Gastrointestinal Events Among Patients Initiating Osteoporosis Therapy: A Retrospective Administrative Claims Database Analysis

Ankita Modi, PhD[1]; Ethel S. Siris, MD[2]; Chun-Po Steve Fan, PhD[3]; and Shiva Sajjan, PhD[1]

[1]Global Health Outcomes, Merck & Co, Inc, Whitehouse Station, New Jersey; [2]Columbia University Medical Center & New York-Presbyterian Hospital, New York, New York; and [3]Asclepius Analytics LLC, Brooklyn, New York

ABSTRACT

Purpose: Our purpose was to characterize the occurrence of gastrointestinal (GI) events among women on oral bisphosphonate therapy.

Methods: This was a retrospective cohort study that used a United States (US) claims database. The study period was from January 1, 2000, to December 31, 2011. The index date was the date of the first oral bisphosphonate (alendronate, ibandronate, or risedronate) prescription and occurred between January 1, 2001, and December 31, 2010. The pre- and post-index periods were the 1-year periods before and after the index date, respectively. The analysis included women with osteoporosis aged ≥55 years at the index date who were naive to all osteoporosis treatments before the index date and were continuously enrolled in the health plan for at least 1 year before and 1 year after the index date. Patients with a diagnosis of malignant neoplasm during the pre- or post-index periods or a diagnosis of Paget disease anytime in the claims history were excluded. The occurrence of GI events (defined as esophagitis; gastroesophageal reflux disease; ulcer, stricture, perforation, or hemorrhage of the esophagus; gastric, duodenal, or peptic ulcer; acute gastritis; duodenitis; GI hemorrhage; nausea/vomiting; or dysphagia) was assessed during the pre-index period and at 3, 6, and 12 months in the post-index period. The rate of GI events was defined as the percentage of patients having at least 1 GI event in each analysis period (ie, pre-index and post-index periods). GI events in the post-index period were also stratified by the presence of GI events in the pre-index period.

Findings: A total of 75,593 women were included in the analysis. The average age at the index date was 64.4 years. Gastroprotective agents were used by 17.9% of patients. Approximately one fourth of patients (26.6%; n = 20,073) had ≥1 GI events in the pre-index period. Approximately the same proportion of patients (28.0%; n = 21,142) experienced GI events in the post-index period. The cumulative rate of GI events during the post-index period was higher among patients who had GI events in the pre-index period (51.2%) than among patients without a GI event in the pre-index period (19.6%).

Implications: Among women with osteoporosis enrolled in a US commercial plan, GI events were common regardless of bisphosphonate use. Approximately one fourth of US women on bisphosphonate therapy experienced GI events within the year after initiation of therapy, and one half of US women with a previous GI event had another event while taking bisphosphonates. (*Clin Ther.* 2015;37:1228–1234)

Key words: adverse effects, bisphosphonates, drug therapy, gastrointestinal diseases, postmenopausal osteoporosis.

INTRODUCTION

Approximately 15% of women in the United States (US) aged ≥50 years have osteoporosis,[1,2] a skeletal disease characterized by loss of bone density and associated with an increased risk of fracture.[3,4] An

Accepted for publication March 14, 2015.
http://dx.doi.org/10.1016/j.clinthera.2015.03.018
0149-2918/$ - see front matter

estimated 30% of women in this age range have a high enough risk of osteoporotic fracture to be considered eligible for pharmacologic treatment.[5] Many therapies are available with proven efficacy for reducing fracture risk in patients with osteoporosis. Among them, the oral bisphosphonates, including alendronate, risedronate, and ibandronate, are the most commonly used agents.

Oral bisphosphonates can cause irritation of the gastrointestinal (GI) tract[6]; however, the clinical relevance of endoscopic findings is uncertain.[7] Clinical trials have found that upper GI adverse events are no more frequent in bisphosphonate users than in recipients of placebo,[8–10] and several observational studies have found that GI events are as common before bisphosphonate use as after.[11–13] Studies of the frequency of GI events among patients who used oral bisphosphonates in real-world clinical practice have found that the experience of a GI event increases the likelihood of discontinuation,[14,15] and discontinuation precludes the reduction of fracture risk.

However, the understanding of the occurrence of GI events and characterization of GI events among patients who used oral bisphosphonates, particularly in the US-managed care population, is limited. It is important for treating physicians to know how many bisphosphonate users, and which ones, will experience GI events so that they can be ready with educational support and regimen adjustments to help these patients maintain their reduction in osteoporosis fracture risk. The objective of this study was therefore to determine the proportion and characteristics of US bisphosphonate users who experience GI events.

METHODS

Data Source

The retrospective cohort study was conducted with the i3 InVision Data Mart (i3, Ann Arbor, Michigan; now the Clinformatics Data Mart; Optum, Eden Prairie, Minnesota). This large, nationwide US claims database contains de-identified patient information, including demographic characteristics and medical and pharmacy claims data. Medical claims include *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis and procedure codes. The outpatient pharmacy claims data contain National Drug Codes for dispensed medications. More than 3 million patients with a diagnosis of osteoporosis, osteoporosis-related fracture, and/or a prescription for a medication used to treat or prevent osteoporosis were included in the database during the study period from January 2000 through December 2011.

Study Design

The index date, which could occur any time between January 1, 2001, and December 31, 2010, was defined as the date of the first oral bisphosphonate prescription. The pre-index period was the 12 months before the index date, and the post-index period was the 12 months after the index date. The analyses used de-identified patient data; thus, informed consent was not required.

Study Sample

Eligible patients were women aged $\geq$55 years with a diagnosis of osteoporosis (ICD-9 code 733.0), 1 new pharmacy claim for an oral bisphosphonate (alendronate, risedronate, or ibandronate) on the index date, and continuous enrollment in the health plan during the pre- and post-index periods. Patients were excluded if they had a pharmacy claim for any osteoporosis therapy at any time during the pre-index claims history, a medical claim for Paget disease (ICD-9 code 731.0x) at any time during the claims history, or a diagnosis of malignant neoplasm (ICD-9 codes 140.xx–171.xx, 174.xx–208.xx, or 230.xx–239.xx) during the pre- or post-index periods.

Study Variables

Patient age was assessed on the index date. Characteristics assessed within 1 year before the index date were the Deyo-Charlson comorbidity index score[16] and the use of gastroprotective agents, glucocorticoids, estrogen, and NSAIDs. Disease diagnoses and comorbidities were identified on the basis of ICD-9 codes, and medications were identified on the basis of National Drug Code numbers. Similar to previous publications,[12,13] GI events were identified on the basis of ICD-9 diagnosis codes for esophagitis; gastroesophageal reflux disease; ulcer, stricture, perforation, or hemorrhage of the esophagus; gastric, duodenal, or peptic ulcers; acute gastritis; duodenitis; GI hemorrhage; nausea/vomiting; or dysphagia. The following codes were defined as severe GI events: 530.21 (ulcer of the esophagus with bleeding), 530.4 (perforation of esophagus), 530.82 (esophageal hemorrhage), 531.x

(acute or chronic gastric ulcer with hemorrhage and/or perforation), 532.x (acute or chronic duodenal ulcer with hemorrhage and/or perforation), 533.x (acute or chronic peptic ulcer with hemorrhage and/or perforation), 535.0x (acute gastritis), and 578.xx (GI hemorrhage).

Statistical Analysis

Patient characteristics and GI event rates were analyzed descriptively. Pre-index patient characteristics were assessed in all patients and compared for patients with versus without post-index GI events. Means and SDs were used for continuous variables, and numbers and percentages were used for categorical variables. Between-cohort differences were assessed with *t* tests for continuous variables and χ^2 tests for categorical variables. The between-cohort difference was considered statistically significant if the *P* value was ≤ 0.05.

The primary outcome of interest was the rate of GI events, which is presented for the pre-index period as the percentage of patients who experienced an event during the 12 months before the index date and, for the post-index period, as the cumulative percentage of patients who experienced GI events at 3, 6, and 12 months after the index date. In addition, the cumulative 3-, 6- and 12-month GI event rates were calculated and reported after stratification by the presence of pre-index GI events

RESULTS

Characteristics of the Study Population

After application of the inclusion and exclusion criteria, 75,593 women were eligible for the analysis (Figure 1). The average age at the index date was 64 years, and 17.9% of patients used gastroprotective agents during the pre-index period (Table). One quarter of the women (25.1%) used NSAIDs (Table). Use of gastroprotective agents in the pre-index period was significantly higher in patients who experienced post-index GI events (34.3% vs 11.5% in patients without post-index GI events; $P < 0.001$; Table). Likewise, a history of NSAID use, glucocorticoid use, and estrogen use was more common in patients with post-index GI events (30.9%, 22.1%, and 22.2%, respectively) than in patients without post-index GI events (22.9%, 15.5%, and 21.0%, respectively; all, $P < 0.001$; Table). Patients with post-index GI events had a higher comorbidity score than patients without GI events (0.8 vs 0.5; $P < 0.001$;

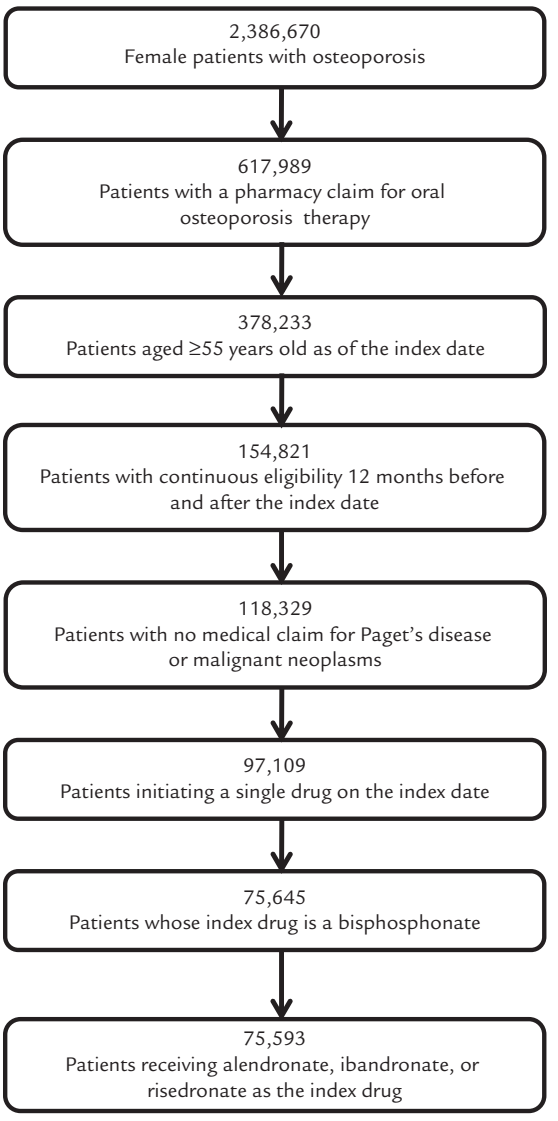

Figure 1. Patient selection.

Table). GI events ranged from mild symptoms such as heartburn to serious events such as perforation of the esophagus, stomach, or duodenum.

Rate of GI Events

A total of 20,073 women (26.6%) had at least 1 GI event in the pre-index period, and 21,142 women (28.0%) had at least 1 GI event in the post-index period. Severe GI events occurred in 2707 women in the pre-index period (3.6%) and in 2966 women in the post-index period (3.9%). Pre-index GI events had

Table. Patient characteristics in the pre-index period.

Patient Characteristics	All Patients (N = 75,593)	Patients With Post-Index GI Events (N = 21,142)	Patients Without Post-Index GI Events (N = 54,451)
Age, mean (SD), y	64.4 (8.4)	64.9 (8.5)	64.3 (8.4)*
CCI score, mean (SD)	0.56 (1.02)	0.8 (1.2)	0.5 (0.9)*
Age distribution, n (%)			
55–59 y	27,820 (36.8)	7267 (34.4)	20,553 (37.8)*
60–69 y	28,770 (38.1)	8223 (38.9)	20,547 (37.7)*
70–79 y	12,038 (15.9)	3558 (16.8)	8480 (15.6)*
≥80 y	6965 (9.2)	2094 (9.9)	4871 (9.0)*
Medication use, n (%)			
Gastroprotective agents	13,523 (17.9)	7254 (34.3)	6269 (11.5)*
Proton pump inhibitors	11,222 (14.9)	6279 (29.7)	4943 (9.1)*
H2 antagonists	2596 (3.4)	1243 (5.9)	1353 (2.5)*
Cytoprotectants	790 (1.1)	399 (1.9)	391 (0.7)*
NSAIDs	18,985 (25.1)	6539 (30.9)	12,446 (22.9)*
Glucocorticoids	13,094 (17.3)	4679 (22.1)	8415 (15.5)*
Estrogen	16,116 (21.3)	4700 (22.2)	11,416 (21.0)*
Pre-index GI events, n (%)	20,073 (26.6)	10,276 (48.6)	9797 (18.0)*
Severe pre-index GI events, n (%)	2707 (3.6)	1380 (6.5)	1327 (2.4)*

CCI = Charlson comorbidity index; GI = gastrointestinal.
*$P < 0.001$ for the comparison between patients with and without post-index GI events.

occurred in 48.6% of patients with a GI event in the post-index period, compared with 18.0% of patients without a post-index GI event ($P < 0.001$; **Table**). The proportion of patients with severe pre-index GI events was higher among patients with post-index GI events than among patients without post-index GI events (6.5% vs 2.4%; $P < 0.001$; **Table**).

Figure 2 shows the rate of GI events at predetermined time points within the post-index period. In the total study population, 10.7%, 17.5%, and 28.0% experienced GI events within the first 3, 6, and 12 months, respectively, of bisphosphonate initiation. Totals of 903 (1.2%), 1653 (2.2%), and 2966 (3.9%) women experienced severe GI events at these respective time points. The frequencies were higher in women who had experienced GI events in the pre-index period (23.0%, 35.3%, and 51.2%, respectively) than in women with no GI events in the pre-index period (6.3%, 11.1%, and 19.6%, respectively).

DISCUSSION

This study found that, in US women who initiated bisphosphonate therapy, the overall rate of GI events after initiating bisphosphonates is approximately the same as before initiation. Post-initiation GI events

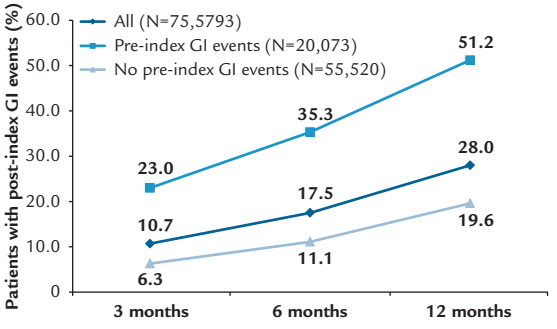

Figure 2. Percentage of patients who experienced a GI event during the post-index period. GI = gastrointestinal.

occurred more frequently in patients with a history of GI events.

GI symptoms are common in populations with osteoporosis, making it difficult to distinguish background GI symptoms from those caused by medication use. In a survey of 497 women from the New York City area, 47% of postmenopausal women reported having upper GI symptoms (compared with 42% of perimenopausal women and 26% of premenopausal women).[17] The US Upper Gastrointestinal Study (N = 9076 women) found that 21% of adult women experienced heartburn on a monthly basis.[18] Vestergaard et al[19] reported that Danish patients who started various osteoporosis therapies were already at increased risk of GI events, such as esophagitis, esophageal ulceration/perforation, and gastroduodenal ulcers, before taking the medications. Similarly, several US observational studies that reported both pre-initiation and post-initiation GI event rates found that the rate in the pre-initiation period was similar to (or greater than) that in the period of bisphosphonate use.[11–13] Our results are consistent with these data.

The rate of GI events among women treated with osteoporosis therapy in our study population (28.0%) was higher than that reported in previous US studies of bisphosphonate users.[11–14,20,21] Values in those studies ranged from <1% for severe GI events[13] and hospitalization for upper GI bleeding[20] to 14% when milder GI symptoms (heartburn, nausea, and/or stomachache) were reported.[14] Differences in sex distribution (ie, percentage of men), the definition of GI events, and the specific bisphosphonate(s) being assessed likely contributed to the differences in the results. Studies of postmenopausal women treated with bisphosphonates in various European countries, however, have reported GI event frequencies in the range of 9.9% to 51.6%,[22–26] indicating that our findings are plausible.

Our observation that GI events among women treated with osteoporosis therapy are more common in patients with a history of GI events confirms the findings of several previous studies. Among UK women taking risedronate, the rates of upper GI adverse effects in women with and without pretreatment GI problems were 32% and 11%, respectively ($P < 0.002$).[22] In another UK population that switched from risedronate to alendronate, a history of upper GI events was associated with a >3-fold increased risk of emergent upper GI events (hazard ratio = 3.18; 95% CI, 2.79–3.63).[27] A Grecian cohort who took alendronate exhibited more than twice the odds of GI-related adverse events if they had a history of GI disease (odds ratio = 2.4; 95% CI, 1.4–3.8).[28] Similarly, our finding that patients with post-index GI events were more frequent users of NSAIDs and glucocorticoids is consistent with previous analyses finding that use of these drugs was predictive of GI events.[29,30]

Limitations of our study design include the typical weaknesses of claims database analyses, such as potential coding errors/omissions and the assumption of compliance on the basis of prescription refills. In addition, our combined analysis of different bisphosphonates does not take into account their individual tolerability profiles. We report here an average effect of the drug class as a whole. Our study population did not include a control group, so we cannot quantitatively distinguish between the competing factors that may be responsible for the relatively stable GI event rates before and after bisphosphonate initiation. Likewise, we cannot say whether the GI event rates in an untreated control group would have remained stable. Finally, the definition of GI events differs across studies, and, as suggested in the third paragraph of this Discussion, the event rate will vary according to the severity of GI events.

CONCLUSIONS

This study found that GI events are common among women with osteoporosis both before and during bisphosphonate use. Among US women enrolled in a commercial health plan and taking bisphosphonate therapy, one fourth experienced a GI event within a year. Approximately one half of US women with a previous GI event had another event while taking bisphosphonates. Prescribing physicians should target their patients with a history of GI events for follow-up about their treatment experience, and future studies should evaluate the burden of GI events as it relates to resource use in the osteoporotic patient population.

ACKNOWLEDGMENTS

We thank Anna Kaufman, MPH, and Melissa Stauffer, PhD, in collaboration with SCRIBCO, for medical writing assistance.

All authors participated in study design, data interpretation, and critical revisions of the manuscript. C.-P. Steve Fan was responsible for data collection and analysis. All authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

A. Modi and S. SSajjan are employees of Merck & Co., Inc. C.-P. Steve Fan is an employee of Asclepius Analytics LLC, which has received financial remuneration from Merck & Co., Inc. to participate in the study. E. Siris received financial remuneration from Merck & Co., Inc. for the design of the study and the clinical analysis of the results. This study was funded by Merck & Co., Inc. Other than through the employer relationship disclosed here, Merck & Co., Inc. did not have a role in the study design, data collection, interpretation of the data, in writing of the manuscript, and in the decision to submit the manuscript for publication.

REFERENCES

1. Wright NC, Looker AC, Saag KG, et al. The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. *J Bone Miner Res*. 2014;29:2520–2526.
2. Looker AC, Borrud LG, Dawson-Hughes B, et al. Osteoporosis or low bone mass at the femur neck or lumbar spine in older adults: United States, 2005-2008. *NCHS Data Brief*. 2012;93:1–8.
3. Management of osteoporosis in postmenopausal women: 2010 position statement of The North American Menopause Society. *Menopause* 2010;17:25-54; quiz 55-56.
4. Watts NB, Bilezikian JP, Camacho PM, et al. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the diagnosis and treatment of postmenopausal osteoporosis. *Endocr Pract*. 2010;16 (Suppl 3):1–37.
5. Dawson-Hughes B, Looker AC, Tosteson AN, et al. The potential impact of the National Osteoporosis Foundation guidance on treatment eligibility in the USA: an update in NHANES 2005-2008. *Osteoporos Int*. 2012;23: 811–820.
6. Graham DY. What the gastroenterologist should know about the gastrointestinal safety profiles of bisphosphonates. *Dig Dis Sci*. 2002;47:1665–1678.
7. Cryer B, Bauer DC. Oral bisphosphonates and upper gastrointestinal tract problems: what is the evidence? *Mayo Clin Proc*. 2002;77:1031–1043.
8. Wells GA, Cranney A, Peterson J, et al. Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. *Cochrane Database Syst Rev*. 2008;(1):CD001155.
9. Wells G, Cranney A, Peterson J, et al. Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. *Cochrane Database Syst Rev*. 2008;(1):CD004523.
10. Epstein S, Delmas PD, Emkey R, et al. Oral ibandronate in the management of postmenopausal osteoporosis: review of upper gastrointestinal safety. *Maturitas*. 2006;54:1–10.
11. Delaney MF, Hurwitz S, Shaw J, LeBoff MS. Bone density changes with once weekly risedronate in postmenopausal women. *J Clin Densitom*. 2003;6:45–50.
12. Miller RG, Bolognese M, Worley K, et al. Incidence of gastrointestinal events among bisphosphonate patients in an observational setting. *Am J Manag Care*. 2004;10: S207–S215.
13. Blumentals WA, Harris ST, Cole RE, et al. Risk of severe gastrointestinal events in women treated with monthly ibandronate or weekly alendronate and risedronate. *Ann Pharmacother*. 2009;43:577–585.
14. Tosteson AN, Grove MR, Hammond CS, et al. Early discontinuation of treatment for osteoporosis. *Am J Med*. 2003;115:209–216.
15. Penning-van Beest FJ, Goettsch WG, Erkens JA, Herings RM. Determinants of persistence with bisphosphonates: a study in women with postmenopausal osteoporosis. *Clin Ther*. 2006;28:236–242.
16. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45:613–619.
17. Infantino M. The prevalence and pattern of gastroesophageal reflux symptoms in perimenopausal and menopausal women. *J Am Acad Nurse Pract*. 2008;20:266–272.
18. Camilleri M, Dubois D, Coulie B, et al. Prevalence and socioeconomic impact of upper gastrointestinal disorders in the United States: results of the US Upper Gastrointestinal Study. *Clin Gastroenterol Hepatol*. 2005;3: 543–552.
19. Vestergaard P, Schwartz K, Pinholt EM, et al. Gastric and esophagus events before and during treatment of osteoporosis. *Calcif Tissue Int*. 2010;86:110–115.
20. Cadarette SM, Katz JN, Brookhart MA, et al. Comparative gastrointestinal safety of weekly oral bisphosphonates. *Osteoporos Int*. 2009;20:1735–1747.
21. Cryer B, Miller P, Petruschke RA, et al. Upper gastrointestinal tolerability of once weekly alendronate 70 mg with concomitant non-steroidal anti-inflammatory drug use. *Aliment Pharmacol Ther*. 2005;21:599–607.
22. Hamilton B, McCoy K, Taggart H. Tolerability and compliance with risedronate in clinical practice. *Osteoporos Int*. 2003;14:259–262.

23. Turbi C, Herrero-Beaumont G, Acebes JC, et al. Compliance and satisfaction with raloxifene versus alendronate for the treatment of postmenopausal osteoporosis in clinical practice: an open-label, prospective, nonrandomized, observational study. *Clin Ther*. 2004;26:245–256.
24. Sewerynek E, Dabrowska K, Skowronska-Jozwiak E, et al. Compliance with alendronate 10 treatment in elderly women with postmenopausal osteoporosis. *Endokrynol Pol*. 2009;60:76–81.
25. Ringe JD, Moller G. Differences in persistence, safety and efficacy of generic and original branded once weekly bisphosphonates in patients with postmenopausal osteoporosis: 1-year results of a retrospective patient chart review analysis. *Rheumatol Int*. 2009;30:213–221.
26. Payer J, Cierny D, Killinger Z, et al. Preferences of patients with postmenopausal osteoporosis treated with bisphosphonates–the VIVA II study. *J Int Med Res*. 2009;37:1225–1229.
27. Ralston SH, Kou TD, Wick-Urban B, et al. Risk of upper gastrointestinal tract events in risedronate users switched to alendronate. *Calcif Tissue Int*. 2010;87:298–304.
28. Anastasilakis AD, Goulis DG, Kita M, Avramidis A. Oral bisphosphonate adverse effects in 849 patients with metabolic bone diseases. *Hormones (Athens)*. 2007;6:233–241.
29. Donahue JG, Chan KA, Andrade SE, et al. Gastric and duodenal safety of daily alendronate. *Arch Intern Med*. 2002;162:936–942.
30. Etminan M, Levesque L, Fitzgerald JM, Brophy JM. Risk of upper gastrointestinal bleeding with oral bisphosphonates and non steroidal anti-inflammatory drugs: a case-control study. *Aliment Pharmacol Ther*. 2009;29:1188–1192.

Address correspondence to: Ankita Modi, PhD, Merck & Co, Inc, Center for Observational and Real-World Evidence (CORE), Supporting Bone Products, 600 Corporate Drive, Mailstop: CRB-205, Whitehouse Station, NJ 08889-0100. E-mail: ankita.modi@merck.com