Osteoporos Int (2010) 21:837–846
DOI 10.1007/s00198-009-1023-x

ORIGINAL ARTICLE

Preference and satisfaction with a 6-month subcutaneous injection versus a weekly tablet for treatment of low bone mass

D. L. Kendler · L. Bessette · C. D. Hill · D. T. Gold · R. Horne · S. F. Varon · J. Borenstein · H. Wang · H.-S. Man · R. B. Wagman · S. Siddhanti · D. Macarios · H. G. Bone

Received: 3 April 2009 / Accepted: 22 June 2009 / Published online: 6 August 2009

Abstract
Summary The Preference and Satisfaction Questionnaire (PSQ) compares patient preference and satisfaction between a 6-month subcutaneous injection and weekly oral tablet for treatment of bone loss. Patients preferred and were more satisfied with a treatment that was administered less frequently, suggesting the acceptability of the 6-month injection for treatment of bone loss.

Electronic supplementary material The online version of this article (doi:10.1007/s00198-009-1023-x) contains supplementary material, which is available to authorized users.

D. L. Kendler (✉)
Prohealth Clinical Research, University of British Columbia,
600–1285 West Broadway,
Vancouver, BC V6H 3X8, Canada
e-mail: kendler@ca.inter.net

L. Bessette
Le Centre Hospitalier Universitaire de Québec, Pavillon CHUL,
2705 Boul. Laurier,
Quebec City, QC, Canada G1V 4G2

C. D. Hill
RTI Health Solutions, RTI International,
200 Park Offices Drive, P.O. Box 12194, Research Triangle Park,
NC 27709, USA

D. T. Gold
Center for Aging, Duke University Medical Center,
P.O. Box 3003, Duke Medical Center,
Durham, NC 27710, USA

R. Horne
Centre for Behavioral Medicine, The School of Pharmacy,
University of London,
29–39 Brunswick Square,
London WC1N 1AX, UK

S. F. Varon · J. Borenstein · H. Wang · S. Siddhanti · D. Macarios
Amgen Inc.,
One Amgen Center Drive,
Thousand Oaks, CA 91320, USA

H.-S. Man
Amgen Inc.,
240 Cambridge Science Park, Milton Road,
Cambridge CB4 0WD, UK

R. B. Wagman
Amgen Inc.,
1120 Veterans Boulevard,
South San Francisco, CA 94080, USA

R. B. Wagman
Stanford University School of Medicine,
Stanford, CA, USA

H. G. Bone
Michigan Bone and Mineral Clinic, P.C.,
22201 Moross Road, Suite 260,
Detroit, MI 48236, USA

Present Address:
S. F. Varon
Allergan,
2525 Dupont Drive,
Irvine, CA 92612, USA

Introduction The PSQ compares patient preference and satisfaction between a 6-month subcutaneous injection and a weekly oral tablet for treatment of bone loss.
Methods Postmenopausal women with low bone mass who enrolled in two separate randomized phase 3 double-blind, double-dummy studies received a 6-month subcutaneous denosumab injection (60 mg) plus a weekly oral placebo or a weekly alendronate tablet (70 mg) plus a 6-month subcutaneous placebo injection. After 12 months, patients completed the PSQ to rate their preference, satisfaction, and degree of bother with each regimen.
Results Most enrolled patients (1,583 out of 1,693; 93.5%) answered ≥1 item of the PSQ. Significantly more patients preferred and were more satisfied with the 6-month injection versus the weekly tablet ($P<0.001$). More patients reported no bother with the 6-month injection (90%) than the weekly tablet (62%).
Conclusion Patients preferred, were more satisfied, and less bothered with a 6-month injection regimen for osteoporosis.

Keywords Injection · Osteoporosis · Preference · Questionnaire · Satisfaction · Tablet

Introduction

Patient compliance and persistence with treatments for chronic conditions is often low [1, 2]. Among patients receiving treatment for osteoporosis, approximately half discontinue therapy within the first 6 months [3, 4]. Analyses of administrative data suggest that more than 50% compliance and persistence with osteoporosis therapy is required for antifracture efficacy, and it is likely that 75% to 80% persistence with therapy is necessary for patients to experience fracture risk reduction consistent with what is seen in clinical trials of osteoporosis medications [5]. Poor compliance and persistence may increase the risk of fracture [5–7], thus adversely affecting patient outcomes and increasing health resource utilization [8–11]. Understanding patient perceptions and preferences of therapies may help in developing strategies to improve compliance and persistence with treatment.

The bisphosphonate alendronate is the most commonly prescribed antiresorptive agent for the treatment of postmenopausal bone loss [12, 13] and is available as a daily or weekly tablet as well as an oral solution. Alendronate binds to the mineralized surface of the bone and inhibits the bone-resorbing activity of mature osteoclasts, thus decreasing bone turnover, increasing bone mineral density (BMD), and reducing the risk for fracture [14, 15]. Recent preference studies with alendronate have shown that patients prefer weekly dosing over daily dosing [16, 17].

Denosumab, a fully human monoclonal antibody, is an antiresorptive agent in late-stage clinical development that neutralizes RANKL, thereby inhibiting osteoclast-mediated bone resorption, by affecting osteoclast development, function, and survival [18–20]. Administered as a subcutaneous injection every 6 months, denosumab has been shown to decrease bone turnover and increase BMD in postmenopausal women with low bone mass or osteoporosis and reduce fracture risk in postmenopausal women with osteoporosis [21–25].

Published studies have described patient preference for once weekly, once monthly, and once annual therapies for osteoporosis [16, 17, 26–28]. However, there have been no data that characterize patient preference and satisfaction with 6-month subcutaneous injections. The Preference and Satisfaction Questionnaire (PSQ) was developed specifically to evaluate patient preference and satisfaction with two different modes and frequency of dosing for the treatment of postmenopausal bone loss: a subcutaneous injection administered every 6 months (Q6M) and an oral tablet taken once weekly (QW) [29]. We report the results of patient responses to the PSQ from two blinded phase 3 head-to-head randomized controlled trials that directly compared denosumab with alendronate [30, 31].

Methods

Patients

Both the Determining Efficacy: Comparison of Initiating Denosumab versus AlEndronate (DECIDE) trial and the Study of Transitioning from AleNdronate to Denosumab (STAND) trial were international, double-blind, double-dummy, randomized, phase 3 head-to-head trials comparing denosumab with alendronate. Details of the design and inclusion and exclusion criteria of these studies have been published [30, 31] and are summarized below. The primary endpoint for both studies was the percent change from baseline in BMD at the proximal femur (total hip) after 12 months of treatment. These studies were approved by the Institutional Review Board or Ethics Committee at each site and were conducted in accordance with the ethical standards of the Declaration of Helsinki.

The DECIDE study was conducted from April 2006 to December 2007 and compared the efficacy and safety of denosumab with weekly oral branded alendronate (Fosamax® 70 mg; Merck) in postmenopausal women with low bone mass (T-score at the total hip or lumbar spine ≤−2.0) with no or very limited previous bisphosphonate use. Patients were excluded if they had a disease or condition known to affect bone metabolism or used drugs known to affect bone

metabolism including any prior intravenous bisphosphonate use, more than 3 months of oral bisphosphonate use within the past 2 years, or 1 month or more of oral bisphosphonate use within the past year. In contrast, the STAND study (conducted October 2006 to March 2008) evaluated the efficacy and safety of denosumab in postmenopausal women with low bone mass (T-score at the total hip or lumbar spine between ≤−2.0 and ≥−4.0) who were receiving bisphosphonate therapy for a minimum of 6 months prior to entering the study. Patients with a disease or condition known to affect bone metabolism were excluded, as well as those with prior intravenous bisphosphonate use. Patients enrolled in STAND had a 1-month run-in period of weekly oral alendronate before being either transitioned from weekly alendronate therapy (Fosamax® 70 mg; Merck) to denosumab (60 mg Q6M) or continued on alendronate therapy. Patients enrolled in both studies were asked to complete the PSQ after 12 months of treatment or upon study discontinuation. Study participants self-administered the tablet (alendronate or placebo), while the injection (denosumab or placebo) was administered by study staff at the scheduled study visits.

PSQ aims and design

The PSQ is a 34-item questionnaire that measures patient preference and satisfaction with a Q6M injection versus weekly tablet for the treatment of low bone mass. Development and validation of the PSQ is reported separately [29]. Briefly, the PSQ was developed from a pool of potential questions derived from a review of the published literature and input from topic experts. Questions were then refined based on feedback from in-depth cognitive interviews with two separate focus groups in the United States. The refined PSQ was then translated from US English into 17 languages and given to all trial participants. The PSQ was designed to compare whether the proportion of subjects who preferred or were more satisfied with the injection was the same as with the tablet within each treatment group. Since participants were blinded to treatment allocation, questions specific to perceptions about denosumab or alendronate treatment were not incorporated into this questionnaire. For the PSQ, preference was defined as the medication or treatment choice made by a patient, based on specific attributes of the medication or treatment. Satisfaction is the degree to which the attributes of a specific medication or treatment actually meets the expectations that the patient had for the medication or treatment. Finally, bother is the degree to which a patient is annoyed or disturbed by certain attributes of the medication. Overall preference was assessed from the question, "Which do you prefer? The weekly pill (tablet), the 6-month injection, or no preference." Satisfaction with the frequency of treatment administration was assessed using the question, "With which frequency of administration have you been more satisfied? The weekly pill, the 6-month injection, or I am not satisfied with one frequency of administration over the other." Six additional preference or satisfaction measures were also evaluated in the PSQ: overall satisfaction, satisfaction with mode of treatment administration, lifestyle fit, convenience, choice for long-term use, and choice for continuation. Subjects were also queried about whether they were bothered by the weekly tablet or the 6-month injection.

Statistical analysis

Patients who completed one or more items of the PSQ were included in the analysis. A complete case approach was used to analyze the PSQ data. Missing data were not imputed and were not included in the within-treatment and between-treatment group analyses. An asymptotic test was used to evaluate whether the proportion of patients who preferred or were more satisfied with the 6-month injection was equal to the proportion of patients who preferred or were more satisfied with the weekly tablet within each treatment group. The Mantel–Haenszel test was used to determine if there were significant differences in the proportion of patients between the two treatment groups (tablet versus injection) adjusting for study (DECIDE versus STAND) on preference and satisfaction items. The same statistical methodologies were also applied to subgroup analyses (such as age [<65 versus ≥65 years old] and prior fracture [yes versus no]) on preference and satisfaction. Analyses of other preference and satisfaction endpoints were exploratory and were summarized using descriptive statistics.

Results

Baseline demographics and disease characteristics

Overall, the demographics of patients enrolled in the two studies were similar. Patients who enrolled in the DECIDE study were younger (mean [SD] age 64.4 years [8.5 years]) than those who enrolled in the STAND study (67.6 years [7.8 years]) and had a shorter average time since menopause (Table 1). Most of the patients enrolled in both studies were Caucasian (84% for DECIDE versus 93% for STAND), and there was a greater percentage of patients who self-identified as Hispanic or Latino in the DECIDE study compared with the patients in the STAND study. Baseline T-scores at the lumbar spine and total hip were similar between studies.

Table 1 Baseline demographics and disease characteristics for the overall study populations

	DECIDE study		STAND study	
	Denosumab 60mg Q6M (*N*=594)	Alendronate 70mg QW (*N*=595)	Denosumab 60mg Q6M (*N*=253)	Alendronate 70mg QW (*N*=251)
Age (years), mean (SD)	64.1 (8.6)	64.6 (8.3)	66.9 (7.8)	68.2 (7.7)
Ethnic group/race, *n* (%)				
White or Caucasian	502 (85)	502 (84)	238 (94)	232 (92)
Hispanic or Latino	66 (11)	69 (12)	11 (4)	12 (5)
Black or African American	7 (1)	9 (2)	0 (0)	2 (<1)
Other[a]	19 (3)	15 (3)	4 (2)	5 (2)
Geographic location, *n* (%)				
North America	330 (56)	332 (56)	137 (54)	139 (55)
Europe	161 (27)	154 (26)	116 (46)	112 (45)
South America	87 (15)	88 (15)	n/a	n/a
Australia	16 (3)	21 (4)	n/a	n/a
Years since menopause, mean (SD)	16.5 (10.2)	17.8 (9.8)	18.8 (9.2)	19.9 (9.9)
Baseline BMD T-score, mean (SD)				
Total hip	−1.75 (0.79)	−1.69 (0.81)	−1.79 (0.82)	−1.81 (0.74)
Lumbar spine	−2.57 (0.75)	−2.57 (0.75)	−2.64 (0.75)	−2.62 (0.79)
History of fracture, *n* (%)				
Vertebral	36 (6)	23 (4)	26 (10)	20 (8)
Nonvertebral	221 (37)	228 (38)	118 (47)	108 (43)

[a] Other includes patients who self-identified as Asian, Japanese, American Indian or Alaskan Native, Native Hawaiian or Other Pacific Islander, Aborigine, or Other

The majority of patients completed 12 months of the study (94% DECIDE and 95% STAND). Reasons for discontinuation were similar, with withdrawal of consent being the most common. Over 93% of patients enrolled in the DECIDE and STAND studies completed at least one item of the PSQ (Fig. 1). Demographics or baseline characteristics were very similar between patients who took the PSQ and those who did not.

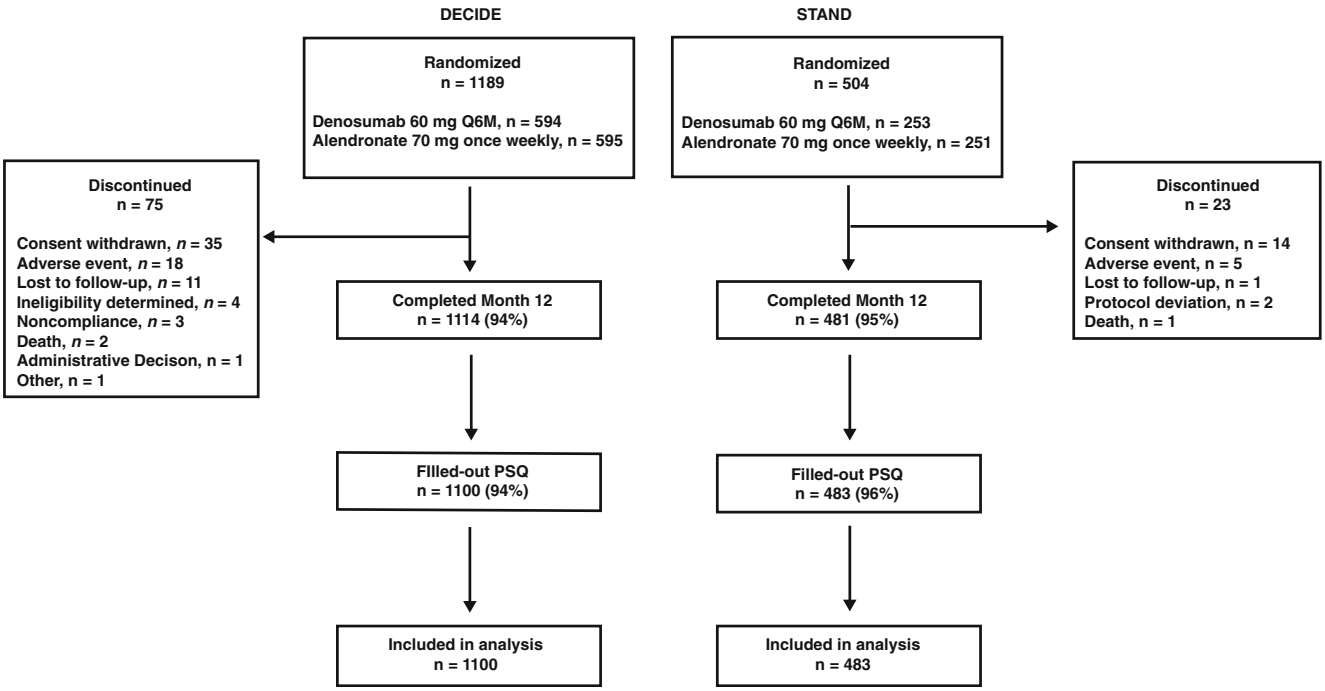

Fig. 1 Patient disposition for the DECIDE and STAND trials

Patient-reported outcomes

The overall study design, medications used, inclusion and exclusion criteria (other than the difference in prior oral bisphosphonate exposure), study length, dates the studies were conducted, and demographics of the study participants were very similar for both the DECIDE and STAND studies. Furthermore, the results of the PSQ given to patients in both studies were very similar. We, therefore, present the combined data analysis.

Preference and satisfaction with dosing frequency

Nearly all patients completed the question regarding preference (99%). Some patients in each treatment group did not indicate a preference for either treatment (16% of denosumab-treated patients; 17% of alendronate-treated patients). Among patients who reported a preference, significantly more patients preferred the 6-month injection (65% of denosumab group; 63% of alendronate group) to the weekly tablet (19% for both treatment groups; $P<0.0001$; Fig. 2a). The proportion of patients choosing the tablet, the injection, or no preference was similar among patients randomized to receive the active injection (denosumab group) or the placebo injection (alendronate group; $P=0.4500$).

The majority of patients also responded to the question regarding satisfaction with the frequency that the treatments were administered (99%). Twenty percent of patients in both treatment groups were not more satisfied with one dosing frequency over the other. Significantly more patients in both the denosumab (64% versus 16%) and alendronate (63% versus 16%) groups were more satisfied with the dosing frequency of the 6-month injection over the weekly tablet ($P<0.0001$; Fig. 2b). For both the denosumab and alendronate treatment groups, similar proportions of patients selected the weekly tablet, 6-month injection, or not satisfied with one over the other ($P=0.9907$).

Additional measures of preference and satisfaction

Six additional measures of preference and satisfaction were also evaluated by the PSQ and are summarized in Fig. 3. Most patients were more satisfied overall and found the 6-month injection to be more convenient and fit better with their lifestyle than the weekly tablet. In addition, more patients indicated that they would choose the 6-month injection for long-term use or continuation of treatment. The findings were similar among patients that received either the active (denosumab group) or placebo (alendronate group) injection.

Preference and satisfaction by demographic, ethnic, and regional differences

Patient responses to the questions about preference and satisfaction with frequency of treatment administration were evaluated by age at enrollment (<65 versus ≥65 years old) and history of fracture. Both younger (<65 years) and older (≥65 years) patients indicated that they preferred and were more satisfied with the dosing frequency of the 6-month injection over the weekly tablet ($P<0.0001$; data not shown). Similarly, patients with or without a prior fracture also preferred and were more satisfied with the frequency of the 6-month injection than the weekly tablet ($P<0.0001$).

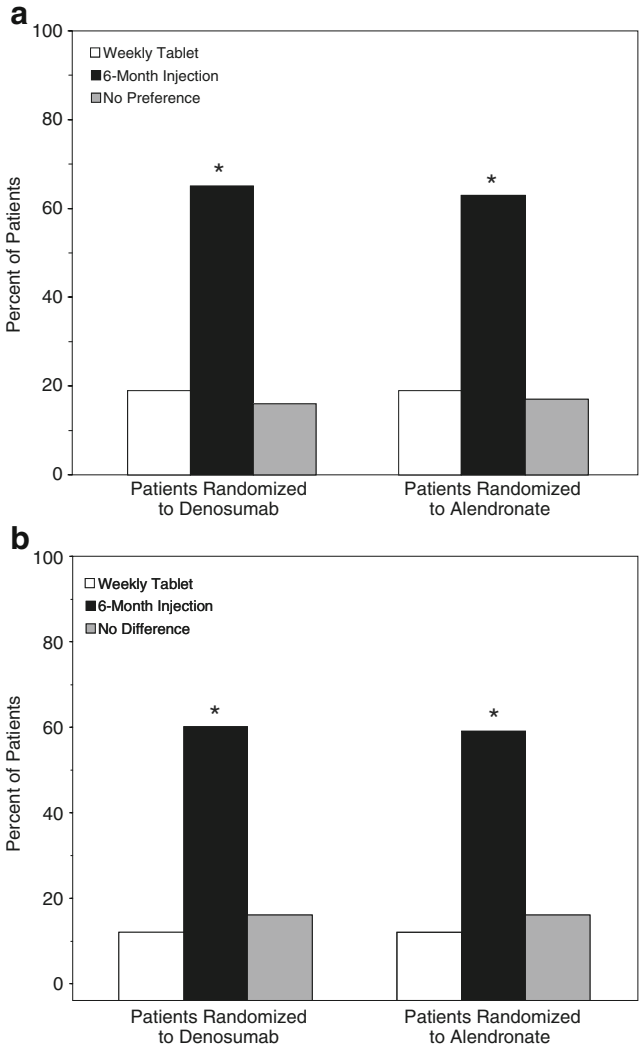

Fig. 2 Patient-reported preference (**a**) and satisfaction with frequency of treatment administration (**b**). The values shown are combined data from the DECIDE and STAND trials.*$P<0.0001$ for 6-month injection versus weekly tablet

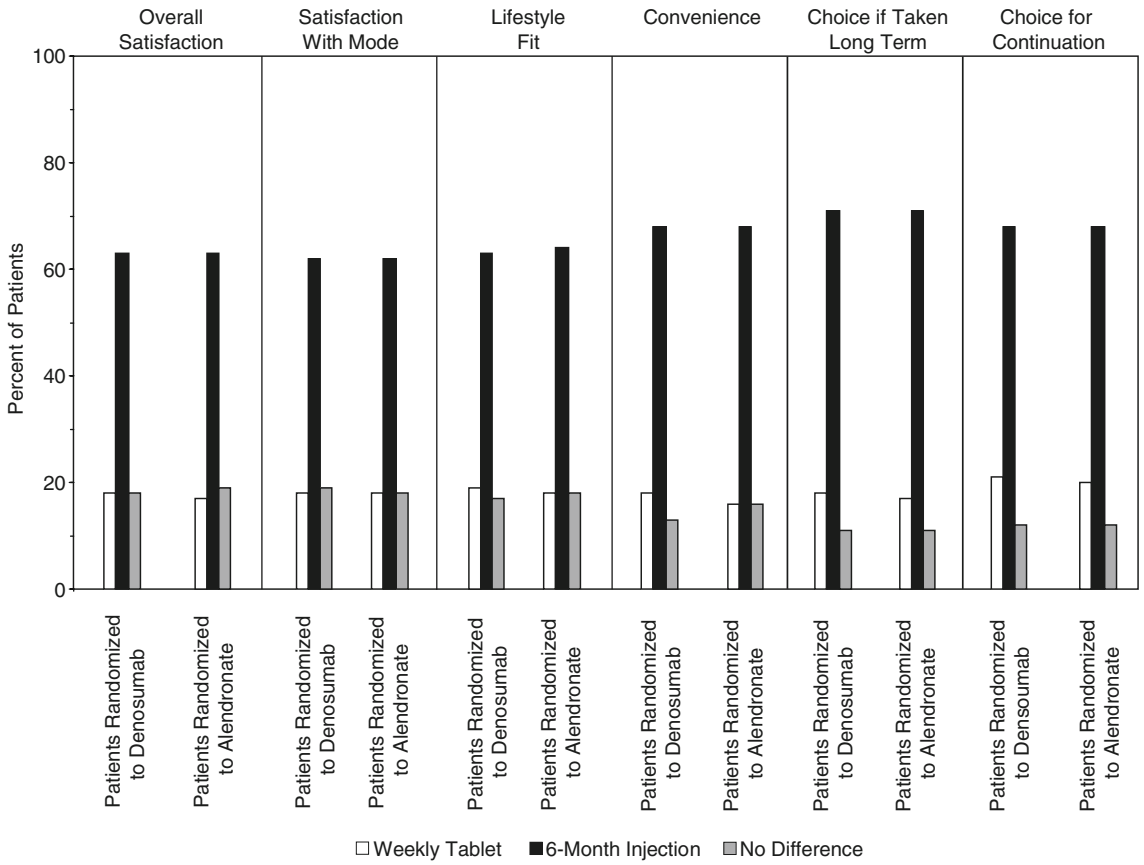

Fig. 3 Patient-reported outcomes for additional preference and satisfaction measures evaluated in the PSQ. The values shown are combined data from the DECIDE and STAND trials.*$P<0.0001$ for 6-month injection versus weekly tablet

The PSQ was administered to patients in 14 countries in 18 languages. The US English version of the PSQ was the most commonly completed (33%), followed by the Danish (11%) and Canadian English (11%) versions [29]. In all 14 countries, more patients preferred the injection over the tablet (Supplementary Table 1). In addition, patients from most countries were also more satisfied with the frequency of the 6-month injection over the weekly tablet (Supplementary Table 1).

The PSQ was given in two languages in Canada, Belgium, and the United States. No differences were noted for preference and satisfaction with frequency of administration between patients who took the Canadian English or Canadian French versions of the PSQ. In Belgium, a somewhat greater percentage of patients completing the Dutch version of the PSQ ($n=17$) preferred and were more satisfied with the frequency of administration of the injection than patients completing the French version ($n=33$), but the sample size was too small for comparison. The largest differences were noted in the United States between patients who took the US English versus the US Spanish version of the PSQ. Over 70% of patients who took the US English version of the PSQ preferred and were more satisfied with the administration frequency of the injection, while slightly more than 50% of patients who took the US Spanish version preferred and were more satisfied with the administration frequency of the injection. However, the English-speaking group was much larger ($n=520$) than the Spanish-speaking group ($n=66$), making comparison difficult.

Treatment bothersomeness

Nearly half of the patients in both studies indicated that one treatment was not more bothersome than the other (44% in denosumab group, 45% in alendronate group). However, among patients who reported a difference in bother between treatments, most indicated the weekly tablet (45% of denosumab-treated patients and 44% of alendronate-treated patients) was more bothersome than the 6-month injection (5% of patients in both treatment groups; Fig. 4). Patients were less likely to claim bother with the injection, if they reported greater satisfaction with the frequency of the injection (data not shown).

The reasons for bother with the 6-month injection or weekly tablet are described in Table 2. Overall, more

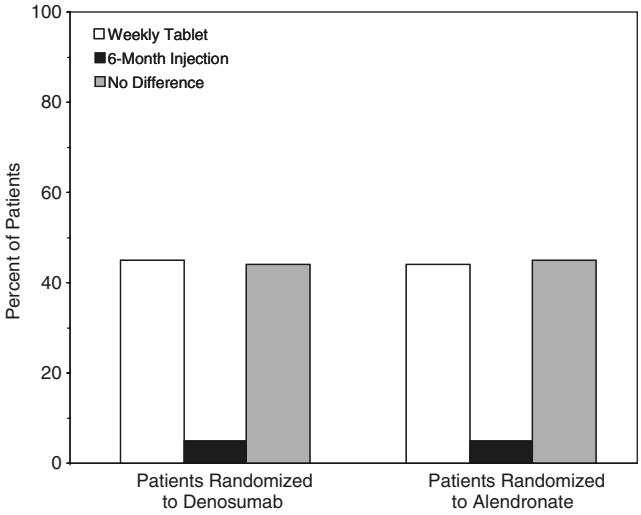

Fig. 4 Patient-reported bothersomeness of treatments. The values shown are combined data from the DECIDE and STAND trials

patients indicated that following the correct routine for the 6-month injection was not bothersome at all compared with following the correct routine for the weekly tablet. Greater numbers of patients reported that they found the weekly tablet to be minimally or moderately bothersome compared with the 6-month injection. In addition, more patients reported experiencing at least some stomach upset after taking the weekly tablet than after receiving the 6-month injection (Table 2). Stomach upset was reported by similar numbers of patients taking placebo and active alendronate tablets.

Approximately 25% of patients reported that they had at least some dislike of the needle. Most patients reported that dislike of the needle was minimal, although a small number of subjects (n=48, 3%) did report that they were quite or severely bothered by the needle. Most patients did not report any pain associated with the injections; however, nine (0.6%) patients did report they had pain that bothered them quite a bit or severely after receiving the injections.

Discussion

In two large randomized, double-blind, double-dummy phase 3 trials of postmenopausal women with bone loss, among patients who expressed a preference, significantly more preferred to receive and were more satisfied with the frequency of administration of a 6-month injection over a weekly tablet after 12 months of treatment. Many patients indicated that they were more likely to continue the 6-month injection long term and that it was better fitted to their lifestyles. Among patients indicating bother with treatments, more patients found the weekly tablet bothersome than the 6-month injection. Although in both trials denosumab treatment significantly increased BMD compared with alendronate [30, 31], patients were blinded to their treatment randomization and BMD results at the time

Table 2 Reasons for bother with treatment

	Denosumab 60mg Q6M (N=798)				Alendronate 70mg QW (N=785)			
	Not at all n (%)	Minimal or moderate n (%)	Quite a bit or severe n (%)	Missing n (%)	Not at all n (%)	Minimal or moderate n (%)	Quite a bit or severe n (%)	Missing n (%)
The weekly pill								
Bother with the weekly pill	497 (62)	264 (33)	29 (4)	8 (1)	478 (61)	268 (34)	33 (4)	6 (<1)
Stomach upset after pill taken	611 (77)	127 (16)	32 (4)	28 (4)	610 (78)	136 (17)	21 (3)	18 (2)
Fasting for 30 min	519 (65)	228 (29)	31 (4)	20 (3)	524 (67)	221 (28)	25 (3)	15 (2)
Taking the pill with water only	697 (87)	73 (9)	11 (1)	17 (2)	673 (86)	86 (11)	11 (1)	15 (2)
Being upright after taking the pill	597 (75)	168 (21)	20 (3)	13 (2)	609 (78)	142 (18)	20 (3)	14 (2)
Overall (follow the correct routine for the pill)	525 (66)	231 (29)	25 (3)	17 (2)	515 (66)	228 (29)	25 (3)	17 (2)
The 6-month injection								
Bother with the 6-month injection	718 (90)	63 (8)	7 (<1)	10 (1)	709 (90)	54 (7)	10 (1)	12 (2)
Stomach upset after injection taken	690 (86)	71 (9)	19 (2)	18 (2)	676 (86)	74 (9)	11 (1)	24 (3)
Pain at the injection site	710 (89)	67 (8)	4 (<1)	17 (2)	710 (90)	53 (7)	2 (<1)	20 (3)
Pain after the injection	728 (91)	53 (7)	0 (0)	17 (2)	717 (91)	46 (6)	3 (<1)	19 (2)
Dislike of needle	599 (75)	158 (20)	20 (3)	21 (3)	583 (74)	152 (19)	28 (4)	22 (3)
Overall (follow the correct routine for the 6-month injection)	735 (92)	42 (5)	3 (<1)	18 (2)	724 (92)	40 (5)	2 (<1)	19 (2)

N number of subjects randomized with observed data for ≥1 question in the questionnaire

they answered the PSQ. Furthermore, there were no significant differences in the fracture rates or incidence of adverse events in these studies, making it unlikely that patients could distinguish which active therapy they were receiving.

Compliance and persistence with therapy are major concerns in the treatment of osteoporosis due to the asymptomatic nature of the disease. While currently available therapies have demonstrated efficacy and safety in the controlled setting of a clinical trial, their use in the community setting has been suboptimal. Adverse effects of treatment, along with complacency with the disease process, may contribute to poor compliance and persistence with treatment regimens, and the resultant loss of antifracture efficacy among patients who discontinue therapy [32–34]. Thus, despite the availability of generally well-tolerated and efficacious therapies, an unmet need exists in the management of osteoporosis. New therapies for osteoporosis will not only need to demonstrate antifracture efficacy, tolerability, and safety in the clinical trial setting, but also convenient administration so that the efficacy may be maximized in the community setting.

Understanding patient preference for the mode and frequency of administration for treatments plays an important role in designing strategies to optimize compliance and persistence with therapy. Considerations that shape patient preference are likely multifactorial and may include perceived treatment effectiveness and safety, specific method of administration (oral versus injection), adverse effects associated with treatment, length of time since regulatory approval for use, physician recommendation, patient experience with and convenience of dosing regimen, and influence on lifestyle [4, 35]. Older patients or individuals with comorbidities who require multiple medications may view a twice yearly subcutaneous injection as more desirable than a weekly oral tablet. Injection of osteoporosis medication may involve a visit to a health care professional, which may be perceived as added value to some patients, but as an inconvenience to others. As all patients in these studies received an injection from a health care provider, we cannot comment on how the interaction with a health care provider might impact patient preference. Furthermore, cultural differences also seem to influence patient preference. For these studies, patients in all countries preferred the injection over the tablet, yet the proportion varied by country. Additionally, differences in percentages of patients preferring the injection were noted among patients in the same country, but who took the PSQ in a different language. The sample size for most countries and ethnic populations were not large enough to allow comparison. Also, no questions included in the PSQ are designed to evaluate how cultural differences may influence patient response. Further studies are needed to understand how ethnic differences may impact preference and satisfaction with mode of treatment administration.

To date, the clinical implications of preference studies remain largely uninvestigated. It has been shown that patients prefer and are more likely to adhere to treatments that are dosed once per day rather than multiple times per day [36]. For the treatment of osteoporosis, patients prefer [16, 17] and have increased compliance and persistence with treatments dosed weekly rather than daily [37–40]. However, compliance and persistence with weekly treatment is still suboptimal [5]. While limited data is available that suggests patients prefer monthly dosing intervals [26, 27, 41], there is little evidence that patients comply and persist with monthly dosing to a greater extent than weekly dosing [42]. When annual intravenous infusion therapy was compared with weekly oral therapy, patients preferred the once yearly treatment [28, 43]. At this time, it is not known if the availability of an annual treatment for postmenopausal bone loss will improve long-term compliance and persistence in the community setting.

In the two studies reported here, overall levels of preference and satisfaction with the injection may be higher than in the community setting based on the self-selection of patients in these studies. As with all studies of preference and satisfaction, the willingness of subjects to accept the treatments offered can potentially confound the interpretation of the results. Subjects in the STAND study were likely accepting and tolerant of bisphosphonate therapy, as ≥6 months prior oral bisphosphonate use and a 1-month run-in period of weekly oral alendronate were requirements for study entry. Similarly, patients in both the DECIDE and STAND studies were aware that they would be receiving two injections. As such, patients with a fear of needles or injections might have declined to participate. Furthermore, some potential prescribers might be concerned that many patients would want to avoid treatments administered by injection [44]. However, patient aversion to injections seems to be more prevalent prior to the first injection, and as patients become familiar with injections, they may be more likely to select this treatment option [45]. Finally, the PSQ was administered at the end of the studies, after patients had had the opportunity to reflect on their experiences with both the injections and tablets.

In summary, patients in these trials indicated that they preferred and had greater satisfaction with an osteoporosis treatment that was administered less frequently. The high prevalence of expressed preference and satisfaction with a 6-month injection over weekly oral medication suggests the acceptability of this route. Positive perceptions of the mode by which treatment for postmenopausal bone loss is administered may increase patient compliance and persistence with and subsequent benefit from prescribed therapy. Based on the results from the DECIDE and STAND studies,

the PSQ is being further refined for use in other clinical trials. Additional research is needed to evaluate whether PSQ results are consistent with increased compliance and persistence to medication in the community setting and improved subsequent clinical outcomes.

Acknowledgements Funding for these studies was provided by Amgen Inc., Thousand Oaks, CA USA. Sacha Satram-Hoang, Ph.D. and Amy Foreman-Wykert, Ph.D. (Amgen, Inc.) provided editorial and writing assistance.

Conflicts of interest The authors have the following disclosures:

David L. Kendler has served as an investigator for Merck, Amgen, Eli Lilly, Novartis, Takeda, GlaxoSmithKline, Pfizer, Servier, Biosante, and Wyeth, and a speaker, consultant, or advisor for and/or received honoraria from Merck, Amgen, Eli Lilly, Novartis, Servier, Nycomed, and Wyeth.

Louis Bessette has served as an investigator and advisory board member for Amgen.

Deborah Gold has served as a consultant for Amgen, Procter & Gamble, GlaxoSmithKline, F. Hoffman-La Roche Ltd., Sanofi-Aventis, Roche Diagnostics, Eli Lilly, and Merck. Additionally, she has received travel grants, speaking or writing fees, or other honoraria, and has served as a member of an advisory board for Amgen, Procter & Gamble, GlaxoSmithKline, F. Hoffman-La Roche Ltd., Sanofi-Aventis, Roche Diagnostics, and Eli Lilly.

Rob Horne has received unrestricted grants to the University of London from Procter & Gamble, Gilead Life Sciences, and Hayward Medical Communications/Shire Pharmaceuticals. Professor Horne also has conducted occasional paid consultancy, medical education lectures, and advisory committees for Abbott, Adelphi, Amgen, Astellas, Astrazeneca, Boehringer Ingelheim, Gilead, GlaxoSmithKlein, Hayward Medical Communications, Merck Outcomes Research, Novartis, Pfizer, Procter & Gamble, and Shire Pharmaceuticals. Some consultancies included travel and accommodations paid by pharmaceutical companies.

Cheryl D. Hill is a paid consultant for Amgen Inc.

Sepideh Farivar-Varon is a former employee of Amgen and current employee of Allergan Inc. Dr. Varon owns stock and/or stock options in both Amgen and Allergan Inc.

Jeff Borenstein, Rachel Wagman, Suresh Siddhanti, David Macarios, Huei Wang, and Hoi-Shen Man are employees and shareholders of Amgen.

Henry G. Bone has served as an investigator for Amgen, Eli Lilly, Merck, Nordic Biosciences, and Zelos; as a consultant for Amgen, Merck, Nordic Bioscience, Osteologix, Pfizer, and Zelos; and has received speaker honoraria from Merck and Novartis.

References

1. Osterberg L, Blaschke T (2005) Adherence to medication. N Engl J Med 353:487–497
2. Wahl C, Gregoire JP, Teo K et al (2005) Concordance, compliance and adherence in healthcare: closing gaps and improving outcomes. Healthc Qual 8:65–70
3. Kothawala P, Badamgarav E, Ryu S et al (2007) Systematic review and meta-analysis of real-world adherence to drug therapy for osteoporosis. Mayo Clin Proc 82:1493–1501
4. Reginster JY, Rabenda V, Neuprez A (2006) Adherence, patient preference and dosing frequency: understanding the relationship. Bone 38:S2–S6
5. Siris ES, Harris ST, Rosen CJ et al (2006) Adherence to bisphosphonate therapy and fracture rates in osteoporotic women: relationship to vertebral and nonvertebral fractures from 2 US claims databases. Mayo Clin Proc 81:1013–1022
6. Gold DT, Martin BC, Frytak JR et al (2007) A claims database analysis of persistence with alendronate therapy and fracture risk in post-menopausal women with osteoporosis. Curr Med Res Opin 23:585–594
7. van den Boogaard CH, Breekveldt-Postma NS, Borggreve SE et al (2006) Persistent bisphosphonate use and the risk of osteoporotic fractures in clinical practice: a database analysis study. Curr Med Res Opin 22:1757–1764
8. Caro JJ, Ishak KJ, Huybrechts KF et al (2004) The impact of compliance with osteoporosis therapy on fracture rates in actual practice. Osteoporos Int 15:1003–1008
9. Huybrechts KF, Ishak KJ, Caro JJ (2006) Assessment of compliance with osteoporosis treatment and its consequences in a managed care population. Bone 38:922–928
10. McCombs JS, Thiebaud P, McLaughlin-Miley C et al (2004) Compliance with drug therapies for the treatment and prevention of osteoporosis. Maturitas 48:271–287
11. Papaioannou A, Ioannidis G, Adachi JD et al (2003) Adherence to bisphosphonates and hormone replacement therapy in a tertiary care setting of patients in the CANDOO database. Osteoporos Int 14:808–813
12. Stafford RS, Drieling RL, Hersh AL (2004) National trends in osteoporosis visits and osteoporosis treatment, 1988–2003. Arch Intern Med 164:1525–1530
13. Watson J, Wise L, Green J (2007) Prescribing of hormone therapy for menopause, tibolone, and bisphosphonates in women in the UK between 1991 and 2005. Eur J Clin Pharmacol 63:843–849
14. Black DM, Thompson DE, Bauer DC et al (2000) Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. FIT Research Group. J Clin Endocrinol Metab 85:4118–4124
15. Cummings SR, Black DM, Thompson DE et al (1998) Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 280:2077–2082
16. Kendler D, Kung AW, Fuleihan Gel H et al (2004) Patients with osteoporosis prefer once weekly to once daily dosing with alendronate. Maturitas 48:243–251
17. Simon JA, Lewiecki EM, Smith ME et al (2002) Patient preference for once-weekly alendronate 70 mg versus once-daily alendronate 10 mg: a multicenter, randomized, open-label, crossover study. Clin Ther 24:1871–1886
18. Burgess TL, Qian Y, Kaufman S et al (1999) The ligand for osteoprotegerin (OPGL) directly activates mature osteoclasts. J Cell Biol 145:527–538
19. Kostenuik P, Nguyen H, McCabe J et al (2009) Denosumab, a fully human monoclonal antibody to RANKL, inhibits bone resorption and increases bone density in knock-in mice that express chimeric (murine/human) RANKL. J Bone Miner Res 24:182–195
20. Lacey DL, Timms E, Tan HL et al (1998) Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. Cell 93:165–176
21. Bone HG, Bolognese MA, Yuen CK et al (2008) Effects of denosumab on bone mineral density and bone turnover in postmenopausal women. J Clin Endocrinol Metab 93:2149–2157
22. Cummings SR, McClung MR, Christiansen C et al (2008) The effects of denosumab on fracture risk in women with osteoporosis. Osteoporos Int 20:167
23. Lewiecki EM, Miller PD, McClung MR et al (2007) Two-year treatment with denosumab (AMG 162) in a randomized phase 2

study of postmenopausal women with low bone mineral density. J Bone Miner Res 22:1832–1841
24. McClung MR, Lewiecki EM, Cohen SB et al (2006) Denosumab in postmenopausal women with low bone mineral density. N Engl J Med 354:821–831
25. Miller PD, Bolognese MA, Lewiecki EM et al (2008) Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: a randomized blinded phase 2 clinical trial. Bone 43:222–229
26. Emkey R, Koltun W, Beusterien K et al (2005) Patient preference for once-monthly ibandronate versus once-weekly alendronate in a randomized, open-label, cross-over trial: the Boniva Alendronate Trial in Osteoporosis (BALTO). Curr Med Res Opin 21:1895–1903
27. Hadji P, Minne H, Pfeifer M et al (2008) Treatment preference for monthly oral ibandronate and weekly oral alendronate in women with postmenopausal osteoporosis: A randomized, crossover study (BALTO II). Joint Bone Spine 75:303–310
28. McClung M, Recker R, Miller P et al (2007) Intravenous zoledronic acid 5 mg in the treatment of postmenopausal women with low bone density previously treated with alendronate. Bone 41:122–128
29. Gold DT, Horne R, Hill C et al (2008) Development, reliability, and validity of a new preference satisfaction questionnaire. J Bone Miner Res 23:S210–S211
30. Kendler DL, Benhamou CL, Brown JP et al (2008) Effects of denosumab in postmenopausal women transitioning from alendronate therapy in comparison with continued alendronate. Osteoporos Int 9(Suppl 2):S385–S386
31. Brown JP, Prince RL, Deal C et al (2008) Comparison of the effect of denosumab and alendronate on bone mineral density and biochemical markers of bone turnover in postmenopausal women with low bone mass: a randomized, blinded, phase 3 trial. J Bone Miner Res . doi:10.1359/jbmr.080910
32. Cramer JA, Gold DT, Silverman SL et al (2007) A systematic review of persistence and compliance with bisphosphonates for osteoporosis. Osteoporos Int 18:1023–1031
33. Reginster JY, Burlet N (2006) Osteoporosis: a still increasing prevalence. Bone 38:S4–S9
34. Solomon DH, Avorn J, Katz JN et al (2005) Compliance with osteoporosis medications. Arch Intern Med 165:2414–2419
35. Saltman DC, Sayer GP, O'Dea NA (2006) Dosing frequencies in general practice—whose decision and why? Aust Fam Physician 35:915–919
36. Claxton AJ, Cramer J, Pierce C (2001) A systematic review of the associations between dose regimens and medication compliance. Clin Ther 23:1296–1310
37. Brankin E, Walker M, Lynch N et al (2006) The impact of dosing frequency on compliance and persistence with bisphosphonates among postmenopausal women in the UK: evidence from three databases. Curr Med Res Opin 22:1249–1256
38. Cramer JA, Amonkar MM, Hebborn A et al (2005) Compliance and persistence with bisphosphonate dosing regimens among women with postmenopausal osteoporosis. Curr Med Res Opin 21:1453–1460
39. Cramer JA, Lynch NO, Gaudin AF et al (2006) The effect of dosing frequency on compliance and persistence with bisphosphonate therapy in postmenopausal women: a comparison of studies in the United States, the United Kingdom, and France. Clin Ther 28:1686–1694
40. Ettinger MP, Gallagher R, MacCosbe PE (2006) Medication persistence with weekly versus daily doses of orally administered bisphosphonates. Endocr Pract 12:522–528
41. Payer J, Killinger Z, Sulkova I et al (2008) Preferences of patients receiving bisphosphonates—how to influence the therapeutic adherence. Biomed Pharmacother 62:122–124
42. Cooper A, Drake J, Brankin E (2006) Treatment persistence with once-monthly ibandronate and patient support vs. once-weekly alendronate: results from the PERSIST study. Int J Clin Pract 60:896–905
43. Saag K, Lindsay R, Kriegman A et al (2007) A single zoledronic acid infusion reduces bone resorption markers more rapidly than weekly oral alendronate in postmenopausal women with low bone mineral density. Bone 40:1238–1243
44. Horne R, Kovacs C, Katlama C et al (2009) Prescribing and using self-injectable antiretrovirals: how concordant are physician and patient perspectives? AIDS Res Ther 6:2
45. Gruffydd-Jones K, Hood CA, Price DB (1997) A within-patient comparison of subcutaneous and oral sumatriptan in the acute treatment of migraine in general practice. Cephalalgia 17:31–36