the Odvina and Lane reports, Merck should have been fully aware of Fosamax's potential to cause serious fractures of the femoral shaft and at a minimum sought to study this serious problem.

VI. MERCK'S ATTEMPT TO ADD LANGUAGE TO THE FOSAMAX LABEL IN SEPTEMBER OF 2008 MISCHARACTERIZED FOR THE FDA THE TRUE NATURE OF THE AFF PROBLEM

59. On September 15, 2008, Merck submitted to the Food and Drug Administration ("FDA") a proposal to update the labeling for Fosamax to include a description in the Precautions section of the label of "Low-Energy Femoral Shaft Fractures." Specifically, Merck proposed the following language be added:

> Low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonate treated patients. Some were stress fractures (also known as insufficiency fractures) occurring in the absence of trauma. Some patients experienced prodromal pain in the affected area, often associated with imaging features of stress fracture, weeks to months before a complete fracture occurred. The number of reports of this condition is very low, and stress fractures with similar clinical features also have occurred in patients not treated with bisphosphonates. Patients with suspected stress fractures should be evaluated, including 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), and receive appropriate orthopaedic care. Interruption of bisphosphonate therapy in patients with stress fractures should be

considered, pending evaluation of the patient, based on individual benefit/risk assessment.

60. Along with this proposed labeling, Merck submitted to the FDA adverse event reports, some of which I describe above, reflecting a number of femoral fractures which Merck labeled as "Atypical Femur Fractures." In addition, Merck submitted to the FDA a document entitled "2.5 Clinical Overview," which appears to contain the purported medical and scientific rationale for the proposed label change. I have reviewed what I believe to be Merck's entire submission to the FDA in September 2008. According to the information I have, Merck did not submit anything else to the FDA in support of this proposed label change.

61. It appears that on May 22, 2009, the FDA sent a letter to Merck informing Merck that it could not "approve these applications in their present form." The FDA informed Merck that its "justification for the proposed **PRECAUTIONS** section language is inadequate." The FDA further informed Merck that "[i]dentification of 'stress fractures' may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature." As I will explain in more detail below, it is not surprising that the FDA made this determination given the inadequate description and justification that Merck provided to the FDA regarding atypical femoral fractures.

62. In 2009 the American Society for Bone and Mineral Research ("ASBMR") convened a Task Force to address the issue of atypical femoral fractures primarily in patients who had been taking bisphosphonates for a long period of time. The Task

Force was asked to review the currently available information to determine what was known and what was not known about atypical femoral fractures and their relationship to BP use, and to recommend a case definition. The Task Force Report was published in the *Journal of Bone and Mineral Research* in 2010 (25:2267–2294.).

63. I, along with a colleague Elizabeth Shane from Columbia University, was selected by the ASBMR to be a co-chairperson of the Task Force. As I discuss above, my work in the field of skeletal fatigue and microcrack-mediated remodeling in bone biomechanical and physiological adaptation makes me particularly suited to marshal the information and resources necessary to adequately understand the issues surrounding atypical femoral fractures.

64. The Task Force Report summarizes what was known at the time about atypical femoral fractures, their relationship to bisphosphonates, and their possible pathogenesis. Table 5 in that report lists 37 published case series and reports on atypical femoral fractures, starting with the initial report by Odvina et al. in 2005. In 2008, 13 of those 37 published case series and reports were available to Merck. By May of 2009, 19 of those 37 were available to Merck. Additionally, the Task Force cited a total of 177 published or available articles and posters. Of those 177, 114 were available in 2008 or earlier and 120 were available before May of 2009.

65. Although the Task Force in 2010 could not conclude that, from a scientific perspective (i.e. very high certainty), bisphosphonate use and atypical femoral fractures were related in a cause and effect

manner, it seemed likely that bisphosphonate use was a substantial factor in causing atypical femoral fractures because (1) more than 90% of cases of AFF occurred in association with BP treatment for osteoporosis, (2) there was no indication of osteoporotic changes in the femurs of this relatively young cohort; indeed the increased cortical thickness that was noted at the time should, from a mechanical standpoint, be associated with increased structural rigidity, not reduced strength, and (3) there were several plausible mechanisms of action which could explain how long-term use of Fosamax and other BPs would lead to an AFF.

A. Merck's September 2008 Submission To The FDA Failed To Demonstrate To The FDA The Potential Underlying Pathogenic Mechanisms Connecting The Long-Term Use Of Fosamax With Insufficiency Stress Fractures.

66. One of the most important aspects to understanding the how and why of AFF is an examination of the possible pathogenesis of this unusual fracture. Indeed, prior to the introduction of Fosamax, subtrochanteric femoral fractures rarely were reported with the clinical criteria associated with AFF.

67. For more than 15 years, I have been examining the relationship between bisphosphonate use and bone material properties. My work, along with dozens of other scientists, shows convincingly that continuous use of Fosamax and other BPs can change important bone characteristics and properties, such as bone toughness. Scientists such as myself have shown that

continuous use of Fosamax and other BPs results in microcrack accumulation, AGE accumulation, increased bone homogeneity, and a greater proportion of older bone, all of which have the effect of decreasing bone toughness, or the bone's ability to withstand repeated low energy forces without breaking.

68. As I discuss above, decreased bone toughness can lead to stress fracture. Additionally, Fosamax and other BPs reduce the body's ability to repair a stress fracture once it has begun, but prior to complete fracture. This might explain why a large number of bisphosphonate-induced stress fractures go on to completion. Indeed, normally a stress fracture will heal itself if the patient simply decreases his/her activity level for a period of time. However, AFFs which begin as stress fractures appear to progress to completion at a much higher rate than would be expected.

69. I have reviewed Merck's September 15, 2008 submission to the FDA, including the "Clinical Overview" document which purports to provide the justification and rationale for the proposed label change. Nowhere in Merck's submission does it provide the FDA with any possible pathogenesis for AFF from long-term Fosamax. By September 15, 2008, there were literally dozens of published scientific articles, including many on which I was an author, which provided evidence for a possible pathogenesis of AFF.

70. An explanation regarding the possible pathogenesis of AFF is particularly important in this context because Fosamax is a drug that was designed

to prevent osteoporotic fractures.[4] Without an adequate explanation to the FDA about why AFFs might be different than other osteoporotic fractures, the FDA and others might conflate the two types of fractures. Importantly, the data suggest that Fosamax may be particularly effective in reducing fractures among women with osteoporosis in the first several years of treatment. By contrast, AFFs generally do not occur until a patient has been taking Fosamax and other bisphosphonates for five years or more (the Task Force Report in 2010 identified the median duration of treatment before fracture as 7 years). Thus, a more detailed presentation to the FDA would have revealed that there is little overlap between the therapeutic use of Fosamax and its harmful side effect of AFFs.

71. By contrast, less than two years later, the Task Force examined the available literature and evidence regarding a possible pathogenesis for AFF and provided the medical community, and the FDA, with a detailed explanation of how long-term use of Fosamax and other BPs could lead to an AFF. This prompted the FDA to take quick action in requiring manufacturers to update the BP labeling with a warning regarding the potential risk for AFF.

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[4] I offer no opinion herein regarding the efficacy of Fosamax in preventing osteoporotic fractures.

B. Merck's September 2008 Submission To The FDA Failed To Explain That AFFs Were Unusual Fractures That Had Rarely Been Reported In The Literature Prior to the Availability of BPs

72. In reviewing the proposed labeling Merck sent to the FDA, as well as the "Clinical Overview" that Merck provided the FDA, Merck repeatedly emphasized that fractures with "similar clinical features" had previously been reported in patients not taking Fosamax. In the "Clinical Overview" document Merck provided to the FDA, Merck stated "[w]hile these fractures are less common than other osteoporotic low-energy fractures (representing about 6% of fractures of the femur), they occur in a similar population of elderly individuals and have been reported prior to the availability of bisphosphonates." Although it is true that stress fractures, including completed stress fractures, had previously been reported in the literature, the nature of AFF is unusual and cannot be identified properly without radiographic evidence. This often was not available prior to the availability of BPs or prior to the identification of AFF as a separate patholology, and so the incidence prior to the availability of bisphosphonates was really unknown. Merck's submission to the FDA fails to acknowledge the crucial distinction between subtrochanteric or femoral shaft fractures, and AFF, and improperly implies a rate of non-bisphosphonate exposed AFF that was unknown, and which conflates the occurrence of any subtrochanteric fracture with fractures that have specific features of atypia.

73. As I discuss above, stress fractures have unique clinical characteristics. First, they are often painful in the affected area. Second, they are often imaged on x-ray as having a periosteal or endosteal reaction indicative of the bone's attempt at repair. Third, they appear on x-ray generally as an incomplete transverse fracture. Finally, they occur not from trauma, but from repeated low energy loading of the bone which is unable to be repaired in sufficient time to prevent the stress fracture from occurring.

74. Importantly, even though Merck knew in September of 2008 that AFFs had a relatively unique clinical appearance, Merck made little effort to describe that to the FDA. In fact, my review of the submission by Merck indicated that Merck told the FDA only that the femoral fractures were "low energy," that some patients experienced "prodromal pain," and that some patients had the "imaging features" of a stress fracture. At that point in time, many authors had adequately described AFFs as being low energy, femoral shaft or subtrochanteric fractures, which a transverse fracture line, a periosteal reaction, associated with cortical thickening, prodromal pain, and bilaterality. In fact, in the reports received by Merck in 2006 from Singapore, the doctors there described these unusual fractures in a very similar way: low (or no) energy, subtrochanteric transverse fractures of the shaft, some with bilaterality, and all taking Fosamax. Likewise, in the Neviaser article which was published in March of 2008, the authors described these fractures as "simple, transverse, or short oblique . . . in areas of thickened cortices with a unicortical beak." In fact, although different studies and authors have used slightly different variations on

how they describe AFF, 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. It was this consistency that allowed the ASBMR Task Force to achieve consensus on the definition for an atypical femoral fracture.

75. It is true that some of the studies which examined AFF identified some individuals with the atypical fracture pattern who had not been taking any BP. About 90% of the patients who had the AFF pattern had previous exposure to BPs. Thus, approximately 10% of those patients had no reported prior exposure to BPs. In the second Task Force Report, the relative risk for an AFF in patients on a BP ranged in different studies from 2.11 to 66.9, with an average adjusted relative risk of 31, suggesting convincingly that BP use increases the risk of sustaining an AFF. The Task Force recognized in its first report that not everyone presenting with an AFF had BP exposure when it stated "[a]lthough atypical femoral fractures have been reported *most prominently* in individuals who have been treated with BPs, such fractures have been reported in individuals with no history of BP exposure." (Italics added). The updated Task Force Report, however, states "Although the task force still holds the opinion that a causal relationship between BPs and AFFs has not been established, evidence for an association has continued to accumulate in the 2 years since the first report was published and is quite robust. Moreover, the fairly consistent magnitude of the association between BPs and AFFs is unlikely to be accounted for by unknown or unmeasured confounders." I believe a statement

such as that accurately conveys the relative frequency with which AFFs had been seen among both exposed and non-exposed individuals.

76. In its submission to the FDA, Merck should have better described this unique fracture to the agency and highlighted that this fracture pattern, particularly in the femoral shaft, was rarely reported prior to the availability of BPs. Instead, Merck appears to have created a submission which suggests that this fracture is much more common in the absence of BPs than it actually is.

C. Merck's September 2008 Submission To The FDA Improperly Attributed Various Risk Factors To AFFs, Including Osteoporosis

77. In its proposed labeling to the FDA, Merck includes the following sentence: "Patients with suspected stress fractures should be evaluated, including 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), and receive appropriate orthopedic care."

78. In the "Clinical Overview" document submitted by Merck to the FDA, Merck further made these statements: (1) "Stress fractures are seen mainly in postmenopausal *osteoporotic* women and are becoming more common with the increase of elderly population and its increasing involvement in relatively intensive physical/fitness activities."; and (2) "In addition to abnormally decreased bone mineral density (BMD) associated with osteoporosis, long-term

immobilization/disuse, and use of glucocorticoids, the presence of joint deformity, leg-length discrepancies, muscle weakness, and spasm with resulting alteration in force distribution across the joints is likely to be very important in the development of insufficiency fractures." (Italics added).

79. When the Task Force examined the actual data, many of the "risk factors" identified by Merck in its submission to the FDA simply were not associated with AFF. Importantly, the Task Force noticed that many of the patients with this fracture pattern had "normal or low BMD, but not osteoporosis in the hip region." We identified the fracture pattern as being distinct from a typical osteoporotic fracture. This is consistent with my opinion regarding the likely pathogenesis of AFF as unrelated to any underlying BMD deficiency. Moreover, Merck failed to identify increased cortical thickness as a risk factor, although it had been widely discussed as associated with occurrence of AFFs. Identifying this association would have made it more clear to the FDA that AFFs were not the typical fracture associated with osteoporosis, which causes cortical thinning. Further, although the Task Force identified rheumatoid arthritis, glucocorticoid use, and PPI use as being possibly related to the fracture pattern, there is little evidence that the myriad other "risk factors" identified by Merck have anything to do with AFFs (i.e. "leg-length discrepancies" and "muscle weakness").

80. Further, as the co-editor of a book which focused almost exclusively on stress fractures, it is my opinion that Merck improperly suggested to the FDA risk factors for stress fracture (generally) which are not supported by the available data. For example, in the

book on stress fracture for which Dr. Milgrom and I are co-editors, the relationship between Bone Mineral Density ("BMD") and stress fractures was considered to be "equivocal and difficult to interpret." This suggests that osteoporosis, if defined by BMD, has little support in the literature as a causative factor for stress fracture. In another book in which I wrote a chapter about stress fractures, I examined the relationship between BMD and stress fracture and concluded the data do not support "the hypothesis of a close relationship between low bone density and stress fracture . . . ."

81. In my opinion, it appears that Merck was attempting to confound the true nature of the association between Fosamax and AFFs by identifying numerous potential risk factors, very few of which were actually grounded in the available data. It appears that the FDA agreed with this as it stated in its May 22, 2009 letter to Merck that "[d]iscussion of the risk factors for stress fractures is not warranted and is not adequately supported by the available literature and post-marketing adverse event reporting."

D. Merck's September 2008 Submission To The FDA Improperly Conflated The Underlying Fracture Mechanism (Stress Fracture) With The Ultimate Outcome (Completed Subtrochanteric Fractures)

82. In its proposed labeling, Merck stated that "[l]ow-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonate treated patients."

Thereafter, however, Merck only identified these fractures as "stress fractures" in its proposed labeling. In the "Clinical Overview" document Merck provided to the FDA, Merck focused much of its discussion in the "Introduction" of the document on stress fractures.

83. I was the co-editor of a book entitled *Musculoskeletal Fatigue and Stress Fractures* (2001), which focused almost exclusively on fatigue-type stress fractures. The fact is that the vast majority of stress fractures never progress to a full and complete fracture. "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. Generally, doctors treat stress fractures in patients by prescribing rest or inactivity in the affected bone. The vast majority of stress fractures heal without any further intervention and do not progress to a complete fracture.

84. By choosing to characterize AFFs as "stress fractures" in its submission to the FDA, Merck improperly conflated the underlying fracture mechanism that leads to AFFs with the ultimate outcome. It is true, as the Task Force has now twice pointed out in its reports, that AFFs are the result of a stress/fatigue type process on the proximal femoral shaft. As I describe in great detail herein, Fosamax and other BPs affect the material properties of bone over time by reducing bone toughness and its ability to repair microcracks. As a result, on the lateral side of the femoral shaft, some women (and men) who have continuously taken Fosamax for several years may

develop a stress lesion. However, Fosamax also prevents the normal repair of those stress lesions, allowing the initial stress fracture lesion to continue to grow until complete fracture of the bone. Even an incomplete AFF is a serious medical condition as many of these patients will require surgical intervention to prevent the eventual complete fracture of the femur. As pointed out by the Task Force, intramedullary rods are the current standard of care in such cases.

85. However, a large percentage of these stress lesions in patients treated with Fosamax and other BPs go on to completion. As the task force noted, AFFs have high morbidity "[b]ecause of the propensity for delayed healing." And because the population of patients who develop AFFs is younger [Shane et al., 2013] and more active, significant lifestyle and workplace limitations are associated with these fractures in a population that might normally still be quite vigorous. Thus, characterizing AFFs as stress fractures in product labeling for Fosamax improperly suggests to medical practitioners that AFFs are much more inconsequential than, in fact, they are.

86. In its May 22, 2009 letter to Merck, the FDA stated that "[i]dentification of 'stress fracture' may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature." It appears that by conflating the underlying fracture mechanism (stress fracture) with the ultimate outcome (a completed subtrochanteric fracture), Merck gave the FDA the impression that AFF are simply stress fractures. As I discuss, because they often will progress to a complete fracture of the largest bone in the body, they are much more significant than "garden-variety" stress fractures, which usually heal

uneventfully with simple rest and without full fracture.

E. Summary

87. Overall, it appears to me that Merck failed to adequately apprise the FDA of the true nature of the AFF problem in September of 2008 given the data that was available to it at that time. It is difficult to appreciate the significance of this fracture in the context of a medication that is supposed to prevent fractures unless a detailed discussion of a possible underlying pathogenesis is provided. Merck failed to inform the FDA of the relative rarity of this fracture prior to the availability of Fosamax and, instead, simply stated that the fracture was seen in patients not taking a BP. It appears that Merck attempted to confound the underlying possible causes of AFF by identifying numerous "risk factors," many of which were not supported by data, and by failing to report potential risk factors (e.g. increased cortical thickness) that would have suggested that these fractures were not "osteoporotic fractures." Finally, Merck improperly equated AFF with stress fractures conflating the underlying fracture mechanism with its ultimate outcome.

88. By contrast, the Task Force undertook to look at the issue of AFFs in a very detailed and systematic manner. We considered all the available literature, examined a possible pathogenesis for the fracture, developed a case definition to assist practitioners, researchers, regulatory agencies, and manufacturers in identifying the fracture, we recommended future research, and we recommended labeling changes to BP medications. After approaching the issue in this

manner, the FDA acted very swiftly by requiring manufacturers to update bisphosphonate labels to reflect this significant risk.

I declare under penalty of perjury pursuant to the laws of the United States of America that the foregoing is true and correct.

Executed this 29th Day of September, 2013.

s/ David B. Burr
David B. Burr

[Exhibit 3 to Ecklund Declaration]

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: FOSAMAX (ALENDRONATE SODIUM) PRODUCTS LIABILITY LITIGATION (No. II) THIS DOCUMENT RELATES TO: ALL CASES	Civil Action No. 08-08(GEB)(LHG) MDL No. 2243

DECLARATION OF CURT DANIEL FURBERG, M.D., PH.D.

I. INTRODUCTION AND QUALIFICATIONS

I, Curt Daniel Furberg, M.D., Ph.D., hereby declare that all of the following are true, to the best of my personal knowledge and upon information and belief.

1. I am a medical doctor admitted to the practice of medicine in Sweden. I received my medical training and a PhD-equivalent at the University of Umea, Umea, Sweden.
2. From 1974 through 1985, I was employed at the National Heart, Lung, and Blood Institute of the National Institutes of Health (NIH) in Bethesda, Maryland. For the first nine (9) years at the NIH, I worked in the Clinical Trials Branch and served as its Chief from 1979 to 1985.

3. I received an academic appointment as Professor of Medicine in 1986 from Wake Forest University School of Medicine in Winston-Salem, North Carolina. I was appointed Director, Center for Prevention Research and Biometry and Head, Section of Prevention Research and Biometry in the Department of Medicine. In 1989, the Department of Public Health Sciences was established and I was appointed Chairman. I served in this capacity until 1999. I retired as Professor of Public Health Sciences at Wake Forest School of Medicine as of June 30, 2012. I am currently Professor Emeritus at the school. A copy of my CV is attached as Appendix A.
4. During my 13-year leadership and direction of the Center and the Department, we grew from one to approximately 300 persons. Three Sections were established within the department — Epidemiology, Biostatistics and Social Sciences and Health Policy. We successfully competed for funding from the National Institutes of Health and, in recent years, we have ranked nationally as one of the top two departments of our type (for NIH funding).
5. I have more than three decades of expertise and experience in the areas of epidemiology and clinical trial design, conduct, monitoring, interpretation and reporting. I am considered by my peers to be a national leader in this field. The following are illustrative of my relevant experience and expertise:
    a. I have served as Principal Investigator or Scientific Project Officer on a large number of

primarily cardiovascular clinical trials, having played a very active role in their design, conduct, monitoring, interpretation and reporting. These trials documented the efficacy and safety of various interventions and led to improvements in the quality of care for millions of patients with coronary heart disease, heart failure, hypertension or other vascular conditions. In addition, I served as the Principal Investigator (recipient) of a grant from the Attorney General Consumers and Prescriber Program to develop educational modules for healthcare professionals. Funding for this program, coordinated by the Attorney General's office in Portland, Oregon, came from a large settlement with Pfizer regarding the illegal off-label promotion of the drug Neurontin.

b. I have served or currently serve on the Data Safety Monitoring Committee for over fifty clinical trials, including several trials sponsored by Merck. These committees monitor the efficacy and safety of treatment and prevention trials in progress and are charged with recommending early trial termination, if efficacy is clearly documented or if harmful effects outweigh the benefits. These trials have been sponsored by the National Institutes of Health, Foundations, the pharmaceutical industry and others. Currently, I am on the Data Safety Monitoring Committee of two industry-sponsored trials. Thus, I am very experienced in the generally accepted approaches to weighing favorable and

unfavorable effects of interventions, primarily medications.

c. I have frequently been consulted on clinical trial issues by colleagues at academic institutions and I have conducted trials sponsored by pharmaceutical companies. I consulted for Wyeth as an expert regarding the combination fenfluramine- phenteramine (so-called "fen-phen") in determining the magnitude of the adverse effects associated with its use. I have also interacted with the World Health Organization.

d. I have also been retained as an expert witness for patients who claim that they have suffered harmful drug effects and for pharmaceutical companies defending themselves against such claims. I served as an expert on behalf of Wyeth in a case against a woman who claimed that her hormone replacement therapy had caused her stroke. I have also been retained as an expert for a pharmaceutical company involving litigation regarding a prescription drug in Canada.

6. In addition, I am a past charter member of the U.S. FDA Drug Safety and Risk Management (DSRM) Advisory Committee. This Committee was established by the FDA to provide expert advice on drug safety issues. My term ended in May, 2006. It was as a member of the DSRM Committee that I participated in the FDA Hearing on COX-2 inhibitors in February, 2005. I have been invited as an expert to serve on FDA hearings in 2007, 2008, 2009, and 2010.

7. In collaboration with four other Committee members, we reported our views about the FDA and drug safety in a recent article entitled "The FDA and Drug Safety: A Proposal for Sweeping Changes" (*Arch Intern Med* 2006;166:1938–42).
8. I have served as chair of the Outpatient Prescription Drug Subcommittee and as a member of the Medical Center's Formulary Committee. I was recently invited to be a member of the United States Medicare Evidence Development & Coverage Advisory Committee. I have also served on the State of North Carolina Drug Utilization Review for Medicaid.
9. As an expert on drug safety, I have testified twice at Congressional Hearings. I was invited in March, 2005 to provide a written testimony for the U.S. Senate Committee on Health, Education, Labor and Pensions regarding how well the pharmaceutical industry pursues safety signals and disseminates safety information to the medical community and to consumers. I also provided live testimony in March, 2007 for the U.S. House Committee on Energy and Commerce, Subcommittee on Oversight and Investigations regarding the pharmaceutical companies' oversight of drug safety, including applicable laws, regulations and the consequences associated with violations thereof.
10. I am the past Chair of the Steering Committee of the Cardiovascular Health Study sponsored by the National Heart, Lung, and Blood Institute. This very large epidemiologic study was initiated approximately twenty-five years ago to investigate

risk factors (predictors) for coronary heart disease and stroke in people 65 years of age or older. I am also past Steering Committee Chair of the Ginkgo Evaluation of Memory Study sponsored by the National Center for Complementary and Alternative Medicine of the National Institutes of Health.

11. I was recently invited to be a member of the Advisory Board of the British Medical Journal, one of the leading medical journals in the world.

12. I served as the Research Subject Advocate Advisor and as a member of the General Clinical Research Center's Human Subject Protection Committee, which monitored high- risk studies conducted at Wake Forest University School of Medicine. My role was to help protect the safety and well-being of study participants by overseeing and monitoring ongoing trials for possible adverse treatment effects. As a result of my work, we promptly facilitated the termination of two local VIOXX trials soon after the drug was taken off the market. I am also Past Chair of an institutional Data Safety Monitoring Committee at Wake Forest.

13. As referenced previously, I have authored numerous publications on the subject of clinical trials. Along with two colleagues from the National Institutes of Health, I co-authored a text book entitled *Fundamentals of Clinical Trials*. The 4th Edition was published in 2010 and we are currently working on the 5th Edition. This is considered a leading text and is used widely for teaching and as a reference for clinical trial researchers. A more recent text is entitled "*Data Monitoring in Clinical*

Trials - A Case Studies Approach," Springer 2006. All 29 cases reviewed in this text address issues of benefit, harm and benefit-to-harm balance. Another text entitled "*Evaluating Clinical Research — All that Glitters is not Gold*," Springer 2007, summarizes many of the clinical trial lessons I have learned over more than three decades. It contains many examples of violations of fundamental principles of medical research. I also have written a book for patients entitled "*Knowing Your Medications – A Guide to Becoming an Informed Patient*". These publication I co-wrote received sponsorships from Merck.

14. I am also the author or co-author of more than four hundred (400) peer-reviewed articles and sixty (60) book chapters on various topics, chiefly including epidemiology and clinical trials. More than seventy (70) of the publications deal with drug safety. In several of them, Merck appointed me to serve on Data Safety Monitoring Committees; in some of them, I was appointed and served as the Chair of the Data Safety Monitoring Committee.

15. Since 1983, I have served on sixteen editorial boards. I am currently a member of the editorial board of one professional journal – *Trials* (dealing with the main subject of clinical trials).

16. I have received the following awards:

    1983 – *Director's Award* from the National Institutes of Health

    1998 – *Women's Health Initiative Achievement Award*, NHLBI

    2001 – *Established Investigator in Clinical Science Award* from Wake Forest University

2002 – *Ancel Keys Lecture Award*, American Heart Association

2004 – *Joseph Stokes III Award*, American Society of Preventive Cardiology

2004 – Honorary degree *Doctor Honoris Causa* from Umea University

2004 – *Rockefeller Foundation Residency Award*, Bellagio, Italy.

2005 – Elected *Fellow of the Society for Clinical Trials.*

2007 – *Health Care Heroes - Lifetime Achievement Award* from the Business Journal

2011 – *Wake Forest School of Medicine Team Science Award.*

2013 – *Wake Forest School of Medicine Team Science Award*

2013 – *Bruce Squires Award*, awarded annually to the authors of the research paper published in the Canadian Medical Association Journal that "was most relevant to the practice of medicine and most likely to impact it in a positive way."

17. I have served as an expert witness in Fosamax litigation for several years on the topics of clinical trials, pharmaceutical efficacy, and pharmacovigilance. My rate of compensation is $500/hour. After extensive *Daubert* hearings and briefing, I was recognized by the presiding District Judge in *In re Fosamax Products Liability Litigation*, MDL No. 1789 (S.D.N.Y.) (Keenan, J., presiding), as an expert competent with sufficient bases and methodology to testify in these areas

(clinical trials, pharmaceutical efficacy, and pharmacovigilance). Further, my opinions on clinical trials and efficacy have been cited by the Fosamax MDL 1789 District Court in published rulings pertaining to Fosamax's lack of efficacy for certain populations of patients. *In re Fosamax Prods. Liab. Litig.*, 742 F.Supp.2d 460, 468–73 (S.D.N.Y. 2010) (citing my testimony about the lack of efficacy for osteopenic patients in affirming the jury's finding that Fosamax was unreasonably dangerous and therefore defectively designed). In an earlier opinion in the same case, after citing my testimony and the testimony of regulatory expert, Dr. Suzanne Parisian, the *Fosamax Products Liability Litigation* MDL Presiding Judge ruled:

> Even if the jury finds that Merck has the benefit of a rebuttable presumption by way of Fosamax's FDA approval, based on this evidence, the jury may reasonably conclude that the risks of Fosamax outweigh its benefits when used for the prevention of osteoporosis by those with a T-score better than -2.5.

In re Fosamax Products Liab. Litig., 2010 WL 1257299, *6 (S.D.N.Y. 2010)

II. ASSIGNMENT AND SUMMARY OF OPINIONS

A. Assignment:

18. As referenced above, I previously have provided the opinions in this Declaration through my trial and deposition testimony in *In re Fosamax Products Liab. Litig.*, MDL No. 1789. For this Declaration, I have been asked to provide my opinions related to

the extent of the proven fracture reduction efficacy of Fosamax as to non-osteoporotic patients and the duration of proven fracture reduction efficacy for osteoporotic patients.

19. In conjunction with the assignment, this expert report includes my opinions regarding the Sponsor's actions related to a) adherence to established standards for the conduct of research, b) dissemination of trial results and c) obligations to inform and warn practicing physicians, research subjects and regular patients.

B. Bases for Opinions:

20. The bases of my opinions derive, in part, from my education, training, experience, research and what is accepted within the community of physicians, scientists and public health professionals who are knowledgeable in the proper conduct and reporting of clinical trials and in the proper dissemination of drug safety information to clinicians and to patients. I have also based my opinions on the review of various clinical studies and materials, many of which are exhibits to my expert report and others which are included in a list attached (Appendix B). My opinions (discussed below) may be further refined, subject to ongoing medical and scientific study and the continuing review of additional information produced from this litigation.

21. I am uniquely qualified to render these opinions, based on my extensive experience in drug evaluation and all aspects of clinical trial methodology and based on my knowledge of regulations, including drug safety and labeling.

C. Summary of Opinions:

22. The following is a brief summary of my opinions:

a. The Sponsor's clinical trials for Fosamax fail to establish that Fosamax is effective in reducing the risk of fracture of any patient who does not have osteoporosis defined either by a femoral neck T-score of -2.5SD or less or a prior vertebral fracture. For osteopenic patients who do not have osteoporosis (defined as a femoral neck T-score of -2.5SD or less or a prior vertebral fracture at baseline), there is no proven fracture reduction benefit conferred through the use of Fosamax. For those patients, any risk of harm would outweigh Fosamax's benefits.

b. Even for osteoporotic patients, the Sponsor's clinical trials for Fosamax fail to establish that Fosamax is effective in reduction the risk of fracture beyond three years of use. For osteoporotic patients, there is no proven fracture reduction benefit after three years of Fosamax use and any risk of harm would outweigh Fosamax's benefits.

III. THE ROLE AND CONDUCT OF CLINICAL TRIALS

23. For regulatory approval of prescription drugs in the United States of America, a drug sponsor is required to conduct clinical trials. A clinical trial is a prospective study comparing the effect and value of a particular intervention against a control in human being. Clinical "studies" differ from clinical "trials" as clinical studies are uncontrolled

whereas a true clinical trial must have a control group.

24. There are several phases of studies which are divided into three phases before the FDA grants New Drug Approval ("NDA"). "Preclinical" studies are conducted in animals, typically, before any human testing is conduct.

    a. Phase I studies are conducted in a small number of humans in order to determine basic information about the drug such as drug tolerance, metabolism, bioavailability, interaction, pharmacokinetics, and pharmacodynamics.

    b. Phase II studies sometimes are conducted as controlled clinical studies with an intervention group and a control group. Phase II studies or trials are therapeutic exploratory studies, looking to establish dose ranges and obtain basic biologic response information, typically through biomarkers. Compared to a Phase III trial, Phase II trials are typically much smaller and of shorter duration and are directed to the initial evaluation of the drug's effectiveness for a particular indication in patients with a disease or condition. Information obtained from Phase II trials are used to then design the Phase III trial or trials.

    c. If the Phase II trials suggest effectiveness, Phase III trials are then conducted in a much larger group of patients and for a longer period of time. Phase III trials are the final phase of clinical trials before an NDA is granted by the FDA. Phase III trials evaluate pre-specified

endpoints in a double-blind methodology. Double-blinding is important because neither the subjects of the study (the patients) nor the person conducting the experiment know whether the patient is receiving the control or the intervention.

d. Phase IV trials are conducted after a drug is on the market and are therapeutic use studies which examine the drug in broad or special populations and seek to identify uncommon adverse events.

25. In the conduct of a clinical trial, each patient in the trial must be followed from a well defined point in time which is referred to as "time zero" or, more frequently, "baseline". In the context of a clinical trial, the term "baseline" typically refers to the starting point of the data collection: i.e., when you actually begin administering an intervention or control to a patient and what that patient's status was at that moment in time. For instance, if you refer to an objective baseline set of entry data (such as a patient's weight, for example), you can measure the change in those data during the conduct of the clinical trial.

26. Clinical trials have three major limitations regarding the discovery or elucidation of risks associated with a drug: l. The trial may not be large enough to detect a rarely occurring adverse event; 2. An adverse may take a long period of time to develop and clinically manifest and the typical manifestation may post-date the trial's study period; 3. Clinical trials typically are not designed to specifically look for unexpected adverse events.

Therefore, there is an adage about adverse events and clinical trials: "The absence of reports does not mean the absence of events."

IV. FOSAMAX HAS LIMITED FRACTURE REDUCTION EFFICACY.

27. The disease for which Merck first proposed the use of Fosamax as an intervention is "osteoporosis". Before 1994, the disease "osteoporosis" was primarily a clinical diagnosis made by clinicians without reference to specified criteria. In 1994, the World Health Organization promulgated a standardized system for the diagnosis of osteoporosis through the measurement of bone mineral density via Dual Energy X-ray Absorptiometry ("DXA") machines. The WHO system referenced the system of comparison between a particular patient's bone mineral density ("BMD") and the reference point which was the average for a healthy thirty year-old white female. Any difference from the patient's score and reference point is referred to via the quantification of the standard deviation, also referred to as the T-score. The reference point on the T-score chart is 0. The further into the negative the particular patient's T-score is, the less bone mineral density the patient has. The WHO system established -2.5 standard deviations as the numerical cut-off for the BMD-based diagnosis of osteoporosis.

28. Under the WHO system, patients with T-scores between -1.0 and -2.5 standard deviations are referred to as osteopenic patients. Osteopenia

itself is not a disease. Osteopenia is simply a way of describing low normal bone mineral density.[1]

29. Osteoporosis, while called a disease, is not itself a disabling condition. Rather, it is the fractures associated with osteoporosis that physicians hope to prevent by prescribing interventions such as Fosamax.

30. Most post-menopausal women are neither osteopenic nor osteoporotic. According to the Merck-sponsored National Osteoporosis Risk Assessment Study, 39.6% of postmenopausal women have osteopenia while only 7.2% have osteoporosis.[2] According to NORA, then, in the postmenopausal women population there are 5.5 times more osteopenic women than osteoporotic women.

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[1] World Health Organization. Assessment of Osteoporotic Fracture Risk and Its Role in Screening for Postmenopausal Osteoporosis. WHO Technical Report series no. 843. Geneva: World Health Organization, 1994. As Merck's Director of Clinical Research for Fosamax, Dr. Arthur Santora, testified in a deposition taken in *In re Fosamax Products Liability Litigation* (MDL No. 1789):

Q: We're talking about osteopenia, but just to be fair, osteopenia is not a disease, is it?
A: Osteopenia is just a way of describing low/normal bone density.
Q: Osteopenia is not a disease, is it?
A: No, it's not a disease.

(Santora MDL 1789 deposition, p. 332.)

[2] Siris ES, Miller PD, et al. Identification and Fracture Outcomes of Undiagnosed Low Bone Mineral Density in Postmenopausal Women: Results from the National Osteoporosis Risk Assessment. *JAMA* 2001; 286:2815–2822.

31. Fosamax (alendronate) is a member of a class of drugs called bisphosphonates that are approved for use in the treatment and prevention of osteoporosis in postmenopausal women; treatment to increase bone mass in men with osteoporosis; treatment of glucocorticoid-induced osteoporosis and treatment of Paget's disease of bone. It contains a nitrogen atom and, thus, belongs to the N-containing bisphosphonate subclass. Other members of this sub-subclass are Aredia (pamidronate), Boniva (ibandronate) and Actonel (risedronate). Fosamax has a remarkably long half-life in bone of more than 10 years, which may have long-term health consequences.

32. Fosamax was approved by the FDA in 1995 for the main indication of treatment of osteoporosis in postmenopausal women. The indication was expanded to the "prevention of osteoporosis" in 1997, again in postmenopausal women. Importantly, the FDA conferred the approval of these two separate indications before Merck had received the full results from its pivotal Phase III trial series, the Fracture Intervention Trial ("FIT"). Remarkably, neither Merck nor the FDA had FIT's complete data on the fracture reduction effects of Fosamax when compared to the control group at the time the treatment and prevention indications were approved in 1995 and 1997. As a result of the indications received by Merck in 1995 and 1997, millions of non-osteoporotic women have been prescribed Fosamax even though there is no proven fracture reduction benefit for that group of patients.

33. The FIT trial program was the pivotal clinical trial series for the Fosamax Phase III program.

34. Through its very broad clinical trial program for Fosamax, Merck has studied osteopenic and osteoporotic post-menopausal women. Based upon my review of Merck's clinical trials for Fosamax, there is evidence of a fracture reduction benefit for only a specific population and only for a specific period of time. The specific population for which Merck has shown a fracture reduction benefit is for patients who have osteoporosis defined by either (1) a baseline T-score of -2.5SD or worse or (2) a baseline, preexisting vertebral fracture. Merck has studied but did not find any fracture reduction benefit for post-menopausal women who did not have either of these two conditions. Further, for those women for whom a fracture-reduction benefit is conferred, the benefit is time-limited and no fracture reduction benefit has been proven by Merck after thirty-six month window of use.

35. Where clinical trial evidence demonstrates a time-limited benefit for a specific subgroup it is inappropriate to extend by inference or extrapolation that benefit to patients outside that subgroup, particularly when the trial Sponsor is in possession of data indicating that the patients outside the subgroup achieve no benefit from the use of the studied intervention, Fosamax.

36. After Merck received for Fosamax both the treatment indication (in 1995), and the prevention indication (in 1997), Merck received and analyzed the fracture reduction data from its FIT program. In 1998, Merck co-authored and published in the

Journal of the American Medical Association titled "Effect of Alendronate on Risk of Fracture in Women with Low Bone Density but Without Vertebral Fractures: Results from the Fracture Intervention Trial", for which the lead author was Steven R. Cummings, M.D.[3] (Hereafter FIT-Cummings). Several Merck employees co-authored this publication including Desmond Thompson, Ph.D., Thomas A. Musliner, M.D., and A. John Yates, M.D.

37. In FIT-Cummings, patients with a femoral neck T-score of -1.6SD or worse were recruited and studied.[4] The patients were divided into "tertiles". "Tertile" means one-third. The patients in FIT-Cummings were divided into thirds, or tertiles, based upon the severity of femoral neck bone mineral density deficits. Importantly, this tertile analysis was pre-specified in the clinical trial protocol and was conducted before unblinding. (FIT-Cummings, p. 2080.)

38. In the FIT study, there was no benefit in the reduction for clinical fractures for the overall trial population. It is only when one starts cutting up

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[3] Cummings SR, Black DM, et al. Effect of Alendronate on Risk of Fracture in Women With Low Bone Density but Without Vertebral Fractures: Results from the Fracture Intervention Trial. *JAMA* 1998; 280:2077–2082.

[4] Initially, the threshold T-score for FIT-Cummings was -2.0SD or worse. After the trial began, however, results from the Third National Health and Nutritional Examination Survey ("NHANES III") indicated that the FIT inclusion criteria corresponded to 1.6SD or more below the normal adult mean, rather than 2.0SD or more below the normal adult mean (FIT-Cummings, p. 2078.)

the data of the study into tertiles is a benefit seen, and that benefit is exclusively limited to those women in the top tertile: i.e., those women with a baseline femoral neck T-score of -2.5SD or worse. The demonstrated benefit for that group, however, dissipated after thirty-six months of use.

39. The FIT-Cummings tertile analysis is presented at Table 3 of the publication. In analyzing this clinical trial evidence, the acronym "RH" stands for "Relative Hazard". When analyzing "Relative Hazards", scientists use a statistical approach known as the "CI" or "Confidence Interval" to determine whether any difference in hazard risk is "statistically significant". The CI is a key issue in the interpretation of clinical trial findings. For an RH result to be "statistically significant", the CI range must not include the number 1.0. If the CI crosses 1.0, then the results, statistically, may be due to chance.

40. The FIT-Cummings tertile analysis shows that the only group that had a statistically significant reduction in the rate of hazard for clinical fractures was those patients who had a baseline femoral neck T-score of -2.5SD or worse. As the tertiles "improve" into the osteopenic range (i.e., better than -2.5SD), Fosamax was not shown to reduce the risk of fractures. For instance, among women in the middle tertile who had a baseline femoral neck T-score of -2.0 to -2.5SD, more women in the Fosamax group had a clinical fracture when compared to those in the placebo group. There is no numerical evidence of any clinical fracture reduction benefit whatsoever for this tertile of women. Further, when comparing the non-clinical

vertebral fractures, the CI crosses 1.0 (1.04) and, thus, no statistically significant benefit is seen for the non-clinical fractures in the middle tertile. In the bottom tertile (the group of women who had a baseline femoral neck T-score of -1.6 to -2.0SD), there were seven more fractures in the Fosamax group than in the placebo group. There is no evidence of any fracture reduction benefit whatsoever for this tertile of women. Further, when comparing the non-clinical vertebral fractures, the CI crosses 1.0 (2.07) and, thus, no statistically significant benefit is seen for the non-clinical fractures in the bottom tertile.

41. In an attempt to broaden the beneficial findings of the FIT trial, the FIT-Cummings authors engaged in a post-hoc analysis. Post-hoc analyses are analyses that are not pre-specified in the clinical trial protocol and usually are conducted after unblinding. Because they are not pre-specified and are done post-hoc after unblinding, post-hoc analyses are scientifically suspect because of the risk of profound bias that can invade the analysis. Post hoc analyses are not accepted by the FDA or the medical community as conclusive.

42. However, even in the FIT-Cummings post hoc analyses, the authors were unable to find a meaningful fracture reduction benefit for those patients with T-scores better than -2.5SD: "In post hoc analyses, alendronate reduced the risk of hip fractures by 56% among women with a femoral neck T-score of -2.5 or less ... There was no reduction in risk among those who femoral neck T-scores were more than -2.5[.]" (FIT-Cummings, p. 2081.) Further: "Alendronate reduced the risk of

clinical fractures by 36% . . . in women whose initial femoral neck T score was -2.5 or less. However, 4 years of alendronate did not significantly affect risk of clinical fracture in those with higher BMD." (FIT-Cummings, p. 2080.)

43. In the same paragraph, however, the authors write: "We observed a 22% lower risk of clinical fractures in those who T-scores were more than 2.0SDs below the normal mean. . . . Alendronate did not decrease the risk of fracture among subjects whose initial T-scores were greater than -2.5." (FIT-Cummings, pp. 2080–81.) These two contradictory sentences about the post-hoc analyses require examination. The only way Merck got to the 22% risk reduction figure was to take one of the two tertiles for which there clearly was no fracture reduction benefit demonstrated (the middle tertile), leave out the other tertile for which there clearly was no fracture reduction benefit demonstrated (the bottom tertile), then average the middle tertile with the top tertile for which there was a fracture reduction benefit demonstrated to come up with a "new score" for 2 of the 3 tertiles. This is analogous to taking one high school class that got an "A" on a standardized exam, grouping it together with another high school class that got an "F" on the exam, and then proclaiming that everyone passes since the average grade is now a "C". Indeed, when one analyzes all three tertiles of the FIT-Cummings study group, the trial fails to demonstrate a statistically benefit for the entire cohort studied. It is not scientifically valid for Merck to pick and choose — on a post hoc, unblinded basis — which groups it will select for

this combined analysis. The trial fails to demonstrate a benefit for the entire study population. It is only by the tertile analysis that any benefit for any pre-specified subgroup is shown: i.e., that group with a baseline femoral neck T-score of -2.5SD or worse.

44. Thus, the only fracture reduction benefit demonstrated in FIT-Cummings is in the top tertile of patients: those who have a baseline femoral neck T-score of -2.5SD or worse. Even for that group of patients, however, the benefit conferred is not infinite in duration of the benefit. The FIT-Cummings article includes, at Figure 3, a "Life Table Graph". The purpose of a "Life Table Graph" is to show the reader when during treatment a benefit first appeared in the trial, and whether and for how long the benefit of intervention was sustained. Because a "Life Table Graph" shows the cumulative number of events, in order to demonstrate a continuing treatment benefit between the control group and the intervention group, the two lines on the graph should continue to diverge. At the point in time when they stop separating, the benefit of intervention has also stopped. At Figure 3 of FIT-Cummings, one can clearly see a divergence of the "Alendronate Sodium" line and the "Placebo" line starting at approximately 18 months of treatment and continuing through approximately 36 months of treatment. At that point, the lines begin narrowing through the remainder of the studied period, showing no continuing fracture reduction benefit after approximately 36 months of treatment.

45. At about the same time as the publication of FIT-Cummings, an FDA biostatistical reviewer named Dr. Anthony Mucci reviewed the FIT results. I received this document from the Plaintiffs Steering Committee for *In re Fosamax Products Liability Litigation*, MDL No. 1789, which I understand received the document through a Freedom of Information Act request to the United States Food & Drug Administration, and which certified the record as an official record from the FDA. The FDA's certification reads: "The following attached document is a true copy of an official record of the United States Food and Drug Administration: 'Statistical review and evaluation, clinical studies, NDA number 20-560 SE8-15, Sponsor: Merck, drug: Fosamax (Alendronate), dated September 4, 1998 by A.G. Mucci, Ph.D:, Statistical Reviewer." (MDL 1789 PSC Exh. 1.0097A.)

46. In his review of the FIT trials' clinical fracture reduction benefits conferred, Dr. Mucci writes: "The performance of Fosamax is especially bad in the restricted nonosteoporotic cohort G, where P equals .22 and where both the relative risk and the difference in cumulative incidences actually favor placebo." (MDL 1789 PSC Exh. 1.0097A, p. 439.) Dr. Mucci also writes: "The clinical fracture trial does not quite attain its primary efficacy goal of a statistically significant decrease in clinical fractures for Fosamax versus placebo unless the patient population is reduced to the osteoporotic cohort." (MDL 1789 PSC Exh. 1.0097A, p. 452.) Dr. Mucci continues: "Furthermore, the nonosteoporotic cohort reveals no efficacy for Fosamax for any category of fracture." (MDL 1789

PSC Exh. 1.0097A, p. 452.) Finally, Dr. Mucci concludes: "Thus, Fosamax can be said to be effective in osteoporotic patients with no prevalent vertebral fracture only if osteoporosis is defined in the more stringent fashion wherein the previous inclusionary criterion, with BMD set at a negative 2 T score, is replaced by a new inclusionary criterion, which sets BMD at a negative 2.5 T score." (MDL 1789 PSC Exh. 1.0097A, p. 452.) This correlates very well with the tertile analysis in FIT-Cummings, which clearly demonstrates the only fracture reduction benefit is for that subgroup of patients with a baseline femoral neck T-score of -2.5SD or worse.

47. In analyzing the 54 months of fracture reduction data from the FIT clinical fracture studies, Dr. Mucci further concludes: "The reviewer's interpretation of these results is: l. Fosamax provides no advantage over placebo in either the first 18 months or the last 18 months; 2. Fosamax does provide protection against fracture in the middle eighteen months." (MDL 1789 PSC Exh. 1.0097A, p. 451.) This analysis is very consistent with the Life Table Graph results presented at Figure 3 of FIT-Cummings, as well as my opinion that Fosamax has no fracture reduction benefit for any subgroup after thirty-six months of use. Dr. Mucci further concludes: "This analysis should cast some doubt on the value of extended use of Fosamax in patients with low BMD but without prevalent vertebral fractures at start of treatment, who, after three years of subsequent treatment, have experienced no fractures." (MDL 1789 PSC Exh. 1.0097A, p. 451.)

48. In litigation, Merck has attempted to answer these studies' shortcomings through other publications on its clinical trials but none of these studies demonstrates that Fosamax has a fracture reduction benefit for post-menopausal women unless they have either a prior vertebral fracture or a T-score of -2.5SD at baseline.

49. These studies frequently cited by Merck include a 1996 publication in *Lancet* titled "Randomized Trial of Effect of Alendronate on Risk of Fracture in Women with Existing Vertebral Fracture", lead author Dennis M. Black, Ph.D (hereafter FIT-Black)[5]. As the title of the FIT-Black publication shows, however, this portion of the FIT program was limited only to that group of patients with a history of vertebral fracture at baseline: i.e., a subgroup of the population at a very high risk for osteoporotic fracture. (FIT-Black, p. 1540.) This portion of the FIT project was not directed to studying patients without a vertebral fracture at baseline and no fracture reduction efficacy can be inferred to the much larger population of post-menopausal women without a prevalent vertebral fracture.

50. Just as with the FIT-Black study, the earlier publication by Liberman, et al., did not pertain to non-osteoporotic patients.[6] The Liberman study

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[5] Black DM, Cummings SR, et al. Randomised Trial of Effect of Alendronate on Risk of Fracture in Women With Existing Vertebral Fracture. *Lancet* 1996; 348:1535–1541.

[6] Liberman UA, Weiss SR, et al. Effect of Oral Alendronate on Bone Mineral Density and the Incidence of Fractures in Postmenopausal Osteoporosis. *NEJM* 1995; 333:1437–1443.

pertained only to patients who had a baseline vertebral T-score of -2.5SD or worse, with or without prevalent vertebral fracture at baseline. (Liberman, et al., p. 1438.) This trial is not directed to studying patients with a non-osteoporotic T-score. Further, the overwhelming majority of new vertebral fractures recorded during the study period occurred in those patients who had a prevalent vertebral fracture at baseline. (Liberman, et al., p.1441.)

51. Because their pre-specified clinical trial results did not demonstrate a fracture reduction benefit for non-osteoporotic patients, Merck sponsored a post hoc data pooling analysis through which it attempted to present some evidence of Fosamax fracture reduction benefit for non-osteoporotic patients. In the post-hoc analysis by Quandt, et al.[7], the study authors, including several from Merck, pooled data from across the FIT program and attempted to divine a vertebral fracture reduction benefit from Fosamax use for patients who had baseline femoral neck T-scores better than -2.5SD. The reviewers pooled the data for patients who had a vertebral fracture at baseline with those who did not have a vertebral fracture at baseline and concluded that there was an overall vertebral fracture reduction benefit. However, when the data are examined appropriately, one can readily see, in both Tables 2 and 3 of the study, that the CI

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[7] Quandt SA, Thompson DE, et al. Effect of Alendronate on Vertebral Fracture Risk in Women With Bone Mineral Density T Scores of -1.6 to -2.5 at the Femoral Neck: The Fracture Intervention Trial. *Mayo Clin Proc* 2005; 80:343–349.

crosses 1.0 for those patients who did not have a prevalent vertebral fracture at baseline. Therefore, there is no statistically significant difference demonstrated, even in this unblinded post-hoc analysis, in vertebral fracture risk for those women who had a femoral neck T-score of -1.6 to -2.5SD but no prevalent vertebral fracture at baseline.

52. Further, at least two Merck officials who are intimately familiar with the Fosamax clinical trial programs have testified that Fosamax has no evidence of fracture risk reduction for women who are not osteoporotic: Dr. Arthur Santora and Dr. Daniel Baran.

53. In my several years as a testifying expert in MDL No. 1789, I have reviewed several depositions key Merck employees taken in that litigation including Dr. Arthur Santora and Dr. Daniel Baran. I understand from Dr. Santora's deposition that he has served as Merck's Director of Clinical Research for Fosamax since 1989. (Santora MDL 1789 depo., pp.14–15.) Dr. Santora served as the head of the clinical development program for Fosamax and was Merck's physician responsible for the Fosamax Phase III clinical trials. (Goldberg MDL 1789 depo., pp. 22–2; 119–121.)

54. Dr. Santora testified that in the Fracture Intervention Trial, "only those who had osteoporosis, defined by a low bone mineral density at the femoral neck, were found to have a significant risk reduction of all clinical fractures." (Santora MDL 1789 depo., p. 709.) Just as I have observed, and Dr. Mucci has observed, Dr. Santora

testified that, when all non-osteoporotic patients studied were combined with the patients with osteoporosis, there was no statistically significant difference found between the placebo arm and the treatment arm in the trial. (Santora MDL 1789 depo., pp. 708–709.)

55. As presented above, Dr. Santora testified that the Non-Osteoporotic Cohort in the FIT included those patients with a baseline T-score better than -2.5SD. (Santora MDL 1789 depo., p. 720.)

56. Regarding the totality of Merck's clinical trial evidence for Fosamax, Dr. Santora explained the following:

Q: It's my understanding, based on the clinical trial evidence that Merck had and presented to the FDA, Merck cannot say that for those patients without osteoporosis that the use of Fosamax prevents fractures, right?

…

Q: Is that right?

A: Merck has stated that the drug works to reduce the risk of fracture in people who have osteoporosis defined as either vertebral fracture or defined as a low bone mineral density. Your question, I think, is related to whether we have promoted or stated the drug works in other populations to reduce the risk of fracture. The answer is no, we have not indicated that Fosamax reduces the risk of fracture in women who don't have osteoporosis.

Q: Because there's no evidence that it does, right?

A: Right. There's no evidence that any drug reduces the risk of fracture in people who don't have osteoporosis.

(Santora MDL 1789 depo., pp. 795–796.)

57. I agree with Dr. Santora's testimony that there is no evidence that Fosamax reduces the risk of fracture in non-osteoporotic patient. Dr. Santora, however, incorrectly testified that Merck does not attempt to indicate that Fosamax reduces the risk of fracture in non-osteoporotic patient as Merck's Fosamax prevention indication language from the Fosamax package insert expressly tells the prescriber that Fosamax can be used for non-osteoporotic patient to "reduce the risk of future fracture".

58. Dr. Santora is not the only Merck official to testify that Fosamax has no evidence of fracture reduction efficacy for non-osteoporotic patients. Dr. Daniel Baran served as Merck's National Science Director for Osteoporosis from 2003 to 2006, and later served as Merck's Senior Regional Medical Director. (Baran MDL 1789 depo., pp. 123–124, 140–141.) As to Fosamax, Dr. Baran testified: "There is—there are no studies showing that treatment of individuals with osteopenia without a prevalent vertebral fracture reduces the risk of fractures, that is correct." (Baran MDL 1789 depo., pp. 320–321.)

59. The FDA has been concerned for a good period of time about the use of Fosamax in the non-osteoporotic population.

60. The FDA also has been concerned about long-term use of Fosamax. The FDA convened a September

9, 2011, Joint Meeting of the Advisory Committee for Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committee pertaining to the long-term use of bisphosphonates, including Fosamax, several FDA officials testified about the lack of fracture reduction benefit for Fosamax after three years of use. FDA Medical Reviewer Dr. Marcea Whitaker testified that there was a plateau in overall fracture reduction benefit after three to four years of use and that "therapy can be safely discontinued without loss of efficacy." (FDAAC 09/09/11 transcript, p. 27.) Further, FDA Clinical Team Leader Dr. Theresa Kehoe testified that even high risk patients do not benefit with continued Fosamax therapy. (FDAAC 09/09/11 transcript, pp. 76–77.)

61. Further, testifying on behalf of Merck, Dr. Santora testified about Fosamax: "These days you wouldn't treat somebody for osteoporosis if their BMD T-score was -1.6." (FDAAC 09/09/11 transcript, p. 59.)

62. Through FDA Clinical Team Leader, Dr. Theresa Kehoe, and in response to a question from an Advisory Committee member, the FDA has indicated the Fosamax prevention indication is outdated and is being "revisited" by the FDA:

> CLIFF ROSEN: So I guess my question though is when we talk about prevention of osteoporosis you commonly hear people say that an indication for using these drugs is osteopenia. Is that correct or incorrect?
>
> THERESA KEHOE: I would imagine that's technically correct, but I think that

> unfortunately the indications have preceded where the standard of is [sic] in the field now, which is that a prevention indication I think is really being revisited all the way around, including by FDA.
>
> CLIFF ROSEN: It's — that's what I wanted to hear, if somebody's looking at this.
>
> THERESA KEHOE: Well I think that might be a topic for later advisory committee, but certainly it's something we're struggling with and dealing with.
>
> (FDAAC 09/09/11 transcript, pp. 86–87.)

63. On June 16, 2013, the FDA sent to Merck a letter titled "INFORMATION REQUEST", indicating as follows: "Given the concerns regarding the long-term safety of bisphosphonates, the Division is considering whether the broad 'prevention of postmenopausal osteoporosis' indication for bisphosphonates is warranted. We would like to hear your perspective on whether there is still utility for a prevention indication for your products. If you believe a prevention indication is still appropriate, address whether the language of the indication should be modified to better define an appropriate target population." (06/16/13 FDA "INFORMATION REQUEST" to Merck Sharpe & Dohme Corp., attn: Elinor Chen, Ph.D., signed by Hylton V. Joffe, M.D., M.M.Sc., Director, Division of Bone, Reproductive, and Urologic Products, FDA.)

V. **CONCLUSION.**

64. Compared to the broad population of post-menopausal women who have actually taken

Fosamax, there exists only a small subgroup of patients for whom there is evidence of a fracture reduction benefit: patients with osteoporosis defined by either a femoral T-score of -2.5SD or worse or by a preexisting vertebral fracture. There is no documented clinical trial evidence of a fracture reduction benefit for the rest of the population of post-menopausal women who have used Fosamax.

65. For patients who do not have preexisting vertebral fracture or a baseline femoral neck T- score of -2.5SD or worse, the clinical trial evidence utterly fails to demonstrate a fracture reduction benefit. Thus, if there is any harm or risk of side effect from Fosamax, Fosamax is unreasonably dangerous because the risk of harm outweighs the benefit conferred.

66. For any group of patients who take Fosamax, the clinical trial evidence fails to demonstrate a fracture reduction benefit beyond three years of use. Thus, if there is any harm or risk of side effect from Fosamax, Fosamax is unreasonably dangerous after three years of use because the risk of harm outweighs the benefit conferred.

I declare under penalty of perjury pursuant to 18 USC § 1746 that the foregoing is true and correct. Executed on September 25, 2013.

/s/ Curt Daniel Furberg
CURT DANIEL FURBERG, M.D., Ph.D.

[Exhibit 7 to Ecklund Declaration]

Fosamax

David Madigan, PhD

October 15, 2012

1. Credentials

1. I am Professor and Chair of Statistics at Columbia University in New York City. I received my bachelor's degree in Mathematical Sciences from Trinity College Dublin in 1984 and was awarded the College's gold medal. In 1990, I received a Ph.D. in Statistics, also from Trinity College. I have worked in the past for KPMG, SkillSoft, University of Washington, AT&T Labs, and Soliloquy Inc. From 2005 to 2007 I was Professor of Statistics and Dean of Physical and Mathematical Sciences at Rutgers University. Prior to serving as Dean I was Director of the Rutgers University Institute of Biostatistics. I am an elected Fellow of both the Institute of Mathematical Statistics and the American Statistical Association and was the 36th most cited mathematician worldwide from 1995–2005. I was an Institute of Mathematical Statistics Medallion Lecturer in 2009. I recently completed a term as the Editor of *Statistical Science*, 2008–2010, the highest impact journal in Statistics.

2. I have published more than 100 technical papers on Bayesian statistics, biostatistics, pharmacovigilance, statistical graphics, Monte Carlo methods, computer-assisted learning, information retrieval, and text mining. Within the last few years I

have consulted for Boehringer-Ingelheim, Jarvik Heart, Novartis, Pfizer, Sanofi-Aventis, Takeda, and Wyeth on a variety of issues, many related to drug safety. I have considerable statistical experience with clinical trials including the design and analysis of pain studies at the University of Washington and the Fred Hutchinson Cancer Research Center, both in Seattle, and service as a statistical consultant to multiple internal and external clients, particularly while I was director of the Institute of Biostatistics at Rutgers University, and continuing with Jarvik Heart.

3. In the last several years, drug safety has been one of my significant research interests with a focus on the development and application of statistical methods for pharmacovigilance. I have published my work in *Drug Safety, Pharmacoepidemiology and Drug Safety, Epidemiology*, and other journals. I also serve as an investigator in the Mini-Sentinel project. Mini-Sentinel is a pilot project sponsored by the FDA to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products. In 2010–11, I lead the Mini-Sentinel Working Group on case-based methods in active surveillance. In addition, I am the methods lead for the Observational Medical Outcomes Partnership, a public-private partnership between the FDA and the pharmaceutical industry. The partnership is conducting a multi-year initiative to research methods that are feasible and useful to analyze existing healthcare databases to identify and evaluate safety and benefit issues of drugs already on the market. I am a member of the FDA's Drug Safety and Risk Management Advisory Committee (DSaRM). DSaRM

advises the FDA Commissioner on risk management, risk communication, and quantitative evaluation of spontaneous reports for drugs for human use and for any other product for which the FDA has regulatory responsibility. From 2010 to 2011 I was a member of a sub-committee of the FDA Science Board charged with reviewing the Center for Drug Evaluation and Research's pharmacovigilance program.

4. Further information concerning my background, training, and experience, including a complete list of my publications, is reflected in my curriculum vitae, a copy of which is attached as Appendix D. A list of the testimony I have provided in the last four years is attached as Appendix E.

2. Research Question

5. I was asked to examine whether a signal of problematic oversuppression of bone turnover and associated atypical femur fracture syndromes existed for Fosamax, using industry standard pharmacovigilance techniques and data sources, and the adverse event terms selected by Merck to internally evaluate the same. I was also asked to assess the strength of that signal, if any, in comparison to the signal, if any, for such events in other products indicated for the prevention and treatment of osteoporosis.

6. The approach I have taken to the work would have been the same had Merck hired me to carry out the analyses. I am being compensated at the rate of $500 per hour for my work on this matter. As I continue to review the data (or review newly provided data) I reserve the right to supplement and refine my

report. All the opinions I express herein I hold to a reasonable degree of scientific certainty.

3. Pharmacovigilance

7. Increasing scientific, regulatory and public scrutiny focuses on the obligation of the medical community, pharmaceutical industry, and health authorities to ensure that marketed drugs have acceptable benefit-risk profiles. This is an intricate and ongoing process that begins with pre-approval studies, but continues after regulatory market authorization when the drug is in widespread clinical use. In the latter environment, surveillance schemes based on spontaneous reporting system (SRS) databases represent a cornerstone for the early detection of drug hazards that are novel by virtue of their clinical nature, severity, and/or frequency. "Pharmacovigilance" is often used to describe the aforementioned surveillance activities.

8. Signal detection algorithms assist pharmacovigilance domain experts to discover potentially relevant drug-event associations. In recent years, data mining in pharmacovigilance has attracted significant attention and has now become routine both in the pharmaceutical industry and amongst regulators worldwide.

9. Pharmaceutical companies, health authorities, and drug monitoring centers use SRS databases for global screening for signals of new adverse events or changes in the frequency, character, or severity of existing adverse events (AEs) after regulatory authorization for use in clinical practice. The precise details of each SRS differ in terms of size and scope, statutory reporting mandates, surveillance selectivity

or intensity, and organizational count of 3[8]. For GPS, Szarfman and her co-authors proposed using a threshold of 2 for the EB05 measure[9] although other authors have suggested that EB05 is intrinsically too conservative in the sense that it could result in delayed detection of relevant signals. A recent review article[10] identified a wide variety of thresholds in actual use.

3.3 Signal Refinement

24. The methods I have just described represent standard approaches to signal detection in SRSs that are used by regulators and pharmaceutical companies worldwide. I note that such signal analyses are not meant to quantify the extent of a drug's increased risks. Once a signal is detected, a wide variety of approaches are used to carry out "signal refinement," a process designed to shed further light on the signal. One standard approach is to compare reporting rates of the drug in question with reporting rates for specific other drugs in the same class (using, for example, the PRR). This was the approach adopted when a signal

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[8] Evans, SJW, Waller, D, Davis, D. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. *Pharmacoepidemiology and Drug Safety*, **10**,(2001) 483–486.

[9] Szarfman A, Machado SG, O'Neill RT: Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. *Drug Saf* (2002) **25**(6):381–392.

[10] Deshpande, G., Gogolak, V., Weiss Smith, S. Data Mining in Drug Safety: Review of Published Threshold Criteria for Defining Signals of Disproportionate Reporting. *Pharmaceutical Medicine*. **24**(1):37–43, February 1, 2010.

was generated for Baycol (cerivastatin) and rhabdomyolysis. In that context, the scientific community focused on the reporting rate for rhabdomyolysis and Baycol as compared with other market-leading statins[11].

4. Methods

25. Using the FDA's AERS database, I examined the possible association between Fosamax and a series of MEDRA preferred terms selected by Merck to evaluate oversuppression of bone turnover and associated atypical femur fracture syndromes. I used two industry-standard signal detection algorithms (MGPS and PRR as described in Section 3) to assess whether or not Fosamax presented a safety signal related to oversuppression of bone turnover. Specifically I considered the EB05, EBGM, and PRR metrics over time. As a comparator, I considered the other approved oral bisphosphonates indicated for the treatment and prevention of osteoporosis (risedronate and ibandronate), as well a non-bisphosphonate drug indicated for the treatment and prevention of osteoporosis (raloxifene)[12]. Risedronate was first approved in March 1998, ibandronate was first approved in May 2003, and raloxifene was first

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[11] Furberg CD, Pitt B. Withdrawal of cerivastatin from the world market. *Curr Control Trials Cardiovasc Med*, **2**(5) 205–207.

[12] FDA Background Document for Meeting of Advisory Committee for Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committee, September 9th, 2011. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials /drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm270958.pdf

approved in December 1997. Since ibandronate is available in both oral and injectable form, I excluded reports where the route of administration was injection. Some analysts have observed declining reporting rates over time. Since alendronate was approved before the comparator drugs, this should result in conservative estimates of the relative risk associated with alendronate.

26. As endpoints, I considered the MedDRA preferred terms that Merck selected in their examination of oversuppression of bone turnover and associated atypical femur fracture syndromes[13]. These terms are:

- bone development abnormal
- bone disorder
- bone formation decreased
- fracture delayed union
- fracture malunion
- fracture nonunion
- low turnover osteopathy
- pathological fracture
- stress fracture
- fracture
- femur fracture

I note an internal Merck email discusses combining three preferred terms that have delayed union as a feature so I also consider the composite endpoint of fracture delayed union, fracture malunion, and

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[13] MRK-FOSMDL-BOL-00008312 at 13, MRK-FOSMDL-BOL-00015857 at 60, MRK-FOSMDL-01020264 at 435,

fracture nonunion[14] and refer to this endpoint as "fracture union issues."

27. To conduct my analyses I used the programming language perl (for data preparation), the statistical software package R (version 2.15.0), and the QScan pharmacovigilance platform provided by DrugLogic Inc. (Reston, VA). Specicially I used QScan to compute EBGM, EB05, and PRR statistics and to generate summary statistics required for my analysis.

28. The QScan software has been in widespread use for over 10 years and has been validated extensively. DrugLogic uses a very detailed validation process (originally set up by an FDA software auditor.) DrugLogic's software development process is CFR 21 Part 11 compliant. Many peer-reviewed publications report results derived from QScan[15].

29. Publications reporting disproportionality analyses often report stratified results. All results presented below are stratified by sex (male, female, unknown) and age (unknown, 0–15, 16–30, 31–50, 51–75, and greater than 75). As a sensitivity analysis, I performed several calculations without stratification

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[14] MRK-FOSMDL-GOL-00017912 at 14

[15] See, for example, Pearson EC, Woosley RL. QT prolongation and torsades de pointes among methadone users: reports to the FDA spontaneous reporting system. *Pharmacoepidemiology and Drug Safety*, **14**,(2005) 747–753 or Alsheikh-Ali AA, Karas RH, Adverse Events With Concomitant Amiodarone and Statin Therapy, *Preventative Cardiology*, **8**, (2005), 95–97 or Ratcliffe S, Younus M, Hauben M, Reich L. Antidepressants that inhibit neuronal norepinephrine reuptake are not associated with increased spontaneous reporting of cardiomyopathy. *Journal of Psychopharmacology*, **24**, (2010), 503–511.

and unstratified PRR and EB05 values never differed by more than 0.5 from their stratified counterparts.

30. Duplicate reports can occur in SRS systems and a number of authors have described algorithms for detecting duplicates. In the analyses presented below I removed duplicates defined as reports having identical manufacturer and control codes.

31. Historically MGPS calculations have often omitted drugs with fewer than 100 reports overall and AEs with fewer than 100 reports. This is largely to reduce the computational burden and has little effect on the analyses. In what follows I do not impose such a limitation.

32. In some of my publications[16] I have expressed concern about confounding bias introduced by the so-called "innocent bystander" effect. The basic problem is as follows. Suppose Drug A causes a particular adverse event and Drug B does not. Further suppose that Drug A is commonly co-prescribed with Drug B. Then any analysis of Drug B will tend to incorrectly show an association with the adverse event. Drug B is an "innocent bystander." Statistical methods do exist to account for this problem[17] although these have yet to find widespread adoption.

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[16] Hauben, M., Madigan, D., Gerrits, C., and Meyboom, R. (2005). The role of data mining in pharmacovigilance. *Expert Opinion in Drug Safety*, **4**(5), 929–948.

[17] Caster, O., Noren, G.N., Madigan, D., and Bate, A. (2010). Large-Scale Regression-Based Pattern Discovery: The Example of Screening the WHO Global Drug Safety Database. *Statistical Analysis and Data Mining*, **3**, 197–208.

33. In the specific case of Fosamax, many different drugs are co-reported. However, the co-reported medications are very similar between Fosamax and the comparator drugs. Thus, if a signal of disproportionate reporting is due to an innocent bystander, the same signal should be present for all the drugs I consider. Since the results below demonstrate differential signals for Fosamax, the innocent bystander effect cannot explain the findings and is not a concern in my analysis.

5. Results

34. Appendix A presents cumulative results as of December 31st each year from 2001 to 2011. I also present results through the end of the first quarter of 2012, which includes the most recent AERS data available. For each endpoint (11 preferred terms and the composite fracture union endpoint) and for each comparator drug, the Tables below provide:

- EB05 (Appendix A1),
- EBGM (Appendix A2),
- PRR (Appendix A3), and
- the observed number of reports (Appendix A4)

for each timepoint.

6. Discussion

35. My analyses clearly demonstrate the existence of early signals for Fosamax for various terms related to oversuppression of bone turnover and associated atypical femur fracture concerns. Focusing on the conservative EB05 measure, and applying a signaling threshold of 2, Table 1 below shows the year when a signal first emerged.

	Alendronate	**Risedronate & Ibandronate**	**Raloxifene**
fracture delayed union	2004	2011	No signal
fracture malunion	2002	2010	No signal
fracture nonunion	2005	2010	No signal
fracture union issues	2002	2009	No signal
bone development abnormal	No signal	No signal	No signal
bone disorder	2001	2007	No signal
bone formation decreased	2004	No signal	No signal
low turnover osteopathy	2005	2010	No signal
fracture	2005	2004	2004
femur fracture	2005	2009	2006
pathological fracture	2009	2010	No signal
stress fracture	2003	2009	2004

For only one of the eleven events selected by Merck as relevant to assessing bone oversuppression and fracture risks was a signal not evident (bone development abnormal). For each of the others, a safety signal was evident. The composite endpoint

fracture union issues revealed a very strong early signal (EB05 = 2.39 in 2002), which only got stronger over time (e.g., EB05 = 20.63 in 2012). With a single exception ("fracture"), alendronate signaled earlier than the comparators for every event considered. For eight of the twelve outcomes considered, Fosamax signaled five or more years before the comparators.

7. Conclusion

36. Based on my review of FDA spontaneous report data for Fosamax, it is apparent that industry standard pharmacovigilance techniques and datasources reveal the presence of a clear signal for oversuppression of bone turnover and associated atypical femur fracture events utilizing the terms selected by Merck for such analysis. By standard metrics of "signal" detection, the signal is strong, consistent, and not ambiguous. Of perhaps greater concern, the signal was striking in comparison to that for other drugs indicated for the prevention and treatment of osteoporosis. As early as 2001–2002, the spontaneous report data for Fosamax provide signals for a number of indicators of suppression of bone turnover. For the comparator drugs, such signals either never appear or appear years later.

s/ David Madigan
David Madigan, PhD
October 15, 2012

[Exhibit 9 to Ecklund Declaration]

Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA 6013411

FOSAMAX®

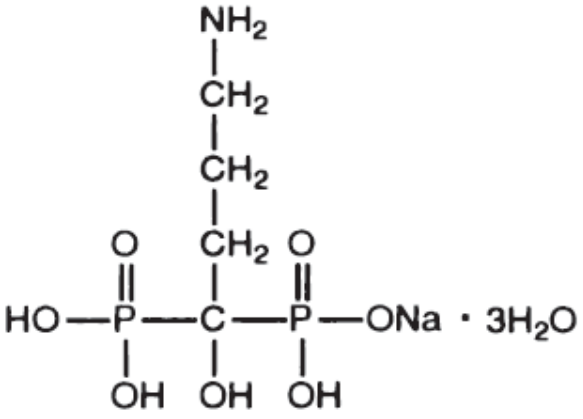
(ALENDRONATE SODIUM) TABLETS AND ORAL SOLUTION

DESCRIPTION

FOSAMAX® (alendronate sodium) is a bisphosphonate that acts as a specific inhibitor of osteoclast-mediated bone resorption. Bisphosphonates are synthetic analogs of pyrophosphate that bind to the hydroxyapatite found in bone.

Alendronate sodium is chemically described as (4-amino-1-hydroxybutylidene) bisphosphonic acid monosodium salt trihydrate.

The empirical formula of alendronate sodium is $C_4H_{12}NNaO_7P_23H_2O$ and its formula weight is 325.12. The structural formula is:



Alendronate sodium is a white, crystalline, nonhygroscopic powder. It is soluble in water, very slightly soluble in alcohol, and practically insoluble in chloroform.

Tablets FOSAMAX for oral administration contain 6.53, 13.05, 45.68, 52.21 or 91.37 mg of alendronate monosodium salt trihydrate, which is the molar equivalent of 5, 10, 35, 40 and 70 mg, respectively, of free acid, and the following inactive ingredients: microcrystalline cellulose, anhydrous lactose, croscarmellose sodium, and magnesium stearate. Tablets FOSAMAX 10 mg also contain carnauba wax.

Each bottle of the oral solution contains 91.35 mg of alendronate monosodium salt trihydrate, which is the molar equivalent to 70 mg of free acid. Each bottle also contains the following inactive ingredients: sodium citrate dihydrate and citric acid anhydrous as buffering agents, sodium saccharin, artificial raspberry flavor, and purified water. Added as preservatives are sodium propylparaben 0.0225% and sodium butylparaben 0.0075%.

CLINICAL PHARMACOLOGY

Mechanism of Action

Animal studies have indicated the following mode of action. At the cellular level, alendronate shows preferential localization to sites of bone resorption, specifically under osteoclasts. The osteoclasts adhere normally to the bone surface but lack the ruffled border that is indicative of active resorption. Alendronate does not interfere with osteoclast recruitment or attachment, but it does inhibit osteoclast activity. Studies in mice on the localization of radioactive [^{3}H]alendronate in bone showed about

10-fold higher uptake on osteoclast surfaces than on osteoblast surfaces. Bones examined 6 and 49 days after [^{3}H]alendronate administration in rats and mice, respectively, showed that normal bone was formed on top of the alendronate, which was incorporated inside the matrix. While incorporated in bone matrix, alendronate is not pharmacologically active. Thus, alendronate must be continuously administered to suppress osteoclasts on newly formed resorption surfaces. Histomorphometry in baboons and rats showed that alendronate treatment reduces bone turnover (i.e., the number of sites at which bone is remodeled). In addition, bone formation exceeds bone resorption at these remodeling sites, leading to progressive gains in bone mass.

Pharmacokinetics

Absorption

Relative to an intravenous (IV) reference dose, the mean oral bioavailability of alendronate in women was 0.64% for doses ranging from 5 to 70 mg when administered after an overnight fast and two hours before a standardized breakfast. Oral bioavailability of the 10 mg tablet in men (0.59%) was similar to that in women when administered after an overnight fast and 2 hours before breakfast.

FOSAMAX 70 mg oral solution and FOSAMAX 70 mg tablet are equally bioavailable.

A study examining the effect of timing of a meal on the bioavailability of alendronate was performed in 49 postmenopausal women. Bioavailability was decreased (by approximately 40%) when 10 mg alendronate was administered either 0.5 or 1 hour before a standardized breakfast, when compared to

dosing 2 hours before eating. In studies of treatment and prevention of osteoporosis, alendronate was effective when administered at least 30 minutes before breakfast.

Bioavailability was negligible whether alendronate was administered with or up to two hours after a standardized breakfast. Concomitant administration of alendronate with coffee or orange juice reduced bioavailability by approximately 60%.

Distribution

Preclinical studies (in male rats) show that alendronate transiently distributes to soft tissues following 1 mg/kg IV administration but is then rapidly redistributed to bone or excreted in the urine. The mean steady-state volume of distribution, exclusive of bone, is at least 28 L in humans. Concentrations of drug in plasma following therapeutic oral doses are too low (less than 5 ng/mL) for analytical detection. Protein binding in human plasma is approximately 78%.

Metabolism

There is no evidence that alendronate is metabolized in animals or humans.

Excretion

Following a single IV dose of [^{14}C]alendronate, approximately 50% of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the feces. Following a single 10 mg IV dose, the renal clearance of alendronate was 71 mL/min (64, 78; 90% confidence interval [CI]), and systemic clearance did not exceed 200 mL/min. Plasma concentrations fell by more than

95% within 6 hours following IV administration. The terminal half-life in humans is estimated to exceed 10 years, probably reflecting release of alendronate from the skeleton. Based on the above, it is estimated that after 10 years of oral treatment with FOSAMAX (10 mg daily) the amount of alendronate released daily from the skeleton is approximately 25% of that absorbed from the gastrointestinal tract.

Special Populations

Pediatric: The oral bioavailability in children was similar to that observed in adults; however, FOSAMAX is not indicated for use in children (see PRECAUTIONS, *Pediatric Use*).

Gender: Bioavailability and the fraction of an IV dose excreted in urine were similar in men and women.

Geriatric: Bioavailability and disposition (urinary excretion) were similar in elderly and younger patients. No dosage adjustment is necessary (see DOSAGE AND ADMINISTRATION).

Race: Pharmacokinetic differences due to race have not been studied.

Renal Insufficiency: Preclinical studies show that, in rats with kidney failure, increasing amounts of drug are present in plasma, kidney, spleen, and tibia. In healthy controls, drug that is not deposited in bone is rapidly excreted in the urine. No evidence of saturation of bone uptake was found after 3 weeks dosing with cumulative IV doses of 35 mg/kg in young male rats. Although no clinical information is available, it is likely that, as in animals, elimination of alendronate via the kidney will be reduced in patients with impaired renal function. Therefore,

somewhat greater accumulation of alendronate in bone might be expected in patients with impaired renal function.

No dosage adjustment is necessary for patients with mild-to-moderate renal insufficiency (creatinine clearance 35 to 60 mL/min). **FOSAMAX is not recommended for patients with more severe renal insufficiency (creatinine clearance <35 mL/min) due to lack of experience with alendronate in renal failure**.

Hepatic Insufficiency: As there is evidence that alendronate is not metabolized or excreted in the bile, no studies were conducted in patients with hepatic insufficiency. No dosage adjustment is necessary.

Drug Interactions

(also see PRECAUTIONS, *Drug Interactions*)

Intravenous ranitidine was shown to double the bioavailability of oral alendronate. The clinical significance of this increased bioavailability and whether similar increases will occur in patients given oral H_2-antagonists is unknown.

In healthy subjects, oral prednisone (20 mg three times daily for five days) did not produce a clinically meaningful change in the oral bioavailability of alendronate (a mean increase ranging from 20 to 44%).

Products containing calcium and other multivalent cations are likely to interfere with absorption of alendronate.

Pharmacodynamics

Alendronate is a bisphosphonate that binds to bone hydroxyapatite and specifically inhibits the activity of osteoclasts, the bone-resorbing cells. Alendronate

reduces bone resorption with no direct effect on bone formation, although the latter process is ultimately reduced because bone resorption and formation are coupled during bone turnover.

Osteoporosis in postmenopausal women

Osteoporosis is characterized by low bone mass that leads to an increased risk of fracture. The diagnosis can be confirmed by the finding of low bone mass, evidence of fracture on x-ray, a history of osteoporotic fracture, or height loss or kyphosis, indicative of vertebral (spinal) fracture. Osteoporosis occurs in both males and females but is most common among women following the menopause, when bone turnover increases and the rate of bone resorption exceeds that of bone formation. These changes result in progressive bone loss and lead to osteoporosis in a significant proportion of women over age 50. Fractures, usually of the spine, hip, and wrist, are the common consequences. From age 50 to age 90, the risk of hip fracture in white women increases 50-fold and the risk of vertebral fracture 15- to 30-fold. It is estimated that approximately 40% of 50-year-old women will sustain one or more osteoporosis-related fractures of the spine, hip, or wrist during their remaining lifetimes. Hip fractures, in particular, are associated with substantial morbidity, disability, and mortality.

Daily oral doses of alendronate (5, 20, and 40 mg for six weeks) in postmenopausal women produced biochemical changes indicative of dose-dependent inhibition of bone resorption, including decreases in urinary calcium and urinary markers of bone collagen degradation (such as deoxypyridinoline and cross-linked N-telopeptides of type I collagen). These

biochemical changes tended to return toward baseline values as early as 3 weeks following the discontinuation of therapy with alendronate and did not differ from placebo after 7 months.

Long-term treatment of osteoporosis with FOSAMAX 10 mg/day (for up to five years) reduced urinary excretion of markers of bone resorption, deoxypyridinoline and cross-linked N-telopeptides of type I collagen, by approximately 50% and 70%, respectively, to reach levels similar to those seen in healthy premenopausal women. Similar decreases were seen in patients in osteoporosis prevention studies who received FOSAMAX 5 mg/day. The decrease in the rate of bone resorption indicated by these markers was evident as early as one month and at three to six months reached a plateau that was maintained for the entire duration of treatment with FOSAMAX. In osteoporosis treatment studies FOSAMAX 10 mg/day decreased the markers of bone formation, osteocalcin and bone specific alkaline phosphatase by approximately 50%, and total serum alkaline phosphatase by approximately 25 to 30% to reach a plateau after 6 to 12 months. In osteoporosis prevention studies FOSAMAX 5 mg/day decreased osteocalcin and total serum alkaline phosphatase by approximately 40% and 15%, respectively. Similar reductions in the rate of bone turnover were observed in postmenopausal women during one-year studies with once weekly FOSAMAX 70 mg for the treatment of osteoporosis and once weekly FOSAMAX 35 mg for the prevention of osteoporosis. These data indicate that the rate of bone turnover reached a new steady-state, despite the progressive increase in the total amount of alendronate deposited within bone.

As a result of inhibition of bone resorption, asymptomatic reductions in serum calcium and phosphate concentrations were also observed following treatment with FOSAMAX. In the long-term studies, reductions from baseline in serum calcium (approximately 2%) and phosphate (approximately 4 to 6%) were evident the first month after the initiation of FOSAMAX 10 mg. No further decreases in serum calcium were observed for the five-year duration of treatment; however, serum phosphate returned toward prestudy levels during years three through five. Similar reductions were observed with FOSAMAX 5 mg/day. In one-year studies with once weekly FOSAMAX 35 and 70 mg, similar reductions were observed at 6 and 12 months. The reduction in serum phosphate may reflect not only the positive bone mineral balance due to FOSAMAX but also a decrease in renal phosphate reabsorption.

Osteoporosis in men

Treatment of men with osteoporosis with FOSAMAX 10 mg/day for two years reduced urinary excretion of cross-linked N-telopeptides of type I collagen by approximately 60% and bone-specific alkaline phosphatase by approximately 40%. Similar reductions were observed in a one-year study in men with osteoporosis receiving once weekly FOSAMAX 70 mg.

Glucocorticoid-induced Osteoporosis

Sustained use of glucocorticoids is commonly associated with development of osteoporosis and resulting fractures (especially vertebral, hip, and rib). It occurs both in males and females of all ages. Osteoporosis occurs as a result of inhibited bone

formation and increased bone resorption resulting in net bone loss. Alendronate decreases bone resorption without directly inhibiting bone formation.

In clinical studies of up to two years' duration, FOSAMAX 5 and 10 mg/day reduced cross-linked N-telopeptides of type I collagen (a marker of bone resorption) by approximately 60% and reduced bone-specific alkaline phosphatase and total serum alkaline phosphatase (markers of bone formation) by approximately 15 to 30% and 8 to 18%, respectively. As a result of inhibition of bone resorption, FOSAMAX 5 and 10 mg/day induced asymptomatic decreases in serum calcium (approximately 1 to 2%) and serum phosphate (approximately 1 to 8%).

Paget's disease of bone

Paget's disease of bone is a chronic, focal skeletal disorder characterized by greatly increased and disorderly bone remodeling. Excessive osteoclastic bone resorption is followed by osteoblastic new bone formation, leading to the replacement of the normal bone architecture by disorganized, enlarged, and weakened bone structure.

Clinical manifestations of Paget's disease range from no symptoms to severe morbidity due to bone pain, bone deformity, pathological fractures, and neurological and other complications. Serum alkaline phosphatase, the most frequently used biochemical index of disease activity, provides an objective measure of disease severity and response to therapy.

FOSAMAX decreases the rate of bone resorption directly, which leads to an indirect decrease in bone formation. In clinical trials, FOSAMAX 40 mg once daily for six months produced significant decreases in

serum alkaline phosphatase as well as in urinary markers of bone collagen degradation. As a result of the inhibition of bone resorption, FOSAMAX induced generally mild, transient, and asymptomatic decreases in serum calcium and phosphate.

Clinical Studies

Treatment of osteoporosis

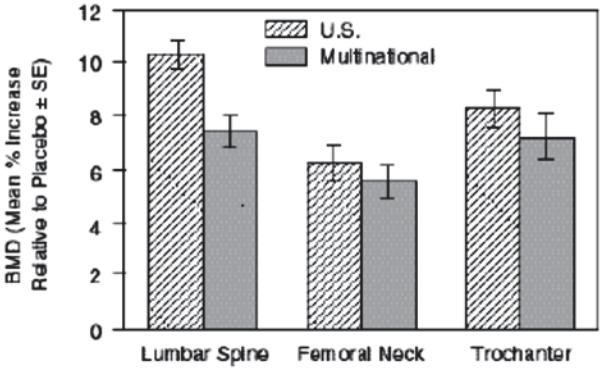
Postmenopausal women

Effect on bone mineral density

The efficacy of FOSAMAX 10 mg once daily in postmenopausal women, 44 to 84 years of age, with osteoporosis (lumbar spine bone mineral density [BMD] of at least 2 standard deviations below the premenopausal mean) was demonstrated in four double-blind, placebo-controlled clinical studies of two or three years' duration. These included two three-year, multicenter studies of virtually identical design, one performed in the United States (U.S.) and the other in 15 different countries (Multinational), which enrolled 478 and 516 patients, respectively. The following graph shows the mean increases in BMD of the lumbar spine, femoral neck, and trochanter in patients receiving FOSAMAX 10 mg/day relative to placebo-treated patients at three years for each of these studies.

Osteoporosis Treatment Studies in Postmenopausal Women

Increase in BMD
FOSAMAX 10 mg/day at Three Years

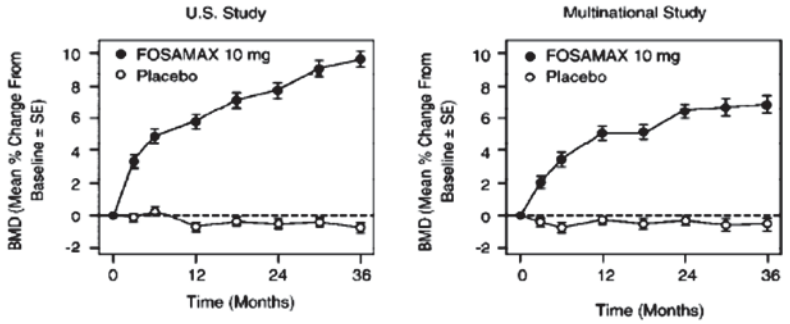


At three years significant increases in BMD, relative both to baseline and placebo, were seen at each measurement site in each study in patients who received FOSAMAX 10 mg/day. Total body BMD also increased significantly in each study, suggesting that the increases in bone mass of the spine and hip did not occur at the expense of other skeletal sites. Increases in BMD were evident as early as three months and continued throughout the three years of treatment. (See figures below for lumbar spine results.) In the two-year extension of these studies, treatment of 147 patients with FOSAMAX 10 mg/day resulted in continued increases in BMD at the lumbar spine and trochanter (absolute additional increases between years 3 and 5: lumbar spine, 0.94%; trochanter, 0.88%). BMD at the femoral neck, forearm and total body were maintained. FOSAMAX was similarly effective regardless of age, race, baseline rate of bone turnover, and baseline BMD in the range studied (at

least 2 standard deviations below the premenopausal mean).

Osteoporosis Treatment Studies in Postmenopausal Women

Time Course of Effect of FOSAMAX 10 mg/day Versus Placebo: Lumbar Spine BMD Percent Change From Baseline



In patients with postmenopausal osteoporosis treated with FOSAMAX 10 mg/day for one or two years, the effects of treatment withdrawal were assessed. Following discontinuation, there were no further increases in bone mass and the rates of bone loss were similar to those of the placebo groups.

The therapeutic equivalence of once weekly FOSAMAX 70 mg (n=519) and FOSAMAX 10 mg daily (n=370) was demonstrated in a one-year, double-blind, multicenter study of postmenopausal women with osteoporosis. In the primary analysis of completers, the mean increases from baseline in lumbar spine BMD at one year were 5.1% (4.8, 5.4%; 95% CI) in the 70-mg once-weekly group (n=440) and 5.4% (5.0, 5.8%; 95% CI) in the 10-mg daily group (n=330). The two treatment groups were also similar with regard to BMD increases at other skeletal sites. The results of the intention-to-treat analysis were consistent with the primary analysis of completers.

Effect on fracture incidence

Data on the effects of FOSAMAX on fracture incidence are derived from three clinical studies: 1) U.S. and Multinational combined: a study of patients with a BMD T-score at or below minus 2.5 with or without a prior vertebral fracture, 2) Three-Year Study of the Fracture Intervention Trial (FIT): a study of patients with at least one baseline vertebral fracture, and 3) Four-Year Study of FIT: a study of patients with low bone mass but without a baseline vertebral fracture.

To assess the effects of FOSAMAX on the incidence of vertebral fractures (detected by digitized radiography; approximately one third of these were clinically symptomatic), the U.S. and Multinational studies were combined in an analysis that compared placebo to the pooled dosage groups of FOSAMAX (5 or 10 mg for three years or 20 mg for two years followed by 5 mg for one year). There was a statistically significant reduction in the proportion of patients treated with FOSAMAX experiencing one or more new vertebral fractures relative to those treated with placebo (3.2% vs. 6.2%; a 48% relative risk reduction). A reduction in the total number of new vertebral fractures (4.2 vs. 11.3 per 100 patients) was also observed. In the pooled analysis, patients who received FOSAMAX had a loss in stature that was statistically significantly less than was observed in those who received placebo (-3.0 mm vs. -4.6 mm).

The Fracture Intervention Trial (FIT) consisted of two studies in postmenopausal women: the Three-Year Study of patients who had at least one baseline radiographic vertebral fracture and the Four-Year

Study of patients with low bone mass but without a baseline vertebral fracture. In both studies of FIT, 96% of randomized patients completed the studies (i.e., had a closeout visit at the scheduled end of the study); approximately 80% of patients were still taking study medication upon completion.

Fracture Intervention Trial: Three-Year Study (patients with at least one baseline radiographic vertebral fracture)

This randomized, double-blind, placebo-controlled, 2027-patient study (FOSAMAX, n=1022; placebo, n=1005) demonstrated that treatment with FOSAMAX resulted in statistically significant reductions in fracture incidence at three years as shown in the table below.

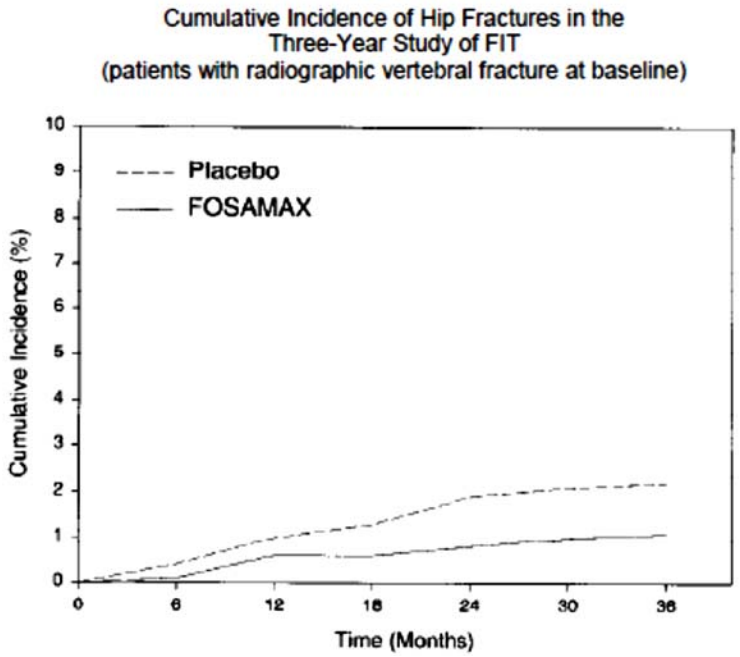
Effect of FOSAMAX on Fracture Incidence in the Three-Year Study of FIT
(patients with vertebral fracture at baseline)

	Percent of Patients			
	FOSAMAX (n=1022)	Placebo (n=1005)	Absolute Reduction in Fracture Incidence	Relative Reduction in Fracture Risk
Patients with:				
Vertebral fractures (diagnosed by X-ray)[1]				
≥ 1 new vertebral fracture	7.9	15.0	7.1	47‡‡
≥ 2 new vertebral fractures	0.5	4.9	4.4	90‡‡
Clinical (symptomatic) fractures				
Any clinical (symptomatic) fracture	13.8	18.1	4.3	26†
≥ 1 clinical (symptomatic) vertebral fracture	2.3	5.0	2.7	54‡
Hip fracture	1.1	2.2	1.1	51‡
Wrist (forearm) fracture	2.2	4.1	1.9	48‡

[1]Number evaluable for vertebral fractures: FOSAMAX, n=984; placebo, n=966
‡p<0.05, ‡‡p<0.01, ‡‡‡p<0.001, †p=0.007

Furthermore, in this population of patients with baseline vertebral fracture, treatment with FOSAMAX significantly reduced the incidence of hospitalizations (25.0% vs. 30.7%).

In the Three-Year Study of FIT, fractures of the hip occurred in 22 (2.2%) of 1005 patients on placebo and 11 (1.1%) of 1022 patients on FOSAMAX, p=0.047. The figure below displays the cumulative incidence of hip fractures in this study.



Fracture Intervention Trial: Four-Year Study (patients with low bone mass but without a baseline radiographic vertebral fracture)

This randomized, double-blind, placebo-controlled, 4432-patient study (FOSAMAX, n=2214; placebo, n=2218) further investigated the reduction in fracture incidence due to FOSAMAX. The intent of the study was to recruit women with osteoporosis, defined as a baseline femoral neck BMD at least two standard deviations below the mean for young adult women. However, due to subsequent revisions to the

normative values for femoral neck BMD, 31% of patients were found not to meet this entry criterion and thus this study included both osteoporotic and non-osteoporotic women. The results are shown in the table below for the patients with osteoporosis.

Effect of FOSAMAX on Fracture Incidence in Osteoporotic[1] Patients in the Four-Year Study of FIT
(patients without vertebral fracture at baseline)

	Percent of Patients			
	FOSAMAX (n=1545)	Placebo (n=1521)	Absolute Reduction in Fracture Incidence	Relative Reduction in Fracture Risk (%)
Patients with:				
Vertebral fractures (diagnosed by X-ray)[2]				
≥ 1 new vertebral fracture	2.5	4.8	2.3	48[**]
≥ 2 new vertebral fractures	0.1	0.6	0.5	78[*]
Clinical (symptomatic) fractures				
Any clinical (symptomatic) fracture	12.9	16.2	3.3	22[*]
≥ 1 clinical (symptomatic) vertebral fracture	1.0	1.6	0.6	41 (NS)[***]
Hip fracture	1.0	1.4	0.4	29 (NS)[***]
Wrist (forearm) fracture	3.9	3.8	-0.1	NS[***]

[1] Baseline femoral neck BMD at least 2 SD below the mean for young adult women
[2] Number evaluable for vertebral fractures: FOSAMAX, n=1426; placebo, n=1428
[***] Not significant. This study was not powered to detect differences at these sites.
[*] p=0.035, [**] p=0.01, [***] p<0.001

Fracture results across studies

In the Three-Year Study of FIT, FOSAMAX reduced the percentage of women experiencing at least one new radiographic vertebral fracture from 15.0% to 7.9% (47% relative risk reduction, p<0.001); in the Four-Year Study of FIT, the percentage was reduced from 3.8% to 2.1% (44% relative risk reduction, p=0.001); and in the combined U.S./Multinational studies, from 6.2% to 3.2% (48% relative risk reduction, p=0.034).

FOSAMAX reduced the percentage of women experiencing multiple (two or more) new vertebral fractures from 4.2% to 0.6% (87% relative risk reduction, p<0.001) in the combined U.S./Multinational studies and from 4.9% to 0.5%

(90% relative risk reduction, $p<0.001$) in the Three-Year Study of FIT. In the Four-Year Study of FIT, FOSAMAX reduced the percentage of osteoporotic women experiencing multiple vertebral fractures from 0.6% to 0.1% (78% relative risk reduction, $p=0.035$).

Thus, FOSAMAX reduced the incidence of radiographic vertebral fractures in osteoporotic women whether or not they had a previous radiographic vertebral fracture.

FOSAMAX, over a three- or four-year period, was associated with statistically significant reductions in loss of height vs. placebo in patients with and without baseline radiographic vertebral fractures. At the end of the FIT studies the between-treatment group differences were 3.2 mm in the Three-Year Study and 1.3 mm in the Four-Year Study.

Bone histology

Bone histology in 270 postmenopausal patients with osteoporosis treated with FOSAMAX at doses ranging from 1 to 20 mg/day for one, two, or three years revealed normal mineralization and structure, as well as the expected decrease in bone turnover relative to placebo. These data, together with the normal bone histology and increased bone strength observed in rats and baboons exposed to long-term alendronate treatment, support the conclusion that bone formed during therapy with FOSAMAX is of normal quality.

Men

The efficacy of FOSAMAX in men with hypogonadal or idiopathic osteoporosis was demonstrated in two clinical studies.

A two-year, double-blind, placebo-controlled, multicenter study of FOSAMAX 10 mg once daily enrolled a total of 241 men between the ages of 31 and 87 (mean, 63). All patients in the trial had either: 1) a BMD T-score ≤-2 at the femoral neck and ≤-1 at the lumbar spine, or 2) a baseline osteoporotic fracture and a BMD T-score ≤-1 at the femoral neck. At two years, the mean increases relative to placebo in BMD in men receiving FOSAMAX 10 mg/day were significant at the following sites: lumbar spine, 5.3%; femoral neck, 2.6%; trochanter, 3.1%; and total body, 1.6%. Treatment with FOSAMAX also reduced height loss (FOSAMAX, -0.6 mm vs. placebo, -2.4 mm).

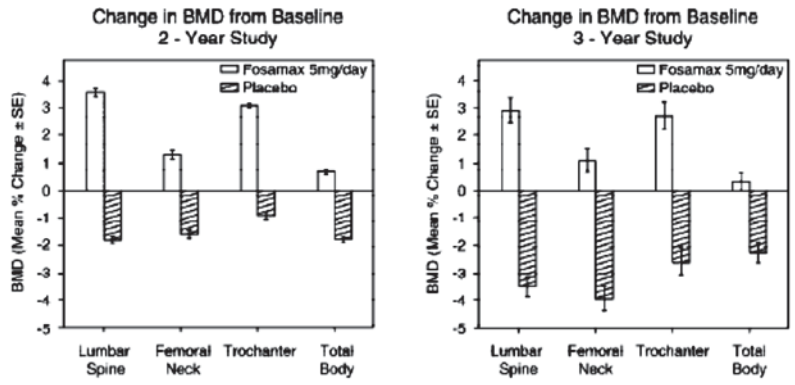
A one-year, double-blind, placebo-controlled, multicenter study of once weekly FOSAMAX 70 mg enrolled a total of 167 men between the ages of 38 and 91 (mean, 66). Patients in the study had either: 1) a BMD T-score ≤-2 at the femoral neck and ≤-1 at the lumbar spine, 2) a BMD T-score ≤-2 at the lumbar spine and ≤-1 at the femoral neck, or 3) a baseline osteoporotic fracture and a BMD T-score ≤-1 at the femoral neck. At one year, the mean increases relative to placebo in BMD in men receiving FOSAMAX 70 mg once weekly were significant at the following sites: lumbar spine, 2.8%; femoral neck, 1.9%; trochanter, 2.0%; and total body, 1.2%. These increases in BMD were similar to those seen at one year in the 10 mg once-daily study.

In both studies, BMD responses were similar regardless of age (≥65 years vs. <65 years), gonadal function (baseline testosterone <9 ng/dL vs. ≥9 ng/dL), or baseline BMD (femoral neck and lumbar spine T-score ≤-2.5 vs. >-2.5).

Prevention of osteoporosis in postmenopausal women

Prevention of bone loss was demonstrated in two double-blind, placebo-controlled studies of postmenopausal women 40–60 years of age. One thousand six hundred nine patients (FOSAMAX 5 mg/day; n=498) who were at least six months postmenopausal were entered into a two-year study without regard to their baseline BMD. In the other study, 447 patients (FOSAMAX 5 mg/day; n=88), who were between six months and three years postmenopause, were treated for up to three years. In the placebo-treated patients BMD losses of approximately 1% per year were seen at the spine, hip (femoral neck and trochanter) and total body. In contrast, FOSAMAX 5 mg/day prevented bone loss in the majority of patients and induced significant increases in mean bone mass at each of these sites (see figures below). In addition, FOSAMAX 5 mg/day reduced the rate of bone loss at the forearm by approximately half relative to placebo. FOSAMAX 5 mg/day was similarly effective in this population regardless of age, time since menopause, race and baseline rate of bone turnover.

Osteoporosis Prevention Studies in Postmenopausal Women



The therapeutic equivalence of once weekly FOSAMAX 35 mg (n=362) and FOSAMAX 5 mg daily (n=361) was demonstrated in a one-year, double-blind, multicenter study of postmenopausal women without osteoporosis. In the primary analysis of completers, the mean increases from baseline in lumbar spine BMD at one year were 2.9% (2.6, 3.2%; 95% CI) in the 35-mg once-weekly group (n=307) and 3.2% (2.9, 3.5%; 95% CI) in the 5-mg daily group (n=298). The two treatment groups were also similar with regard to BMD increases at other skeletal sites. The results of the intention-to-treat analysis were consistent with the primary analysis of completers.

Bone histology

Bone histology was normal in the 28 patients biopsied at the end of three years who received FOSAMAX at doses of up to 10 mg/day.

Concomitant use with estrogen/hormone replacement therapy (HRT)

The effects on BMD of treatment with FOSAMAX 10 mg once daily and conjugated estrogen (0.625 mg/day) either alone or in combination were assessed in a two-year, double-blind, placebo- controlled study of hysterectomized postmenopausal osteoporotic women (n=425). At two years, the increases in lumbar spine BMD from baseline were significantly greater with the combination (8.3%) than with either estrogen or FOSAMAX alone (both 6.0%).

The effects on BMD when FOSAMAX was added to stable doses (for at least one year) of HRT (estrogen ± progestin) were assessed in a one-year, double-blind, placebo-controlled study in postmenopausal osteoporotic women (n=428). The addition of

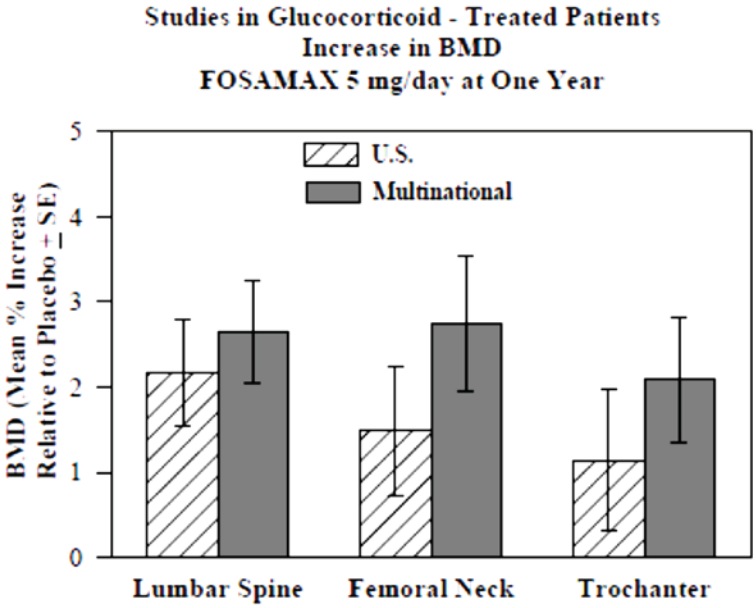
FOSAMAX 10 mg once daily to HRT produced, at one year, significantly greater increases in lumbar spine BMD (3.7%) vs. HRT alone (1.1%).

In these studies, significant increases or favorable trends in BMD for combined therapy compared with HRT alone were seen at the total hip, femoral neck, and trochanter. No significant effect was seen for total body BMD.

Histomorphometric studies of transiliac biopsies in 92 subjects showed normal bone architecture. Compared to placebo there was a 98% suppression of bone turnover (as assessed by mineralizing surface) after 18 months of combined treatment with FOSAMAX and HRT, 94% on FOSAMAX alone, and 78% on HRT alone. The long-term effects of combined FOSAMAX and HRT on fracture occurrence and fracture healing have not been studied.

Glucocorticoid-induced osteoporosis

The efficacy of FOSAMAX 5 and 10 mg once daily in men and women receiving glucocorticoids (at least 7.5 mg/day of prednisone or equivalent) was demonstrated in two, one-year, double-blind, randomized, placebo-controlled, multicenter studies of virtually identical design, one performed in the United States and the other in 15 different countries (Multinational [which also included FOSAMAX 2.5 mg/day]). These studies enrolled 232 and 328 patients, respectively, between the ages of 17 and 83 with a variety of glucocorticoid-requiring diseases. Patients received supplemental calcium and vitamin D. The following figure shows the mean increases relative to placebo in BMD of the lumbar spine, femoral neck, and trochanter in patients receiving FOSAMAX 5 mg/day for each study.



After one year, significant increases relative to placebo in BMD were seen in the combined studies at each of these sites in patients who received FOSAMAX 5 mg/day. In the placebo-treated patients, a significant decrease in BMD occurred at the femoral neck (-1.2%), and smaller decreases were seen at the lumbar spine and trochanter. Total body BMD was maintained with FOSAMAX 5 mg/day. The increases in BMD with FOSAMAX 10 mg/day were similar to those with FOSAMAX 5 mg/day in all patients except for postmenopausal women not receiving estrogen therapy. In these women, the increases (relative to placebo) with FOSAMAX 10 mg/day were greater than those with FOSAMAX 5 mg/day at the lumbar spine (4.1% vs. 1.6%) and trochanter (2.8% vs. 1.7%), but not at other sites. FOSAMAX was effective regardless of dose or duration of glucocorticoid use. In addition, FOSAMAX was similarly effective regardless of age

(<65 vs. ≥65 years), race (Caucasian vs. other races), gender, underlying disease, baseline BMD, baseline bone turnover, and use with a variety of common medications.

Bone histology was normal in the 49 patients biopsied at the end of one year who received FOSAMAX at doses of up to 10 mg/day.

Of the original 560 patients in these studies, 208 patients who remained on at least 7.5 mg/day of prednisone or equivalent continued into a one-year double-blind extension. After two years of treatment, spine BMD increased by 3.7% and 5.0% relative to placebo with FOSAMAX 5 and 10 mg/day, respectively. Significant increases in BMD (relative to placebo) were also observed at the femoral neck, trochanter, and total body.

After one year, 2.3% of patients treated with FOSAMAX 5 or 10 mg/day (pooled) vs. 3.7% of those treated with placebo experienced a new vertebral fracture (not significant). However, in the population studied for two years, treatment with FOSAMAX (pooled dosage groups: 5 or 10 mg for two years or 2.5 mg for one year followed by 10 mg for one year) significantly reduced the incidence of patients with a new vertebral fracture (FOSAMAX 0.7% vs. placebo 6.8%).

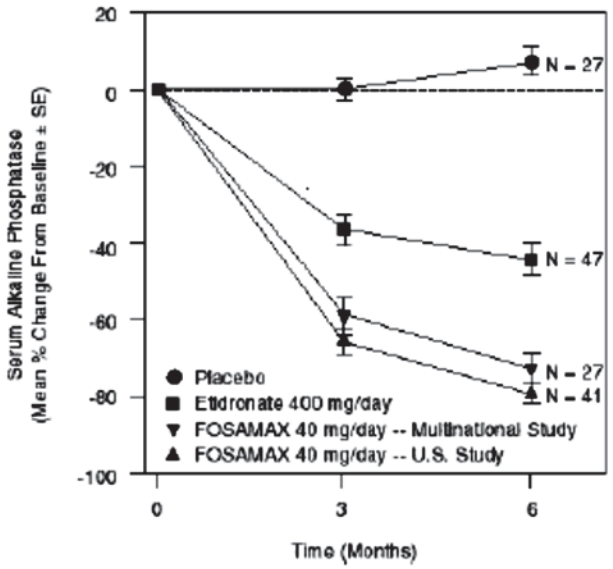
Paget's disease of bone

The efficacy of FOSAMAX 40 mg once daily for six months was demonstrated in two double-blind clinical studies of male and female patients with moderate to severe Paget's disease (alkaline phosphatase at least twice the upper limit of normal): a placebo-controlled, multinational study and a U.S. comparative study

with etidronate disodium 400 mg/day. The following figure shows the mean percent changes from baseline in serum alkaline phosphatase for up to six months of randomized treatment.

Studies in Paget's Disease of Bone

Effect on Serum Alkaline Phosphatase of FOSAMAX 40 mg/day Versus Placebo or Etidronate 400 mg/day



At six months the suppression in alkaline phosphatase in patients treated with FOSAMAX was significantly greater than that achieved with etidronate and contrasted with the complete lack of response in placebo-treated patients. Response (defined as either normalization of serum alkaline phosphatase or decrease from baseline >60%) occurred in approximately 85% of patients treated with FOSAMAX in the combined studies vs. 30% in the etidronate group and 0% in the placebo group. FOSAMAX was similarly effective regardless of age,

gender, race, prior use of other bisphosphonates, or baseline alkaline phosphatase within the range studied (at least twice the upper limit of normal).

Bone histology was evaluated in 33 patients with Paget's disease treated with FOSAMAX 40 mg/day for 6 months. As in patients treated for osteoporosis (see *Clinical Studies, Treatment of osteoporosis in postmenopausal women, Bone histology*), FOSAMAX did not impair mineralization, and the expected decrease in the rate of bone turnover was observed. Normal lamellar bone was produced during treatment with FOSAMAX, even where preexisting bone was woven and disorganized. Overall, bone histology data support the conclusion that bone formed during treatment with FOSAMAX is of normal quality.

ANIMAL PHARMACOLOGY

The relative inhibitory activities on bone resorption and mineralization of alendronate and etidronate were compared in the Schenk assay, which is based on histological examination of the epiphyses of growing rats. In this assay, the lowest dose of alendronate that interfered with bone mineralization (leading to osteomalacia) was 6000-fold the antiresorptive dose. The corresponding ratio for etidronate was one to one. These data suggest that alendronate administered in therapeutic doses is highly unlikely to induce osteomalacia.

INDICATIONS AND USAGE

FOSAMAX is indicated for:

- Treatment and prevention of osteoporosis in postmenopausal women
  - For the treatment of osteoporosis, FOSAMAX increases bone mass and reduces

the incidence of fractures, including those of the hip and spine (vertebral compression fractures). Osteoporosis may be confirmed by the finding of low bone mass (for example, at least 2 standard deviations below the premenopausal mean) or by the presence or history of osteoporotic fracture. (See CLINICAL PHARMACOLOGY, *Pharmacodynamics*.)

- For the prevention of osteoporosis, FOSAMAX may be considered in postmenopausal women who are at risk of developing osteoporosis and for whom the desired clinical outcome is to maintain bone mass and to reduce the risk of future fracture.

  Bone loss is particularly rapid in postmenopausal women younger than age 60. Risk factors often associated with the development of postmenopausal osteoporosis include early menopause; moderately low bone mass (for example, at least 1 standard deviation below the mean for healthy young adult women); thin body build; Caucasian or Asian race; and family history of osteoporosis. The presence of such risk factors may be important when considering the use of FOSAMAX for prevention of osteoporosis.

- Treatment to increase bone mass in men with osteoporosis
- Treatment of glucocorticoid-induced osteoporosis in men and women receiving glucocorticoids in a daily dosage equivalent to

7.5 mg or greater of prednisone and who have low bone mineral density (see PRECAUTIONS, *Glucocorticoid-induced osteoporosis*). Patients treated with glucocorticoids should receive adequate amounts of calcium and vitamin D.

- Treatment of Paget's disease of bone in men and women
  - Treatment is indicated in patients with Paget's disease of bone having alkaline phosphatase at least two times the upper limit of normal, or those who are symptomatic, or those at risk for future complications from their disease.

The safety and effectiveness of FOSAMAX for the treatment of osteoporosis are based on clinical data of four years duration. The optimal duration of use has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis.

CONTRAINDICATIONS

- Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia
- Inability to stand or sit upright for at least 30 minutes (see WARNINGS)
- Patients at increased risk of aspiration should not receive FOSAMAX oral solution.
- Hypersensitivity to any component of this product
- Hypocalcemia (see PRECAUTIONS, *General*)

WARNINGS

FOSAMAX, like other bisphosphonates administered orally, may cause local irritation of the

upper gastrointestinal mucosa. Because of these possible irritant effects and a potential for worsening of the underlying disease, caution should be used when FOSAMAX is given to patients with active upper gastrointestinal problems (such as known Barrett's esophagus, dysphagia, other esophageal diseases, gastritis, duodenitis, or ulcers).

Esophageal adverse experiences, such as esophagitis, esophageal ulcers and esophageal erosions, occasionally with bleeding and rarely followed by esophageal stricture or perforation, have been reported in patients receiving treatment with oral bisphosphonates including FOSAMAX. In some cases these have been severe and required hospitalization. Physicians should therefore be alert to any signs or symptoms signaling a possible esophageal reaction and patients should be instructed to discontinue FOSAMAX and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn.

The risk of severe esophageal adverse experiences appears to be greater in patients who lie down after taking oral bisphosphonates including FOSAMAX and/or who fail to swallow oral bisphosphonates including FOSAMAX with the recommended full glass (6–8 oz) of water, and/or who continue to take oral bisphosphonates including FOSAMAX after developing symptoms suggestive of esophageal irritation. Therefore, it is very important that the full dosing instructions are provided to, and understood by, the patient (see DOSAGE AND ADMINISTRATION). In patients who cannot comply with dosing instructions due to mental disability,

therapy with FOSAMAX should be used under appropriate supervision.

There have been post-marketing reports of gastric and duodenal ulcers with oral bisphosphonate use, some severe and with complications, although no increased risk was observed in controlled clinical trials.

PRECAUTIONS

General

Causes of osteoporosis other than estrogen deficiency, aging, and glucocorticoid use should be considered.

Hypocalcemia must be corrected before initiating therapy with FOSAMAX (see CONTRAINDICATIONS). Other disorders affecting mineral metabolism (such as vitamin D deficiency) should also be effectively treated. In patients with these conditions, serum calcium and symptoms of hypocalcemia should be monitored during therapy with FOSAMAX.

Presumably due to the effects of FOSAMAX on increasing bone mineral, small, asymptomatic decreases in serum calcium and phosphate may occur, especially in patients with Paget's disease, in whom the pretreatment rate of bone turnover may be greatly elevated and in patients receiving glucocorticoids, in whom calcium absorption may be decreased.

Ensuring adequate calcium and vitamin D intake is especially important in patients with Paget's disease of bone and in patients receiving glucocorticoids.

Musculoskeletal Pain

In post marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates that are approved for the prevention and treatment of osteoporosis (see ADVERSE REACTIONS). This category of drugs includes FOSAMAX (alendronate). Most of the patients were postmenopausal women. The time to onset of symptoms varied from one day to several months after starting the drug. Discontinue use if severe symptoms develop. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

In placebo-controlled clinical studies of FOSAMAX, the percentages of patients with these symptoms were similar in the FOSAMAX and placebo groups.

Dental

Osteonecrosis of the jaw (ONJ), which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing, and has been reported in patients taking bisphosphonates, including FOSAMAX. Known risk factors for osteonecrosis of the jaw include invasive dental procedures (e.g., tooth extraction, dental implants, boney surgery), diagnosis of cancer, concomitant therapies (e.g., chemotherapy, corticosteroids), poor oral hygiene, and co-morbid disorders (e.g., periodontal and/or other pre-existing dental disease, anemia, coagulopathy, infection, ill-fitting dentures).

For patients requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk for ONJ. Clinical judgment of the treating physician and/or oral surgeon should guide the management plan of each patient based on individual benefit/risk assessment.

Patients who develop osteonecrosis of the jaw while on bisphosphonate therapy should receive care by an oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition. Discontinuation of bisphosphonate therapy should be considered based on individual benefit/risk assessment.

Atypical Subtrochanteric and Diaphyseal Femoral Fractures

Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.

Atypical femur fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture.

Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patients presenting with an atypical fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.

Renal insufficiency

FOSAMAX is not recommended for patients with renal insufficiency (creatinine clearance <35 mL/min). (See DOSAGE AND ADMINISTRATION.)

Glucocorticoid-induced osteoporosis

The risk versus benefit of FOSAMAX for treatment at daily dosages of glucocorticoids less than 7.5 mg of prednisone or equivalent has not been established (see INDICATIONS AND USAGE). Before initiating treatment, the hormonal status of both men and women should be ascertained and appropriate replacement considered.

A bone mineral density measurement should be made at the initiation of therapy and repeated after 6 to 12 months of combined FOSAMAX and glucocorticoid treatment.

The efficacy of FOSAMAX for the treatment of glucocorticoid-induced osteoporosis has been shown in patients with a median bone mineral density which was 1.2 standard deviations below the mean for healthy young adults.

The efficacy of FOSAMAX has been established in studies of two years' duration. The greatest increase

in bone mineral density occurred in the first year with maintenance or smaller gains during the second year. Efficacy of FOSAMAX beyond two years has not been studied.

The efficacy of FOSAMAX in respect to fracture prevention has been demonstrated for vertebral fractures. However, this finding was based on very few fractures that occurred primarily in postmenopausal women. The efficacy for prevention of non-vertebral fractures has not been demonstrated.

Information for Patients

General

Physicians should instruct their patients to read the Medication Guide before starting therapy with FOSAMAX and to reread it each time the prescription is renewed.

Patients should be instructed to take supplemental calcium and vitamin D, if daily dietary intake is inadequate. Weight-bearing exercise should be considered along with the modification of certain behavioral factors, such as cigarette smoking and/or excessive alcohol consumption, if these factors exist.

Dosing Instructions

Patients should be instructed that the expected benefits of FOSAMAX may only be obtained when it is taken with plain water the first thing upon arising for the day at least 30 minutes before the first food, beverage, or medication of the day. Even dosing with orange juice or coffee has been shown to markedly reduce the absorption of FOSAMAX (see CLINICAL PHARMACOLOGY, *Pharmacokinetics, Absorption*).

To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation patients should be instructed to swallow each tablet of FOSAMAX with a full glass of water (6–8 oz). To facilitate gastric emptying patients should drink at least 2 oz (a quarter of a cup) of water after taking FOSAMAX oral solution. Patients should be instructed not to lie down for at least 30 minutes and until after their first food of the day. Patients should not chew or suck on the tablet because of a potential for oropharyngeal ulceration. Patients should be specifically instructed not to take FOSAMAX at bedtime or before arising for the day. Patients should be informed that failure to follow these instructions may increase their risk of esophageal problems. Patients should be instructed that if they develop symptoms of esophageal disease (such as difficulty or pain upon swallowing, retrosternal pain or new or worsening heartburn) they should stop taking FOSAMAX and consult their physician.

Patients should be instructed that if they miss a dose of once weekly FOSAMAX, they should take one dose on the morning after they remember. They should not take two doses on the same day but should return to taking one dose once a week, as originally scheduled on their chosen day.

Drug Interactions
(also see CLINICAL PHARMACOLOGY,
Pharmacokinetics, Drug Interactions)

Estrogen/hormone replacement therapy (HRT)

Concomitant use of HRT (estrogen ± progestin) and FOSAMAX was assessed in two clinical studies of one or two years' duration in postmenopausal osteoporotic

women. In these studies, the safety and tolerability profile of the combination was consistent with those of the individual treatments; however, the degree of suppression of bone turnover (as assessed by mineralizing surface) was significantly greater with the combination than with either component alone. The long-term effects of combined FOSAMAX and HRT on fracture occurrence have not been studied (see CLINICAL PHARMACOLOGY, *Clinical Studies, Concomitant use with estrogen/hormone replacement therapy (HRT)* and ADVERSE REACTIONS, *Clinical Studies, Concomitant use with estrogen/hormone replacement therapy*).

Calcium Supplements/Antacids

It is likely that calcium supplements, antacids, and some oral medications will interfere with absorption of FOSAMAX. Therefore, patients must wait at least one-half hour after taking FOSAMAX before taking any other oral medications.

Aspirin

In clinical studies, the incidence of upper gastrointestinal adverse events was increased in patients receiving concomitant therapy with daily doses of FOSAMAX greater than 10 mg and aspirin-containing products.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

FOSAMAX may be administered to patients taking NSAIDs. In a 3-year, controlled, clinical study (n=2027) during which a majority of patients received concomitant NSAIDs, the incidence of upper gastrointestinal adverse events was similar in patients taking FOSAMAX 5 or 10 mg/day compared to those taking placebo. However, since NSAID use is

associated with gastrointestinal irritation, caution should be used during concomitant use with FOSAMAX.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Harderian gland (a retro-orbital gland not present in humans) adenomas were increased in high-dose female mice (p=0.003) in a 92-week oral carcinogenicity study at doses of alendronate of 1, 3, and 10 mg/kg/day (males) or 1, 2, and 5 mg/kg/day (females). These doses are equivalent to 0.12 to 1.2 times a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/m2. The relevance of this finding to humans is unknown.

Parafollicular cell (thyroid) adenomas were increased in high-dose male rats (p=0.003) in a 2-year oral carcinogenicity study at doses of 1 and 3.75 mg/kg body weight. These doses are equivalent to 0.26 and 1 times a 40 mg human daily dose based on surface area, mg/m^2. The relevance of this finding to humans is unknown.

Alendronate was not genotoxic in the *in vitro* microbial mutagenesis assay with and without metabolic activation, in an *in vitro* mammalian cell mutagenesis assay, in an *in vitro* alkaline elution assay in rat hepatocytes, and in an *in vivo* chromosomal aberration assay in mice. In an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, however, alendronate gave equivocal results.

Alendronate had no effect on fertility (male or female) in rats at oral doses up to 5 mg/kg/day (1.3 times a 40 mg human daily dose based on surface area, mg/m^2).

Pregnancy

Pregnancy Category C:

Reproduction studies in rats showed decreased postimplantation survival at 2 mg/kg/day and decreased body weight gain in normal pups at 1 mg/kg/day. Sites of incomplete fetal ossification were statistically significantly increased in rats beginning at 10 mg/kg/day in vertebral (cervical, thoracic, and lumbar), skull, and sternebral bones. The above doses ranged from 0.26 times (1 mg/kg) to 2.6 times (10 mg/kg) a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/m^2. No similar fetal effects were seen when pregnant rabbits were treated at doses up to 35 mg/kg/day (10.3 times a 40 mg human daily dose based on surface area, mg/m^2).

Both total and ionized calcium decreased in pregnant rats at 15 mg/kg/day (3.9 times a 40 mg human daily dose based on surface area, mg/m^2) resulting in delays and failures of delivery. Protracted parturition due to maternal hypocalcemia occurred in rats at doses as low as 0.5 mg/kg/day (0.13 times a 40 mg human daily dose based on surface area, mg/m^2) when rats were treated from before mating through gestation. Maternotoxicity (late pregnancy deaths) occurred in the female rats treated with 15 mg/kg/day for varying periods of time ranging from treatment only during pre-mating to treatment only during early, middle, or late gestation; these deaths were lessened but not eliminated by cessation of treatment. Calcium supplementation either in the drinking water or by minipump could not ameliorate the hypocalcemia or prevent maternal and neonatal

deaths due to delays in delivery; calcium supplementation IV prevented maternal, but not fetal deaths.

Bisphosphonates are incorporated into the bone matrix, from which they are gradually released over a period of years. The amount of bisphosphonate incorporated into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the dose and duration of bisphosphonate use. There are no data on fetal risk in humans. However, there is a theoretical risk of fetal harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on the risk has not been studied.

There are no studies in pregnant women. FOSAMAX should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

Nursing Mothers

It is not known whether alendronate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FOSAMAX is administered to nursing women.

Pediatric Use

The efficacy and safety of FOSAMAX were examined in a randomized, double-blind, placebo-controlled two-year study of 139 pediatric patients, aged 4-18 years, with severe osteogenesis imperfecta. One-hundred-and-nine patients were randomized to 5

mg FOSAMAX daily (weight <40 kg) or 10 mg FOSAMAX daily (weight ≥40 kg) and 30 patients to placebo. The mean baseline lumbar spine BMD Z-score of the patients was -4.5. The mean change in lumbar spine BMD Z-score from baseline to Month 24 was 1.3 in the FOSAMAX-treated patients and 0.1 in the placebo-treated patients. Treatment with FOSAMAX did not reduce the risk of fracture. Sixteen percent of the FOSAMAX patients who sustained a radiologically-confirmed fracture by Month 12 of the study had delayed fracture healing (callus remodeling) or fracture non-union when assessed radiographically at Month 24 compared with 9% of the placebo-treated patients. In FOSAMAX-treated patients, bone histomorphometry data obtained at Month 24 demonstrated decreased bone turnover and delayed mineralization time; however, there were no mineralization defects. There were no statistically significant differences between the FOSAMAX and placebo groups in reduction of bone pain.

FOSAMAX is not indicated for use in children.

(For clinical adverse experiences in children, see ADVERSE REACTIONS, *Clinical Studies, Osteogenesis Imperfecta.*)

Geriatric Use

Of the patients receiving FOSAMAX in the Fracture Intervention Trial (FIT), 71% (n=2302) were ≥65 years of age and 17% (n=550) were ≥75 years of age. Of the patients receiving FOSAMAX in the United States and Multinational osteoporosis treatment studies in women, osteoporosis studies in men, glucocorticoid-induced osteoporosis studies, and Paget's disease studies (see CLINICAL PHARMACOLOGY, *Clinical*

Studies), 45%, 54%, 37%, and 70%, respectively, were 65 years of age or over. No overall differences in efficacy or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Clinical Studies

In clinical studies of up to five years in duration adverse experiences associated with FOSAMAX usually were mild, and generally did not require discontinuation of therapy.

FOSAMAX has been evaluated for safety in approximately 8000 postmenopausal women in clinical studies.

Treatment of osteoporosis

Postmenopausal women

In two identically designed, three-year, placebo-controlled, double-blind, multicenter studies (United States and Multinational; n=994), discontinuation of therapy due to any clinical adverse experience occurred in 4.1% of 196 patients treated with FOSAMAX 10 mg/day and 6.0% of 397 patients treated with placebo. In the Fracture Intervention Trial (n=6459), discontinuation of therapy due to any clinical adverse experience occurred in 9.1% of 3236 patients treated with FOSAMAX 5 mg/day for 2 years and 10 mg/day for either one or two additional years and 10.1% of 3223 patients treated with placebo. Discontinuations due to upper gastrointestinal adverse experiences were: FOSAMAX, 3.2%; placebo, 2.7%. In these study populations, 49–54% had a history of gastrointestinal disorders at baseline and

54–89% used nonsteroidal anti-inflammatory drugs or aspirin at some time during the studies. Adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either FOSAMAX or placebo are presented in the following table.

Osteoporosis Treatment Studies in Postmenopausal Women
Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1 of Patients

	United States/Multinational Studies		Fracture Intervention Trial	
	FOSAMAX	Placebo	FOSAMAX	Placebo
	(n=196)	(n=397)	(n=3236)	(n=3223)
Gastrointestinal				
abdominal pain	6.6	4.8	1.5	1.5
nausea	3.6	4.0	1.1	1.5
dyspepsia	3.6	3.5	1.1	1.2
constipation	3.1	1.8	0.0	0.2
diarrhea	3.1	1.8	0.6	0.3
flatulence	2.6	0.5	0.2	0.3
acid regurgitation	2.0	4.3	1.1	0.9
esophageal ulcer	1.5	0.0	0.1	0.1
vomiting	1.0	1.5	0.2	0.3
dysphagia	1.0	0.0	0.1	0.1
abdominal distention	1.0	0.8	0.0	0.0
gastritis	0.5	1.3	0.6	0.7
Musculoskeletal				
musculoskeletal (bone, muscle or joint) pain	4.1	2.5	0.4	0.3
muscle cramp	0.0	1.0	0.2	0.1
Nervous System/Psychiatric				
headache	2.6	1.5	0.2	0.2
dizziness	0.0	1.0	0.0	0.1
Special Senses				
taste perversion	0.5	1.0	0.1	0.0

10 mg/day for three years
5 mg/day for 2 years and 10 mg/day for either 1 or 2 additional years

Rarely, rash and erythema have occurred.

One patient treated with FOSAMAX (10 mg/day), who had a history of peptic ulcer disease and gastrectomy and who was taking concomitant aspirin developed an anastomotic ulcer with mild hemorrhage, which was considered drug related. Aspirin and FOSAMAX were discontinued and the patient recovered.

The adverse experience profile was similar for the 401 patients treated with either 5 or 20 mg doses of

FOSAMAX in the United States and Multinational studies. The adverse experience profile for the 296 patients who received continued treatment with either 5 or 10 mg doses of FOSAMAX in the two-year extension of these studies (treatment years 4 and 5) was similar to that observed during the three-year placebo-controlled period. During the extension period, of the 151 patients treated with FOSAMAX 10 mg/day, the proportion of patients who discontinued therapy due to any clinical adverse experience was similar to that during the first three years of the study.

In a one-year, double-blind, multicenter study, the overall safety and tolerability profiles of once weekly FOSAMAX 70 mg and FOSAMAX 10 mg daily were similar. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients in either treatment group are presented in the following table.

Osteoporosis Treatment Studies in Postmenopausal Women
Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1 of Patients

	Once Weekly FOSAMAX 70 mg (n=519)	FOSAMAX 10 mg/day (n=370)
Gastrointestinal		
abdominal pain	3.7	3.0
dyspepsia	2.7	2.2
acid regurgitation	1.9	2.4
nausea	1.9	2.4
abdominal distention	1.0	1.4
constipation	0.8	1.6
flatulence	0.4	1.6
gastritis	0.2	1.1
gastric ulcer	0.0	1.1
Musculoskeletal		
musculoskeletal (bone, muscle, joint) pain	2.9	3.2
muscle cramp	0.2	1.1

Men

In two placebo-controlled, double-blind, multicenter studies in men (a two-year study of FOSAMAX 10 mg/day and a one-year study of once weekly

FOSAMAX 70 mg) the rates of discontinuation of therapy due to any clinical adverse experience were 2.7% for FOSAMAX 10 mg/day vs. 10.5% for placebo, and 6.4% for once weekly FOSAMAX 70 mg vs. 8.6% for placebo. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥2% of patients treated with either FOSAMAX or placebo are presented in the following table.

Osteoporosis Studies in Men
Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥2 of Patients

	Two-year Study		One-year Study	
	FOSAMAX 10 mg/day (n=146)	Placebo (n=95)	Once Weekly FOSAMAX 70 mg (n=109)	Placebo (n=58)
Gastrointestinal				
acid regurgitation	4.1	3.2	0.0	0.0
flatulence	4.1	1.1	0.0	0.0
gastroesophageal reflux disease	0.7	3.2	2.8	0.0
dyspepsia	3.4	0.0	2.8	1.7
diarrhea	1.4	1.1	2.8	0.0
abdominal pain	2.1	1.1	0.9	3.4
nausea	2.1	0.0	0.0	0.0

Prevention of osteoporosis in postmenopausal women

The safety of FOSAMAX 5 mg/day in postmenopausal women 40–60 years of age has been evaluated in three double-blind, placebo-controlled studies involving over 1,400 patients randomized to receive FOSAMAX for either two or three years. In these studies the overall safety profiles of FOSAMAX 5 mg/day and placebo were similar. Discontinuation of therapy due to any clinical adverse experience occurred in 7.5% of 642 patients treated with FOSAMAX 5 mg/day and 5.7% of 648 patients treated with placebo.

In a one-year, double-blind, multicenter study, the overall safety and tolerability profiles of once weekly FOSAMAX 35 mg and FOSAMAX 5 mg daily were similar.

The adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either once weekly FOSAMAX 35 mg, FOSAMAX 5 mg/day or placebo are presented in the following table.

Osteoporosis Prevention Studies in Postmenopausal Women
Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1% of Patients

	Two/Three-Year Studies		One-Year Study	
	FOSAMAX 5 mg/day (n=642)	Placebo (n=648)	FOSAMAX 5 mg/day (n=361)	Once Weekly FOSAMAX 35 mg (n=362)
Gastrointestinal				
dyspepsia	1.9	1.4	2.2	1.7
abdominal pain	1.7	3.4	4.2	2.2
acid regurgitation	1.4	2.5	4.2	4.7
nausea	1.4	1.4	2.5	1.4
diarrhea	1.1	1.7	1.1	0.6
constipation	0.9	0.5	1.7	0.3
abdominal distention	0.2	0.3	1.4	1.1
Musculoskeletal				
musculoskeletal (bone, muscle or joint) pain	0.8	0.9	1.9	2.2

Concomitant use with estrogen/hormone replacement therapy

In two studies (of one and two years' duration) of postmenopausal osteoporotic women (total: n=853), the safety and tolerability profile of combined treatment with FOSAMAX 10 mg once daily and estrogen ± progestin (n=354) was consistent with those of the individual treatments.

Treatment of glucocorticoid-induced osteoporosis

In two, one-year, placebo-controlled, double-blind, multicenter studies in patients receiving glucocorticoid treatment, the overall safety and tolerability profiles of FOSAMAX 5 and 10 mg/day were generally similar to that of placebo. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in >1% of patients treated with either FOSAMAX 5 or 10 mg/day or placebo are presented in the following table.

One-Year Studies in Glucocorticoid-Treated Patients
Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1% of Patients

	FOSAMAX 10 mg/day (n=157)	FOSAMAX 5 mg/day (n=161)	Placebo (n=159)
Gastrointestinal			
abdominal pain	3.2	1.9	0.0
acid regurgitation	2.5	1.9	1.3
constipation	1.3	0.6	0.0
melena	1.3	0.0	0.0
nausea	0.6	1.2	0.6
diarrhea	0.0	0.0	1.3
Nervous System/Psychiatric			
headache	0.6	0.0	1.3

The overall safety and tolerability profile in the glucocorticoid-induced osteoporosis population that continued therapy for the second year of the studies (FOSAMAX: n=147) was consistent with that observed in the first year.

Paget's disease of bone

In clinical studies (osteoporosis and Paget's disease), adverse experiences reported in 175 patients taking FOSAMAX 40 mg/day for 3–12 months were similar to those in postmenopausal women treated with FOSAMAX 10 mg/day. However, there was an apparent increased incidence of upper gastrointestinal adverse experiences in patients taking FOSAMAX 40 mg/day (17.7% FOSAMAX vs. 10.2% placebo). One

case of esophagitis and two cases of gastritis resulted in discontinuation of treatment.

Additionally, musculoskeletal (bone, muscle or joint) pain, which has been described in patients with Paget's disease treated with other bisphosphonates, was considered by the investigators as possibly, probably, or definitely drug related in approximately 6% of patients treated with FOSAMAX 40 mg/day versus approximately 1% of patients treated with placebo, but rarely resulted in discontinuation of therapy. Discontinuation of therapy due to any clinical adverse experience occurred in 6.4% of patients with Paget's disease treated with FOSAMAX 40 mg/day and 2.4% of patients treated with placebo.

Osteogenesis Imperfecta

FOSAMAX is not indicated for use in children.

The overall safety profile of FOSAMAX in OI patients treated for up to 24 months was generally similar to that of adults with osteoporosis treated with FOSAMAX. However, there was an increased occurrence of vomiting in OI patients treated with FOSAMAX compared to placebo. During the 24-month treatment period, vomiting was observed in 32 of 109 (29.4%) patients treated with FOSAMAX and 3 of 30 (10%) patients treated with placebo.

In a pharmacokinetic study, 6 of 24 pediatric OI patients who received a single oral dose of FOSAMAX 35 or 70 mg developed fever, flu-like symptoms, and/or mild lymphocytopenia within 24 to 48 hours after administration. These events, lasting no more than 2 to 3 days and responding to acetaminophen, are consistent with an acute-phase response that has been reported in patients receiving bisphosphonates,

including FOSAMAX. See ADVERSE REACTIONS, *Post-Marketing Experience, Body as a Whole*.

Laboratory Test Findings

In double-blind, multicenter, controlled studies, asymptomatic, mild, and transient decreases in serum calcium and phosphate were observed in approximately 18% and 10%, respectively, of patients taking FOSAMAX versus approximately 12% and 3% of those taking placebo. However, the incidences of decreases in serum calcium to <8.0 mg/dL (2.0 mM) and serum phosphate to ≤2.0 mg/dL (0.65 mM) were similar in both treatment groups.

Post-Marketing Experience

The following adverse reactions have been reported in post-marketing use:

Body as a Whole: hypersensitivity reactions including urticaria and rarely angioedema. Transient symptoms of myalgia, malaise, asthenia and rarely, fever have been reported with FOSAMAX, typically in association with initiation of treatment. Rarely, symptomatic hypocalcemia has occurred, generally in association with predisposing conditions. Rarely, peripheral edema.

Gastrointestinal: esophagitis, esophageal erosions, esophageal ulcers, rarely esophageal stricture or perforation, and oropharyngeal ulceration. Gastric or duodenal ulcers, some severe and with complications have also been reported (see WARNINGS, PRECAUTIONS, *Information for Patients*, and DOSAGE AND ADMINISTRATION).

Localized osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection

with delayed healing, has been reported rarely (see PRECAUTIONS, *Dental*).

Musculoskeletal: bone, joint, and/or muscle pain, occasionally severe, and rarely incapacitating (see PRECAUTIONS, Musculoskeletal Pain); joint swelling; low-energy femoral shaft and subtrochanteric fractures (see PRECAUTIONS, Atypical Subtrochanteric and Diaphyseal Femoral Fractures).

Nervous system: dizziness and vertigo.

Skin: rash (occasionally with photosensitivity), pruritus, alopecia, rarely severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Special Senses: rarely uveitis, scleritis or episcleritis.

OVERDOSAGE

Significant lethality after single oral doses was seen in female rats and mice at 552 mg/kg (3256 mg/m^2) and 966 mg/kg (2898 mg/m^2), respectively. In males, these values were slightly higher, 626 and 1280 mg/kg, respectively. There was no lethality in dogs at oral doses up to 200 mg/kg (4000 mg/m^2).

No specific information is available on the treatment of overdosage with FOSAMAX. Hypocalcemia, hypophosphatemia, and upper gastrointestinal adverse events, such as upset stomach, heartburn, esophagitis, gastritis, or ulcer, may result from oral overdosage. Milk or antacids should be given to bind alendronate. Due to the risk of esophageal irritation, vomiting should not be induced and the patient should remain fully upright.

Dialysis would not be beneficial.

DOSAGE AND ADMINISTRATION

FOSAMAX must be taken at least one-half hour before the first food, beverage, or medication of the day with plain water only (see PRECAUTIONS, *Information for Patients*). Other beverages (including mineral water), food, and some medications are likely to reduce the absorption of FOSAMAX (see PRECAUTIONS, *Drug Interactions*). Waiting less than 30 minutes, or taking FOSAMAX with food, beverages (other than plain water) or other medications will lessen the effect of FOSAMAX by decreasing its absorption into the body.

FOSAMAX should only be taken upon arising for the day. To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation, a FOSAMAX tablet should be swallowed with a full glass of water (6–8 oz). To facilitate gastric emptying FOSAMAX oral solution should be followed by at least 2 oz (a quarter of a cup) of water. Patients should not lie down for at least 30 minutes and until after their first food of the day. FOSAMAX should not be taken at bedtime or before arising for the day. Failure to follow these instructions may increase the risk of esophageal adverse experiences (see WARNINGS, PRECAUTIONS, *Information for Patients*).

Patients should receive supplemental calcium and vitamin D, if dietary intake is inadequate (see PRECAUTIONS, *General*).

No dosage adjustment is necessary for the elderly or for patients with mild-to-moderate renal insufficiency (creatinine clearance 35 to 60 mL/min). FOSAMAX is not recommended for patients with more severe renal

insufficiency (creatinine clearance <35 mL/min) due to lack of experience.

Treatment of osteoporosis in postmenopausal women (see INDICATIONS AND USAGE)

The recommended dosage is:

- one 70 mg tablet once weekly

  or

- one bottle of 70 mg oral solution once weekly

  or

- one 10 mg tablet once daily

Treatment to increase bone mass in men with osteoporosis

The recommended dosage is:

- one 70 mg tablet once weekly

  or

- one bottle of 70 mg oral solution once weekly

  or

- one 10 mg tablet once daily

Prevention of osteoporosis in postmenopausal women (see INDICATIONS AND USAGE)

The recommended dosage is:

- one 35 mg tablet once weekly

  or

- one 5 mg tablet once daily

The safety of treatment and prevention of osteoporosis with FOSAMAX has been studied for up to 7 years.

Treatment of glucocorticoid-induced osteoporosis in men and women

The recommended dosage is one 5 mg tablet once daily, except for postmenopausal women not receiving estrogen, for whom the recommended dosage is one 10 mg tablet once daily.

Paget's disease of bone in men and women

The recommended treatment regimen is 40 mg once a day for six months.

Retreatment of Paget's disease

In clinical studies in which patients were followed every six months, relapses during the 12 months following therapy occurred in 9% (3 out of 32) of patients who responded to treatment with FOSAMAX. Specific retreatment data are not available, although responses to FOSAMAX were similar in patients who had received prior bisphosphonate therapy and those who had not. Retreatment with FOSAMAX may be considered, following a six-month post-treatment evaluation period in patients who have relapsed, based on increases in serum alkaline phosphatase, which should be measured periodically. Retreatment may also be considered in those who failed to normalize their serum alkaline phosphatase.

HOW SUPPLIED

No. 3759 — Tablets FOSAMAX, 5 mg, are white, round, uncoated tablets with an outline of a bone image on one side and code MRK 925 on the other. They are supplied as follows:

NDC 0006-0925-31 unit-of-use bottles of 30

NDC 0006-0925-58 unit-of-use bottles of 100.

No. 3797 — Tablets FOSAMAX, 10 mg, are white, oval, wax-polished tablets with code MRK on one side and 936 on the other. They are supplied as follows:

NDC 0006-0936-31 unit-of-use bottles of 30

NDC 0006-0936-58 unit-of-use bottles of 100

NDC 0006-0936-28 unit dose packages of 100

NDC 0006-0936-82 bottles of 1,000.

No. 3813 — Tablets FOSAMAX, 35 mg, are white, oval, uncoated tablets with code 77 on one side and a bone image on the other. They are supplied as follows:

NDC 0006-0077-44 unit-of-use blister package of 4

NDC 0006-0077-21 unit dose packages of 20.

No. 8457 — Tablets FOSAMAX, 40 mg, are white, triangular-shaped, uncoated tablets with code MSD 212 on one side and FOSAMAX on the other. They are supplied as follows:

NDC 0006-0212-31 unit-of-use bottles of 30.

No. 3814 — Tablets FOSAMAX, 70 mg, are white, oval, uncoated tablets with code 31 on one side and an outline of a bone image on the other. They are supplied as follows:

NDC 0006-0031-44 unit-of-use blister package of 4

NDC 0006-0031-21 unit dose packages of 20.

No. 3833 — Oral Solution FOSAMAX, 70 mg, is a clear, colorless solution with a raspberry flavor and is supplied as follows:

NDC 0006-3833-34 unit-of-use cartons of 4 single-dose bottles containing 75 mL each.

Storage

FOSAMAX Tablets:

Store in a well-closed container at room temperature, 15–30°C (59–86°F).

FOSAMAX Oral Solution:

Store at 25°C (77°F), excursions permitted to 15–30°C (59–86°F). [See USP Controlled Room Temperature.] Do not freeze.

Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

FOSAMAX
(alendronate sodium) Tablets and Oral Solution

Issued January 2011

Printed in USA

[Exhibit 13 to Ecklund Declaration]

FDA **U.S. Food and Drug Administration**

Protecting and Promoting Your Health

Drugs

FDA Drug Safety Communication: Safety update for osteoporosis drugs, bisphosphonates, and atypical fractures

Safety Announcement

[**10-13-2010**] The U.S. Food and Drug Administration (FDA) is updating the public regarding information previously communicated describing the risk of atypical fractures of the thigh, known as subtrochanteric and diaphyseal femur fractures, in patients who take bisphosphonates for osteoporosis. This information will be added to the *Warnings and Precautions* section of the labels of all bisphosphonate drugs approved for the prevention or treatment of osteoporosis.

Bisphosphonates are a class of medicines that can be effective at preventing or slowing the loss of bone mass (osteoporosis) in postmenopausal women, thus reducing the risk of common osteoporotic bone fracture. Osteoporotic fractures can result in pain, hospitalization, and surgery.

Atypical subtrochanteric femur fractures are fractures in the bone just below the hip joint. Diaphyseal femur fractures occur in the long part of the thigh bone. These fractures are very uncommon and appear to account for less than 1% of all hip and

femur fractures overall. Although it is not clear if bisphosphonates are the cause, these unusual femur fractures have been predominantly reported in patients taking bisphosphonates.

The bisphosphonates affected by this notice are only those approved to treat osteoporosis, including Fosamax, Fosamax Plus D, Actonel, Actonel with Calcium, Boniva, Atelvia, and Reclast[1] (and their generic products).

This notice does not affect bisphosphonate drugs that only are used to treat Paget's disease or high blood calcium levels due to cancer (i.e., Didronel, Zometa, Skelid, and their generic products).

Although the optimal duration of bisphosphonate use for osteoporosis is unknown, these atypical fractures may be related to long-term term bisphosphonate use. FDA will require a new Limitations of Use statement in the *Indications and Usage* section of the labels for these drugs. This statement will describe the uncertainty of the optimal duration of use of bisphosphonates for the treatment and/or prevention of osteoporosis.

A Medication Guide will also be required to be given to patients when they pick up their bisphosphonate prescription. This Medication Guide will describe the symptoms of atypical femur fracture and recommend that patients notify their healthcare professional if they develop symptoms.

These actions are part of an ongoing safety review of bisphosphonate use and the occurrence of atypical subtrochanteric and diaphyseal femur fractures, as previously announced in a Drug Safety Communication on March 10, 2010[2].

Additional Information for Patients

If you currently take a bisphosphonate, you should:

- Continue to take your medication unless you are told to stop by your healthcare professional.
- Talk to your healthcare professional if you develop new hip or thigh pain (commonly described as dull or aching pain), or have any concerns with your medications.
- Report any side effects with your bisphosphonate medication to FDA's MedWatch program using the information at the bottom of the page in the "Contact Us" box.

Additional Information for Healthcare Professionals

FDA recommends that healthcare professionals should:

- Be aware of the possible risk of atypical subtrochanteric and diaphyseal femur fractures in patients taking bisphosphonates.
- Continue to follow the recommendations in the drug label when prescribing bisphosphonates.
- Discuss the known benefits and potential risks of using bisphosphonates with patients.
- Evaluate any patient who presents with new thigh or groin pain to rule out a femoral fracture.
- Discontinue potent antiresorptive medications (including bisphosphonates) in patients who have evidence of a femoral shaft fracture.
- Consider periodic reevaluation of the need for continued bisphosphonate therapy, particularly

in patients who have been treated for over 5 years.

- Report any adverse events with the use of bisphosphonates to FDA's MedWatch program using the information at the bottom of the page in the "Contact Us" box.

Any information provided to MedWatch should be as detailed as possible and include information concerning fracture location/configuration, magnitude of trauma, fracture details (complete or incomplete, bilateral, or comminuted), presence and duration of prodromal thigh or groin pain, duration of bisphosphonate use, relevant medical history, and concomitant use of other medications.

Data Summary

FDA has reviewed all available data, including data summarized in the American Society for Bone and Mineral Research (ASBMR) Task Force report regarding bisphosphonates and atypical subtrochanteric and diaphyseal femur fractures[1], released on September 14, 2010. These atypical femur fractures can occur anywhere in the femoral shaft, from just below the lesser trochanter to above the supracondylar flare, and are transverse or short oblique in orientation without evidence of comminution. The fractures can be complete (involving both cortices) or incomplete (involving the lateral cortex only), and may be bilateral. Many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. The exact incidence of atypical femoral fractures is unknown but appears to account for less than one percent of hip and

femoral fractures overall. Therefore, atypical fractures are very uncommon. Although atypical femoral fractures have been predominantly reported in patients taking bisphosphonates, they have also been reported in patients who have not taken bisphosphonates.

The optimal duration of bisphosphonate treatment for osteoporosis is unknown. Bisphosphonate medications approved for the prevention and/or treatment of osteoporosis have clinical trial data supporting fracture reduction efficacy through at least 3 years of treatment and, in some cases, through 5 years. The FDA is continuing its evaluation of data supporting the safety and effectiveness of long term use (greater than 3 to 5 years) of bisphosphonates for the treatment and prevention of osteoporosis and will provide additional guidance at the completion of our review.

In summary, FDA is continuing its ongoing safety review of bisphosphonate use and the occurrence of atypical femur fractures. As of this notice, the FDA is notifying patients and healthcare professionals of new *Warnings and Precautions* information that is being added regarding this risk to the labels of all bisphosphonate products approved for the prevention or treatment of osteoporosis. A new Limitations of Use statement will describe the uncertainty of the optimal duration of use of bisphosphonates for the treatment and/or prevention of osteoporosis. In addition, the FDA will require that a Medication Guide be included with all bisphosphonate medications approved for osteoporosis indications to better inform patients of the risk for atypical femur fracture.

References:

1. Shane E, Burr D, Ebeling PR, et al. Atypical subtrochanteric and diaphyseal femoral fractures: Report of a task force of the American Society for Bone and Mineral Research [published online ahead of print]. *Journal of Bone and Mineral Research*. 2010; http://onlinelibrary.wiley.com/doi/10.1002/jbmr.253/pdf[3]. Accessed September 17, 2010.

Related Information

- Bisphosphonates (marketed as Actonel, Actonel+Ca, Aredia, Boniva, Didronel, Fosamax, Fosamax+D, Reclast, Skelid, and Zometa) Information[4]
- FDA Drug Safety Communication: Ongoing safety review of oral bisphosphonates and atypical subtrochanteric femur fractures[5]
- Possible Fracture Risk With Osteoporosis Drugs[6]
- FDA: Possible increased risk of thigh bone fracture with bisphosphonates[7] [ARCHIVED]
- Risk Evaluation and Mitigation Strategies (REMS) Letters to Sponsor/Applicants Requesting Labeling Changes[8]

Contact FDA

1-800-332-1088
1-800-FDA-0178 Fax
Report a Serious Problem

MedWatch Online[9]

Regular Mail: Use postage-paid FDA Form 3500[10]

Mail to: MedWatch 5600 Fishers Lane

Rockville, MD 20857

Page Last Updated: 10/14/2010

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
Ph. 1-888-INFO-FDA (1-888-463-6332)
Email FDA

[Exhibit 14 to Ecklund Declaration]

MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

9635609
9636809

FOSAMAX ®

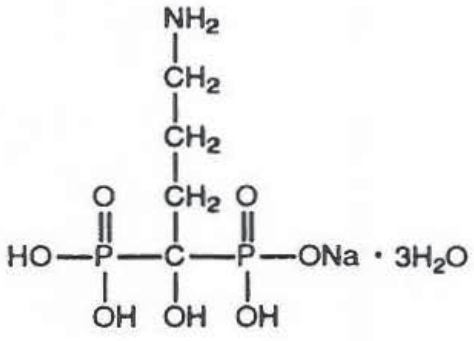
(ALENDRONATE SODIUM) TABLETS AND ORAL SOLUTION

DESCRIPTION

FOSAMAX (alendronate sodium) is a bisphosphonate that acts as a specific inhibitor of osteoclast-mediated bone resorption. Bisphosphonates are synthetic analogs of pyrophosphate that bind to the hydroxyapatite found in bone.

Alendronate sodium is chemically described as (4-amino-1-hydroxybutylidene) bisphosphonic acid monosodium salt trihydrate.

The empirical formula of alendronate sodium is $C_4H_{12}NNaO_7P_2 \cdot 3H2O$ and its formula weight is 325.12. The structural formula is:



Alendronate sodium is a white, crystalline, nonhygroscopic powder. It is soluble in water, very slightly soluble in alcohol, and practically insoluble in chloroform.

Tablets FOSAMAX for oral administration contain 6.53, 13.05, 45.68, 52.21 or 91.37 mg of alendronate monosodium salt trihydrate, which is the molar equivalent of 5, 10, 35, 40 and 70 mg, respectively, of free acid, and the following inactive ingredients: microcrystalline cellulose, anhydrous lactose, croscarmellose sodium, and magnesium stearate. Tablets FOSAMAX 10 mg also contain carnauba wax.

Each bottle of the oral solution contains 91.35 mg of alendronate monosodium salt trihydrate, which is the molar equivalent to 70 mg of free acid. Each bottle also contains the following inactive ingredients: sodium citrate dihydrate and citric acid anhydrous as buffering agents, sodium saccharin, artificial raspberry flavor, and purified water. Added as preservatives are sodium propylparaben 0.0225% and sodium butylparaben 0.0075 %.

CLINICAL PHARMACOLOGY

Mechanism of Action

Animal studies have indicated the following mode of action. At the cellular level, alendronate shows preferential localization to sites of bone resorption, specifically under osteoclasts. The osteoclasts adhere

* * *

- For the prevention of osteoporosis, FOSAMAX may be considered in postmenopausal women who are at risk of developing osteoporosis and for whom the

desired clinical outcome is to maintain bone mass and to reduce the risk of future fracture.

Bone loss is particularly rapid in postmenopausal women younger than age 60. Risk factors often associated with the development of postmenopausal osteoporosis include early menopause; moderately low bone mass (for example, at least 1 standard deviation below the mean for healthy young adult women); thin body build; Caucasian or Asian race; and family history of osteoporosis. The presence of such risk factors may be important when considering the use of FOSAMAX for prevention of osteoporosis.

- Treatment to increase bone mass in men with osteoporosis
- Treatment of glucocorticoid-induced osteoporosis in men and women receiving glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and who have low bone mineral density (see PRECAUTIONS, *Glucocorticoid-induced osteoporosis*). Patients treated with glucocorticoids should receive adequate amounts of calcium and vitamin D.
- Treatment of Paget's disease of bone in men and women
    - Treatment is indicated in patients with Paget's disease of bone having alkaline phosphatase at least two times the upper limit of normal, or those who are

symptomatic, or those at risk for future complications from their disease.

CONTRAINDICATIONS

- Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia
- Inability to stand or sit upright for at least 30 minutes
- Patients at increased risk of aspiration should not receive FOSAMAX oral solution.
- Hypersensitivity to any component of this product
- Hypocalcemia (see PRECAUTIONS, *General*)

WARNINGS

FOSAMAX, like other bisphosphonates, may cause local irritation of the upper gastrointestinal mucosa.

Esophageal adverse experiences, such as esophagitis, esophageal ulcers and esophageal erosions, occasionally with bleeding and rarely followed by esophageal stricture or perforation, have been reported in patients receiving treatment with FOSAMAX. In some cases these have been severe and required hospitalization. Physicians should therefore be alert to any signs or symptoms signaling a possible esophageal reaction and patients should be instructed to discontinue FOSAMAX and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn.

The risk of severe esophageal adverse experiences appears to be greater in patients who lie down after taking FOSAMAX and/or who fail to swallow it with the recommended amount of water, and/or who continue to take FOSAMAX after developing

symptoms suggestive of esophageal irritation. Therefore, it is very important that the full dosing instructions are provided to, and understood by, the patient (see DOSAGE AND ADMINISTRATION). In patients who cannot comply with dosing instructions due to mental disability, therapy with FOSAMAX should be used under appropriate supervision.

Because of possible irritant effects of FOSAMAX on the upper gastrointestinal mucosa and a potential for worsening of the underlying disease, caution should be used when FOSAMAX is given to patients with active upper gastrointestinal problems (such as dysphagia, esophageal diseases, gastritis, duodenitis, or ulcers).

There have been post-marketing reports of gastric and duodenal ulcers, some severe and with complications, although no increased risk was observed in controlled clinical trials.

PRECAUTIONS

General

Causes of osteoporosis other than estrogen deficiency, aging, and glucocorticoid use should be considered.

Hypocalcemia must be corrected before initiating therapy with FOSAMAX (see CONTRAINDICATIONS). Other disorders affecting mineral metabolism (such as vitamin D deficiency) should also be effectively treated. In patients with these conditions, serum calcium and symptoms of hypocalcemia should be monitored during therapy with FOSAMAX.

Presumably due to the effects of FOSAMAX on increasing bone mineral, small, asymptomatic

decreases in serum calcium and phosphate may occur, especially in patients with Paget's disease, in whom the pretreatment rate of bone turnover may be greatly elevated and in patients receiving glucocorticoids, in whom calcium absorption may be decreased.

Ensuring adequate calcium and vitamin D intake is especially important in patients with Paget's disease of bone and in patients receiving glucocorticoids.

Musculoskeletal Pain

In post marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates that are approved for the prevention and treatment of osteoporosis (see ADVERSE REACTIONS). This category of drugs includes FOSAMAX (alendronate). Most of the patients were postmenopausal women. The time to onset of symptoms varied from one day to several months after starting the drug. Discontinue use if severe symptoms develop. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

In placebo-controlled clinical studies of FOSAMAX, the percentages of patients with these symptoms were similar in the FOSAMAX and placebo groups.

Dental

Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, often with delayed healing, has been reported in patients taking bisphosphonates. Most reported cases of bisphosphonate-associated osteonecrosis have been in cancer patients treated with intravenous

bisphosphonates, but some have occurred in patients with postmenopausal osteoporosis. Known risk factors for osteonecrosis include a diagnosis of cancer, concomitant therapies (e.g., chemotherapy, radiotherapy, corticosteroids), poor oral hygiene, and co-morbid disorders (e.g., pre-existing dental disease, anemia, coagulopathy, infection).

Patients who develop osteonecrosis of the jaw (ONJ) while on bisphosphonate therapy should receive care by an oral surgeon. Dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk for ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Renal insufficiency

FOSAMAX is not recommended for patients with renal insufficiency (creatinine clearance <35 mL/min). (See DOSAGE AND ADMINISTRATION.)

Glucocorticoid-induced osteoporosis

The risk versus benefit of FOSAMAX for treatment at daily dosages of glucocorticoids less than 7.5 mg of prednisone or equivalent has not been established (see INDICATIONS AND USAGE). Before initiating treatment, the hormonal status of both men and women should be ascertained and appropriate replacement considered.

A bone mineral density measurement should be made at the initiation of therapy and repeated after 6 to 12 months of combined FOSAMAX and glucocorticoid treatment.

The efficacy of FOSAMAX for the treatment of glucocorticoid-induced osteoporosis has been shown in patients with a median bone mineral density which was 1.2 standard deviations below the mean for healthy young adults.

The efficacy of FOSAMAX has been established in studies of two years' duration. The greatest increase in bone mineral density occurred in the first year with maintenance or smaller gains during the second year. Efficacy of FOSAMAX beyond two years has not been studied.

The efficacy of FOSAMAX in respect to fracture prevention has been demonstrated for vertebral fractures. However, this finding was based on very few fractures that occurred primarily in postmenopausal women. The efficacy for prevention of non-vertebral fractures has not been demonstrated.

Information for Patients

General

Physicians should instruct their patients to read the patient package insert before starting therapy with FOSAMAX and to reread it each time the prescription is renewed.

Patients should be instructed to take supplemental calcium and vitamin D, if daily dietary intake is inadequate. Weight-bearing exercise should be considered along with the modification of certain behavioral factors, such as cigarette smoking and/or excessive alcohol consumption, if these factors exist.

Dosing Instructions

Patients should be instructed that the expected benefits of FOSAMAX may only be obtained when it is

taken with plain water the first thing upon arising for the day at least 30 minutes before the first food, beverage, or medication of the day. Even dosing with orange juice or coffee has been shown to markedly reduce the absorption of FOSAMAX (see CLINICAL PHARMACOLOGY, *Pharmacokinetics, Absorption*).

To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation patients should be instructed to swallow each tablet of FOSAMAX with a full glass of water (6–8 oz). To facilitate gastric emptying patients should drink at least 2 oz (a quarter of a cup) of water after taking FOSAMAX oral solution. Patients should be instructed not to lie down for at least 30 minutes and until after their first food of the day. Patients should not chew or suck on the tablet because of a potential for oropharyngeal ulceration. Patients should be specifically instructed not to take FOSAMAX at bedtime or before arising for the day. Patients should be informed that failure to follow these instructions may increase their risk of esophageal problems. Patients should be instructed that if they develop symptoms of esophageal disease (such as difficulty or pain upon swallowing, retrosternal pain or new or worsening heartburn) they should stop taking FOSAMAX and consult their physician.

Patients should be instructed that if they miss a dose of once weekly FOSAMAX, they should take one dose on the morning after they remember. They should not take two doses on the same day but should return to taking one dose once a week, as originally scheduled on their chosen day.

Drug Interactions (also see CLINICAL PHARMACOLOGY, *Pharmacokinetics, Drug Interactions)*

Estrogen/hormone replacement therapy (HRT)

Concomitant use of HRT (estrogen ± progestin) and FOSAMAX was assessed in two clinical studies of one or two years' duration in postmenopausal osteoporotic women. In these studies, the safety and tolerability profile of the combination was consistent with those of the individual treatments; however, the degree of suppression of bone turnover (as assessed by mineralizing surface) was significantly greater with the combination than with either component alone. The long-term effects of combined FOSAMAX and HRT on fracture occurrence have not been studied (see CLINICAL PHARMACOLOGY, *Clinical Studies, Concomitant use with estrogen/hormone replacement therapy (HRT)* and ADVERSE REACTIONS, *Clinical Studies, Concomitant use with estrogen/hormone replacement therapy*).

Calcium Supplements/Antacids

It is likely that calcium supplements, antacids, and some oral medications will interfere with absorption of FOSAMAX. Therefore, patients must wait at least one-half hour after taking FOSAMAX before taking any other oral medications.

Aspirin

In clinical studies, the incidence of upper gastrointestinal adverse events was increased in patients receiving concomitant therapy with daily doses of FOSAMAX greater than 10 mg and aspirin-containing products.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

FOSAMAX may be administered to patients taking NSAIDs. In a 3-year, controlled, clinical study (n=2027) during which a majority of patients received concomitant NSAIDs, the incidence of upper gastrointestinal adverse events was similar in patients taking FOSAMAX 5 or 10mg/day compared to those taking placebo. However, since NSAID use is associated with gastrointestinal irritation, caution should be used during concomitant use with FOSAMAX.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Harderian gland (a retro-orbital gland not present in humans) adenomas were increased in high-dose female mice (p=0.003) in a 92-week oral carcinogenicity study at doses of alendronate of 1, 3, and 10 mg/kg/day (males) or 1, 2, and 5 mg/kg/day (females). These doses are equivalent to 0.12 to 1.2 times a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/m^2 The relevance of this finding to humans is unknown.

Parafollicular cell (thyroid) adenomas were increased in high-dose male rats (p=0.003) in a 2-year oral carcinogenicity study at doses of 1 and 3.75 mg/kg body weight. These doses are equivalent to 0.26 and 1 times a 40 mg human daily dose based on surface area, mg/m^2. The relevance of this finding to humans is unknown.

Alendronate was not genotoxic in the *in vitro* microbial mutagenesis assay with and without metabolic activation, in an *in vitro* mammalian cell mutagenesis assay, in an *in vitro* alkaline elution assay in rat hepatocytes, and in an *in vivo*

chromosomal aberration assay in mice. In an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, however, alendronate gave equivocal results.

Alendronate had no effect on fertility (male or female) in rats at oral doses up to 5 mg/kg/day (13 times a 40 mg human daily dose based on surface area, mg/m^2).

Pregnancy

Pregnancy Category C:

Reproduction studies in rats showed decreased postimplantation survival at 2 mg/kg/day and decreased body weight gain in normal pups at 1 mg/kg/day. Sites of incomplete fetal ossification were statistically significantly increased in rats beginning at 10 mg/kg/day in vertebral (cervical, thoracic, and lumbar), skull, and sternebral bones. The above doses ranged from 0.26 times (1 mg/kg) to 2.6 times (10 mg/kg) a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/m^2. No similar fetal effects were seen when pregnant rabbits were treated at doses up to 35 mg/kg/day (10.3 times a 40 mg human daily dose based on surface area, mg/m^2).

Both total and ionized calcium decreased in pregnant rats at 15 mg/kg/day (3.9 times a 40 mg human daily dose based on surface area, mg/m^2) resulting in delays and failures of delivery. Protracted parturition due to maternal hypocalcemia occurred in rats at doses as low as 0.5 mg/kg/day (0.13 times a 40 mg human daily dose based on surface area, mg/m^2) when rats were treated from before mating through gestation. Maternotoxicity (late pregnancy deaths) occurred in the female rats treated with 15 mg/kg/day

for varying periods of time ranging from treatment only during pre-mating to treatment only during early, middle, or late gestation; these deaths were lessened but not eliminated by cessation of treatment. Calcium supplementation either in the drinking water or by minipump could not ameliorate the hypocalcemia or prevent maternal and neonatal deaths due to delays in delivery; calcium supplementation IV prevented maternal, but not fetal deaths.

Bisphosphonates are incorporated into the bone matrix, from which they are gradually released over a period of years. The amount of bisphosphonate incorporated into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the dose and duration of bisphosphonate use. There are no data on fetal risk in humans. However, there is a theoretical risk of fetal harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on the risk has not been studied.

There are no studies in pregnant women. FOSAMAX should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

Nursing Mothers

It is not known whether alendronate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FOSAMAX is administered to nursing women.

Pediatric Use

The efficacy and safety of FOSAMAX were examined in a randomized, double-blind, placebo-controlled two-year study of 139 pediatric patients, aged 4–18 years, with severe osteogenesis imperfect. One-hundred-and-nine patients were randomized to 5 mg FOSAMAX daily (weight <40 kg) or 10 mg FOSAMAX daily (weight ≥40 kg) and 30 patients to placebo. The mean baseline lumbar spine BMD Z-score of the patients was -4.5. The mean change in lumbar spine BMD Z-score from baseline to Month 24 was 1.3 in the FOSAMAX-treated patients and 0.1 in the placebo-treated patients. Treatment with FOSAMAX did not reduce the risk of fracture. Sixteen percent of the FOSAMAX patients who sustained a radiologically-confirmed fracture by Month 12 of the study had delayed fracture healing (callus remodeling) or fracture non-union when assessed radiographically at Month 24 compared with 9% of the placebo-treated patients. In FOSAMAX-treated patients, bone histomorphometry data obtained at Month 24 demonstrated decreased bone turnover and delayed mineralization time; however, there were no mineralization defects. There were no statistically significant differences between the FOSAMAX and placebo groups in reduction of bone pain.

FOSAMAX is not indicated for use in children.

(For clinical adverse experiences in children, see ADVERSE REACTIONS, *Clinical Studies*, *Osteogenesis Imperfecta*.)

Geriatric Use

Of the patients receiving FOSAMAX in the Fracture Intervention Trial (FIT), 71% (n=2302) were ≥65 years

of age and 17% (n=550) were ≥75 years of age. Of the patients receiving FOSAMAX in the United States and Multinational osteoporosis treatment studies in women, osteoporosis studies in men, glucocorticoid-induced osteoporosis studies, and Paget's disease studies (see CLINICAL PHARMACOLOGY, *Clinical Studies*), 45%, 54%, 37%, and 70%, respectively, were 65 years of age or over. No overall differences in efficacy or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Clinical Studies

In clinical studies of up to five years in duration adverse experiences associated with FOSAMAX usually were mild, and generally did not require discontinuation of therapy.

FOSAMAX has been evaluated for safety in approximately 8000 postmenopausal women in clinical studies.

Treatment of osteoporosis

Postmenopausal women

In two identically designed, three-year, placebo-controlled, double-blind, multicenter studies (United States and Multinational; n=994), discontinuation of therapy due to any clinical adverse experience occurred in 4.1% of 196 patients treated with FOSAMAX 10 mg/day and 6.0% of 397 patients treated with placebo. In the Fracture Intervention Trial (n=6459), discontinuation of therapy due to any clinical adverse experience occurred in 9.1% of 3236 patients treated with FOSAMAX 5 mg/day for 2 years

and 10 mg/day for either one or two additional years and 10.1% of 3223 patients treated with placebo. Discontinuations due to upper gastrointestinal adverse experiences were: FOSAMAX, 3.2%; placebo, 2.7%. In these study populations, 49–54% had a history of gastrointestinal disorders at baseline and 54–89% used nonsteroidal anti-inflammatory drugs or aspirin at some time during the studies. Adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in $\geq$1% of patients treated with either FOSAMAX or placebo are presented in the following table.

* * *

Osteoporosis Prevention Studies in Postmenopausal Women Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥ 1% of Patients

	Two/Three-Year Studies		One-Year Study	
	FOSAMAX 5 mg/day % (n=642)	Placebo % (n=648)	FOSAMAX 5 mg/day % (n=361)	Once Weekly FOSAMAX 35 mg % (n=362)
Gastrointestinal				
dyspepsia	1.9	1.4	2.2	1.7
abdominal pain	1.7	3.4	4.2	2.2
acid regurgitation	1.4	2.5	4.2	4.7
nausea	1.4	1.4	2.5	1.4
diarrhea	1.1	1.7	1.1	0.6
constipation	0.9	0.5	1.7	0.3
abdominal distention	0.2	0.3	1.4	1.1
Musculoskeletal				
musculoskeletal (bone, muscle or joint) pain	0.8	0.9	1.9	2.2

Concomitant use with estrogen/hormone replacement therapy

In two studies (of one and two years' duration) of postmenopausal osteoporotic women (total: n=853), the safety and tolerability profile of combined treatment with FOSAMAX 10 mg once daily and estrogen ± progestin (n=354) was consistent with those of the individual treatments.

Treatment of glucocorticoid-induced osteoporosis

In two, one-year, placebo-controlled, double-blind, multicenter studies in patients receiving glucocorticoid treatment, the overall safety and tolerability profiles of FOSAMAX 5 and 10 mg/day were generally similar to that of placebo. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either FOSAMAX 5 or 10 mg/day or placebo are presented in the following table.

One-Year Studies in Glucocorticoid-Treated Patients Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥ 1% of Patients			
	FOSAMAX 10 mg/day % (n=157)	FOSAMAX 5 mg/day % (n=161)	Placebo % (n=159)
Gastrointestinal			
abdominal pain	3.2	1.9	0.0
acid regurgitation	2.5	1.9	1.3
constipation	1.3	0.6	0.0
melena	1.3	0.0	0.0
nausea	0.6	1.2	0.6
diarrhea	0.0	0.0	1.3
Nervous System / Psychiatric			
headache	0.6	0.0	1.3

The overall safety and tolerability profile in the glucocorticoid-induced osteoporosis population that continued therapy for the second year of the studies (FOSAMAX: n=147) was consistent with that observed in the first year.

Paget's disease of bone

In clinical studies (osteoporosis and Paget's disease), adverse experiences reported in 175 patients taking FOSAMAX 40 mg/day for 3–12 months were similar to those in postmenopausal women treated with FOSAMAX 10 mg/day. However, there was an apparent increased incidence of upper gastrointestinal adverse experiences in patients taking FOSAMAX 40 mg/day (17.7% FOSAMAX vs. 10.2% placebo). One case of esophagitis and two cases of gastritis resulted in discontinuation of treatment.

Additionally, musculoskeletal (bone, muscle or joint) pain, which has been described in patients with Paget's disease treated with other bisphosphonates, was considered by the investigators as possibly, probably, or definitely drug related in approximately 1% of patients treated with FOSAMAX 40 mg/day versus approximately 1% of patients treated with placebo, but rarely resulted in discontinuation of therapy. Discontinuation of therapy due to any clinical adverse experience occurred in 6.4% of patients with Paget's disease treated with FOSAMAX 40 mg/day and 2.4% of patients treated with placebo.

Osteogenesis Imperfecta

FOSAMAX is not indicated for use in children.

The overall safety profile of FOSAMAX in OI patients treated for up to 24 months was generally similar to that of adults with osteoporosis treated with FOSAMAX. However, there was an increased occurrence of vomiting in OI patients treated with FOSAMAX compared to placebo. During the 24-month treatment period, vomiting was observed in 32 of 109 (29.4%) patients treated with FOSAMAX and 3 of 30 (10%) patients treated with placebo.

In a pharmacokinetic study, 6 of 24 pediatric OI patients who received a single oral dose of FOSAMAX 35 or 70 mg developed fever, flu-like symptoms, and/or mild lymphocytopenia within 24 to 48 hours after administration. These events, lasting no more than 2 to 3 days and responding to acetaminophen, are consistent with an acute-phase response that has been reported in patients receiving bisphosphonates, including FOSAMAX. See

ADVERSE REACTIONS, *Post-Marketing Experience*, *Body as a Whole*.

Laboratory Test Findings

In double-blind, multicenter, controlled studies, asymptomatic, mild, and transient decreases in serum calcium and phosphate were observed in approximately 18% and 10%, respectively, of patients taking FOSAMAX versus approximately 12% and 3% of those taking placebo. However, the incidences of decreases in serum calcium to <8.0 mg/dL (2.0 mM) and serum phosphate to ≤2.0 mg/dL (0.65 mM) were similar in both treatment groups.

Post-Marketing Experience

The following adverse reactions have been reported in post-marketing use:

Body as a Whole: hypersensitivity reactions including urticaria and rarely angioedema. Transient symptoms of myalgia, malaise, asthenia and rarely, fever have been reported with FOSAMAX, typically in association with initiation of treatment. Rarely, symptomatic hypocalcemia has occurred, generally in association with predisposing conditions. Rarely, peripheral edema.

Gastrointestinal: esophagitis, esophageal erosions, esophageal ulcers, rarely esophageal stricture or perforation, and oropharyngeal ulceration. Gastric or duodenal ulcers, some severe and with complications have also been reported (see WARNINGS, PRECAUTIONS, *Information for Patients*, and DOSAGE AND ADMINISTRATION).

Localized osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection,

often with delayed healing, has been reported rarely (see PRECAUTIONS, *Dental*).

Musculoskeletal: bone, joint, and/or muscle pain, occasionally severe, and rarely incapacitating (see PRECAUTIONS, *Musculoskeletal Pain*), joint swelling; low-energy femoral shaft and subtrochanteric fractures.

Nervous system: dizziness and vertigo.

Skin: rash (occasionally with photosensitivity), pruritus, alopecia, rarely severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Special Senses: rarely uveitis, scleritis or episcleritis.

OVERDOSAGE

Significant lethality after single oral doses was seen in female rats and mice at 552 mg/kg (3256 mg/m^2) and 966 mg/kg (2898 mg/m^2), respectively. In males, these values were slightly higher, 626 and 1280 mg/kg, respectively. There was no lethality in dogs at oral doses up to 200 mg/kg (4000 mg/m^2).

No specific information is available on the treatment of overdosage with FOSAMAX. Hypocalcemia, hypophosphatemia, and upper gastrointestinal adverse events, such as upset stomach, heartburn, esophagitis, gastritis, or ulcer, may result from oral overdosage. Milk or antacids should be given to bind alendronate. Due to the risk of esophageal irritation, vomiting should not be induced and the patient should remain fully upright.

Dialysis would not be beneficial.

DOSAGE AND ADMINISTRATION

FOSAMAX must be taken *at least* one-half hour before the first food, beverage, or medication of the day with plain water only (see PRECAUTIONS, *Information for Patients*). Other beverages (including mineral water), food, and some medications are likely to reduce the absorption of FOSAMAX (see PRECAUTIONS, *Drug Interactions*). Waiting less than 30 minutes, or taking FOSAMAX with food, beverages (other than plain water) or other medications will lessen the effect of FOSAMAX by decreasing its absorption into the body.

FOSAMAX should only be taken upon arising for the day. To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation, a FOSAMAX tablet should be swallowed with a full glass of water (6–8 oz). To facilitate gastric emptying FOSAMAX oral solution should be followed by at least 2 oz (a quarter of a cup) of water. Patients should not lie down for at least 30 minutes and until after their first food of the day. FOSAMAX should not be taken at bedtime or before arising for the day. Failure to follow these instructions may increase the risk of esophageal adverse experiences (see WARNINGS, PRECAUTIONS, *Information for Patients*).

Patients should receive supplemental calcium and vitamin D, if dietary intake is inadequate (see PRECAUTIONS, *General*).

No dosage adjustment is necessary for the elderly or for patients with mild-to-moderate renal insufficiency (creatinine clearance 35 to 60 mL/min). FOSAMAX is not recommended for patients with more severe renal

insufficiency (creatinine clearance <35 mL/min) due to lack of experience.

Treatment of osteoporosis in postmenopausal women (see INDICATIONS AND USAGE)

The recommended dosage is:

- one 70 mg tablet once weekly

  or

- one bottle of 70 mg oral solution once weekly

  or

- one 10 mg tablet once daily

Treatment to increase bone mass in men with osteoporosis

The recommended dosage is:

- one 70 mg tablet once weekly

  or

- one bottle of 70 mg oral solution once weekly

  or

- one 10 mg tablet once daily

Prevention of osteoporosis in postmenopausal women (see INDICATIONS AND USAGE)

The recommended dosage is:

- one 35 mg tablet once weekly

  or

- one 5 mg tablet once daily

The safely of treatment and prevention of osteoporosis with FOSAMAX has been studied for up to 7 years.

Treatment of glucocorticoid-induced osteoporosis in men and women

The recommended dosage is one 5 mg tablet once daily, except for postmenopausal women not receiving estrogen, for whom the recommended dosage is one 10 mg tablet once daily.

Paget's disease of bone in men and women

The recommended treatment regimen is 40 mg once a day for six months.

Retreatment of Paget's disease

In clinical studies in which patients were followed every six months, relapses during the 12 months following therapy occurred in 9% (3 out of 32) of patients who responded to treatment with FOSAMAX. Specific retreatment data are not available, although responses to FOSAMAX were similar in patients who had received prior bisphosphonate therapy and those who had not. Retreatment with FOSAMAX may be considered, following a six-month post-treatment evaluation period in patients who have relapsed, based on increases in serum alkaline phosphatase, which should be measured periodically. Retreatment may also be considered in those who failed to normalize their serum alkaline phosphatase.

HOW SUPPLIED

No. 3759 — Tablets FOSAMAX, 5 mg, are white, round, uncoated tablets with an outline of a bone image on one side and code MRK 925 on the other. They are supplied as follows:

NDC 0006-0925-31 unit-of-use bottles of 30

NDC 0006-0925-58 unit-of-use bottles of 100.

No. 3797 — Tablets FOSAMAX, 10 mg, are white, oval, wax-polished tablets with code MRK on one side and 936 on the other. They are supplied as follows:

NDC 0006-0936-31 unit-of-use bottles of 30

NDC 0006-0936-58 unit-of-use bottles of 100

NDC 0006-0936-28 unit dose packages of 100

NDC 0006-0936-82 bottles of 1,000.

No. 3813 — Tablets FOSAMAX, 35 mg, are white, oval, uncoated tablets with code 77 on one side and a bone image on the other. They are supplied as follows:

NDC 0006-0077-44 unit-of-use blister package of 4

NDC 0006-0077-21 unit dose packages of 20.

No. 8457 — Tablets FOSAMAX, 40 mg, are white, triangular-shaped, uncoated tablets with code MSD 212 on one side and FOSAMAX on the other. They are supplied as follows:

NDC 0006-0212-31 unit-of-use bottles of 30.

No. 3814 — Tablets FOSAMAX, 70 mg, are white, oval, uncoated tablets with code 31 on one side and an outline of a bone image on the other. They are supplied as follows:

NDC 0006-0031-44 unit-of-use blister package of 4

NDC 0006-0031-21 unit dose packages of 20.

No. 3833 — Oral Solution FOSAMAX, 70 mg, is a clear, colorless solution with a raspberry flavor and is supplied as follows:

NDC 0006-3833-34 unit-of-use cartons of 4 single-dose bottles containing 75 mL each.

Storage

FOSAMAX Tablets:

Store in a well-closed container at room temperature, 15–30°C (59–86°F).

FOSAMAX Oral Solution:

Store at 25°C (77°F), excursions permitted to 15–30°C (59–86°F). [See USP Controlled Room Temperature.] Do not freeze.

MERCK & CO., INC.

Whitehouse Station, NJ 08889, USA

Issued June 2009
Printed in USA

[Exhibit 15 to Ecklund Declaration]

* * *

response for the team review by July 7th. Please let me know if you have any concerns regarding the timeline.

Jim

———

From: Marchick, Julie
[mailto:Julie.Marchick @fda.hhs.gov]
Sent: Friday, June 13, 2008 12:24 PM
To: Adams, James H (WRG)
Subject: Fosamax Information Request - Atypical Fractures

Jim,

We are aware of reports regarding the occurrence of subtrochanteric hip fractures in patients using bisphosphonates (1–5). The subtrochanteric type of hip or femoral fracture is reportedly rare in patients with osteoporosis not on bisphosphonates. We are concerned about this developing safety signal. Please submit any investigations that you have conducted regarding the occurrence of atypical fractures with bisphosphonate use as well as any investigational plans. Please submit all hip and femoral fracture case reports you have received. Where possible, efforts should be made to clarify the fracture location and the duration of bisphosphonate exposure for all case reports.

We request a written response by Friday, July 11, 2008.

Please contact me if you have any questions.

Thanks,

Julie

Julie Marchick
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
301 -796-1280 (phone)
301 -796-9712 (fax)
julie.marchick@fda.hhs.gov

References:

1) Neviaser AS, et. al. Low-energy femoral shaft fractures associated with alendronate use. J Orthop Trauma. 2008; 22:346–350.

2) Goh SK, et. al. Subtrochanteric insufficiency fractures in patients on alendronate therapy: A caution. J Bone Joint Surg Br. 2007; 89:349–353.

3) Odvina CV, et. al. Severely suppressed bone turnover: a potential complication of alendronate therapy. J Clin Endocrinol Metab 2005; 90: 1294–1301.

4) Lee P. van der Wall H, Seibel MJ. Looking beyond low bone mineral density: Multiple insufficiency fractures in a woman with post-menopausal osteoporosis on alendronate therapy. J Endocrinol Invest 2007; 30:590–597.

5) Visekruna M, Wilson D, McKiernan FE. Severely suppressed bone turnover and atypical skeletal

fragility. J Clin Endocrinol Metab. 2008 epublished ahead of print 6/3/2008.

[Exhibit 21 to Ecklund Declaration]

PERSPECTIVE **JBMR**

Atypical Subtrochanteric and Diaphyseal Femoral Fractures: Report of a Task Force of the American Society for Bone and Mineral Research

Elizabeth Shane,* David Burr,* Peter R Ebeling, Bo Abrahamsen, Robert A Adler, Thomas D Brown, Angela M Cheung, Felicia Cosman, Jeffrey R Curtis, Richard Dell, David Dempster, Thomas A Einhorn, Harry K Genant, Piet Geusens, Klaus Klaushofer, Kenneth Koval, Joseph M Lane, Fergus McKiernan, Ross McKinney, Alvin Ng, Jeri Nieves, Regis O'Keefe, Socrates Papapoulos, Howe Tet Sen, Marjolein CH van der Meulen, Robert S Weinstein, and Michael Whyte

Author affiliations appear on pp. 2288–2289

ABSTRACT

Reports linking long-term use of bisphosphonates (BPs) with atypical fractures of the femur led the leadership of the American Society for Bone and Mineral Research (ASBMR) to appoint a task force to address key questions related to this problem. A multidisciplinary expert group reviewed pertinent published reports concerning atypical femur fractures, as well as preclinical studies that could provide insight into their pathogenesis. A case definition was developed so that subsequent studies report on the same condition. The task force defined major and minor features of complete and incomplete atypical femoral fractures and recommends that all major

features, including their location in the subtrochanteric region and femoral shaft, transverse or short oblique orientation, minimal or no associated trauma, a medial spike when the fracture is complete, and absence of comminution, be present to designate a femoral fracture as atypical. Minor features include their association with cortical thickening, a periosteal reaction of the lateral cortex, prodromal pain, bilaterality, delayed healing, comorbid conditions, and concomitant drug exposures, including BPs, other antiresorptive agents, glucocorticoids, and proton pump inhibitors. Preclinical data evaluating the effects of BPs on collagen cross-linking and maturation, accumulation of microdamage and advanced glycation end products, mineralization, remodeling, vascularity, and angiogenesis lend biologic plausibility to a potential association with long-term BP use. Based on published and unpublished data and the widespread use of BPs, the incidence of atypical femoral fractures associated with BP therapy for osteoporosis appears to be very low, particularly compared with the number of vertebral, hip, and other fractures that are prevented by BPs. Moreover, a causal association between BPs and atypical fractures has not been established. However, recent observations suggest that the risk rises with increasing duration of exposure, and there is concern that lack of awareness and underreporting may mask the true incidence of the problem. Given the relative rarity of atypical femoral fractures, the task force recommends that specific diagnostic and procedural codes be created and that an international registry be established to facilitate studies of the clinical and genetic risk factors and optimal surgical and medical

management of these fractures. Physicians and patients should be made aware of the possibility of atypical femoral fractures and of the potential for bilaterality through a change in labeling of BPs. Research directions should include development of animal models, increased surveillance, and additional epidemiologic and clinical data to establish the true incidence of and risk factors for this condition and to inform orthopedic and medical management.

KEY WORDS: OSTEOPOROSIS; BONE; PAIN; FRACTURE; ATYPICAL; SUBTROCHANTERIC; FEMORAL DIAPHYSIS; BISPHOSPHONATES

Received in original form July 19, 2010; revised form August 23, 2010; accepted September 7, 2010. Published online September 14, 2010.

Address correspondence to: Elizabeth Shane, MD, Columbia University, College of Physicians and Surgeons, PH 8 West 864, 630 West 168th Street, New York, NY 10032, USA. E-mail: es54@columbia.edu; David Burr, PhD, Indiana University School of Medicine, Department of Anatomy and Cell Biology, MS 5035, 635 Barnhill Drive, Indianapolis, IN 46202, USA. E-mail: dburr@iupui.edu

*Co-Chairs.

How to cite this paper:

Shane E, Burr D, Ebeling PR, et al. Atypical subtrochanteric and diaphyseal femoral fractures: Report of a task force of the American Society for

Bone and Mineral Research. J Bone Miner Res. 2010;25:2267–2294. DOI: 10.1002/jbmr.253

Journal of Bone and Mineral Research, Vol. 25, No. 11, November 2010, pp 2267–2294

DOI: 10.1002/jbmr.253

Introduction

Reports of atypical femoral fractures, predominantly in patients receiving long-term bisphosphonates (BPs), led the leadership of the American Society for Bone and Mineral Research (ASBMR) to appoint a task force to address a number of key questions related to this disorder. Specifically, the task force was asked to

1. Make a recommendation for a provisional case definition of atypical femoral fractures so that subsequent studies report on the same condition.
2. Review carefully the currently available information in order to assess what is actually known and what is not known about atypical femoral fractures and their potential relationship with BP usage.
3. Recommend the development of noninvasive diagnostic and imaging techniques with which to better characterize and diagnose the disorder.
4. Identify the key questions that the scientific community should address and recommend a research agenda to elucidate incidence, pathophysiology, and etiology of atypical femoral

fractures and their potential relationship with BP usage.

5. Recommend clinical orthopedic and medical management of atypical femoral fractures based on available information.

This report summarizes the findings and recommendations of the task force.

Methods

The expert committee

The expert committee consisted of an international multidisciplinary group of 28 individuals with expertise in clinical and basic bone biology, endocrinology, epidemiology, radiology, biomechanics, and orthopedic surgery. The expert committee also included a basic scientist (TDB) working in the bone field but not in the areas of osteoporosis and BPs and a physician and bioethicist (RM) with expertise in conflict issues affecting biomedical researchers.

Review of the literature/data acquisition

A literature search using PubMed and OVID sought English-language articles with full text abstracts during the period January 1990 to April 30, 2010. The search terms specified included *atypical fracture, subtrochanteric fracture, femoral fracture, diaphyseal fracture, shaft fracture, cortical fracture, bilateral fracture, transverse fracture, low-energy fracture, spontaneous fracture, insufficiency fracture, stress fracture, bisphosphonates, antiresorptive, bone turnover, alendronate, pamidronate, etidronate, ibandronate, risedronate, zoledronate, zoledronic acid, Didronel, Actonel, Fosamax, Reclast,* and *Boniva*. The abstracts retrieved were reviewed by one coauthor

(PRE) to assess their relevance to atypical fractures or long-term complications of BPs, and full text articles of each abstract selected were reviewed subsequently by four members of the ASBMR task force in order to construct the relevant sections of this article. The numbers of subjects in each study; the age and sex of subjects; the specific BP(s) used (if any); the dose and duration of BP exposure; the clinical presentation; a prodrome of pain; the characteristics of the reported fracture(s); the level of trauma; the presence of either bilateral fractures or bilateral radiologic changes and comorbid conditions such as rheumatoid arthritis (RA) and diabetes (DM); the concomitant use of other antiresorptive drugs, glucocorticoids (GCs), or proton pump inhibitors (PPIs); the presence of vitamin D deficiency (<20 ng/ mL); the presence of a bone mineral density (BMD) *T*-score greater than –2.5 (osteopenia or normal BMD); information on bone histology; management and outcome; and any other information were included, when available. Identification of case duplication between studies was achieved by cross-referencing studies whenever possible. The anatomic regions and locations of hip fractures are illustrated in Fig. 1.

Results and Discussion

Make a recommendation for a provisional case definition of atypical femoral fractures so that subsequent studies report on the same condition

Atypical femoral fractures are observed most commonly in the proximal one-third of the femoral shaft but may occur anywhere along the femoral diaphysis from just distal to the lesser trochanter to proximal to the supracondylar flare of the distal

femoral metaphysis. The fracture usually occurs as a result of no or minimal trauma, equivalent to a fall from a standing height or less. The fracture may be complete, extending across the entire femoral shaft, often with the formation of a medial spike (Fig. 2*A*). Complete atypical femoral fractures generally are transverse, although they may have a short oblique configuration, and are not comminuted. Alternatively, the fracture may be incomplete, manifested by a transverse radiolucent line in the lateral cortex. Both complete and incomplete fractures are commonly associated with a periosteal stress reaction and thickening of the lateral cortex at the fracture site (Fig. 2*B*), abnormalities indicative of a stress fracture. In addition, there may be generalized bilateral thickening of both the medial and lateral cortices. Either complete or incomplete atypical fractures may be bilateral. Healing of the fractures may be delayed. There are often prodromal symptoms such as a pain in the groin or thigh. Atypical fractures may be associated with a variety of comorbid conditions and the use of pharmaceutical agents. The diagnosis of atypical femoral fractures should specifically exclude fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, pathologic fractures associated with local primary or metastatic bone tumors, and periprosthetic fractures.

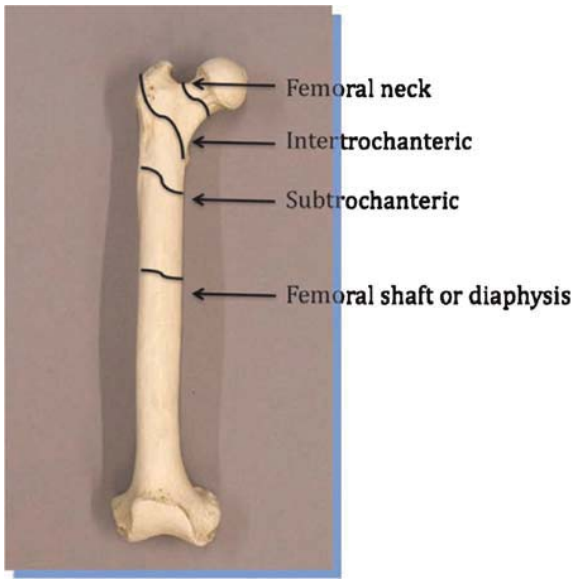


Fig. 1. Locations of common hip and femur fractures. (*Courtesy of Thomas Einhorn, MD.*)

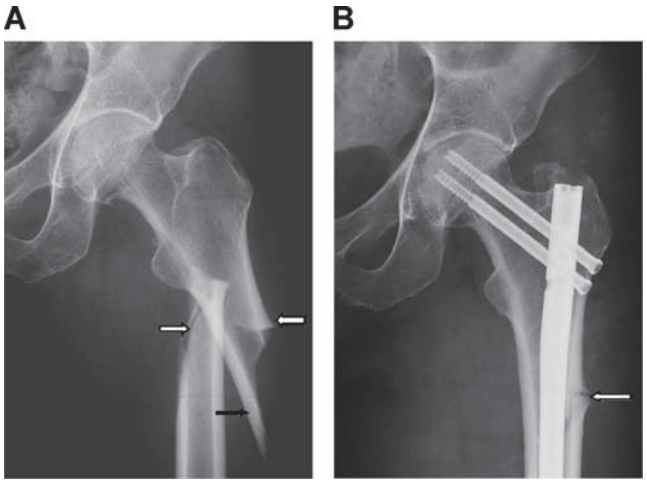


Fig. 2. Anteroposterior (AP) radiographs showing an atypical femoral shaft fracture (*A*) pre- and (*B*) postoperatively from the same individual. Note the oblique and transverse components (*white arrows*) and a medial "spike" (*black arrow*) on the preoperative

view and the lateral, transverse, lucent fracture line and associated focal cortical thickening with a "beaked" appearance (*arrow*) on the postoperative view. (*Courtesy of Thomas Einhorn, MD*.)

To assist in case finding and reporting, the task force defined major and minor features for complete and incomplete atypical fractures of the femur (Table 1). All major features should be present in order to designate a fracture as atypical and distinguish it from more common hip fractures (ie, femoral neck, intertrochanteric). Minor features commonly have been described in association with atypical fractures but may or may not be present in individual patients. Although atypical femoral fractures have been reported most prominently in individuals who have been treated with BPs, such fractures have been reported in individuals with no history of BP exposure. Therefore, to facilitate studies comparing the frequency of atypical femoral fractures in patients with and without BP therapy, association with BP therapy was included as a minor feature.

Review carefully the currently available information in order to assess what is actually known and what is not known about atypical femoral fractures and their potential relationship with BP usage

The task force recognized that the incidence of atypical femoral fractures has come to medical attention principally in the setting of BP use and that the incidence in the general population not exposed to BPs is unknown. Although the association between BP use and atypical femoral fractures is consistent

with a role for BPs, they have not been proven to be causal. To address this charge, the task force considered both preclinical and epidemiologic data, reviewed all case reports and series of atypical femoral fractures, and conducted interviews with physician and scientist representatives of pharmaceutical companies that market drugs for osteoporosis and the US Food and Drug Administration (USFDA).

Table 1. Atypical Femoral Fracture: Major and Minor Features[a]

Major features[b]

- Located anywhere along the femur from just distal to the lesser trochanter to just proximal to the supracondylar flare
- Associated with no trauma or minimal trauma, as in a fall from a standing height or less
- Transverse or short oblique configuration
- Noncomminuted
- Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex.

Minor features

- Localized periosteal reaction of the lateral cortex[c]
- Generalized increase in cortical thickness of the diaphysis
- Prodromal symptoms such as dull or aching pain in the groin or thigh
- Bilateral fractures and symptoms
- Delayed healing

- Comorbid conditions (eg, vitamin D deficiency, RA, hypophosphatasia)
- Use of pharmaceutical agents (eg, BPs, GCs, PPIs)

[a]Specifically excluded are fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, pathologic fractures associated with primary or metastatic bone tumors, and periprosthetic fractures.

[b]All major features are required to satisfy the case definition of atypical femoral fracture. None of the minor features are required but sometimes have been associated with these fractures.

[c]Often referred to in the literature as *beaking* or *flaring*.

Insights into the pathogenesis of atypical femoral fractures from basic studies

The radiologic presentation of atypical femoral fractures bears striking similarities to that of stress fractures[1] and also may resemble that of pseudofractures.[2] About 70% of patients with a confirmed stress fracture of the femur report prodromal pain for a period of weeks before the diagnosis. Radiographic features of stress fractures typically include a periosteal callus that appears hazy and indistinct initially and later solidifies. The periosteal callus is clear evidence of an attempt at repair prior to overt fracture and also occurs in atypical femoral fractures adjacent to the evolving fracture on the lateral cortex (Fig. 2*B*). Rats,[3,4] rabbits,[5,6] dogs,[7] and horses[8,9] all have been used to

study stress fractures and, because of the similarities between stress fractures and atypical femoral fractures, could be useful models to study the pathogenesis of atypical femoral fractures.

Patients with atypical femoral fractures often also have a more generalized thickening of both the medial and lateral cortices bilaterally. This may be a normal genetically determined variant of femoral shape but has been observed often in those who have sustained an atypical femoral fracture. However, there is no evidence that BPs are associated with this more generalized cortical thickening because they are not known to stimulate periosteal apposition, nor do their antiremodeling effects lead to enhanced endosteal formation.

Atypical femoral fractures in patients on BPs have occurred in the setting of comorbid conditions with known adverse effects on bone quality (eg, DM).[10–13] A relatively large proportion of patients also has taken GCs in addition to BPs. GCs reduce osteoblast activity, increase osteoblast apoptosis,[14–16] and are also associated with osteonecrosis of the femoral head.[14,17] In DM, high glucose levels cause the accumulation of advanced glycation end products (AGEs) that have been associated with an increased risk of fracture.[18] In vitro[19] and in vivo studies[20,21] demonstrate that AGE accumulation increases the brittleness of bone.

BP effects on collagen. The organic matrix is the principal determinant of toughness, a measure of the intrinsic energy–absorption capacity of bone.[22–24] Bone collagen contains both enzymatic and nonenzymatic collagen cross-links; both stabilize the matrix and have significant impact on the bone's

mechanical properties. Enzymatic cross-links are first formed as immature divalent cross-links that are eventually converted to mature trivalent cross-links, pyridinoline (PYD), deoxypyridinoline (DPD), and pyrroles. Nonenzymatic cross-links are formed through the interaction of collagen and sugars via oxidation reactions. They are associated with the accumulation of AGEs in bone.

BPs are associated with both positive and negative effects on bone's organic matrix by altering both collagen maturity and cross-linking. Following 1 year of treatment with a wide range of BP doses, the PYD/DPD ratio was increased significantly in vertebral cancellous bone and tibial cortical bone from BP–treated dogs compared with untreated controls.[20,21] An increased PYD/DPD ratio has been associated with increased strength and stiffness of bone,[25,26] and subsequent mechanical analyses of vertebrae confirmed this in dogs. However, reducing bone turnover also increases pentosidine levels, a marker for AGEs. AGEs are associated with tissue that is more brittle[25] and cause reductions in postyield deformation,[19,26] energy to fracture,[21,27] and toughness.[20] Indeed, tissue from both vertebral[28] and tibial[21] bone from BP-treated animals was less tough than bone from animals not treated with BPs. Pentosidine levels also were increased in the ribs of dogs after 3 years of treatment with incadronate.[29] However, caution should be exercised when interpreting the results of these studies because they involved BP administration to normal rather than osteoporotic dogs.

There are limited data on collagen cross-links in humans treated with BPs. Using Fourier-transformed

infrared spectroscopy (FTIR), Durchschlag and colleagues[30] showed that BP treatment prevented the maturation of collagen found in patients not treated with BPs and reduced collagen maturity in newly formed bone. Boskey and colleagues[31] reported no change in collagen maturity in women treated with alendronate. Donnelly and colleagues[32] showed similar mean values but a narrowed distribution of collagen maturity and enzymatic crosslinks in a small number of women with common proximal femoral fractures without features of atypia who had been treated with BPs for an average of 7 years.

BP effects on bone mineralization density distribution (BMDD). BMDD is a measure of the degree and heterogeneity of mineralization in bone tissue.[33–35] In the healthy adult population, BMDD of cancellous bone shows only minor variations with age, gender, ethnicity, and skeletal site,[36] indicating that the normal BMDD corresponds to a biologic and mechanical optimum. Therefore, even small deviations from the normal BMDD may have biologic meaning. Because the effectiveness of bone in stopping cracks is directly proportional to the stiffness ratio across its internal interfaces, a homogeneous material will be less effective in slowing or stopping cracks initiated in the bone matrix, permitting cracks to grow more quickly to critical size and ultimately increase fracture risk.[37]

BP treatment reduces bone turnover, increases overall mineralization, but leaves mineral particle shape, thickness, and orientation unaffected, narrows the BMDD, and increases bone strength and stiffness.[33,34] BP effects on BMDD have been studied only in transiliac bone biopsies, so there is limited

knowledge about their effects on cortical bone from other sites. However, Donnelly and colleagues[38,39] have shown that the range of mineral distribution at the proximal femur is significantly narrower than that in the iliac crest and that postmenopausal women treated with BPs for an average of 8 years demonstrated substantially less tissue heterogeneity in terms of mineralization, crystal size, and crystal perfection than those who had not been treated. Cortical tissue seemed to be affected preferentially. Narrowing of the BMDD by BPs may be transient. After 5 to 10 years of BP treatment, BMDD was restored to within the normal premenopausal range.[40–43]

Effects of reducing remodeling on microdamage accumulation. Excessive bone remodeling results in microarchitectural deterioration and consequent loss of bone mass and strength and increased susceptibility to fragility fractures. BPs increase bone strength and decrease fracture risk by suppressing excessive bone remodeling. Reduction of remodeling, however, is also associated with increased microdamage accumulation because cracks are not removed efficiently. Even in the absence of BP treatment, age-related reductions in bone turnover result in microdamage accumulation.[28] There is a threefold increase in damage accumulation in the vertebrae of dogs between 2 and 5 years of age that is associated with a 50% reduction in turnover.[28] Damage also accumulates significantly in humans with age, particularly after the age of 70 years,[44,45] although there is broad interindividual variability in the amount. BPs may exacerbate damage accumulation because they impair targeted remodeling to a greater extent than remodeling not

targeted to damage repair (ie, stochastic remodeling),[46,47] thereby allowing microdamage to persist for longer compared with untreated bone. This accumulation of damage is nonlinear and increases more quickly the more that remodeling is suppressed.[48] However, marked reduction of turnover is not necessary to induce a significant accumulation of microdamage. Reducing trabecular bone activation frequency in the canine vertebra by approximately 40% with risedronate is associated with a threefold increase in microdamage compared with untreated controls,[48] and suppression by approximately 20% with raloxifene is associated with a doubling of microdamage.[49]

Studies of iliac crest biopsies provide conflicting data about whether microdamage accumulates with BP treatment in humans. One study that evaluated women treated for an average of 5 years with alendronate showed significant microcrack accumulation in a subsample, but the study is inconclusive because the analyses of biopsies from the two different clinical sites associated with the study differed.[50] A second study did not find an association between BP treatment and damage accumulation in the iliac crest.[51] Neither study evaluated samples from the femoral cortex, and because the accumulation of microdamage is site-specific, it is unknown whether damage accumulates in the cortex of the femoral diaphysis.

Effects of reducing remodeling on tissue mechanical properties. Not only is microdamage accumulation with BP treatment a function of reduced repair, but BP-treated bone also is more susceptible to increased crack initiation,[52] perhaps because AGE

accumulation causes bone tissue to become more brittle. In one study, dogs were treated for 1 year with either risedronate or alendronate at doses equivalent to those used to treat postmenopausal osteoporosis.[52] Vertebrae then were removed and loaded cyclically in compression (5 Hz for 100,000 cycles at loads ranging from 100% to 300% of body weight); cracks were significantly more likely to initiate, but not necessarily to grow, in bone treated with alendronate than in those treated either with risedronate or with saline.[52]

Preclinical studies show that treatment with BPs is associated with reduced bone toughness.[48,53,54] Following 1 to 3 years of BP treatment at doses similar to or greater than those used in postmenopausal women, toughness was 20% to 30% lower than in control animals.[48,53] It was thought initially that the decline in toughness was related to the well-documented accumulation of microdamage that was observed in lumbar vertebrae and other bones of dogs treated with BPs,[48,54,55] although changes to both mineralization and collagen cross-linking also occur. More recent data show that toughness continues to decline in animals with long-term BP treatment without an increase in micro–damage accumulation or a further increase in secondary mineralization.[28] In a 1-year study using various doses of alendronate or risedronate, there was minimal correspondence between changes in micro-damage accumulation and material-level toughness in vertebrae from several groups of BP-treated dogs.[48] Likewise, animals not treated with BPs have an age-related threefold increase in microdamage accumulation without a change in bone toughness.[28] These lines of evidence suggest that neither microdamage nor increased

secondary mineralization is solely responsible for the change in bone material properties with BP therapy, leaving changes in collagen or interactions among all these properties as likely reasons for the progressive decline in toughness. However, the evidence also suggests that decreased remodeling is not solely responsible for reduced toughness, implicating a specific effect of BPs that is independent of reduced turnover.

The mechanical effect of BPs to decrease tissue toughness is countered by their capacity to increase bone mass and mineralization, promote collagen matrix maturation, and prevent microarchitectural deterioration of bone. These factors lead to increases in bone strength and stiffness that offset reduced toughness and make bone stronger at the structural level.

Affinity and retention of BPs in bone. The high affinity of BPs for bone mineral[56] and their long-term retention in bone[57] are of some concern because continued accumulation of BPs or persistent reduction of remodeling for prolonged treatment periods eventually could increase the risk of fracture, even in the face of increased bone mass. However, the toughness of the femoral diaphysis in nonosteoporotic dogs treated for as long as 3 years was not reduced, even with high doses of alendronate.[58] Moreover, cortical thickening, a feature of atypical femoral fractures, was not detected. In the absence of estrogen deficiency, the turnover rate in cortical bone has been estimated at approximately 3% per year,[59] based on biopsies from the rib, which is known to have a relatively high rate of turnover compared with other cortical bone sites. This is about one-tenth the rate of

turnover in cancellous bone.[59] The turnover rate of the femoral diaphysis is undoubtedly even slower than cortical bone from the rib. In 5-year-old beagle dogs, which have cortical bone that is structurally very similar to human bone, the rate of turnover in the femoral cortex is about 1% per year,[58] very much like that found in cortical bone from the femoral neck.[60] While this slow turnover makes the possibility of oversuppression of cortical bone remodeling in the femur unlikely, it is possible that prolonged reduction of remodeling could have an additive effect over time, especially if BPs continue to accumulate in the tissue. This may be relevant to atypical femoral fractures, where case series suggest a potentially significant effect of duration of treatment and a median treatment period of 5 years, according to Giusti and colleagues,[11] and 7 years, according to the current review.

Effects of BPs on fracture healing. Stress fractures and acute fractures of long bones heal by different mechanisms. Complete fractures heal via endochondral ossification, with an initial inflammatory response and the formation of a cartilage callus. BPs do not impair the initial phases of fracture healing or the development of a proliferative callus.[61–63] They only slow the remodeling phase, delaying the remodeling of the calcified cartilage callus to mature bone. In contrast, stress fractures heal by normal bone remodeling, which is reduced by BP treatment. BPs in the form of technetium-99m are used for bone scintigraphy and localize at sites of high bone turnover, microdamage, and fractures.[1,64] The localization of BPs at sites of stress injury would not affect periosteal callus

formation but could compromise intracortical bone repair of the damage itself by lowering the activation of new remodeling even further. Consistent with this hypothesis, treatment with BPs during military training did not lower the risk for stress fractures.[65] Animal studies using repetitive ulnar loading in combination with BP treatment also show that prior alendronate treatment does not protect against a fatigue-related reduction in mechanical properties.[66] However, prior alendronate treatment did eliminate the adaptive remodeling response, suggesting that BP treatment could impair the healing response to a stress fracture. Therefore, it is possible that in the case of a developing stress fracture, reduction of bone remodeling would prevent or delay the repair of the stress reaction without suppressing the appearance of a periosteal callus and that this may result eventually in consolidation of the damage and a complete fracture of the stressed site.

Effects of BPs on angiogenesis. The effects of BPs on stress fracture repair could be exacerbated if BPs are also antiangiogenic. The periosteum of the femoral shaft is thick and highly vascularized.[67] An effective stress fracture healing response requires an increase in periosteal vascularity. Although some observations identify a direct suppression of vasculogenesis by BPs,[68] it can be difficult in bone to distinguish between inhibition of new vessel growth and suppression of osteoclastic activity because both are coupled. However, dissociation between the two is possible during skeletal development in animal models, and studies of growing animals showed no antiangiogenic effect of clodronate.[69] Still, primary studies in nonskeletal tissues suggest that

angiogenesis indeed may be reduced by BPs over and above the normal reduction that would occur because of the absence of effective osteoclastic tunneling.[70] Interestingly, in a rat model of stress fracture, there is upregulation of vascular endothelial growth factor (VEGF) mRNA within 1 to 4 hours of initiation of the stress fracture[71,72] and upregulation of osteogenic genes in the cambium layer of the periosteum within 3 days. Early upregulation of interleukin 6 (IL-6) and IL-11 suggest the importance of remodeling in stress fracture healing.[72] These responses may well be coordinated, and any agent that suppresses angiogenesis could inhibit the repair of an impending stress fracture.

Summary of preclinical studies. The preclinical data provide a mixed picture of the effects of BPs on bone's matrix composition and mechanical properties. BPs reduce bone remodeling, preventing the loss of bone and deterioration of cancellous microarchitecture that accompany it. By reducing the number of new remodeling sites, BPs increase bone density, mineralization, and strength. Increases in fully mature collagen cross-links further contribute to the increased strength and stiffness associated with these other changes. However, at the same time, lowering of remodeling by BPs allows the accumulation of microdamage and increases the formation of AGEs, both of which reduce tissue toughness or the energy-absorbing capacity of bone tissue. Reduced remodeling also increases the homogeneity of the bone tissue, which could permit further damage accumulation, although this effect may be transient and not associated with long-term BP use. However, changes that reduce energy-absorbing capacity may be

particularly significant if a person sustains a low-energy impact such as a fall. Reduced remodeling may impair the healing of a stress fracture without altering the callus bridging that is the adaptation to and accompanies the stress fracture itself. Reduced angiogenesis would contribute to this delay in healing. While the preclinical studies reviewed here provide some insights regarding the possible pathogenesis of atypical femoral fractures, additional studies are required to identify potential pathogenic mechanisms that involve pathologic changes to bone matrix (Table 2), and animal models that more accurately mimic atypical fractures need to be developed.

Epidemiology of Subtrochanteric and Femoral Shaft Fractures

General epidemiology of subtrochanteric and femoral shaft fractures. Fractures located in the subtrochanteric region or femoral shaft (diaphysis) account for 7% to 10% of all hip/femoral diaphyseal fractures.[73,74] Approximately 75% of complete subtrochanteric and femoral shaft fractures are associated with major trauma such as motor vehicle accidents,[73] in which the energy transmitted to the bone results in the propagation of multiple fracture lines, thus producing comminution. Especially in older patients, femoral shaft fractures may occur below the stem of the prosthesis after total hip replacement.[75] In adults of all ages, more than half of femoral shaft fractures are spiral fractures, with the remainder presenting with a transverse or oblique configuration.[73,76]

Subtrochanteric fractures have important effects on mortality and morbidity. A study of 87 patients with

subtrochanteric fractures showed a mortality rate of 14% at 12 months and 25% at 24 months. Moreover, by 24 months, almost half had not achieved their prefracture functioning in terms of walking and performing other activities of daily living. In addition, many (71%) were unable to live in conditions similar to those before the fracture.[77] These outcomes are similar to long-term outcomes for people with femoral neck fractures.[78–81]

Table 2. Possible Pathogenetic Mechanisms Associated With Atypical Subtrochanteric Femoral Fractures

- Alterations to the normal pattern of collagen cross-linking
  - Changes to maturity of cross-links formed by enzymatic processes
  - Advanced glycation end-product accumulation
- Microdamage accumulation
- Increased mineralization
- Reduced heterogeneity of mineralization
- Variations in rates of bone turnover
- Reduced vascularity and antiangiogenic effects

A comprehensive review of 6409 femoral shaft fractures in Swedish inpatients showed a bimodal age distribution of incidence in both males and females,[82] similar to that reported by Singer and colleagues.[83] The age-specific incidence rates (per 100,000) for subtrochanteric fractures increased between the 65– and 85– year categories in both males and females in

Iran,[84] in the United States,[85] and in the United Kingdom.[86] Although femoral shaft fractures were more common among males than among females up to age 49, this gender difference was reversed in the 60– to 69– year age group.[82] Thus subtrochanteric fractures share features of typical osteoporosis-related fractures, including (1) higher incidence among women than among men, (2) a steep increase in incidence with age, and (3) more common occurrence in the elderly after low-energy trauma.[82,87–89] The number of admissions for femoral shaft fractures was unchanged from 1998 to 2004 in Sweden[82] and from 1996 to 2006 in the United States.[74]

The epidemiology of femoral neck and trochanteric and intertrochanteric hip fractures was compared with that of subtrochanteric and femoral shaft fractures in the United States among people 50 years of age and older using both the National Hospital Discharge Survey from 1996 to 2006 and MarketScan, a large medical claims database, from 2002 to 2006.[74] In women, hospital discharge rates of hip fracture (femoral neck and trochanteric and intertrochanteric regions) decreased from about 600 per 100,000 to 400 per 100,000 person-years in the decade after 1996. In contrast, subtrochanteric and femoral shaft fracture rates did not change, with an annual incidence of less than 30 per 100,000 person-years.[74] These findings confirmed that hip fracture incidence has declined since BPs were approved for use, whereas subtrochanteric and femoral shaft fractures have remained stable. Another US study of hospitalizations between 1996 and 2007 for hip (ie, femoral neck, intertrochanteric) and subtrochanteric fractures confirmed that femoral neck/intertrochanteric

fractures declined by 12.8% (263,623 in 1996 to 229,942 in 2007).[90] However, in contrast to the study by Nieves and colleagues,[74] subtrochanteric fractures increased from 8273 to 10,853 over the same period.[90] Neither study could ascertain specific radiologic features of atypia discussed in the case series.[74,90]

Recent data from the Study of Osteoporotic Fractures (SOF), a prospective population-based US study of 9704 white women 65 years of age and older followed for as long as 24 years indicate that the incidence of subtrochanteric fractures is very low (3 per 10,000 person-years) compared with the overall incidence of hip fracture (103 per 10,000 person-years).[91] After excluding high–energy, pathologic, and periprosthetic fractures, 48 subtrochanteric fractures occurred in 45 women (3.4% of hip fractures), 9 of whom received BPs. Predictors of subtrochanteric hip fracture were older age, lower total hip BMD, and a history of falls. In multivariate models, only increasing age remained significant. Predictors of femoral neck fracture were similar in this largely BP–naive group. Since fracture radiographs were not available, features of atypia were not ascertained. However, in 33 of the 45 women from the SOF with subtrochanteric fractures, baseline pelvis radiographs were available. When compared with 388 randomly selected controls, women with the thickest medial femoral shaft cortices were at lower risk of subtrochanteric and femoral neck fracture than those with the thinnest cortices.[92] Although lateral cortical thickening is described commonly in patients with atypical fractures, thickness of the lateral cortex was not related to fracture risk. Since only 6 women in the subset with pelvic radiographs had taken BPs, more

data are required on the role of cortical thickness in atypical femoral fractures in BP users.

Subtrochanteric and femoral shaft fractures and BP use. In a retrospective case-control study of postmenopausal women,[93] 41 cases of low-trauma subtrochanteric and femoral shaft fractures were identified and matched by age, race, and body mass index (BMI) to one intertrochanteric and one femoral neck fracture patient who presented during the same time period (2000–2007). BP use was documented in 15 of the 41 (37%) subtrochanteric and femoral shaft fracture patients compared with 9 of the 82 (11%) intertrochanteric and femoral neck fracture patients, resulting in an odds ratio (OR) of 4.44 [95% confidence interval (CI) 1.77–11.35]. Long-term BP use was more likely and duration of BP use was longer in subtrochanteric and femoral shaft fracture patients than in both hip fracture control groups ($p = .001$). Radiographs showed fractures with a transverse or oblique orientation, cortical thickening, and localized diffuse bone formation on the lateral cortex in 10 of the 15 fracture patients on a BP and in 3 of 26 fracture patients who were not taking a BP (OR = 15.33, 95% CI 3.06–76.90, $p < .001$).

In a cross-sectional study of 11,944 Danish people over age 60, Abrahamsen and colleagues[94] compared age-specific fracture rates and BP exposure in various kinds of proximal femur fractures identified by International Classification of Diseases (ICD)– 10 codes. Alendronate exposure was the same in patients with subtrochanteric fractures (ICD-10, S72.2; 6.7%), femoral diaphyseal fractures (S72.3; 7.1%), and the more common femoral neck (S72.0) and intertrochanteric fractures (S72.1; both 6.7%). They

tested the hypothesis that increased risk of subtrochanteric and femoral shaft fractures in patients treated with alendronate exceeded the increased risk of femoral neck and intertrochanteric fractures. Each patient who received alendronate for at least 6 months (n = 5187) was matched with two controls (n = 10,374). In this register-based matched-cohort study, the hazard ratio (HR) for subtrochanteric or diaphyseal fracture with alendronate was 1.46 (95% CI 0.91–2.35, p = .12), similar to the hazard ratio of 1.45 (95% CI 1.21–1.74, p < .001) for femoral neck and intertrochanteric fractures; both estimates were adjusted for comorbidity and concurrent medications. Patients with subtrochanteric and diaphyseal fractures were no more likely to be on alendronate but were more likely to use oral GCs than those with typical hip fractures.

In another national register-based Danish cohort study, 4854 patients without prior hip fracture were followed for a mean of 6.6 years after starting alendronate; data also were obtained from a large matched-cohort analysis of 31,834 alendronate users and 63,668 comorbidity-matched controls over a mean follow-up period of 3.5 years.[95] The overall incidence of subtrochanteric and diaphyseal fractures did not differ between patients in the lowest quartile of cumulative alendronate use (mean 0.2 dose – years) and those in the highest quartile of use (mean 8.7 dose– years), 4.7 per 1000 versus 3.1 per 1000, respectively. In contrast, there was a decline in femoral neck/intertrochanteric hip fracture incidence with increasing dose-years of alendronate from lowest (22.8 of 1000) to highest quartile (10.9 of 1000). The hazard ratio for subtrochanteric/diaphyseal fracture

with alendronate was 1.50 (95% CI 1.31–1.72) compared with 1.29 (95% CI 1.21–1.37) for femoral neck/intertrochanteric hip fracture. Although rates of all fractures were higher in alendronate users than in nonusers, highly compliant patients had significantly lower risk of femoral neck/intertrochanteric fractures (HR = 0.47, 95% CI 0.34–0.65) and subtrochanteric/diaphyseal fractures (HR = 0.28, 95% CI 0.12–0.63).[94] Furthermore, in a small subset of persons who remained highly compliant long term (>6 years), subtrochanteric/ diaphyseal fractures comprised 10% of fractures compared with 12.5% in the control cohort. Consistent with these results, data from another Danish cohort suggest that the risk of subtrochanteric/ diaphyseal fractures and all fractures is present before BP initiation.[96]

In summary, the Danish data indicate no greater risk for a subtrochanteric or diaphyseal femoral fracture in alendronate–treated patients than for an osteoporosis-related fracture of any part of the femur (including the hip).[94,95] Studies of this type provide important broad and contextual data on the epidemiologic characteristics and incidence of subtrochanteric and diaphyseal femoral fractures. However, there is no adjudication of radiographs, and thus they cannot provide specific information on the clinical and radiographic features of the atypical fractures described in case reports and series versus the more typical fractures seen at the same sites.

No cases of subtrochanteric fractures were reported in preclinical studies or placebo-controlled registration trials of oral BPs involving more than 17,000 patients. However, the maximum duration of BP exposure for most subjects in these trials was less than 4 years.

Recently, however, Black and colleagues[97] reported a secondary analysis of three large randomized clinical trials of BPs, two of oral alendronate, the Fracture Intervention Trial (FIT) and its long-term extension (FLEX), and one of zoledronate (HORIZON-PFT). FIT randomized women to alendronate or placebo for 3 to 4.5 years. In FLEX, 1099 women originally randomized to alendronate were rerandomized to alendronate 5 or 10 mg/day or placebo. The total duration of alendronate was 10 years for those randomized to alendronate and 5 years for those randomized to placebo. In the HORIZON trial, 7736 women were randomized to zoledronate 5 mg or placebo and followed for 3 years. All 284 hip and femur fractures were reevaluated to identify femoral shaft fractures and assess features of atypia. However, the reevaluation was based on the radiographic report because radiographs were available for only one subject. Twelve subtrochanteric/diaphyseal fractures (4%) were found in 10 subjects, 3 of whom had not received BPs. The relative hazard ratios of alendronate versus placebo were 1.03 (95% CI 0.06–16.5) in FIT and 1.33 (95% CI 0.12–14.7) in FLEX. The relative hazard ratio of zoledronate versus placebo was 1.5 (95% CI 0.25–9.0). The authors concluded that the risk of subtrochanteric/diaphyseal fracture was not significantly increased, even among women treated for as long as 10 years. Although the FLEX data that compare 5 and 10 years of alendronate treatment provide some reassurance regarding reported associations of subtrochanteric/diaphyseal fracture with long-term BP treatment, this study had a number of very important limitations.[98] Radiographs were

not available to evaluate features of atypia. Only a minority received more than 4 years of BP, and some received a lower dose of alendronate (5 mg) than commonly prescribed. Most important, because of the rarity of these fractures, statistical power was extremely low.

Preliminary data are now available on the incidence of atypical femoral fractures from a large US health maintenance organization (HMO) that serves 2.6 million people over age 45.[99] Using electronic data sources, 15,000 total hip and femur fractures were identified by both ICD-9 and Current Procedural Terminology (CPT) coding in patients older than 45 years over a 3-year period between 2007 and 2009. After excluding fractures above the subtrochanteric region and below the distal femoral flair and periprosthetic, pathologic, and high-trauma fractures, 600 radiographs were reviewed, of which 102 (~17%) had features of atypia (ie, transverse fracture with short oblique extension medially, cortical thickening, periosteal callus on the lateral cortex). Most (97 of 102) patients had taken a BP. Based on the number of patients receiving BPs in the HMO, preliminary estimates of atypical femoral fracture incidence increased progressively from 2 per 100,000 cases per year for 2 years of BP use to 78 per 100,000 cases per year for 8 years of BP use. These data suggest that atypical femoral fractures are rare in both the general population and BP-treated patients, but their incidence may increase with increasing duration of BP exposure. However, there was no age-matched control group of patients who did not use BPs, and it is possible that the incidence of all fractures in women at this age would increase over 6 years. Important

strengths of this study include the expert adjudication of all 600 radiographs of the region of interest and availability of data on filled prescriptions for oral BPs.

Summary of epidemiologic studies. It is important not to equate the anatomic entity of subtrochanteric/diaphyseal femoral fracture with that of atypical femoral fractures. In addition to location, the latter diagnosis should include all other major features outlined in the case definition (Table 1). The interest in subtrochanteric and diaphyseal fractures in an epidemiologic context is that the total number of these fractures marks the upper boundary of any potential harm owing to atypical femoral fractures. Notably, subtrochanteric and diaphyseal fractures together account for only about 5% to 10% of all hip/femoral fractures; of these, only a subset is atypical (17% to 29%). The proportion of subtrochanteric and diaphyseal fractures that have features of atypia depends on whether fractures owing to high-impact trauma or periprosthetic fractures are excluded and varies in the different patient series from 17%(99) to 29%.[100] It is this subset of fractures that has been associated with the use of BPs, an association that may or may not be causal. It is also important to note that atypical fractures have been reported in patients who have not been exposed to BPs. This occurred in 3 of the 8 patients with atypical fragility fractures of the femur reported by Schilcher and colleagues,[101] in 1 of 20 patients in the Neviaser case series,[100] in 5 of 102 patients reported by Dell and colleagues,[99] in 1 of 4 patients reported by Bunning and colleagues,[102] and in 3 of 26 patients in the Lenart study,[93] as well as in patients with hypophosphatasia.[2,103]

Epidemiologic studies show that fractures of the subtrochanteric region of the femur and the femoral shaft follow an age and sex distribution similar to osteoporotic fractures. However, decreases in age-specific hip fracture rates in the community have not been accompanied by decreases in the rates of subtrochanteric or diaphyseal femoral fractures despite similarities in epidemiology and an association with BMD. While register–based studies provide useful information on the prevalence and incidence of subtrochanteric/diaphyseal fractures, it is important to recognize that these studies rely on diagnostic codes for case finding that may misclassify fracture location[104] and do not assess the radiologic hallmarks of atypia. Thus a stable total number of subtrochanteric fractures potentially could mask a shift from typical osteoporotic subtrochanteric fractures toward more atypical fractures, as might be suggested by Dell's results[99] and those reported by Wang and Bhattacharyya.[90]

If BPs are targeted to patients with a fracture risk similar to that in FIT,[105] using alendronate in women without baseline vertebral fractures, about 700 nonvertebral and 1000 clinical vertebral fractures would be avoided per 100,000 person-years on treatment. In women with prior vertebral fractures, the corresponding numbers are 1000 and 2300.[106] Based on the assumption that up to one in three subtrochanteric fractures is atypical, these numbers are 13 and 29 times higher, respectively, than the 78 per 100,000 incidence figure reported by Dell and colleagues[99] and 10 and 23 times higher, respectively, than the highest estimate of the rate of atypical subtrochanteric/ diaphyseal fractures of 100 per

100,000 in long-term users of alendronate from the Danish study.[95] Thus the risk-benefit ratio clearly favors BP treatment in women at high risk of fracture.

Atypical subtrochanteric and femoral shaft fractures: Clinical data

In its review of published case reports and series as described in "Methods," the task force recognized that the quality of the evidence reported in a substantial proportion was poor, with missing important historical or clinical information. The task force recommends that a hierarchy of data quality should be established for all future studies reporting cases of atypical femoral fractures. The data quality for a case would be based on the quality in seven areas, as indicated in Tables 3 and 4.

Case series and case reports. The total number of reported cases was 310 after overlapping case reports had been excluded (Table 5); 286 cases occurred in association with BP treatment for osteoporosis and 5 in patients with BP treatment for malignancy (ie, myeloma or metastatic renal cell carcinoma). In 19 cases, BP use was not identified. The subjects ranged in age from 36 to 92 years. Only nine fractures were in men, but gender was not identified in three large case series.[100,107,108] The majority (160 of 189) occurred after oral alendronate monotherapy: 12 patients were treated with oral risedronate (of these, 1 was followed by oral alendronate, whereas 2 were treated previously with alendronate and another was treated previously with pamidronate), 4 with a combination of intravenous pamidronate followed by intravenous zoledronic acid (myeloma), 4 with either oral or intravenous pamidronate (osteoporosis), 2 with

intravenous zoledronic acid (renal cell carcinoma and osteoporosis), 2 with oral alendronate followed by oral ibandronate, and 102 with an unspecified oral BP.

Table 3. Hierarchy of Data Quality for Atypical Femoral Fractures

The quality of evidence should be assessed for the following key areas:

1. Patient characteristics
   a. Age
   b. Gender
2. Description of atypical subtrochanteric and femoral shaft fracture
   a. Location in femoral shaft from just distal to the lesser trochanter to just proximal to the supracondylar flair of the distal femoral metaphysis
   b. Presence of transverse or short oblique configuration of fracture
   c. Low level of trauma
   d. Noncomminuted
   e. Presence of thickened cortices with or without a periosteal callus
3. Bisphosphonate exposure history
   a. Specific drug(s)
   b. Specific dose history
   c. Duration of and adherence to therapy before diagnosis of fracture
4. Bisphosphonate therapy indication
   a. Disease (osteoporosis, osteopenia, myeloma, etc.)

b. History of prior low-trauma fracture

5. Comorbid conditions
   a. Presence of vitamin D deficiency (<20 ng/mL)
   b. Presence of other comorbid conditions
      - RA
      - Other diseases requiring corticosteroids
      - Diabetes
      - Cancer
      - Hypophosphatasia
6. Concomitant medication history
   a. Identity of concomitant medications, including
      - Glucocorticoids
      - Proton pump inhibitors
      - Other antiresorptive drugs (eg, estrogen, raloxifene, calcitonin, denosumab)
   b. Doses of concomitant medications and duration of therapy prior to subtrochanteric fracture
7. Investigations
   a. Bone densitometry
   b. Bone turnover markers
   c. Bone histomorphometry, including an assessment of bone turnover

The duration of BP therapy ranged from 1.3 to 17 years, although duration was not identified in 1 patient. The median duration was 7 years. The presence or absence of prodromal pain was assessed in 227 of 310 patients; it was present in 70% (158 of 227). Concomitant GC use was assessed in 76 of 310 patients; it was present in 34% (26 of 76) and increased the risk of subtrochanteric fractures in one large series

(OR = 5.2).[107] Bilateral fractures were assessed in 215 of the 310 patients and were present in 28% (60 of 215). Bilateral radiologic changes were assessed in 224 of the 310 patients and were present in 28% (63 of 224). Healing was assessed in 112 of the 310 patients and was reported to be delayed in 26% (29 of 112).[13,102,109–119] In one large series, other historical risk factors associated with subtrochanteric fractures were a prior low-trauma fracture (OR = 3.2), age younger than 65 years (OR = 3.6), and active RA (OR = 16.5). PPI use was assessed in 36 of the 310 patients and was noted in 14 (39%) [112,119–121]

Table 4. Classification of Data Quality

The overall hierarchy of evidence quality for a case would be based on the quality of these seven areas:

Best evidence:

Information complete for all seven categories

Good evidence:

Information complete for categories 1–5, 6a, and 7a

Acceptable evidence:

Information complete for categories 1–4, but 5, 6a, and 7a not all complete

Marginal evidence:

Information complete only for categories 2a and 3a

Insufficient evidence:

Information unavailable for categories 2a, 3a, and 4a regardless of other information provided

Serum 25-hydroxyvitamin D [25(OH)D] concentrations were measured in 84 patients, and 5 (6%) had vitamin D deficiency [25(OH)D < 20 ng/mL]. In one large series, serum 25(OH)D concentrations of less than 16 ng/mL increased the risk of subtrochanteric fractures (OR = 3.2). Of the 67 patients who had bone densitometry recorded, 45 (67%) had osteopenia or normal BMD.

Relatively few reports included bone turnover markers (BTMs).[13,109,113–116,122,123] When measured, however, bone resorption markers are usually within the normal premenopausal range[109,114–116,123,124] and occasionally are elevated.[114,115,122] In only a minority of cases have BTMs been suppressed.[13,109,116] Thus BTMs, at least when measured after atypical femoral fractures have occurred, do not suggest oversuppression of bone turnover in the majority of patients. However, since fractures per se are associated with increased BTMs, measurements obtained after a fracture may reflect fracture healing rather than the rate of bone remodeling throughout the skeleton. BTM determination prior to the fracture would be more informative.

Summary of case series and case reports. Several case series and multiple individual case reports suggest that subtrochanteric and femoral shaft fractures occur in patients who have been treated with long-term BPs. However, these fractures also may occur in BP-naive patients. Several unique radiographic and clinical features have emerged from these case reports and series. All the individual case reports of atypical femoral fractures[118,119,122,125–129] illustrate one or more radiographic features suggestive of a fracture distinct from the common osteoporosis-, prosthesis-, or major

trauma–related fractures. These include lack of precipitating trauma,[118,122,127] bilaterality (either simultaneous or sequential),[118,119,122,129] transverse fractures,[127] cortical hypertrophy or thickness,[118] stress reaction on the affected and/or unaffected side,[118,122,125,127,129] and poor fracture healing.[118,128] Other features include prodromal pain in the thigh or groin for weeks or months prior to the fracture,[118,122,127] use of an additional antiresorptive agent (eg, estrogen, raloxifene, or calcitonin), use of GCs or PPIs in addition to the BP,[118,119,125] presence of RA or DM, serum 25(OH)D concentrations less than 20 ng/mL, and normal or low BMD but not osteoporosis in the hip region.[13,115,119] Several reports describe iliac crest biopsies with very low bone turnover rates (Table 6); however, this is not a distinguishing feature of patients with atypical fractures on BPs because even short-term use of a BP results in dramatic reductions in rates of bone turnover.[119,130] BTMs have not shown any consistent pattern but are often not suppressed. In sharp contrast to prior experience with osteonecrosis of the jaw,[131] the number of cases of atypical fracture reported in cancer patients receiving high-dose intravenous BPs is substantially lower than those in patients being treated for osteoporosis. Whether this is a reporting bias remains to be seen. However, if true, this would argue against a simple causal relationship with the amount of BP received and perhaps suggests that duration may be more important than amount.

Guisti and colleagues conducted a systematic review of 141 women with postmenopausal osteoporosis treated with BPs who sustained

subtrochanteric/diaphsyeal fractures.[11] Their results are generally comparable with this task force report with regard to age, mean duration of BP use, proportions with bilateral fractures, prodromal pain, comorbid conditions (ie, DM or RA), and concomitant use of estrogen, raloxifene, tamoxifen, and GCs. They also reported that patients with subtrochanteric versus femoral shaft fractures had a higher number of comorbid conditions, were more likely to have bilateral fractures, and were more often using PPIs. Patients who had used BPs for less than 5 years were more likely to be Asian and to have had a femoral shaft fracture prior to initiating BP therapy.[11]

It is highly likely that case reports and case series of atypical femur fractures will continue to accumulate. In this regard, abstracts submitted to the 2010 Annual Meeting of the ASBMR[132–136] reported another 47 cases not included in this analysis. Many physicians who treat substantial numbers of patients with osteoporosis have described additional cases anecdotally, the majority of which are unlikely to be published. Similarly, cases may not be reported owing to lack of recognition by clinicians. Thus there is concern that the reported cases represent a minority of the actual number of cases that exist.

Bone histology and histomorphometry. A substantial number of the case studies have included histomorphometric analysis of iliac crest bone biopsies (Table 6). However, only a few reports have included histology or histomorphometry of bone taken from or close to the subtrochanteric fracture site. Iliac crest biopsies generally have revealed extremely low bone turnover, a finding consistent with BP treatment,[137--139] especially in patients treated concomitantly with a

BP and another antiresorptive agent, such as estrogen,[140] or with BPs and GCs.[141] Although a number of reports mention lack of double tetracycline labels in the biopsy, this too is a common and expected finding in BP-treated subjects,[138,139] even in those who have been treated for only 6 months.[130] Moreover, lack of double label or so little double label that mineral apposition rate cannot be evaluated reliably is seen in a significant proportion of untreated postmenopausal women.[142,143] Static parameters of bone formation are also low in biopsies from patients with atypical femoral fractures, consistent with those seen in BP– treated patients with osteoporosis. It is important to note that a finding of low turnover in biopsies from BP-treated patients with atypical femoral fractures has not been universal.[109,119] In most cases, only a single transiliac biopsy, usually taken soon after the fracture, has been studied. Therefore, the turnover status prior to the fracture or before beginning BPs is not known. However, in one report,[126] a 35-year-old man was biopsied before beginning alendronate and again 7 years later, after a low-trauma subtrochanteric femur fracture. The first biopsy revealed low trabecular bone volume, reduced trabecular connectivity, and increased osteoid surface and tetracycline uptake, consistent with high-turnover osteoporosis. In contrast, the postfracture biopsy showed lack of osteoid and tetracycline labels, confirming conversion of high– to low-turnover bone.

Table 5. Case Series and Reports of Atypical Fractures

[see next page for table]

Author/date/reference	Number of patients	Age (range)	Gender (M/F)	BP exposure	BP duration (years)	Bilateral fractures/ radiographic changes (*n*)	Prodrome (*n*)	Oral GCs (*n*)	Serum 25 (OH)D < 20 ng/mL (*n*/available)	Hip *T*-score > −2.5 (*n*/available)
Goh, 2007[10]	9	55–71	0M/9F	9 ALN	2.5–5	1/3 (thick cortex)	5	1	NA	5/5
Kwek, 2008[12]	17[a]	55–77	0M/17F	16 ALN, 1 ALN > RIS	2–10	4/5	13	1	NA	8/12
Neviaser, 2008[100]	19[b]	NA	NA	19 ALN	Mean 6.9 (in 10 patients)	NA/NA	NA	NA	NA	NA
Wernecke, 2008[123]	1[c]	72	0M/1F	ZA > PAM	11	1/0	1	0	NA	1
Odvina, 2005[116]	5	52–68	1M/4F	5 ALN	3–8	2/NA	NA	2	None (range 28–180)	3/3
Odvina, 2010[115]	11	38–77	0M/11F	9 ALN 2 RIS	2–11	3/NA	5	4	2/9 (range 17.0–33.0)	5/8
Visekruna, 2008[13]	3	51–75	0M/3F	3 ALN	5–10	2/NA	2	3	None (range 32–48)	3
Somford, 2009[119]	1	76	0M/1F	ALN	8	1/0	1	1	1 (16.8)	1
Demiralp, 2007[125]	1	65	0M/1F	ALN	7	1/0	1	1	NA	0
Armamento-Villareal, 2009[109]	7	43–75	1M/6F	6 ALN 1 RIS	2–10	2/NA	NA	0	(30.6)	4/5
Lee, 2007[170]	1	73	0M/1F	ALN	1.6	0/1 (thick lateral cortex)	1	0	None (24)	1
Schilcher, 2009[101]	5	>75	0M/5F	NA	3.5–8.5 (mean 5.8)	1/NA	NA	NA	NA	NA
Ing-Lorenzini, 2009[112]	8	57–86	1M/7F	5 ALN 1 RIS > ALN 1 ALN > IBN 1 PAM	1.3–10.3	4/3 (thick lateral cortex)	2	3	NA	3/4
Schneider, 2006[118]	1	59	0M/1F	ALN	7	0/0	1	NA	NA	1
Sayed Noor, 2008[117]	1	72	0M/1F	ALN	7	0/1 (thick cortex with local lateral cortical reaction)	1	NA	NA	NA
Sayed Noor, 2009[128]	2	55–78	0M/2F	2 ALN	9	0/1 (cortical hypertrophy with lateral cortical reaction)	2	0	NA	NA
Goddard, 2009[171]	1	67	0M/1F	ALN > IBN	17	1/0	0	0	NA	NA
Cheung, 2007[122]	1	82	0M/1F	ALN	10	1/0	0	0	"Normal"	1
Bush, 2008[145]	1	61	1M/0F	ZA	1.5	0/1 (thick diaphyseal cortex)	0	0	NA	NA
Capeci, 2009[110]	7	53–75	0M/7F	7 ALN	5–13	3/4 (cortical stress reaction)	4	NA	0/3 (21–39)	NA

Author/date/reference	Number of patients	Age (range)	Gender (M/F)	BP exposure	BP duration (years)	Bilateral fractures/ radiographic changes (*n*)	Prodrome (*n*)	Oral GCs (*n*)	Serum 25 (OH)D < 20 ng/mL (*n*/available)	Hip *T*-score > −2.5 (*n*/available)
Husada, 2005[129]	1	72	0M/1F	ALN	NA	1/0	1	NA	NA	NA
Edwards, 2010[172]	1	60	0M/1F	ALN	6	1/1	1	1	NA	1
Cermak, 2009[111]	3	59–70	0M/3F	ALN	5.5–12	1/1	2	0	NA	NA
Ali, 2009[173]	1	82	0M/1F	ALN	8	0/0	0	0	"Normal"	1
Koh, 2010[174]	32[d]	47–91	0M/32F	30 ALN 1 ALN > RIS 1 ZA	2–10	NA/NA	NA	NA	8/32 (median 26.7 μg/L)	NA
Grasko, 2009[175]	1	57	1M/0F	PAM > ZA	9	0/0	1	1	NA	1
Napoli, 2010[144]	1	56	0M/1F	PAM > ZA	6	0/0	1	1	0	1
Issacs, 2010[108]	40	NA	NA	40 ALN	7.1 (mean)	NA/18	29	NA	NA	NA
Girgis, 2010[107]	20	78	NA	15 ALN 2 RIS	5.1 ALN (mean) 3.0 RIS (mean)	NA/NA	NA	OR 5.2	OR 3.5	NA
Glennon, 2009[176]	6	60–87	0M/6F	5 ALN 1 RIS	1.5–16 ALN 3.0 RIS	0/1 (cortical hypertrophy with lateral cortical reaction)	5	NA	"Normal"	NA
Bunning, 2010[102]	4	49–59	1M/3F	1 PAM > ZA 2 ALN 1 No BP	5–5.5	1/1 1 (cortical hypertrophy with lateral cortical reaction)	4	NA	NA	3
Lee, 2009[113]	1	82	0M/1F	ALN	8	1/1	NA	NA	None	1
Leung, 2009[114]	6	73–81	0M/6F	ALN	0.5–6	0/0	1	0	2	2
Schneider, 2009[177]	3	59–66	0M/3F	ALN	5–9	0/2 (cortical hypertrophy with lateral cortical reaction)	2	NA	NA	NA
Somford, 2009[121]	3	65–79	0M/3F	ALN	4–12	1/1	3	3	0	1
Giusti, 2010[11]	8	36–75	0M/8F	ALN (3) PAM (2) PAM -> RIS (1) RIS (2)	2.5–8 ALN 5–6 RIS 3–7 PAM	2/2 3 (cortical hypertrophy with lateral cortical reaction)	5	5	0	3
Dell, 2010[99]	102	45–92	3M/99F	Oral BPs (97) No BPs (5)	5.5	26 (complete fracture or stress fracture)	71	NA	NA	NA

NA = data not available; *n* = number; None = no cases outside the range; BP = bisphosphonate; ALN = alendronate; RIS = risedronate; IBN = ibandronate; ZA = zoledronate; PAM = pamidronate; GC = gluco-glucocorticoid; OR = odds ratio.

[a]This report included 8 from Goh, with substantial overlap likely.[10]

[b]This report included 10 from Lenart.[172]

[c]Unclear whether included in Neviaser.[100]

[d]This report included 17 from Kwek.[12]

Table 6. Histomorphometric and Pathologic Assessments.

Author/date /reference	Number of patients biopsied	Site	Parameters	Findings
Goh, 2007	5	Fracture site	Qualitative	No malignancy
Bush, 2008 (a)	1	Fracture site	Qualitative	No malignancy; no osteoclasts
Wemecke, 2008 (a)	1	L Femoral head, neck, marrow R Fracture site	Qualitative	L: No myeloma R: Thin, sclerotic trabeculae Absent osteoclast/osteoblast activity
Somford, 2009	2	Fracture site	Qualitative	No malignancy; no "osteoporosis"
Ing-Lorenzini, 2009	2	Fracture site	Qualitative	Absent fracture healing/remodeling in cortex ½; periosteal bridging
Aspenberg, 2010	1	Fracture site	Qualitative	Few osteocytes distant from fracture; increased Oc.N and Ot.N near fracture; loss of osteonal regular structure indicating enhanced remodeling

Samford, 2009	1	Fracture site and iliac crest	Static	Increased resorption and reduced formation at both sides; Oc.N sixfold higher at femoral cortex than iliac crest
Lee, 2009	1	Fracture site	Static	Absence of osteoclasts and osteoblasts; few osteocytes; hypercellular marrow No inflammation or malignancy; irregular/disorganized collagen matrix
Donnelly, 2010	14(c)	Fracture site	Static, Material Properties	Normal architecture and OS; reduced heterogeneity
Odvina, 2005	9	Iliac crest	Static and Dynamic	Reduced bone turnover in all; no double labels 9/9; single labels 5/9
Cheung, 2007	1	Iliac crest	Static and Dynamic	Reduced osteoblast/osteoclast activity; thin but extensive osteoid
Visekruna, 2008	2	Iliac crest	Static and Dynamic	Case 1: Increased Oc.N; lower OS and O.Wi; no double labels; limited single labels Case 3: increased Oc.N and Ob.N; lower OS and O.Wi; double and single labels; low activation frequency
Armamento -Villareal, 2009	7(b)	Iliac crest	Static and Dynamic	Reduced bone turnover 5/7; normal turnover 2/7
Odvina, 2010	6	Iliac crest	Static and Dynamic	Ob.S and OS absent or low 6/6; Oc.S absent or low 3/6; ES normal 5/5; double labels absent 4/6; single labels present 4/6

Giusti, 2010	1	Iliac crest	Static and Dynamic	Decreased Oc.N, ES, and OS; reduced turnover; few labels
Armamento -Villareal, 2006	1	Iliac crest	Qualitative	Pre-ALN: increased OS and labels; post-ALN: 6 years, no osteoid or labels
Leung, 2009	1	Iliac crest	Qualitative	Decreased Oc.N and Ob.N; reduced bone turnover; no labels
Napoli, 2010	1	Iliac crest		Unsuccessful; bone too "hard"

Oc.N = osteoclast number; Ob.N = osteoblast number; OS = osteoid surface; O.Wi = osteoid width; Oc.S = osteoclast surface; Ob.S = osteoblast surface.

(a) Cancer patients treated with high-dose BPs, i.v.

(b) Biopsies performed on 15 patients, but only 7 had femoral shaft fractures.

(c) All BP treated, average duration 7.4 years; 4 atypical femoral fractures, 1 subtrochanteric, 9 intertrochanteric

In several cases, biopsy samples were obtained at or close to the site of the subtrochanteric fracture, the location that is likely to provide more information on the underlying pathogenetic mechanism, although there is no opportunity for tetracycline labeling and dynamic assessment of bone turnover in this setting. Moreover, analysis at the biopsy site may be misleading because the fracture itself will lead to an acceleration of remodeling in the region of the fracture. Caution should be used in interpreting measurements of bone turnover taken from a biopsy at the fracture site. Ing-Lorenzini and colleagues[112] obtained biopsies from two patients but described the histologic appearance of only one of those, a 65-year-old postmenopausal woman who had received alendronate for 5 years and ibandronate for 1 year before suffering a subtrochanteric right femoral shaft insufficiency fracture. Five years earlier and 2 years after starting alendronate, she had sustained a subtrochanteric fracture of her left femur. This patient also had been treated with tibolone, inhaled GCs, and a PPI. A biopsy taken from the lateral cortex exactly at the level of the second fracture showed a fracture line extending from the periosteal to the endosteal surface with evidence of partial bone bridging across the fracture line on the periosteal surface. The fracture line was filled with blood, and there was no evidence of intracortical remodeling.

Lee[113] obtained a biopsy of endocortical bone from the proximal end of the fracture in an 82-year-old woman who had sustained bilateral atypical femoral fractures. She had been treated with alendronate for 8 years. Osteoclasts were not seen in the sample, and osteocytes were few in number. Polarized light

revealed the presence of both lamellar and woven bone. The bone marrow was hypercellular, but there was no evidence of inflammation, malignancy, or myelosclerosis. Goh and colleagues[10] performed qualitative histology on biopsies removed intraoperatively during repair of subtrochanteric fractures in 5 alendronate-treated patients, but they simply reported that there was no evidence of neoplasia.

Napoli and colleagues [144] described one of the few reported cases of atypical femoral fracture in a cancer patient (multiple myeloma) treated with high-dose intravenous BPs. Following a stem cell transplant, the patient was given pamidronate for 2 years and zoledronate for 4 years, in addition to high-dose GCs. An attempt to obtain an iliac crest biopsy was unsuccessful because the biopsy needle was unable to penetrate the "rock hard" bone. Wernecke and colleagues[123] reported another case of a patient with multiple myeloma who had been treated with intravenous BPs (pamidronate and zoledronate) for 9 years and presented with sequential, bilateral subtrochanteric stress fractures. Histologic examination of a biopsy taken from the femoral head during repair of the second fracture revealed an almost complete lack of osteoclasts and osteoblasts. A similar finding was described in curettage samples from the fracture site of a patient who had been treated with intravenous zoledronate for 1.5 years to prevent metastatic bone disease secondary to renal carcinoma.[145]

In contrast to the preceding cases, the biopsy from the subtrochanteric fracture site obtained by Somford and colleagues[119] revealed a very different cellular

profile. This biopsy was taken from a 76-year-old woman with RA who had been treated with alendronate for 8 years prior to admission for a subtrochanteric stress fracture of her left femur, which subsequently fractured completely. She also had received GCs and methotrexate for 11 years and infliximab for 3 years before the fracture. Nine months after the left femur fracture, she sustained a subtrochanteric fracture of her right femur. At that time, biopsies were obtained from the iliac crest and the right femur approximately 1 cm above the fracture. In the ilium, cancellous bone microarchitecture was normal for her age, but static bone formation indices, such as osteoid surface and volume, were reduced substantially to within the range previously reported for patients with alendronate-treated, GC– induced osteoporosis.[141] Unexpectedly, the eroded surface was about threefold higher than that of controls and 6.5 to 13 times the levels seen in patients with GC-induced osteoporosis and postmenopausal osteoporosis, respectively. Osteoclast number also was about four times higher than that recorded in alendronate-treated patients; however, this is not surprising because normal or elevated numbers of osteoclasts have been reported from biopsies of BP-treated patients.[146] In a biopsy taken close to the fracture site, eroded surface and osteoclast number were high, and static parameters of bone formation were low, although there are no normative data for this skeletal site. Osteoclast number at the fracture site was sixfold higher than at the iliac crest. At both sites, the morphologic appearance of the osteoclasts suggested that they were actively resorbing. The imbalance between resorption

and formation displayed by this patient differs from the prevailing hypothesis regarding the pathogenesis of atypical fractures, which invokes severe suppression of turnover. It is possible that the excessive resorption was related to the fracture itself, but this seems unlikely, given that it also was evident in the iliac crest biopsy and that the femoral biopsy was located 1 cm above the fracture and was taken within 12 hours of the event. MRI evidence for excessive resorption at the site of atypical fractures also has been reported in a BP-treated patient,[12] and the same phenomenon injuries.[147,148] Somford and colleagues[11] also took the opportunity to assess the mineralization density of the bone tissue at the fracture site because some have suggested that prolonged BP treatment may lead to hypermineralized and, therefore, brittle bone matrix. There was no evidence of hypermineralization and no change in hydroxyapatite crystal size, although the crystals were more mature than in control subjects, consistent with the known effects of alendronate on bone turnover and secondary mineralization.[119]

Summarizing the small amount of histologic data currently available in patients with atypical fractures, most, but not all, studies indicate very low turnover at both the iliac crest and the fracture site, although reports of increased turnover may be influenced by the fracture itself. Also, only static and qualitative histomorphometry analyses at the fracture site are available. Whether turnover at the iliac crest is lower than in the vast majority of BP-treated patients who have not sustained such fractures is not known. Double tetracycline labels are usually absent, but single labels are present in many cases, indicating

that turnover is not always absent at the ilium. Also, where available, biochemical markers of bone turnover are often not reduced to the same degree as that seen in the biopsy and may be within the normal range.[13,109,113–116,122,123] The findings of Somford and colleagues[119] at both the ilium and the fracture site and of Visekruna and colleagues[12] at the ilium suggest an alternate pathogenetic mechanism that involves increased resorption coupled with reduced bone formation. Clearly, more information is needed about bone histopathology at the site of atypical femur fractures (see "Key Research Questions" below).

Input from the pharmaceutical industry. Four members of the task force (DB, TB, RM, and ES) conducted teleconference sessions with representatives of companies that market drugs used to treat osteoporosis in the United States (ie, Amgen, Eli Lilly, Genentech, Merck, Novartis, and Warner-Chilcott). These sessions were informational; they permitted the task force to develop some understanding of the number of atypical fracture cases reported to the industry and the steps being taken by the individual companies to adjudicate cases reported to them. The sessions also permitted experts from the industry to provide their input on the case definition for consideration by the task force.

Most of the companies had examined the data from their large registration trials, and very few cases of atypical femoral fractures were detected. However, this approach was limited in most cases by reliance on diagnostic codes to search for subtrochanteric and diaphyseal fractures and lack of availability of radiographs to examine features of atypia in any subtrochanteric/diaphyseal fractures that occurred.

Also, maximum treatment duration in these trials was lower than the median treatment duration in the published cases of atypical fractures. Most cases were from the postmarketing reporting system. These are unsolicited reports of medical events temporally associated with use of a pharmaceutical product and originating from health care professionals, patients, regulatory agencies, the scientific literature, and the lay press. Although this system is useful for identifying rare events that are not detected in clinical trials, important limitations include underreporting and poor-quality reports with missing critical information. Additionally, it is impossible to calculate incidence rates; the numerator is uncertain because of under–reporting, and the denominator generally is based on the amount of drug distributed. There was considerable variability among companies in the mechanisms in place to identify atypical femoral fractures and in the amount of information that was shared with the task force. The number of patient-years of exposure to drugs that are currently on the market for osteoporosis varied between 2 million and 54 million. In general, reporting rates of subtrochanteric and diaphyseal fractures, with or without atypical features, were very low (1 to 3 per 1 million patient-years of exposure). However, as expected, the pharmaceutical companies were aware of cases that had not been reported in the medical literature.

Input from the USFDA. Two task force members (DB and ES) conducted a teleconference with representatives of the FDA. Data from the FDA were consistent with industry and task force estimates of the number of atypical femoral fractures. However,

officials emphasized that adverse-event reporting was subject to the same limitations noted earlier, particularly substantial underreporting.

Recommend the development of noninvasive diagnostic and imaging techniques with which to better characterize and diagnose the disorder

Imaging of the atypical femoral shaft fracture is relatively straightforward. Conventional radiography is the first line of approach, with more sophisticated imaging such as bone scintigraphy, magnetic resonance imaging (MRI), or computed tomography (CT) useful principally for detecting early or subtle prefracture features.[12,93,100,119,145]

Conventional radiographs of the femur, acquired in anteroposterior and lateral projections, usually suffice to demonstrate a range of characteristic findings in complete or incomplete fractures[149–152] (Fig. 2*A*). These consist of a substantially transverse fracture line, at least laterally, with variable obliquity extending medially (Fig. 3). There is often associated focal or diffuse cortical thickening, especially of the lateral cortex, where the fracture process generally initiates. When it is focal and substantial, this lateral cortical thickening may produce an appearance of cortical "beaking" or "flaring" adjacent to a discrete transverse fracture line[12,93,100,145] (Fig. 2*B*). As the fracture evolves and propagates medially, ultimately displacing and becoming a complete fracture, an oblique component may be observed as a prominent medial "spike" (Fig. 2*A*). Conventional radiography also may show diffuse cortical thickening, suggesting chronic stress response, which may be unilateral or bilateral (Fig. 3). Similarly, discrete linear lateral

cortical translucencies may be observed in the pre–fracture displacement phase, often with adjacent focal cortical thickening from periosteal new bone apposition[12,93,100,145] In contrast, femoral stress fractures of athletes usually involve the medial cortex in the proximal one-third of the diaphysis.[149–152]

While conventional radiographs may be suggestive or diagnostic of these stress or insufficiency fractures even in moderately early evolution, the findings may be quite subtle and nondiagnostic[149,150] (Figs. 4*A*, *C*, and 5*A*). In the setting of prodromal symptoms of aching deep thigh or groin pain and normal or equivocal radiographs, additional, more advanced diagnostic imaging procedures may be useful. Radionuclide bone scintigraphy may be employed to document the presence of an evolving stress or insufficiency fracture.[119,145,149–153] Typically, the appearance will be that of unilateral or bilateral increased uptake with a broad diffuse zone and a centrally located, focal region of extreme uptake usually in the lateral cortex (Figs. 4*B* and 5*B*). When only the diffuse pattern is observed, the differential diagnosis includes primary or secondary malignancy, bone infarction, and osteomyelitis. However, these conditions usually are centered in the medullary space of the femur and do not show the lateral cortical predilection of stress fractures.

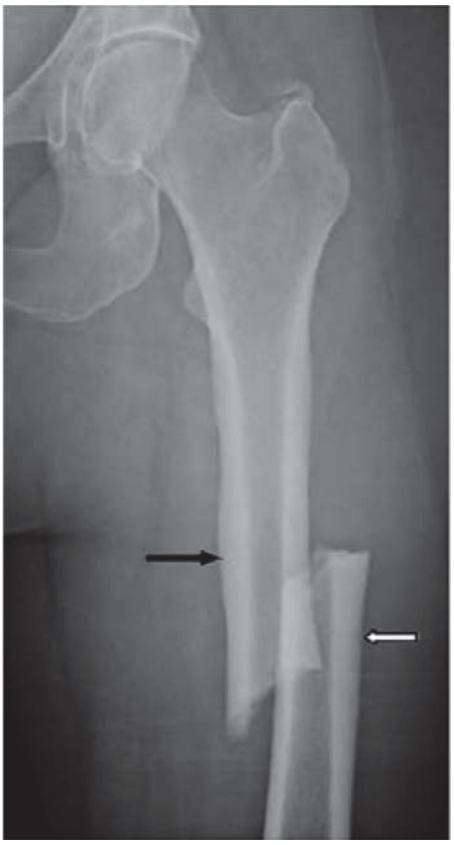


Fig. 3. AP radiograph of the left femur demonstrates a substantially transverse femoral fracture and associated diffuse periosteal new bone formation (*black arrow*) and focal cortical thickening (*white arrow*) consistent with atypical femoral shaft fracture. (*Courtesy of Joseph Lane, MD.*)

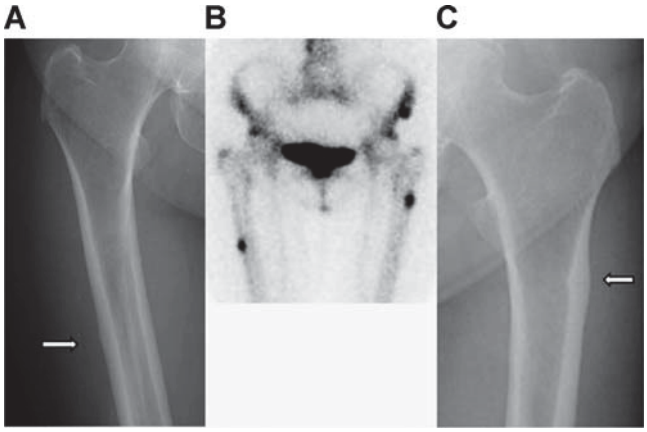


Fig. 4. Conventional AP radiographs of the right (*A*) and left femurs (*C*) demonstrate subtle focal cortical thickening on both periosteal and endosteal surfaces, as well callus on the periosteal surface (*arrows*), whereas bone scintigraphy (B) demonstrates focal increased radionuclide uptake in the corresponding proximal lateral femoral cortices, findings consistent with early, evolving, bilateral femoral insufficiency fractures. (*Courtesy of Piet Geusens, MD.*)

Like bone scintigraphy, MRI can detect the reactive hyperemia and periosteal new bone formation of an evolving stress or insufficiency fracture[151–155] (Fig. 5*C*). Typically, on T1-weighted images there will be diffuse decreased signal owing to both water partially replacing the normal fatty marrow components and the focal cortical thickening that creates little signal on this sequence. On T2-weighted images with fat saturation, there may be diffuse increased signal related to the associated inflammation and hyperemia. With relatively high resolution and multiplanar imaging, the evolving fracture line in the lateral cortex may be discerned on T2-weighted

images or on T1– weighted images obtained with fat saturation and gadolinium–based contrast enhancement. The ability to image thin sections in multiple planes creates both high sensitivity and high specificity, generally surpassing that of bone scintigraphy.

Similarly, the application of advanced multislice or spiral CT imaging with its thin sections, relatively high resolution, and multiplanar re-formation capability renders this technique quite useful in detecting subtle reactive periosteal new bone formation and the small, discrete radiolucency of the evolving fracture and its focal intracortical bone resorption.[156–158]

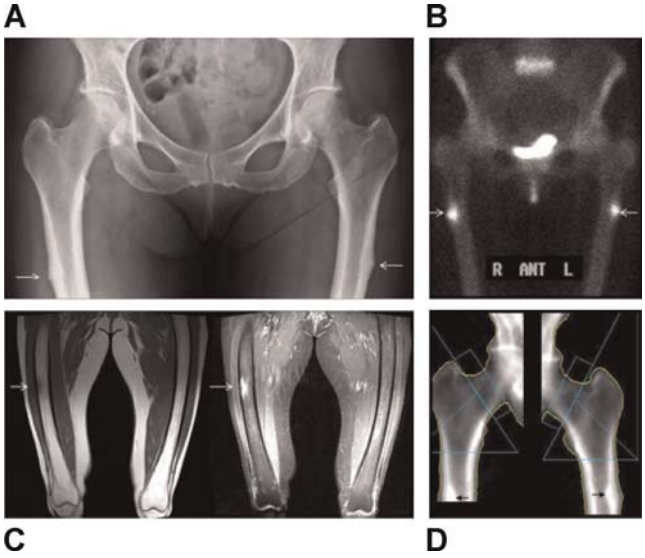


Fig. 5. Conventional AP radiograph of the pelvis (*A*) shows bilateral focal cortical thickening from periosteal new bone formation (*arrows*). Corresponding bone scintigraphy (*B*) demonstrates focal increased radionuclide uptake in the proximal

lateral femoral cortices (*arrows*). MRI images of the femurs (*C*) demonstrate subtle decreased signal on T1-weighted and increased signal on T2-weighted images only of the right femur on this section. Similar findings on AP DXA hip images (*D*) show focal bilateral cortical thickening consistent with early, evolving femoral insufficiency fractures. (*Courtesy of Fergus McKiernan, MD.*)

While scintigraphy, MRI, and CT scanning are more costly and less convenient than conventional radiography, these advanced imaging techniques provide superior sensitivity and specificity for detecting early stages of stress or insufficiency fractures and therefore, in selected instances, could improve the clinical management of atypical femoral shaft fractures (Fig. 5*A*–*C*). Even the lower-resolution images of dual-energy X-ray absorptiometry (DXA) occasionally may detect the hypertrophic new bone formation of an evolving proximal subtrochanteric femoral shaft fracture and aid in the differentiation of proximal thigh pain in this condition[104] (Fig. 5*D*).

Identify the key questions that the scientific community should address, and recommend a research agenda to elucidate incidence, pathophysiology, and etiology of atypical femoral fractures and their potential relationship with BP usage

Recommendations to facilitate future research

Create specific diagnostic and procedural codes for cases of atypical femoral fractures. To facilitate case ascertainment in administrative data sets and identification of incident cases, specific diagnostic and

procedural codes (ICD and/or CPT code) should be created for atypical femoral fractures based on the major features summarized in the case definition, as has been done recently for osteonecrosis of the jaw (ONJ, ICD-9 733.45). Such codes would facilitate preliminary case ascertainment in administrative data sets, which then would result in more efficient and targeted review of medical records and radio–graphic images. Having a specific code would permit better understanding of the relative incidence of these fractures compared with other osteoporotic fractures of the lower extremity that otherwise could be coded similarly. Without such a code, it will be more difficult to identify and confirm atypical fractures efficiently in future large population databases where the population at risk can be enumerated. Better precision in determining incidence rates of atypical fractures in large populations will permit examination of health economics and harm/benefit modeling.

Develop an international registry for cases of atypical femoral fractures. Because of the generally low incidence of these fractures, a centralized repository of standardized information will be required to generate the kinds of data and sufficient numbers of cases to understand the incidence, risk factors, and pathophysiology of atypical femoral fractures. The task force strongly recommends the establishment of an international registry spanning interested countries and health care plans with different patterns of BP usage. Local and national databases should be established to maximize case ascertainment. Data sources that contribute to the registry will be most informative if they can enumerate the population at risk (ie, a denominator).

The registry must use a uniform case definition of atypical fractures. All future studies using patients treated or untreated for osteoporosis should collect radiographs of all femoral fractures. Some formal means should be established to collect all radiographs in an electronic repository to allow for review of the variability in fracture pattern. There should be independent review of the radiographic studies to distinguish classic comminuted spiral fractures from noncomminuted transverse or short oblique atypical fractures of the femoral subtrochanteric and diaphyseal regions. Administrative data may be useful to assist in identifying possible cases, and an ideal scenario would link administrative data to medical and pharmacy records and radiographic images (not simply radiographic reports). Certain information on risk factors for fracture should be available from both administrative and clinical data sources (Table 7). An external agency also could follow up and validate FDA adverse– drug-report data in detail both to confirm all reported cases and to accumulate further accurate information on the epidemiology of this rare but important condition. This was considered to be a good model for national regulatory agencies to consider.

The registry should develop a focused standardized case report form to be completed for each case. A balance must be achieved in the recording of vital information because requiring too much information will make it time consuming to report cases and mean that fewer cases will be reported. Ideally, a case report should include information on demographics, fractures, BP exposure (if any), comorbid diseases, and concomitant medications, as summarized in Table 7.

Key research questions

Define measurable characteristics that are associated with atypical femoral fractures. To develop a clinical profile and to determine which patients are susceptible, it is important to define quantitatively features that are considered part of the etiopathology of atypical femoral fractures. For example, case reports and series suggest that cortical thickening at the fracture site is one feature of atypia. However, because cortical thickness varies throughout the diaphysis and also by age, gender, and possibly race, studies that evaluate this characteristic must specify the specific regions for analysis and measurement. A normal range by age, gender, and diaphyseal location should be developed as a first step toward identifying the significance of cortical thickening in the pathogenesis of atypical fractures. It also would be important to determine prospectively the frequency of other characteristics reported in conjunction with atypical femoral fractures, such as

- The frequency of periosteal reaction (ie, callus) associated with a fracture, including the incidence of such reactions in the contralateral nonfractured femur
- The incidence and duration of prodromal thigh pain
- The frequency of bilateral fractures and symptoms

Table 7. Information That Should Be Included in Future Reports of Atypical Femoral Fractures

- Standard demographic data (age, gender, height, weight, race, ethnicity)
- Anatomic location of the fracture (subtrochanteric or diaphyseal)
- Key radiographic features of atypia (see Table 1)
- Information on osteoporosis therapies
  - Doses, routes, duration of, and adherence to osteoporosis therapy
  - Indication for therapy (eg, osteoporosis, osteopenia, bone loss prevention, cancer, Paget disease)
- Prior fracture history
- Concomitant medications: GCs, thiazolidenediones, PPIs, anticonvulsants, statins, HRT, SERMs
- Comorbid medical conditions: Diabetes, RA, chronic kidney disease, malabsorption, errors of phosphate metabolism, joint replacement
- Family history (for genetic studies)
- Bone mineral density: before treatment and at time of fracture
- Biochemistries
  - Serum calcium, creatinine, 25(OH)D, PTH
  - Biochemical markers of bone turnover (P1NP, osteocalcin, total or bone alkaline phosphatase, C-telopeptide)

- Surgical management of the fracture (intramedullary rod, locking plates): documentation of delayed healing

Identify the true incidence of atypical femoral fractures and their association with BPs and/or other conditions characterized by low bone turnover. The precise incidence of atypical femoral fractures is unknown. To clarify the pathogenesis and causality, it is necessary to understand the true incidence of these fractures in the general population of patients without known osteoporosis who are unexposed to BPs, in patients with osteoporosis both exposed and unexposed to BPs and other agents used to treat osteoporosis, and in specific populations distinguished by concomitant drug exposures and comorbid diseases. Without these data, it is possible to misinterpret an association between treatment and fractures as causation. Patients with Paget disease receiving intermittent courses of BPs and patients with malignancies receiving high doses of intravenous BPs also should be assessed, with appropriate controls for duration of treatment, BMD, and other relevant parameters. To determine whether atypical femoral fractures are a class effect of BPs or generally related to low bone turnover, it is essential to determine whether such fractures occur with other antiresorptive drugs, such as estrogen, raloxifene, and denosumab, or in diseases characterized by extremely low bone turnover, such as osteopetrosis, hypoparathyroidism, myxedema, and certain forms of renal bone disease. It also will be important to determine whether the risk of atypical femoral fractures increases with greater inhibition of remodeling. The association between atypical femoral

fractures and concomitant GC therapy is a concern and requires investigation. BPs represent the cornerstone of strategies for the prevention and treatment of bone loss and fractures associated with GCs. However, there are no studies of long-term (>2 to 3 years) BP treatment in patients receiving GCs. Thus, while short-term (1 to 2 years) BP administration lowers the risk of typical osteoporotic fractures in patients with glucocorticoid-induced osteoporosis (GIOP), it is possible that prolonged administration of two classes of drugs that suppress bone formation may increase the risk of atypical femoral fractures.

Acquisition of biopsy data, especially from the site of fracture. Bone biopsy data should be collected whenever possible. Both specimens from the fracture site and tetracycline double-labeled transiliac bone biopsies would be desirable, although the former may be misleading as an indicator of the bone-remodeling rate prior to the fracture. Guidelines for the biopsy size and quality control should be developed. A concerted effort should be made to gather normative data for all these variables from the subtrochanteric femoral shaft. Carefully selected autopsy material would serve for all but the dynamic indices of bone formation. In addition, however, it might be helpful to assess local BMD using microradiographs, micro–computed tomography (mCT), or quantitative backscattered electron microscopy to provide some assessment of collagen organization and to evaluate necrotic bone by measurements of osteocyte apoptosis and/or lacunar density. The information that ideally should be collected from biopsy specimens is summarized in Table 8. Measurement of mechanical

properties, especially tissue properties, would be desirable. It is also important to know whether microcracks accumulate at the site of the femoral fracture and whether there is evidence of healing at the site.

Genetics. Although patients with X-linked hypophosphatemia (XLH) can have pseudofractures that resemble atypical femoral fractures,[2] XLH is usually obvious and only rarely could explain this problem. However, because atypical femoral fractures may resemble the pseudofractures that characterize adult hypophosphatasia,[2] studies to examine the gene that encodes the tissue nonspecific (bone) isoenzyme of alkaline phosphatase (TNSALP) for mutations or polymorphisms will be of research interest for atypical femoral fracture patients. This could clarify whether carriers for hypophosphatasia develop atypical femoral fractures from antiresorptive agents. Genome-wide association studies probably will not be helpful because DNA samples from many atypical femoral fracture patients would be necessary.

Table 8. Information to Be Collected from Transiliac and/or Femoral Fracture Biopsies

- Cortical and cancellous microarchitecture: Bone volume (BV/TV), trabecular thickness (Tb.Th), separation (Tb.Sp) and number (Tb.N); cortical area (Ct.Ar), thickness (Ct.Th), and porosity (Ct.Po)
- Mineral and matrix quality, including mineral density distribution, heterogeneity of matrix characteristics, and mineral particle size and shape

- Collagen cross-links and advanced glycation end products
- Collagen organization (lamellar/woven)
- Osteoblast and osteoclast surface
- Osteoblast and osteoclast numbers, with surface referent
- Prevalence of osteoblast and osteocyte apoptosis per total number of cells
- Amount of necrotic bone, as determined by measurements of lacunar density and empty lacunae
- Osteoid surface, volume, and average thickness
- Reversal surface, with bone surface referent
- Bone-formation rates and activation frequency, when possible
- Bone vascularity
- Tissue mechanical properties

Bone turnover markers. Retrospective analysis of BTM data from fracture patients but prior to the introduction of BP therapy and before the fracture should be performed where possible. Although specific BTMs may not be available, serum total alkaline phosphatase is a commonly performed test and may be useful in assessing whether bone turnover was low before or became suppressed during therapy in these individuals.

The development of an animal model to study pathogenesis. It is unlikely that pathogenesis and fracture mechanism can be fully understood from clinical data alone given the low incidence of these

fractures and the variability in patient characteristics. Once the risk factors contributing to atypical femoral fractures are better understood, animal models incorporating risk factors may provide insights into mechanisms at the cellular and tissue levels. Because bone remodeling is likely an important component of the response, in vivo animal models that exhibit intracortical remodeling are particularly critical. Several different animal models have been used to study the pathogenesis of stress fractures. Existing rodent models[3,4,66] may not be appropriate because of their lack of haversian remodeling, but attempts should be made to adapt fatigue–loading techniques that have been developed in rodents to larger animals. Nonhuman primates would be acceptable but are expensive. Several smaller animal models, such as rabbits and dogs, that have substantial intracortical bone remodeling may be appropriate. However, these animals cannot be studied in conjunction with the osteoporotic condition because attempts to make them estrogen-deficient generally do not result in bone loss. Sheep have some intracortical remodeling and can be made estrogen-deficient. However, they have some reproductive anomalies and are seasonal breeders, which may limit their usefulness. Minipigs might offer a suitable alternative, although adult minipigs can be difficult to handle and are expensive.

Because of the similarity of the signs and symptoms preceding atypical femoral fractures to stress fractures, it may be desirable to combine variable loading regimens (eg, increased mechanical loading or fatigue injury) with a concurrent pharmacologic regimen that could accelerate the development of bone fragility. Animals do not appear to fracture

spontaneously, even following prolonged treatment with high doses of second– and third– generation BPs. For this reason, the endpoints of such studies should not be overt fracture. Rather, animal models can be used to investigate alterations in the structural and material properties of the bone under different conditions, such as coadministration of GCs and BPs or administration of BPs to diabetic animals. They also could be used to explore possible regional differences in the biodistribution of various BPs, bone histomorphometry and microarchitecture, bone healing, and bone vascularity. Efforts at management of stress-induced lesions (eg, treatment with parathyroid hormone) also should be examined in such models.

Recommend clinical orthopedic and medical management of atypical femoral fractures based on available information

Surgical treatment strategy for atypical subtrochanteric and femoral shaft fractures

Because of the propensity for delayed healing, the morbidity of these fractures is particularly high. The task force recognized that there are no controlled studies evaluating surgical treatment strategies for atypical subtrochanteric and femoral shaft fractures. The recommendations outlined here therefore are opinion-based and represent the consensus of the orthopedic surgeons who served on the task force. The task force developed a hierarchical approach to management that depends on whether the fracture is complete or incomplete.

History of thigh or groin pain in a patient on BP therapy. A femoral fracture must be ruled

out.[10,12,93,100,110,115,124,159] Anteroposterior and lateral plain radiographs of the hip, including the full diaphysis of the femur, should be performed. If the radiograph is negative and the level of clinical suspicion is high, a technetium bone scan or MRI of the femur should be performed to detect a periosteal stress reaction. The advantage of the technetium bone scan is that both legs will be imaged.

Complete subtrochanteric/diaphyseal femoral fracture. Orthopedic management includes stabilizing the fracture and addressing the medical management[10,12,93,100,110,115,124,159] (see below). Since BPs inhibit osteoclastic remodeling, endochondral fracture repair is the preferred method of treatment. Intramedullary reconstruction full-length nails accomplish this goal and protect the entire femur. Locking plates preclude endochondral repair, have a high failure rate, and are not recommended as the method of fixation. The medullary canal should be overreamed (at least 2.5 mm larger than the nail diameter) to compensate for the narrow intramedullary diameter (if present), facilitate insertion of the reconstruction nail, and prevent fracture of the remaining shaft. The proximal fragment may require additional reaming to permit passage of the nail and avoid malalignment. The contralateral femur must be evaluated radiographically, including scintigraphy or MRI, whether or not symptoms are present.[110]

Incomplete subtrochanteric/femoral shaft fractures. Prophylactic reconstruction nail fixation is recommended for incomplete fractures accompanied by pain.[10,12,93,100,110,115,124,159] If the patient has minimal pain, a trial of conservative therapy, in which

weight bearing is limited through the use of crutches or a walker, may be considered. However, if there is no symptomatic and radiographic improvement after 2 to 3 months of conservative therapy, prophylactic nail fixation should be strongly considered because these patients may progress to a complete fracture. For patients with incomplete fractures and no pain, weight bearing may be continued but should be limited and vigorous activity avoided. Reduced activity should be continued until there is no bone edema on MRI.

Medical management of atypical subtrochanteric/femoral shaft fractures

There are also no controlled studies evaluating medical treatment strategies for atypical subtrochanteric and femoral shaft fractures. The recommendations outlined here therefore are opinion-based and represent the consensus of the clinicians who served on the task force. The task force considered two main aspects of medical management:

Prevention. Decisions to initiate pharmacologic treatment, including BPs, to manage patients with osteoporosis should be made based on an assessment of benefits and risks. Patients who are deemed to be at low risk of osteoporosis-related fractures should not be started on BPs. For patients with osteoporosis in the spine and normal or only moderately reduced femoral neck or total-hip BMD, one could consider alternative treatments for osteoporosis, such as raloxifene or teriparatide, depending on the severity of the patient's condition. It is apparent that therapy must be individualized and clinical judgment must be used because there will not always be sufficient

evidence for specific clinical situations. BP therapy should be strongly considered to protect patients from rapid bone loss and increased fracture rates associated with clinical scenarios such as organ transplantation, endocrine or chemotherapy for breast or prostate cancer, and initiation of aromatase inhibitors and GCs. However, long-term BP therapy may not always be necessary in these clinical conditions.[160,161] More research is needed to determine the most effective dose and duration of BPs in patients with secondary causes of rapid bone loss.

The optimal duration of BP treatment is not known. Based on studies with alendronate[162] and risedronate,[163,164] patients with osteoporosis will have an antifracture benefit for at least 5 years. However, continued use of BP therapy beyond that time should be reevaluated annually, assessing factors such as BMD, particularly in the hip region, fracture history, newly diagnosed underlying conditions or initiation of other medications known to affect skeletal status, and new research findings in a rapidly evolving field. For those who are considered to remain at moderately elevated fracture risk, continuation of BP therapy should be strongly considered. Recent or multiple fractures (including asymptomatic vertebral fractures on lateral DXA imaging or lateral spine X-ray at the time of reevaluation) should suggest assessment or reassessment for underlying secondary causes and reevaluation of the treatment plan. Such patients are known to be at high risk of future fracture, and thus discontinuation of osteoporosis treatment is inadvisable. However, whether continuing BPs beyond 5 years will reduce that risk is unclear. In the FLEX trial, the incidence of clinical (but not

morphometric) vertebral fractures was significantly lower in those on 10 years of continued alendronate versus those who stopped after 5 years[162]; reduction in nonvertebral fracture incidence was limited to women without a fracture history but with femoral neck T-scores that were –2.5 or less.[165] While conclusions from this trial need to be tempered by its limitations, primarily the small study sample, these are the only long-term fracture data available with alendronate treatment. With regard to risedronate, 7 years of therapy did not further reduce the incidence of vertebral fractures below that observed with 3 and 5 years of therapy.[163] Models to help determine absolute risk of fracture in patients who have already been treated for 4 to 5 years are needed to help guide these decisions.

Based on current case reports and series, the median BP treatment duration in patients with atypical subtrochanteric and femoral shaft fractures is 7 years. For patients without a recent fracture and with femoral neck T-scores greater than –2.5 after the initial therapeutic course, consideration may be given to a "drug holiday" from BPs. Because some patients with atypical femoral fractures while on BPs were on concomitant therapy with GCs, estrogen, tamoxifen, or PPIs, continued BP therapy should be reevaluated, particularly in those deemed to be at low or only modestly elevated fracture risk. Whether discontinuation of BPs after 4 to 5 years in the lower-risk group will lead to fewer atypical subtrochanteric fractures is not known.

If BPs are discontinued, there are no data to guide when or whether therapy should be restarted. However, patients should be followed by clinical

assessment, bone turnover markers, and BMD determination. Restarting osteoporosis therapy, either with BPs or with a different class of agent, can be considered in patients who appear to be at increasing fracture risk. Models to help assess risk in previously treated patients, after 1 or more years off therapy, are needed to help guide these therapeutic decisions. It seems apparent that there can be no general rule and that decisions to stop and/or restart therapy must be individualized.

More than half of patients reported with atypical femoral fractures have had a prodrome of thigh or groin pain before suffering an overt break. Thus it is important to educate physicians and patients about this symptom and for physicians to ask patients on BPs and other potent antiresorptive agents about thigh or groin pain. Complaints of thigh or groin pain in a patient on BPs require urgent radiographic evaluation of both femurs (even if pain is unilateral). If plain radiographs are normal or equivocal and clinical suspicion is high, MRI or radionuclide scintigraphy should be performed to identify stress reaction, stress fracture, or partial fracture of either femur. Other disorders, such as forms of osteomalacia, also should be considered.[2]

Medical management. For patients with a stress reaction, stress fracture, or incomplete or complete subtrochanteric or femoral shaft fracture, potent antiresorptive agents should be discontinued. Dietary calcium and vitamin D status should be assessed, and adequate supplementation should be prescribed. A few case reports and anecdotal findings suggest that teriparatide therapy can improve or hasten healing of these fractures.[13,123] Additionally, consistent with a

large body of animal data,[166] some clinical evidence[167,168] indicates that teriparatide benefits nonunion of fractures, although a controlled trial in patients with Colles' fracture showed little effect.[169] Given the relative rarity of atypical femoral fractures and ethical issues surrounding potential randomization to placebo, it seems unlikely that there will be a randomized, controlled trial of teriparatide for subtrochanteric and femoral shaft fractures. Therefore, the level of evidence for efficacy likely will remain low. However, in the absence of evidence-based approaches, teriparatide should be considered in patients who suffer these fractures, particularly if there is little evidence of healing by 4 to 6 weeks after surgical intervention.

Summary and Conclusions

BPs are highly effective at reducing the risk of spine and nonspine fractures, including typical and common femoral neck and intertrochanteric fractures. However, there is evidence of a relationship between long-term BP use and a specific type of subtrochanteric and femoral shaft fracture. These fractures are characterized by unique radiographic features (ie, transverse or short oblique orientation, absence of comminution, cortical thickening, stress fracture or stress reaction on the symptomatic and/or contralateral side, and delayed healing) and unique clinical features (ie, prodromal pain and bilaterality). The apparent increased risk for atypical femoral fractures in patients receiving GCs is a concern because BPs are the mainstay for prevention of GC-induced osteoporotic fractures. Bone biopsies from the iliac crest and/or fracture site generally show reduced bone formation consistent with BP action.

Paradoxically, some patients show biopsy evidence of enhanced bone resorption. Biochemical BTMs are often normal but may be increased. These fractures can occur in patients who have not been treated with BPs, and their true incidence in both treated and untreated patients is unknown. However, they appear to be more common in patients who have been exposed to long-term BPs, usually for more than 3 years (median treatment 7 years). It must be emphasized that these fractures are rare, particularly when considered in the context of the millions of patients who have taken BPs and also when compared with typical and common femoral neck and intertrochanteric fractures. It also must be emphasized that BPs are important drugs for the prevention of common osteoporotic fractures. However, atypical femoral fractures are of concern, and more information is urgently needed both to assist in identifying patients at particular risk and to guide decision making about duration of BP therapy. Physicians and patients should be made aware of the possibility of atypical femoral fractures and of the potential for bilaterality through a change in labeling of BPs. Given the relative rarity of atypical femoral fractures, to facilitate future research, specific diagnostic and procedural codes should be created for cases of atypical femoral fractures, an international registry should be established, and the quality of case reporting should be improved. Research directions should include development of animal models, increased surveillance, and additional epidemiologic data to establish the true incidence of and risk factors for this condition and studies to address their surgical and medical management.

Disclosures

The American Society for Bone and Mineral Research (ASBMR) is well served by the fact that many of those responsible for policy development and implementation have diverse interests and are involved in a variety of activities outside the Society. The ASBMR protects itself and its reputation by ensuring impartial decision making. Accordingly, the ASBMR requires that all ASBMR officers, councilors, committee chairs, editors-in-chief, associate editors, and certain other appointed representatives disclose any real or apparent conflicts of interest (including investments or positions in companies involved in the bone and mineral metabolism field), as well as any duality of interests (including affiliations, organizational interests, and/or positions held in entities relevant to the bone and mineral metabolism field and/or the ASBMR).

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Relationship key: (1) Research grant or financial support from commercial entities; (2) consultant or member of advisory board to a commercial entity; (3) participant in a speakers' bureau; (4) employment or executive positions in pharmaceutical, medical device, or diagnostic companies, including industry scientists in the bone and mineral field; (5) stock holdings in pharmaceutical, medical device, or diagnostic companies; (6) any other situation or transaction in which you have a formal role or interest (eg, you serve on a bone-related organization's board, committee, or journal; a family member contracts with ASBMR; etc.).

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The American Society for Bone and Mineral Research (ASBMR) is the premier professional, scientific, and medical society established to promote excellence in bone and mineral research and to facilitate the translation of that research into clinical practice. The ASBMR has a membership of nearly 4000 physicians, basic research scientists, and clinical investigators from around the world. The ASBMR has a hard-earned reputation for scientific integrity.

Most of the Society's revenue comes from membership dues, fees paid to attend the Society's annual meeting, and subscriptions to ASBMR publications. Like many scientific, professional, and medical organizations, ASBMR also accepts grants from pharmaceutical companies, the federal government, and other entities to support its mission. ASBMR receives corporate support in the form of unrestricted educational grants from pharmaceutical companies, rental of exhibit space at its annual

meeting, and paid advertisements in its journal. To ensure that the Society adheres to the highest ethical practices, ASBMR has an ethics committee, consults with experts in health care ethics, and periodically reviews its practices with regard to managing potential conflict of interest.

Although task force members were required to disclose their potential conflicts of interest and their disclosures are published with this document, ASBMR recognizes that this might not go far enough to demonstrate to some that the final output of the task force is free of all bias. In an effort to address this concern, two additional individuals were assigned to the Atypical Femoral Fractures Task Force—an ethicist and a scientist knowledgeable about the musculoskeletal system who does not work directly on osteoporosis or bisphosphonates or with pharmaceutical companies who make or market bisphosphonates. The role of these individuals was to provide ethical oversight to the work of the task force. Both individuals have verified and attested that they witnessed no commercial bias during the task force's deliberations, during discussions with the pharmaceutical industry, or in the preparation of the final document by the task force.

[Conflicts Table Omitted]

References

1. Chisin R. The role of various imaging modalities in diagnosing stress fractures. In: Burr DB, Milgrom C, eds. Musculoskeletal Fatigue and Stress Fractures. Boca Raton, FL: CRC Press, 2001:279–294.

2. Whyte MP. Atypical femoral fractures, bisphosphonates, and adult hypophosphatasia. J Bone Miner Res. 2009;24:1132–1134.

3. Li J, Waugh LJ, Hui SL, Burr DB, Warden SJ. Low-intensity pulsed ultrasound and nonsteroidal anti-inflammatory drugs have opposing effects during stress fracture repair. J Orthop Res. 2007;25:1559– 1567.

4. Uthgenannt BA, Kramer MH, Hwu JA, Wopenka B, Silva MJ. Skeletal self-repair: stress fracture healing by rapid formation and densification of woven bone. J Bone Miner Res. 2007;22:1548–1556.

5. Burr DB, Milgrom C, Boyd RD, Higgins WL, Robin G, Radin EL. Experimental stress fractures of the tibia: biological and mechanical aetiology in rabbits. J Bone Joint Surg Br. 1990;72:370–375.

6. Li GP, Zhang SD, Chen G, Chen H, Wang AM. Radiographic and histologic analyses of stress fracture in rabbit tibias. Am J Sports Med. 1985;13:285–294.

7. Muir P, Johnson KA, Ruaux-Mason CP. In vivo matrix microdamage in a naturally occurring canine fatigue fracture. Bone. 1999;25:571– 576.

8. Nunamaker D. Bucked Shins in Horses. In: Burr DB, Milgrom C, eds. Musculoskeletal Fatigue and Stress Fractures. Boca Raton: CRC Press, 2001: 279–294.

9. Verheyen K, Price J, Lanyon L, Wood J. Exercise distance and speed affect the risk of fracture in racehorses. Bone. 2006;39:1322–1330.

10. Goh SK, Yang KY, Koh JS, et al. Subtrochanteric insufficiency fractures in patients on alendronate therapy: a caution. J Bone Joint Surg Br. 2007;89:349–353.
11. Guisti A, Hamdy NAT, Papapoulos SE. Atypical fractures of the femur and bisphosphonate therapy: a systematic review of case/case series studies. Bone. 2010;24:1736–1740.
12. Kwek EB, Goh SK, Koh JS, Png MA, Howe TS. An emerging pattern of subtrochanteric stress fractures: a long-term complication of alendronate therapy? Injury. 2008;39:224–231.
13. Visekruna M, Wilson D, McKiernan FE. Severely suppressed bone turnover and atypical skeletal fragility. J Clin Endocrinol Metab. 2008;93:2948–2952.
14. Jilka RL, Weinstein RS, Parfitt AM, Manolagas SC. Quantifying osteoblast and osteocyte apoptosis: challenges and rewards. J Bone Miner Res. 2007;22:1492–1501.
15. Plotkin LI, Lezcano V, Thostenson J, Weinstein RS, Manolagas SC, Bellido T. Connexin 43 is required for the anti-apoptotic effect of bisphosphonates on osteocytes and osteoblasts in vivo. J Bone Miner Res. 2008;23:1712–1721.
16. Wang FS, Ko JY, Yeh DW, Ke HC, Wu HL. Modulation of Dickkopf-1 attenuates glucocorticoid induction of osteoblast apoptosis, adipocytic differentiation, and bone mass loss. Endocrinology. 2008;149: 1793–1801.
17. Asada T, Kushida T, Umeda M, et al. Prevention of corticosteroid–induced osteonecrosis in rabbits

by intra-bone marrow injection of autologous bone marrow cells. Rheumatology (Oxford). 2008;47: 591–596.

18. Saito M, Marumo K. Collagen cross-links as a determinant of bone quality: a possible explanation for bone fragility in aging, osteoporosis, and diabetes mellitus. Osteoporos Int. 21:195–214.
19. Vashishth D, Gibson GJ, Khoury JI, Schaffler MB, Kimura J, Fyhrie DP. Influence of nonenzymatic glycation on biomechanical properties of cortical bone. Bone. 2001;28:195–201.
20. Allen MR, Gineyts E, Leeming DJ, Burr DB, Delmas PD. Bisphosphonates alter trabecular bone collagen cross-linking and isomerization in beagle dog vertebra. Osteoporos Int. 2008;19:329–337.
21. Tang SY, Allen MR, Phipps R, Burr DB, Vashishth D. Changes in non–enzymatic glycation and its association with altered mechanical properties following 1-year treatment with risedronate or alendronate. Osteoporos Int. 2009;20:887–894.
22. Hernandez CJ, Tang SY, Baumbach BM, et al. Trabecular micro–fracture and the influence of pyridinium and non-enzymatic glycation-mediated collagen cross-links. Bone. 2005;37:825–832.
23. Wang X, Shen X, Li X, Agrawal CM. Age-related changes in the collagen network and toughness of bone. Bone. 2002;31:1–7.

24. Zioupos P, Currey JD, Hamer AJ. The role of collagen in the declining mechanical properties of aging human cortical bone. J Biomed Mater Res. 1999;45:108–116.

25. Vashishth D. Advanced glycation end-products and bone fractures. BoneKey. 2009;6:268–278.

26. Tang SY, Zeenath U, Vashishth D. Effects of non-enzymatic glycation on cancellous bone fragility. Bone. 2007;40:1144–1151.

27. Viguet-Carrin S, Roux JP, Arlot ME, et al. Contribution of the advanced glycation end product pentosidine and of maturation of type I collagen to compressive biomechanical properties of human lumbar vertebrae. Bone. 2006;39:1073–1079.

28. Allen MR, Burr DB. Three years of alendronate treatment results in similar levels of vertebral microdamage as after one year of treatment. J Bone Miner Res. 2007;22:1759–1765.

29. Saito M, Mori S, Mashiba T, Komatsubara S, Marumo K. Collagen maturity, glycation induced-pentosidine, and mineralization are increased following 3-year treatment with incadronate in dogs. Osteoporos Int. 2008;19:1343–1354.

30. Durchschlag E, Paschalis EP, Zoehrer R, et al. Bone material properties in trabecular bone from human iliac crest biopsies after 3– and 5-year treatment with risedronate. J Bone Miner Res. 2006;21:1581– 1590.

31. Boskey AL, Spevak L, Weinstein RS. Spectroscopic markers of bone quality in

alendronate-treated postmenopausal women. Osteoporos Int. 2009;20:793–800.

32. Donnelly E, Meredith DS, Gladnick BP, Rebolledo BJ, Lane JM, Boskey AL. Reduced matrix heterogeneity with bisphosphonate treatment in postmenopausal women with proximal femoral fractures. American Society of Bone and Mineral Research Annual Meeting, Toronto, Canada. 2010.

33. Boivin GY, Chavassieux PM, Santora AC, Yates J, Meunier PJ. Alendronate increases bone strength by increasing the mean degree of mineralization of bone tissue in osteoporotic women. Bone. 2000; 27:687–694.

34. Roschger P, Rinnerthaler S, Yates J, Rodan GA, Fratzl P, Klaushofer K. Alendronate increases degree and uniformity of mineralization in cancellous bone and decreases the porosity in cortical bone of osteoporotic women. Bone. 2001;29:185–191.

35. Roschger P, Paschalis EP, Fratzl P, Klaushofer K. Bone mineralization density distribution in health and disease. Bone. 2008;42:456–466.

36. Roschger P, Gupta HS, Berzlanovich A, et al. Constant mineralization density distribution in cancellous human bone. Bone. 2003;32:316– 323.

37. Turner CH, Burr DB. Principles of Bone Biomechanics. In: Lane NE, Sambrook PN, eds. Osteoporosis and the Osteoporosis of Rheumatic Diseases. Mosby. Philadelphia: Elsevier, 2006: 41–53.

38. Donnelly E, Gladnick BP, Meredith DS, Lane JM, Boskey AL. Bisphosphonate treatment reduces cortical tissue heterogeneity in post–menopausal women with fractures. Transactions Orthopaedic Research Society 56th Annual Meeting, New Orleans. 2010.

39. Donnelly E, Meredith DS, Nguyen JT, et al. Mean bone tissue composition, but not heterogeneity, is consistent across iliac crest and trochanteric sites. American Society for Bone and Mineral Research, 23nd Annual Meeting, Toronto, Canada. 2010.

40. Borah B, Dufresne TE, Ritman EL, et al. Long-term risedronate treatment normalizes mineralization and continues to preserve trabecular architecture: sequential triple biopsy studies with micro-computed tomography. Bone. 2006;39:345–352.

41. Roschger P, Lombardi A, Misof BM, et al. Mineralization density distribution of postmenopausal osteoporotic bone is restored to normal after long-term alendronate treatment: qBEI and sSAXS data from the fracture intervention trial long-term extension (FLEX). J Bone Miner Res. 2010;25:48–55.

42. Ruffoni D, Fratzl P, Roschger P, Phipps R, Klaushofer K, Weinkamer R. Effect of temporal changes in bone turnover on the bone mineralization density distribution: a computer simulation study. J Bone Miner Res. 2008;23:1905–1914.

43. Zoehrer R, Roschger P, Paschalis EP, et al. Effects of 3– and 5-year treatment with

risedronate on bone mineralization density distribution in triple biopsies of the iliac crest in postmenopausal women. J Bone Miner Res. 2006;21:1106–1112.

44. Mori S, Harruff R, Ambrosius W, Burr DB. Trabecular bone volume and microdamage accumulation in the femoral heads of women with and without femoral neck fractures. Bone. 1997;21:521–526.
45. Schaffler MB, Choi K, Milgrom C. Aging and matrix microdamage accumulation in human compact bone. Bone. 1995;17:521–525.
46. Li J, Mashiba T, Burr DB. Bisphosphonate treatment suppresses not only stochastic remodeling but also the targeted repair of micro–damage. Calcif Tissue Int. 2001;69:281–286.
47. Parfitt AM. Targeted and nontargeted bone remodeling: relationship to basic multicellular unit origination and progression. Bone. 2002;30:5–7.
48. Allen MR, Iwata K, Phipps R, Burr DB. Alterations in canine vertebral bone turnover, microdamage accumulation, and biomechanical properties following 1-year treatment with clinical treatment doses of risedronate or alendronate. Bone. 2006;39:872–879.
49. Allen MR, Iwata K, Sato M, Burr DB. Raloxifene enhances vertebral mechanical properties independent of bone density. Bone. 2006;39: 1130–1135.

50. Stepan JJ, Burr DB, Pavo I, et al. Low bone mineral density is associated with bone microdamage accumulation in postmenopausal women with osteoporosis. Bone. 2007;41:378–385.

51. Chapurlat RD, Arlot M, Burt-Pichat B, et al. Microcrack frequency and bone remodeling in postmenopausal osteoporotic women on long–term bisphosphonates: a bone biopsy study. J Bone Miner Res. 2007; 22:1502–1509.

52. Iwata K, Allen MR, Phipps R, Burr DB. Microcrack initiation occurs more easily in vertebrae from beagles treated with alendronate than with risedronate. Bone. 2006;38(Suppl):42.

53. Allen MR, Reinwald S, Burr DB. Alendronate reduces bone toughness of ribs without significantly increasing microdamage accumulation in dogs following 3 years of daily treatment. Calcif Tissue Int. 2008;82:354–360.

54. Mashiba T, Turner CH, Hirano T, Forwood MR, Johnston CC, Burr DB. Effects of suppressed bone turnover by bisphosphonates on micro–damage accumulation and biomechanical properties in clinically relevant skeletal sites in beagles. Bone. 2001;28:524–531.

55. Mashiba T, Hirano T, Turner CH, Forwood MR, Johnston CC, Burr DB. Suppressed bone turnover by bisphosphonates increases micro–damage accumulation and reduces some biomechanical properties in dog rib. J Bone Miner Res. 2000;15:613–620.

56. Nancollas GH, Tang R, Phipps RJ, et al. Novel insights into actions of bisphosphonates on bone:

differences in interactions with hydro–xyapatite. Bone. 2006;38:617–627.

57. Bagger YZ, Tanko LB, Alexandersen P, Ravn P, Christiansen C. Alendronate has a residual effect on bone mass in postmenopausal Danish women up to 7 years after treatment withdrawal. Bone. 2003;33:301–307.

58. Burr DB, Diab T, Koivunemi A, Koivunemi M, Allen MR. Effects of 1 to 3 years' treatment with alendronate on mechanical properties of the femoral shaft in a canine model: implications for subtrochanteric femoral fracture risk. J Orthop Res. 2009;27:1288–1292.

59. Parfitt AM. The physiologic and clinical significance of bone histomorphometric data. In: Recker RR, ed. Bone Histomorphometry: Techniques and Interpretation. Boca Raton: CRC Press, 1983:143–224.

60. Forwood MR, Burr DB, Takano Y, Eastman DF, Smith PN, Schwardt JD. Risedronate treatment does not increase microdamage in the canine femoral neck. Bone. 1995;16:643–650.

61. Cao Y, Mori S, Mashiba T, et al. Raloxifene, estrogen, and alendronate affect the processes of fracture repair differently in ovariectomized rats. J Bone Miner Res. 2002;17:2237–2246.

62. MacDonald MM, Schindeler A, Little DG. Bisphosphonate treatment and fracture repair. BoneKey. 2007;4:236–251.

63. Martinez MD, Schmid GJ, McKenzie JA, Ornitz DM, Silva MJ. Healing of non-displaced

fractures produced by fatigue loading of the mouse ulna. Bone. 2010;46:1604–1612.

64. Li J, Miller MA, Hutchins GD, Burr DB. Imaging bone microdamage in vivo with positron emission tomography. Bone. 2005;37:819–824.

65. Milgrom C, Finestone A, Novack V, et al. The effect of prophylactic treatment with risedronate on stress fracture incidence among infantry recruits. Bone. 2004;35:418–424.

66. Barrett JG, Sample SJ, McCarthy J, Kalscheur VL, Muir P, Prokuski L. Effect of short-term treatment with alendronate on ulnar bone adaptation to cyclic fatigue loading in rats. J Orthop Res. 2007;25: 1070–1077.

67. Allen MR, Burr DB. Human femoral neck has less cellular periosteum, and more mineralized periosteum, than femoral diaphyseal bone. Bone. 2005;36:311–316.

68. Wood J, Bonjean K, Ruetz S, et al. Novel antiangiogenic effects of the bisphosphonate compound zoledronic acid. J Pharmacol Exp Ther. 2002;302:1055–1061.

69. Deckers MM, Van Beek ER, Van Der Pluijm G, et al. Dissociation of angiogenesis and osteoclastogenesis during endochondral bone formation in neonatal mice. J Bone Miner Res. 2002;17:998–1007.

70. Fournier P, Boissier S, Filleur S, et al. Bisphosphonates inhibit angiogenesis in vitro and testosterone-stimulated vascular regrowth in the ventral prostate in castrated rats. Cancer Res. 2002; 62:6538–6544.

71. Kidd LJ, Stephens AS, Kuliwaba JS, Fazzalari NL, Wu AC, Forwood MR. Temporal pattern of gene expression and histology of stress fracture healing. Bone. 2010;46:369–378.

72. Wohl GR, Towler DA, Silva MJ. Stress fracture healing: fatigue loading of the rat ulna induces upregulation in expression of osteogenic and angiogenic genes that mimic the intramembranous portion of fracture repair. Bone. 2009;44:320–330.

73. Salminen S, Pihlajamaki H, Avikainen V, Kyro A, Bostman O. Specific features associated with femoral shaft fractures caused by low–energy trauma. J Trauma. 1997;43:117–122.

74. Nieves JW, Bilezikian JP, Lane JM, et al. Fragility fractures of the hip and femur: incidence and patient characteristics. Osteoporos Int. 2010;21:399–408.

75. Mullaji AB, Thomas TL. Low-energy subtrochanteric fractures in elderly patients: results of fixation with the sliding screw plate. J Trauma. 1993;34:56–61.

76. Salminen ST, Pihlajamaki HK, Avikainen VJ, Bostman OM. Population based epidemiologic and morphologic study of femoral shaft fractures. Clin Orthop Relat Res. 2000;372:241–249.

77. Ekstrom W, Nemeth G, Samnegard E, Dalen N, Tidermark J. Quality of life after a subtrochanteric fracture: a prospective cohort study on 87 elderly patients. Injury. 2009;40:371–376.

78. Abrahamsen B, van Staa T, Ariely R, Olson M, Cooper C. Excess mortality following hip fracture: a systematic epidemiological review. Osteoporos Int. 2009;20:1633–1650.

79. Holt G, Smith R, Duncan K, Hutchison JD, Gregori A. Gender differences in epidemiology and outcome after hip fracture: evidence from the Scottish Hip Fracture Audit. J Bone Joint Surg Br. 2008;90:480–483.

80. Penrod JD, Litke A, Hawkes WG, et al. The association of race, gender, and comorbidity with mortality and function after hip fracture. J Gerontol A Biol Sci Med Sci. 2008;63:867–872.

81. Johnell O, Kanis JA. An estimate of the worldwide prevalence, mortality and disability associated with hip fracture. Osteoporos Int. 2004;15:897–902.

82. Weiss RJ, Montgomery SM, Al Dabbagh Z, Jansson KA. National data of 6409 Swedish inpatients with femoral shaft fractures: stable incidence between 1998 and 2004. Injury. 2009;40:304–308.

83. Singer BR, McLauchlan GJ, Robinson CM, Christie J. Epidemiology of fractures in 15,000 adults: the influence of age and gender. J Bone Joint Surg Br. 1998;80:243–248.

84. Soveid M, Serati AR, Masoompoor M. Incidence of hip fracture in Shiraz, Iran. Osteoporos Int. 2005;16:1412–1416.

85. Melton LJ 3rd, Crowson CS, O'Fallon WM. Fracture incidence in Olmsted County, Minnesota: comparison of urban with rural rates

and changes in urban rates over time. Osteoporos Int. 1999;9:29–37.

86. Knowelden J, Buhr AJ, Dunbar O. Incidence of fractures in persons over 35 years of age. A report to the M.R.C. working party on fractures in the elderly. Br J Prev Soc Med. 1964;18:130–141.

87. Baron JA, Karagas M, Barrett J, et al. Basic epidemiology of fractures of the upper and lower limb among Americans over 65 years of age. Epidemiology. 1996;7:612–618.

88. Donaldson LJ, Cook A, Thomson RG. Incidence of fractures in a geographically defined population. J Epidemiol Community Health. 1990;44:241–245.

89. Wong PC. Fracture epidemiology in a mixed southeastern Asian community (Singapore). Clin Orthop Relat Res. 1966;45:55–61.

90. Wang Z, Bhattacharyya T. Trends in incidence of subtrochanteric fragility fractures and bisphosphonate use among the US elderly, 1996–2007. J Bone Miner Res. 2010: doi: 10.1002/ibmr.233 [e-pub ahead of print].

91. Kelly MP, Wustrack R, Bauer DC, et al. Incidence of subtrochanteric and diaphyseal fractures in older while women: Data from the Study of Osteoporotic Fractures. ASBMR 2010 Annual Meeting, Toronto, Canada. 2010.

92. Wustrack R, Black DM, Burch S, et al. Are women with thicker cortices in the femoral shaft at higher risk of subtrochanteric/ diaphyseal fractures?: The Study of Osteoporotic Fractures.

ASBMR 2010 Annual Meeting, Toronto, Canada. 2010.

93. Lenart BA, Neviaser AS, Lyman S, et al. Association of low-energy femoral fractures with prolonged bisphosphonate use: a case control study. Osteoporos Int. 2009;20:1353–1362.

94. Abrahamsen B, Eiken P, Eastell R. Subtrochanteric and diaphyseal femur fractures in patients treated with alendronate: a register–based national cohort study. J Bone Miner Res. 2009;24:1095– 1102.

95. Abrahamsen B, Eiken P, Eastell R. Subtrochanteric and diaphyseal femur fractures in patients during long-term alendronate therapy: expanded and extended national register-based cohort study 37th European Symposium on Calcified Tissues (ECTS 2010), Glasgow, Scotland, United Kingdom. 2010.

96. Vestergaard P, Amtssygehus A. Risk of femoral shaft and subtrochanteric fractures in users of bisphophonates, raloxifene and strontium ranelate. ASBMR 2010 Annual Meeting, Toronto, Canada. 2010.

97. Black DM, Kelly MP, Genant HK, et al. Bisphosphonates and fractures of the subtrochanteric or diaphyseal femur. N Engl J Med. 2010; 362:1761–1771.

98. Shane E. Evolving data about subtrochanteric fractures and bisphosphonates. N Engl J Med. 2010;362:1825–1827.

99. Dell R, Greene D, Ott S, et al. A retrospective analysis of all atypical femur fractures seen in a

large California HMO from the years 2007 to 2009. ASBMR 2010 Annual Meeting, Toronto, Canada. 2010.

100. Neviaser AS, Lane JM, Lenart BA, Edobor-Osula F, Lorich DG. Low–energy femoral shaft fractures associated with alendronate use. J Orthop Trauma. 2008;22:346–350.

101. Schilcher J, Aspenberg P. Incidence of stress fractures of the femoral shaft in women treated with bisphosphonate. Acta Orthop. 2009;80: 413–415.

102. Bunning RD, Rentfro RJ, Jelinek JS. Low-energy femoral fractures associated with long-term bisphosphonate use in a rehabilitation setting: a case series. PM&R. 2010;2:76–80.

103. Gagnon C, Sims NA, Mumm S, et al. Lack of sustained response to teriparatide in a patient with adult hypophosphatasia. J Clin Endocrinol Metab. 2010;95:1007–1012.

104. McKiernan FE, Ton Q, Neviaser A, Lane JM. Searching for atypical subtrochanteric femoral shaft fractures. ASBMR 2010 Annual Meeting, Toronto, Canada. 2010.

105. Liberman UA, Weiss SR, Broll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. N Engl J Med. 1995;333:1437–1443.

106. Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral

fractures. Fracture Intervention Trial Research Group. Lancet. 1996; 348:1535–1541.

107. Girgis CM, Sher D, Seibel MJ. Atypical femoral fractures and bisphosphonate use. N Engl J Med. 2010;362:1848–1849.

108. Issacs JD, Shidiak L, Harris I. Femoral insufficiency fractures associated with prolonged alendronate therapy. Annual Meeting of the American Academy of Orthopedic Surgeons, New Orleans, LA, USA. 2010.

109. Armamento-Villareal R, Napoli N, Diemer K, et al. Bone turnover in bone biopsies of patients with low-energy cortical fractures receiving bisphosphonates: a case series. Calcif Tissue Int. 2009;85:37–44.

110. Capeci CM, Tejwani NC. Bilateral low-energy simultaneous or sequential femoral fractures in patients on long-term alendronate therapy. J Bone Joint Surg Am. 2009;91:2556–2561.

111. Cermak K, Shumelinsky F, Alexiou J, Gebhart MJ. Case reports: subtrochanteric femoral stress fractures after prolonged alendronate therapy. Clin Orthop Relat Res. 2009;468:1991–1996.

112. Ing-Lorenzini K, Desmeules J, Plachta O. Low-energy femoral fractures associated with the long-term use of bisphosphonates: a case series from a Swiss university hospital. Drug Saf. 2009;32:775– 785.

113. Lee JK. Bilateral atypical femoral diaphyseal fractures in a patient treated with alendronate sodium. Int J Rheum Dis. 2009;12:149–154.

114. Leung F, Lau TW, To M, Luk KDK, Kung AWC. Atypical femoral diaphyseal and subtrochanteric fractures and their association with bisphosphonates. BMJ Case Reports. 2009; (epub March 5).

115. Odvina CV, Levy S, Rao S, Zerwekh JE, Rao DS. Unusual mid-shaft fractures during long-term bisphosphonate therapy. Clin Endocrinol (Oxf). 2010;72:161–168.

116. Odvina CV, Zerwekh JE, Rao DS, Maalouf N, Gottschalk FA, Pak CY. Severely suppressed bone turnover: a potential complication of alendronate therapy. J Clin Endocrinol Metab. 2005;90:1294–1301.

117. Sayed-Noor AS, Sjoden GO. Subtrochanteric displaced insufficiency fracture after long-term alendronate therapy--a case report. Acta Orthop. 2008;79:565–567.

118. Schneider JP. Should bisphosphonates be continued indefinitely? An unusual fracture in a healthy woman on long-term alendronate. Geriatrics. 2006;61:31–33.

119. Somford MP, Draijer FW, Thomassen BJ, Chavassieux PM, Boivin G, Papapoulos SE. Bilateral fractures of the femur diaphysis in a patient with rheumatoid arthritis on long-term treatment with alendronate: clues to the mechanism of increased bone fragility. J Bone Miner Res. 2009;24:1736–1740.

120. Giusti A, Hamdy NA, Papapoulos SE. Atypical fractures of the femur and bisphosphonate therapy: a systematic review of case/case series studies. Bone. 2010;47:169–180.

121. Somford MP, Geurts GF, den Teuling JW, Thomassen BJ, Draijer WF. Long-Term Alendronate Use Not without Consequences? Int J Rheumatol. 2009:253432.

122. Cheung RK, Leung KK, Lee KC, Chow TC. Sequential non-traumatic femoral shaft fractures in a patient on long-term alendronate. Hong Kong Med J. 2007;13:485–489.

123. Wernecke G, Namduri S, Dicarlo EF, Schneider R, Lane J. Case report of spontaneous, nonspinal fractures in a multiple myeloma patient on long-term pamidronate and zoledronic acid. HSS J. 2008;4:123– 127.

124. Lenart BA, Lorich DG, Lane JM. Atypical fractures of the femoral diaphysis in postmenopausal women taking alendronate. N Engl J Med. 2008;358:1304–1306.

125. Demiralp B, Ilgan S, Ozgur Karacalioglu A, Cicek EI, Yildrim D, Erler K. Bilateral femoral insuffiency fractures treated with inflatable intra–medullary nails: a case report. Arch Orthop Trauma Surg. 2007;127: 597–601.

126. Armamento-Villareal R, Napoli N, Panwar V, Novack D. Suppressed bone turnover during alendronate therapy for high-turnover osteoporosis. N Engl J Med. 2006;355:2048–2050.

127. Kumm DA, Rack C, Rutt J. Subtrochanteric stress fracture of the femur following total knee arthroplasty. J Arthroplasty. 1997;12: 580–583.

128. Sayed-Noor AS, Sjoden GO. Case reports: two femoral insufficiency fractures after long-term

alendronate therapy. Clin Orthop Relat Res. 2009;467:1921–1926.

129. Husada G, Libbeerecht K, Peeters T, Populaire J. Bilateral middiaphyseal femoral stress fractures in the elderly. European J Trauma. 2005;1:68–71.

130. Arlot M, Meunier PJ, Boivin G, et al. Differential effects of teriparatide and alendronate on bone remodeling in postmenopausal women assessed by histomorphometric parameters. J Bone Miner Res. 2005;20:1244–1253.

131. Khosla S, Burr D, Cauley J, et al. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2007;22:1479–1491.

132. Cheung AM, Adachi JD, Josse RG, Bleakney R, Khan A, Jamal SA. Bone density and structure of patients on bisphosphonates with atypical femur fractures. ASBMR 2010 Annual Meeting, Toronto, Canada. 2010.

133. Juby A, Davis S. Subtrochanteric hip fracture in Edmonton, Alberta, Canada –case reports. ASBMR 2010 Annual Meeting, Toronto, Canada. 2010.

134. Nitche J, Sagebien C, Masella R, Redziniak D, Wimalawansa SJ. Subtrochanteric femoral stress fractures in patients on chronic bisphosphonate therapy: A case series ASBMR. 2010 Annual Meeting, Toronto, Canada. 2010.

135. Warren C, Gilchrist NL, Coates M, Helmore J, McKie J, Hooper G. Atypical subtrochanteric and

shaft of femur fractures – are they related to bisphosphonate therapy?: Blinded Radiological Review. ASBMR 2010 Annual Meeting, Toronto, Canada. 2010.

136. Zanchetta MB, Sarli M, Massari FE, et al. Bone microarchitecture assessment in postmenopausal women with atypical fractures and long term bisphosphonate use. ASBMR 2010 Annual Meeting, Toronto, Canada. 2010.

137. Chavassieux PM, Arlot ME, Reda C, Wei L, Yates AJ, Meunier PJ. Histomorphometric assessment of the long-term effects of alendronate on bone quality and remodeling in patients with osteoporosis. J Clin Invest. 1997;100:1475–1480.

138. Eriksen EF, Melsen F, Sod E, Barton I, Chines A. Effects of long-term risedronate on bone quality and bone turnover in women with postmenopausal osteoporosis. Bone. 2002;31:620–625.

139. Recker RR, Delmas PD, Halse J, et al. Effects of intravenous zoledronic acid once yearly on bone remodeling and bone structure. J Bone Miner Res. 2008;23:6–16.

140. Bone HG, Greenspan SL, McKeever C, et al. Alendronate and estrogen effects in postmenopausal women with low bone mineral density. Alendronate/Estrogen Study Group. J Clin Endocrinol Metab. 2000;85:720–726.

141. Chavassieux PM, Arlot ME, Roux JP, et al. Effects of alendronate on bone quality and remodeling in glucocorticoid-induced osteoporosis: a histomorphometric analysis of

transiliac biopsies. J Bone Miner Res. 2000;15:754–762.

142. Hauge E, Mosekilde L, Melsen F. Missing observations in bone histomorphometry on osteoporosis: implications and suggestions for an approach. Bone. 1999;25:389–395.
143. Whyte MP, Bergfeld MA, Murphy WA, Avioli LV, Teitelbaum SL. Postmenopausal osteoporosis. A heterogeneous disorder as assessed by histomorphometric analysis of Iliac crest bone from untreated patients. Am J Med. 1982;72:193–202.
144. Napoli N, Novack D, Armamento-Villareal R. Bisphosphonate-associated femoral fracture: implications for management in patients with malignancies. Osteoporos Int. 2010; 21:705–708.
145. Bush L, Chew F. Subtrochanteric femoral insufficiency fracture following bisphosphonate therapy for osseous metastases. Radiology Case Reports. 2008;3:232.
146. Weinstein RS, Roberson PK, Manolagas SC. Giant osteoclast formation and long-term oral bisphosphonate therapy. N Engl J Med. 2009;360:53–562.
147. Gaeta M, Minutoli F, Scribano E, et al. CT and MR imaging findings in athletes with early tibial stress injuries: comparison with bone scintigraphy findings and emphasis on cortical abnormalities. Radiology. 2005;235:553–561.
148. Mori S, Kawaguchi Y. The Histological Appearance of Stress Fractures. In: Burr DB, Milgrom C, eds. Musculoskeletal Fatigue and

Stress Fractures. Boca Raton: CRC Press, 2001: 151–159.

149. Clement DB, Ammann W, Taunton JE, et al. Exercise-induced stress injuries to the femur. Int J Sports Med. 1993;14:347–352.

150. Ivkovic A, Bojanic I, Pecina M. Stress fractures of the femoral shaft in athletes: a new treatment algorithm. Br J Sports Med. 2006;40:518– 520; discussion 520.

151. Deutsch AL, Coel MN, Mink JH. Imaging of stress injuries to bone. Radiography, scintigraphy, and MR imaging. Clin Sports Med. 1997;16:275–290.

152. Spitz DJ, Newberg AH. Imaging of stress fractures in athletes. Radiol ClinNorlh Am. 2002;40:313–331.

153. Zwas ST, Elkanovitch R, Frank G. Interpretation and classification of bone scintigraphic findings in stress fractures. J Nucl Med. 1987;28: 452–457.

154. Lee JK, Yao L. Stress fractures: MR imaging. Radiology. 1988;169: 217–220.

155. Shin AY, Morin WD, Gorman JD, Jones SB, Lapinsky AS. The superiority of magnetic resonance imaging in differentiating the cause of hip pain in endurance athletes. Am J Sports Med. 1996;24:168–176.

156. Tyrrell PN, Davies AM. Magnetic resonance imaging appearances of fatigue fractures of the long bones of the lower limb. Br J Radiol. 1994;67:332–338.

157. Yousem D, Magid D, Fishman EK, Kuhajda F, Siegelman SS. Computed tomography of stress fractures. J Comput Assist Tomogr. 1986;10:92–95.

158. Berger FH, de Jonge MC, Maas M. Stress fractures in the lower extremity. The importance of increasing awareness amongst radiologists. Eur J Radiol. 2007;62:16–26.

159. Das De S, Setiobudi T, Shen L. A rational approach to management of alendronate-related subtrochanteric fractures. J Bone Joint Surg Br. 92:679–686.

160. Cohen A, Addesso V, McMahon DJ, et al. Discontinuing antiresorptive therapy one year after cardiac transplantation: effect on bone density and bone turnover. Transplantation. 2006;81:686–691.

161. Hershman DL, McMahon DJ, Crew KD, et al. Prevention of bone loss by zoledronic acid in premenopausal women undergoing adjuvant chemotherapy persist up to one year following discontinuing treatment. J Clin Endocrinol Metab. 95:559–566.

162. Black DM, Schwartz AV, Ensrud KE, et al. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. JAMA. 2006;296:2927–2938.

163. Mellstrom DD, Sorensen OH, Goemaere S, Roux C, Johnson TD, Chines AA. Seven years of treatment with risedronate in women with postmenopausal osteoporosis. Calcif Tissue Int. 2004;75:462– 468.

164. Sorensen OH, Crawford GM, Mulder H, et al. Long-term efficacy of risedronate: a 5-year placebo-controlled clinical experience. Bone. 2003;32:120–126.

165. Schwartz AV, Bauer DC, Cummings SR, et al. Efficacy of continued alendronate for fractures in women with and without prevalent vertebral fracture: The FLEX trial. J Bone Miner Res. 2010;25:976– 982.

166. Alkhiary YM, Gerstenfeld LC, Krall E, et al. Enhancement of experimental fracture-healing by systemic administration of recombinant human parathyroid hormone (PTH 1–34). J Bone Joint Surg Am. 2005;87:731–741.

167. Rubery PT, Bukata SV. Teriparatide may accelerate healing in delayed union of Type III odontoid fractures: a report of 3 cases. J Spinal Disord Tech. 2010;23:151–155.

168. Chintamaneni S, Finzel K, Gruber BL. Successful treatment of sternal fracture nonunion with teriparatide. Osteoporos Int. 2010;21:1059–1063.

169. Aspenberg P, Genant HK, Johansson T, et al. Teriparatide for acceleration of fracture repair in humans: A prospective, randomized, double-blind study of 102 postmenopausal women with distal radial fractures. J Bone Miner Res. 2010;25:404–414.

170. Lee P, van der Wall H, Seibel MJ. Looking beyond low bone mineral density: multiple insufficiency fractures in a woman with post-menopausal osteoporosis on alendronate therapy. J Endocrinol Invest. 2007;30:590–597.

171. Goddard MS, Reid KR, Johnston JC, Khanuja HS. Atraumatic bilateral femur fracture in long-term bisphosphonate use. Orthopedics. 2009;32:8.

172. Edwards MH, McCrae FC, Young-Min SA. Alendronate-related femoral diaphysis fracture--what should be done to predict and prevent subsequent fracture of the contralateral side? Osteoporos Int. 2010;21:701–703.

173. Ali T, Jay RH. Spontaneous femoral shaft fracture after long-term alendronate. Age Ageing. 2009;38:625–626.

174. Koh JS, Goh SK, Png MA, Kwek EB, Howe TS. Femoral cortical stress lesions in long-term bisphosphonate therapy: a herald of impending fracture? J Orthop Trauma. 2010;24:75–81.

175. Grasko JM, Herrmann RP, Vasikaran SD. Recurrent low-energy femoral shaft fractures and osteonecrosis of the jaw in a case of multiple myeloma treated with bisphosphonates. J Oral Maxillofac Surg. 2009;67:645–649.

176. Glennon DA. Subtrochanteric stress fractures in six patients on long term bisphosphonate therapy: a case series. Bone. 2009;44 (Suppl 1): S77–S78.

177. Schneider JP. Bisphosphonates and low-impact femoral fractures: current evidence on alendronate-fracture risk. Geriatrics. 2009;64: 18–23.

[Exhibit 45 to Ecklund Declaration]

ORIGINAL ARTICLE

Low-Energy Femoral Shaft Fractures Associated With Alendronate Use

Andrew S. Neviaser, MD, Joseph M. Lane, MD, Brett A. Lenart, BS, Folorunsho Edobor-Osula, MD, MPH, and Dean G. Lorich, MD

Objective: Increasing evidence suggests long-term alendronate use may overly suppress bone metabolism, limiting repair of micro-damage and creating risk for insufficiency fractures. The purpose of this study is to demonstrate an association between alendronate use and a specific pattern of low-energy femoral shaft fracture.

Design, Setting, and Patients: A retrospective review was performed of patients with femoral shaft fractures admitted to a Level 1 trauma center between January 2002 and March 2007. Seventy low-energy fractures were identified.

Main Outcome Measure: The medical records were reviewed, and the incidence and duration of alendronate use were recorded. The incidence of a specific femoral shaft fracture in those patients taking alendronate compared with those not being treated was determined.

Results: There were 59 females and 11 males. The average age was 74.7 years. Twenty-five (36%) were being treated with alendronate. None of the patients had used or were using other bisphosphonates. Nineteen (76%) of these 25 patients demonstrated a simple, transverse fracture with a unicortical beak in an area of cortical hypertrophy. This fracture pattern

was seen in only 1 patient (2%) not being treated with alendronate. Alendronate use was a significant risk factor for the fracture pattern (odds ratio [OR]) 139.33, 95% CI [19.0–939.4], $P < 0.0001$). This pattern was 98% specific to alendronate users. The average duration of alendronate use in those with the pattern was significantly longer than those who did not exhibit the pattern but were taking alendronate, 6.9 years versus 2.5 years of use, respectively ($P = 0.002$). Only 1 patient with the fracture pattern had been taking alendronate for less than 4 years.

Conclusions: 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.

Key Words: alendronate, osteoporosis, insufficiency fractures, subtrochanteric fracture, femur fractures, bisphosphonates

(*J Orthop Trauma* 2008;22:346–350)

Accepted for publication March 4, 2008.

From the Hospital for Special Surgery, New York, New York and Weill Medical College of Cornell University, New York, New York.

Dr. Joseph M. Lane is on the Speaker's Bureau for the following: Novartis, Lilly, Proctor & Gamble, Sanofi-Aventis, and Rosche/GSK. There are no other financial disclosures to report. Reprints: Joseph M. Lane, MD, Osteoporosis and Metabolic Bone Disease Service, 535 E. 70th Street, New York, New York, 10021 (e-mail: lanej@ hss.edu).

INTRODUCTION

Alendronate has been widely and successfully used to treat osteoclast-mediated metabolic bone diseases, such as osteoporosis. It has been proved effective in improving all clinical measures of osteoporosis, including increasing bone-mineral density, reducing laboratory markers of bone turnover, and reducing the number of fractures in the spine and long bones.[1,2] Alendronate targets osteoclasts by binding to the inorganic component of bone. Bound alendronate is released during resorption and endocytosed by osteoclasts. Once inside the cell, alendronate inhibits the mevalonate pathway for cholesterol synthesis and induces osteoclast apoptosis.[3] Bone resorption and remodeling rates are diminished as a result of osteoclast death. The sequelae of long-term alendronate use on bone metabolism, however, remain unclear. Studies in experimental animals treated with alendronate demonstrate reduced bony repair and accumulation of microdamage, leading to reduced bone toughness.[4,5] Odvina and Goh have each reported on patients sustaining low-energy fractures after prolonged therapy.[6,7] They warn that prolonged treatment with alendronate may lead to adynamic, fragile bone. We have empirically recognized a number of patients, treated with alendronate, who have sustained fractures of the proximal femoral shaft after minimal or no trauma. These fractures are characterized by a simple, transverse pattern, beaking of the cortex on one side, and hypertrophy of the diaphyseal cortex (Fig. 1). We retrospectively reviewed all low-energy sub-trochanteric and midshaft femur fractures admitted to our Level 1 trauma center in the last 5 years. We hypothesized

that this specific femoral shaft fracture is associated with long-term alendronate use.

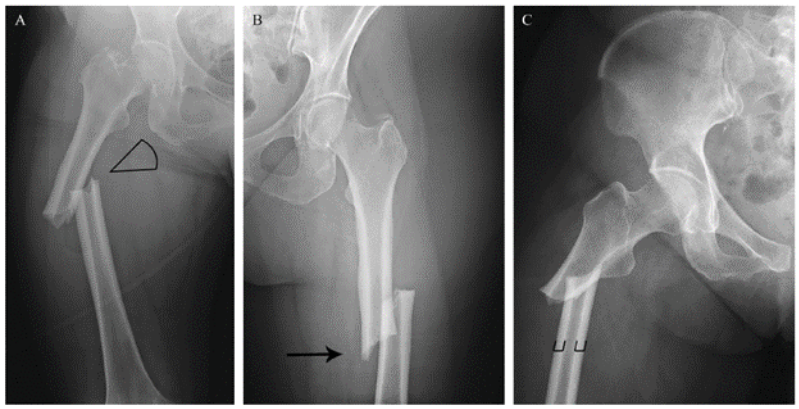

FIGURE 1. Representative radiographs of femoral shaft fractures sustained from minimal trauma in patients taking alendronate. Although each radiograph demonstrates the pattern in its entirety, we have highlighted the following features. A, Fracture pattern pictured with an arch measuring 30 degrees to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

PATIENTS AND METHODS

After approval from the internal review board, a retrospective review was undertaken of all low-energy subtrochanteric and midshaft femur fractures admitted to a Level 1 trauma center between January 2002 and March 2007. Potential patients were identified through ICD-9 codes 820.2 through 821.01, inclusive. All AO Type 32, as well as Type 31 A3, fractures that involved or extended distally to the lesser trochanter, were eligible for inclusion. Low-energy fractures were defined as those caused by the equivalent to a fall from a standing height or less, as

documented in the medical record. Fractures caused by higher-energy trauma (motor vehicle accidents, falls from greater heights, blunt trauma, etc) or by bone tumors, either metastatic or primary, were excluded. Fractures at or beyond the distal third of the femoral shaft (AO Type 33) and pertrochanteric (Type 31 A1–2) were also excluded. Seventy low-energy fractures below the lesser trochanter and above the distal one third of the diaphysis were identified. The medical records were reviewed, and the incidence and duration of alendronate use were recorded. Confirmation of alendronate use and duration was obtained via phone contact with patients or their primary medical doctor. Two experienced attending orthopaedic surgeons and 1 orthopaedic resident independently reviewed the injury radiographs of these patients on 2 separate occasions. Each observer was blinded to patient characteristics, including alendronate use. The reviewers were asked to identify fractures that had a simple, transverse, or short oblique pattern in areas of thickened cortices with a unicortical beak. There was no communication among reviewers. The radiographs were shown in a computer-based slide presentation to each reviewer separately. The order of the radiographs was random and changed between the 2 sessions. Fleiss's and Cohen's kappa coefficients for interobserver and intraobserver agreement, respectively, were calculated by comparing the proportion of agreement in relation to the agreement as a result of chance. Kappa values of less than 0.40 indicate poor agreement, whereas values greater than 0.81 indicate near-perfect agreement. Risk estimates for association of bisphosphonate use and the fracture

pattern were represented as odds ratios (OR) with 95% confidence intervals (CI)

RESULTS

There were 59 females and 11 males. Baseline characteristics are described in Table 1. The average age was 74.7 years. Of the patients, 25 (36%) were being treated with alendronate. We were able to contact 15 patients and 3 primary care physicians to confirm alendronate use in 18 of the 25 patients (72%) being treated. We confirmed the duration of use in 16 of these patients (64%). All patients who were contacted confirmed the record to be accurate. None of the patients had used or were using other bisphosphonates. None of the males were being treated with alendronate.

A total of 31 patients (44%) had a diagnosis of osteoporosis, Of the 25 patients being treated with alendronate, 21 had been diagnosed with osteoporosis (84%). The 4 patients who had not been documented as having osteoporosis in the medical record did not have any other condition typically treated with alendronate. Ten patients had a diagnosis of osteoporosis but had not been treated with alendronate or any other antiresorptive medications. Breakdown of all described subgroups is summarized in Figure 2.

TABLE 1. Baseline Characteristics for Patients With Low-Energy Femoral Shaft Fractures (Differences Between Means for Patients Receiving Alendronate Treatment, Those Receiving Alendronate With Characteristic x-ray Pattern, and Those not Receiving Alendronate Treatment Were Calculated Using the Student's *t*-test)

	Age	Race	History of Osteoporosis (%)
All	74.4	68 W, 2 A	44.3
Female	76.5	57 W, 2 A	50.8
Male	63.5	11 W	9.1
Alendronate	69.4*	23 W, 2 A	84.0
Female	69.4	23 W, 2 A	84.0
Male	—	—	—
Nonalendronate	77.1	45 W	22.2
Female	81.4	34 W	26.4
Male	63.5	11 W	9.1
Alendronate + x-ray	69.5†	17 W, 2 A	84.2
Alendronate − x-ray	69.4	6 W	83.3

W, white; A, Asian; + x-ray, patients with characteristic x-ray pattern; − x-ray, patients without characteristic x-ray pattern.

*$P = 0.058$ for age of bisphosphonate versus nonbisphosphonate.

†$P = 0.065$ for age of bisphosphonate + x-ray vs nonbisphosphonate.

Fifty of the fractures were subtrochanteric, and 20 were located in the femoral shaft. Further classification is provided in Figure 3. The reviewers identified 20 patients with a simple, transverse, or short oblique pattern in areas of thickened cortices with a unicortical beak, represented in Figure 1. Nineteen of the 25 (76%) patients taking alendronate exhibited this fracture pattern. One patient of the 45 not taking alendronate (2.2%) was identified as having the fracture pattern. This patient was diagnosed with multiple myeloma several years after her fracture but had no lesions on her injury radiographs. Thus, 19 of 20 patients identified as having the fracture pattern were taking alendronate (95%). Alendronate use was a significant risk factor for having the fracture pattern in question (OR 139.33, 95% CI [19.0–939.4], $P < 0.0001$). This pattern was 98% specific to alendronate users. Identification of the fracture was consistent.

The interobserver kappa coefficient was 0.93. Intraobserver kappa values ranged from 0.87 to 1.0.

The duration of alendronate use was established in 16 patients and averaged 6.2 years (range 1–10 years). Ten of these patients demonstrated the fracture pattern. Six did not. Of the 6 patients who were taking alendronate but did not exhibit the pattern, the average duration of alendronate use was 2.5 years. This was significantly shorter compared with the 10 patients who had the fracture pattern (average 6.9 years of use, $P = 0.002$). There were no differences in age, race, body mass index (BMI), or osteoporosis history between these groups or among the entire study population.

The fracture pattern was not present in the 10 untreated patients with osteoporosis. No significant difference was found in the mean BMI of those taking and those not taking alendronate. The patients taking alendronate were, on average, younger than those not taking the drug by 8.9 years, but this difference was not significant.

DISCUSSION

The treatment of osteoporosis remains a highly successful intervention for reducing fractures in the elderly. Alendronate was the first oral bisphosphonate available in the United States and remains the most common antiresorptive medication used in treating this disease. The Fracture Intervention Trial, a multicenter randomized control study, demonstrated that alendronate reduced the risk of clinically significant fractures by more than 50% compared to placebo.[1]

We identify a fracture that is specific to patients being treated with alendronate and tends to occur after use of more than 4 years. Fractures associated with alendronate were AO type 32 A3 (simple, transverse). A unicortical beak was typically present, and the diaphyseal cortex was hypertrophied. Although we have not established a causal relationship, the association is sufficiently strong to consider alendronate's effect on bony metabolism when treating these patients.

The clinical utility of recognizing this fracture is recognition of the underlying pathophysiology that led to the fracture. The proximal femoral shaft is an area subject to high stress and would not be expected to fracture from minimal trauma without underlying metabolic bone pathology, such as osteoporosis. The fracture pattern was not seen in the 11 untreated patients with osteoporosis, suggesting that osteoporosis alone is not sufficient to cause this specific failure of the femoral shaft. Further investigation is needed to determine if alendronate is indeed the cause of this fracture. However, reports of insufficiency fractures in patients taking alendronate and studies in experimental animals suggest that adynamic metabolism from impaired resorption may be the underling pathophysiology that leads to these fractures.[4–9]

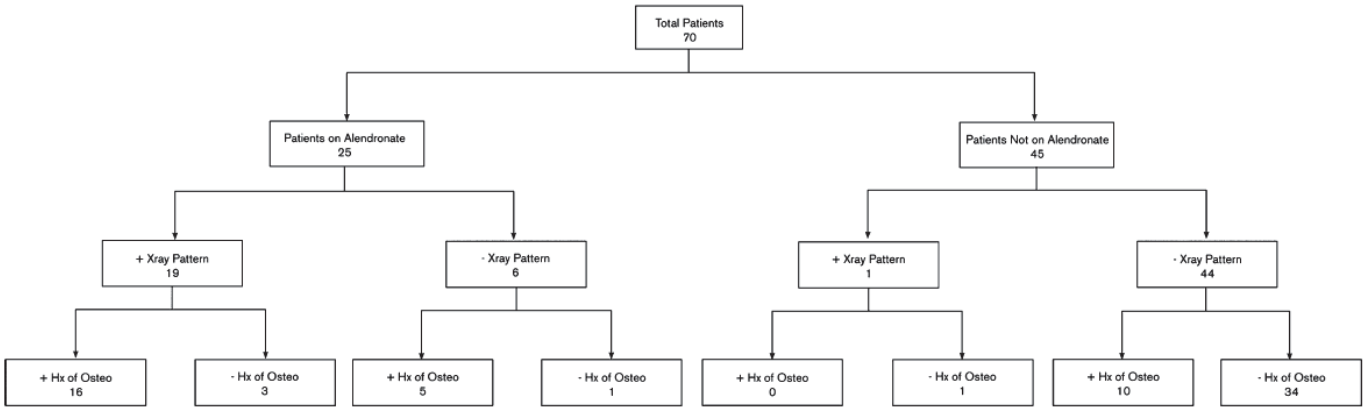

FIGURE 2. Subgroup breakdown of patients in the analysis. + *x-ray pattern*, patients with presence of the x-ray pattern; – *x-ray pattern*, patients without presence of the x-ray pattern; + *Hx of osteo*, patients with a history of osteoporosis; – *Hx of osteo*, patients without a history of osteoporosis.

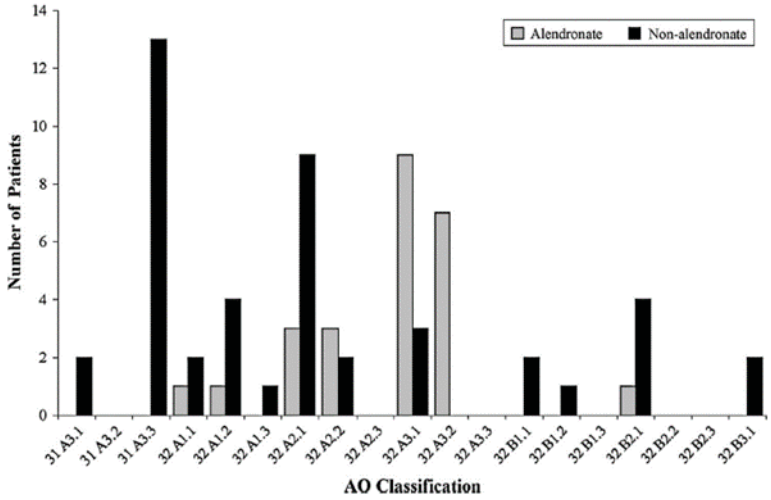

FIGURE 3. Classification of femoral shaft fractures. All 70 fractures were classified based on the Muller AO classification. Gray bars represent patients taking alendronate; black bars represent patients not taking alendronate. 32A3.1 and 32A3.2 represent simple, transverse subtrochanteric and midshaft fractures, respectively. 31A3.3 represents intertrochanteric fractures that extend into the subtrochanteric region.

In 2005 Odvina et al reported on 9 patients who had sustained spontaneous, nontraumatic, nonpathologic fractures while receiving prolonged alendronate therapy (longer than 3 years).[7] All 9 were engaged in normal activities of daily living, such as walking, standing, or turning around, at the time of fracture. Fracture sites included the pubic ramus, femoral shaft, ischium, rib, and sacrum. Six of these patients displayed either delayed healing or histomorphometric evidence of severely suppressed bone turnover. The bone surface was virtually devoid

of cellular elements, bone formation rate was reduced, and matrix formation was severely impaired. The authors raised the possibility that severe suppression of bone turnover may develop during long-term alendronate therapy, resulting in increased susceptibility to, and delayed healing of, nontraumatic, nonpathologic fractures. Studies in experimental animals treated with alendronate have demonstrated reduced repair and accumulation of microdamage in bone, as well as impaired fracture healing.[4,5,8,9]

Goh et al recently reported on 13 subtrochanteric insufficiency fractures over a 10-month period, 9 of which were in patients being treated with alendronate.[6] Eight of the 9 fractures had a pattern similar to what we describe and were associated with the cortical hypertrophy. The patients taking alendronate were younger and more active than those not being treated. They also reported prodromal thigh pain in 5 patients.

We have expanded on this case series by demonstrating a statistically significant association between alendronate use and this type of low-energy femur fracture. The simple transverse pattern, cortical hypertrophy, and prodrome of pain suggest that this injury may result from propagation of a stress fracture, which patients with suppressed microdamage repair are unable to heal. Minimal trauma is then required to produce a complete fracture. Optimal treatment will likely need to address the depressed bone metabolism. Further investigation is needed to validate the role of osteobiologics and anabolic osteoporosis agents in

these patients, both of which would theoretically appear to be important components of treatment.

Alendronate is an appropriate and highly successful first-line therapy for postmenopausal osteoporosis. This study was done to highlight a potential consequence of long-term therapy that may not be unique to alendronate. The potential for suppression of repair exists for all bisphosphonate drugs and may only be apparent with alendronate because it has been available for the longest time and is the most widely used.

This study carries all the shortcomings of a retrospective review. Using the medical record as the gold standard for determining alendronate incidence and use, as well as fracture mechanism, holds some inherent inaccuracy. This inaccuracy was minimized by contacting those patients taking alendronate. The uniform agreement between these patients and the record demonstrates that the record is accurate.

In conclusion, we describe a fracture pattern of the femoral shaft that is specific for patients being treated with alendronate. This fracture is characterized by (1) a simple, transverse pattern; (2) beaking of the cortex on one side; (3) hypertrophied diaphyseal cortices; and (4) resulting from minimal or no trauma. These fractures may be a consequence of alendronate use and its impact on bony metabolism, although further investigation is necessary.

REFERENCES

1. Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral

fractures. Fracture Intervention Trial Research Group. *Lancet*. 1996;348:1535–1541.

2. Bone HG, Hosking D, Devogelaer JP, et al. Ten years' experience with alendronate for osteoporosis in postmenopausal women. *N Engl J Med*. 2004;350:1189–1199.
3. Luckman SP, Hughes DE, Coxon FP, et al. Nitrogen-containing bisphosphonates inhibit the mevalonate pathway and prevent posttranslational prenylation of GTP-binding proteins, including Ras. *J Bone Miner Res*. 1998;13:581–589.
4. Mashiba T, Mori S, Burr DB, et al. The effects of suppressed bone remodeling by bisphosphonates on microdamage accumulation and degree of mineralization in the cortical bone of dog rib. *J Bone Miner Metab*. 2005; 23:36–42.
5. Mashiba T, Turner CH, Hirano T, et al. Effects of suppressed bone turnover by bisphosphonates on microdamage accumulation and biomechanical properties in clinically relevant skeletal sites in beagles. *Bone*. 2001;28:524–531.
6. Goh SK, Yang KY, Koh JS, et al. Subtrochanteric insufficiency fractures in patients on alendronate therapy: A caution. *J Bone Joint Surg Br*. 2007;89:349–353.
7. Odvina CV, Zerwekh JE, Rao DS, et al. Severely suppressed bone turnover: potential complication of alendronate therapy. *J Clin Endocrinol Metab*. 2005;90:1294–1301.
8. Burr DB, Forwood MR, Fyhrie DP, et al. Bone microdamage and skeletal fragility in osteoporotic

and stress fractures. *J Bone Miner Res*. 1997;12:6–15.

9. Cao, Y, Mori S, Mashiba T, et al. Raloxifene, estrogen, and alendronate affect the processes of fracture repair differently in ovariectomized rats. *J Bone Miner Res*. 2002;17:2237–2246.