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REVIEW

Challenges for the Development of Bone-Forming Agents in Europe

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In recent years, significant advances have been made in the management of osteoporosis, particularly with respect to the development of pharmacological interventions to reduce fracture risk. Approved pharmacological interventions in Europe include bisphosphonates, strontium ranelate, raloxifene, bazedoxifene, denosumab, and parathyroid hormone peptides [1–4] (Table 1). Treatments are approved for osteoporosis in postmenopausal women, but alendronate, etidronate, risedronate zoledronic acid, and teriparatide are also approved for the prevention and treatment of glucocorticoid-induced osteoporosis in Europe [3], and alendronate, risedronate, zoledronic acid, strontium ranelate, and teriparatide are approved for the treatment of osteoporosis in men.

Most of these agents are primarily inhibitors of bone turnover, sometimes referred to as anticatabolic agents [5], whereas teriparatide, parathyroid hormone (PTH), and, arguably, strontium ranelate act in part or predominately by the stimulation of bone formation (anabolic agents). There is now a number of bone-forming agents in clinical development, including agents targeting the endogenous inhibitors of bone formation sclerostin and dickkopf-1, cathepsin K inhibitors, new formulations of PTH and PTH related protein (PTHrp) analogs, and calcilytics.

The clinical use of these agents in the management of osteoporosis is dependent on marketing authorization from the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency. Guidelines for product development are available and are regularly updated. The last revision came into effect in 2007 [6]. In phase 3 (the demonstration of efficacy), authorization is dependent on the demonstration of significant efficacy on fracture risk reduction and acceptable safety in postmenopausal women at high or imminent risk of experiencing osteoporotic fractures on the basis of an increased 10-year probability of fractures. Because treatment to prevent fractures may be regarded as a long-term treatment, the CHMP recommends that a duration of randomized

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Table 1 Pharmacological interventions used in the EU for the prevention of osteoporotic fractures [4]

Intervention	Year of market approval	Dosing regimen	Route of administration
Alendronate	1995	70 mg once weekly or 5 or 10 mg once daily	Oral
Etidronate	1980	400 mg daily for 2 weeks every 3 months	Oral
Ibandronate (I)	2005	150 mg once monthly	Oral
Ibandronate (II)	2005	3 mg once every 3 months	Intravenous injection
Risedronate	2000	35 mg once weekly or 5 mg once daily	Oral
Zoledronic acid	2005	5 mg once yearly	Intravenous infusion
Denosumab	2010	60 mg twice yearly	Subcutaneous injection
Raloxifene	1998	60 mg once daily	Oral
Bazedoxifene[a]	2009	20 mg once daily	Oral
Strontium ranelate	2004	2 g once daily	Oral
Teriparatide	2003	20 μg once daily	Subcutaneous injection
Parathyroid hormone 1–84[a]	2006	100 μg once daily	Subcutaneous injection

[a] Registered but not marketed widely

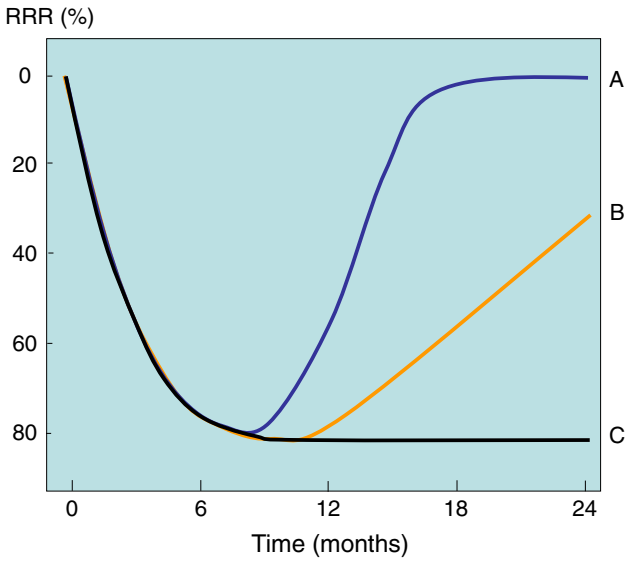

Fig. 1 Schematic diagram showing the effects of a bone-forming agent on the relative fracture risk reduction (RRR) compared with placebo. In scenario *A*, treatment with a bone-forming agent induces a marked effect on fracture risk over a 9 months exposure compared with placebo. On stopping the agent, the effect on fracture wears off over a similar time interval of 9 months. In scenario *C*, the treatment group is treated after the exposure with an inhibitor of bone turnover which maintains the efficacy to 2 years. In scenario *B*, both the treatment and the placebo groups are treated after the exposure with an inhibitor of bone turnover

treatment of at least 2 years is usually appropriate. Indeed, the efficacy after 1 year is considered a secondary outcome variable, and the maintenance of the effect during the second year should be addressed. The maintenance of prevention of fractures with treatment after the second year (e.g., 3–5 years) should be studied, although data may be submitted after registration. Catch-up bone loss after withdrawal of treatment has been described with some drugs. Data that show what occurs after stopping treatment are also considered necessary but can be submitted after registration.

These requirements, which are well rehearsed for inhibitors of bone turnover, pose some problems in the development of bone-forming agents. These are briefly reviewed, and our consensus view is presented, which might be considered in future guidelines.

Assessment of Response

The typical expectation of bone-forming agents is that intervention will induce marked increases in bone mineral density (BMD) and reductions in fracture risk over a short exposure (e.g., 6–12 months) [7, 8]. This is illustrated conceptually in terms of the relative risk reduction in fracture outcome (Fig. 1, scenario A). Treatment with a bone-forming agent induces a marked effect on fracture risk over a 9-month exposure compared with placebo. On stopping the agent, the effect on fracture wears off—in this example, over a similar time interval of 9 months. Thus, significant efficacy, demonstrable at 1 year, is no longer evident at 2 years, which is the time point where the primary end point is assessed.

To mitigate this risk, the treatment group is treated after the exposure with an inhibitor of bone turnover, which maintains the efficacy to 2 years (scenario C). In this instance, efficacy is evident at the pivotal analysis but at the expense of not demonstrating the offset of effect of the bone-forming agent. In practice, it may not always be possible to maintain a placebo group with no intervention over 2 years. The administration of an inhibitor of bone turnover is likely to attenuate the comparative efficacy at the 2-year time point (scenario B).

Below, the term “holding agent” is used so as not to preclude the use of agents that are not classical inhibitors of bone resorption.

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Safety

Market authorization depends on both efficacy and safety. Safety should be evaluated considering the intended exposure with the anabolic agent, but for a chronic condition such as osteoporosis requiring prolonged treatment, a monitoring period for at least 2 years at the time of submission and 3 years at the time of approval is expected. A potential problem with bone-forming agents is their short exposure time and the consequent reduction in patient-years of exposure. This risk should be mitigated by an adequate number of patients recruited. Safety of any holding agent should also be evaluated but summarized separately from the safety profile of the anabolic agent.

Population

The identification of individuals at high risk for treatment is an important principle in the delivery of health care to those most at need, particularly where health care resources are limited. Indeed, current regulatory requirements for the development of treatments for osteoporosis in Europe demand that studies of efficacy in osteoporosis preferentially enroll patients with a high 10-year probability of fracture [6]. Probability ranges included 15–25 % for spine, 5–7.5 % for hip, and 10–15 % for major nonvertebral fractures. These probabilities, set before the completion of FRAX (http://www.shef.ac.uk), do not conform to the output of probability models.

An approach to remedying the issue can be taken from the development of intervention thresholds that are based on fracture probability. The use of such intervention thresholds seems appropriate in the context of development guidelines because new drugs should be developed in the population setting for which their use is intended.

Many guidelines recommend that women with a prior fragility fracture may be considered for intervention without the necessity for a BMD test (other than to monitor treatment) [2]. Thus, a prior fracture can be considered to carry a sufficient risk that treatment can be recommended. For this reason, the intervention threshold in women without a prior fracture can be set at the age-specific fracture probability equivalent to women with a prior fragility fracture and therefore rises with age from a 10-year probability of 8–33 % in the UK [9]. In other words, the intervention threshold is set at the fracture threshold. The same principles have been applied to European guidance and in the management of glucocorticoid-induced osteoporosis [1–3]. Under this scheme, assuming an average age of 65 years, the population studied should have an average probability of approximately 12 % for a major fracture or 3.0 % for a hip fracture, depending on the primary outcome variable (Table 2). These fracture probabilities are marginally higher than those derived from selecting a study population based on presence of osteoporosis (BMD defined) and are marginally lower than those derived from selecting a study population on the basis of established (severe) osteoporosis (World Health Organization defined). We recommend that such thresholds be used for all agents, irrespective of their mode of action. It is important, however, to test efficacy over a spectrum of baseline fracture probability [10].

Table 2 Ten-year probabilities of a major fracture and hip fracture in women aged 65 years in the five major EU countries according to a prior fragility fracture (Prior Fx), a femoral neck T score of -2.5 SD, or a combination

Country	Prior Fx		$T = -2.5$		Prior Fx and $T = -2.5$	
	Major	Hip	Major	Hip	Major	Hip
France	9.3	2.6	6.7	2.1	11	3.5
Germany	12	3.3	8.5	2.7	14	4.5
Italy	12	3.5	8.5	2.9	14	4.8
Spain	7.5	2.1	5.4	1.7	9.0	2.8
UK	17	3.6	12	2.9	19	4.9
Average	11.6	3.0	8.2	2.5	13.4	4.1

Adapted from [2]

Outcome Variables

Current regulatory requirements in Europe demand that studies of efficacy in osteoporosis document vertebral and nonvertebral fracture outcomes separately [6]. The reason is that the methods of data acquisition differ. Thus, clinical fractures are recorded by the date on which they occur, whereas vertebral fractures assessed by quantitative morphometry are recorded by the date of the radiograph; the incident fracture may have occurred at any time between radiographs. From a clinical perspective, the distinction is artificial in that both vertebral and nonvertebral fractures contribute to the morbidity—and indeed mortality—of osteoporosis [11–17]. There is therefore interest in combining fracture outcomes in order to define thresholds of probability at which treatment overall becomes effective to better inform practice guidelines. The reduction of multiple end points to a single outcome variable has obvious attractions in increasing the power of phase 3 studies.

Consensus View

In general, the regulatory guidance for anabolic treatments should follow the same principles and apply a similar level

of detail to that currently provided in the osteoporosis guidance document.

Target Population

The level of risk should be consistent with the intended label (i.e., "at increased risk for fracture"). It is acknowledged that the acceptable risk of the population in a placebo-controlled study is limited by ethical considerations. In active controlled studies, subjects at higher risk may be studied as long as an acceptable active comparator is used and the trial is operationally feasible. Appropriate levels of risk should be consistent with commonly used intervention thresholds.

Duration of Exposure

Duration of exposure is driven by mechanism of action and persistence of pharmacodynamic effects. The optimal time of exposure may vary among different anabolic agents. The proper timing for the evaluation of the effect on disease activity will depend on the time it takes the study drug to achieve its optimal stable effect, as well as on the severity of the disease and its intended place in a therapeutic regimen [18]. Regardless of the duration of exposure to the anabolic agent, safety and efficacy data over at least 2 years should be available at the time of submission and safety data for an additional year at the time of approval. Consideration should be given to the assessment of fracture efficacy at the end of exposure to a bone-forming agent as a primary end point, provided that continued benefit can be shown over 2-year duration with or without a holding agent.

Duration of Studies

Regardless of duration of exposure to the anabolic agent, the studies should provide efficacy data over at least 2 years at the time of submission. Data for treatment duration of at least 2 years should be available at filing, supplemented by safety data for an additional year at the time of registration. This principle should be applied regardless of whether the 3 years of treatment are the result of a single treatment or a sequential treatment regimen, which may include a holding agent.

Primary End Points

In addition to the separate demonstration of the effects on vertebral fracture risk (assessed by morphometry) and major nonvertebral fractures, clinical major fractures are an important end point of interest (i.e., symptomatic vertebral fractures and major nonvertebral fractures). The outcome reflects the clinical burden to patients and also includes the events usually captured in observational databases and can be considered a primary end point. Outcomes might theoretically differ—for example, at cortical sites (wrist, hip)—and allowances must be made for this to be addressed.

Onset and Offset of Action

Data on offset of effect when treatment is stopped is particularly important in the context of bone-forming agents. Offset time can be assessed with sequential measures of BMD and supported where justifiable with measurements of biochemical markers of bone turnover. Data on offset may be submitted after registration (current recommendation), but studies available at the time of registration may aid in the assessment of efficacy. Studies of offset may be obtained in a high-risk population or may be obtained in other populations.

Safety

Regardless of duration of exposure to the anabolic agent, studies should provide safety and efficacy data over at least 2 years at the time of submission. Safety data for an additional year should be available at the time of approval. Where a holding agent is used, safety should additionally be examined separately over the exposure to the bone-forming agent and the holding agent.

Summary of Product Characteristics (SmPC)

For bone-forming agents, the label language should indicate in the clinical section the duration of use that was studied and that formed the basis for approval. If retreatment is not precluded by specific safety concerns, information on the efficacy and safety of a retreatment regimen can be provided after approval and may lead to a variation of the existing label.

If the studies on efficacy include a sequential treatment regimen (e.g., bone-forming agent followed by an inhibitor of bone turnover), then this should be recognized in the drug label. Where justified, the effects of agents studied as holding agents may be generalized across a class in the label of the anabolic agent (e.g., when a holding treatment with a specific bisphosphonate has been evaluated, the observations may be extended to other bisphosphonates).

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References

1. Hernlund E, Svedbom A, Ivergård M, Compston J, Cooper C, Stenmark J, McCloskey EV, Jönsson B, Kanis JA (2013) Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos 8:136
2. Kanis JA, McCloskey EV, Johansson H, Cooper C, Rizzoli R, Reginster JY, Scientific Advisory Board of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO); Committee of Scientific Advisors of the International Osteoporosis Foundation (IOF) (2013) European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int 24:23–57
3. Lekamwasam S, Adachi JD, Agnusdei D, Bilezikian J, Boonen S, Borgström F, Cooper C, Diez Perez A, Eastell R, Hofbauer LC, Kanis JA, Langdahl BL, Lesnyak O, Lorenc R, McCloskey E, Messina OD, Napoli N, Obermayer-Pietsch B, Ralston SH, Sambrook PN, Silverman S, Sosa M, Stepan J, Suppan G, Wahl DA, Compston JE, Joint IOF-ECTS GIO Guidelines Working Group (2012) A framework for the development of guidelines for the management of glucocorticoid-induced osteoporosis. Osteoporos Int 23:2257–2276
4. Strom O, Borgstrom F, Kanis JA, Compston J, Cooper C, McCloskey EV, Jonsson B (2011) Osteoporosis: burden, health care provision and opportunities in the EU: a report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos 6:59–155
5. Riggs BL, Parfitt AM (2005) Drugs used to treat osteoporosis: the critical need for a uniform nomenclature based on their action on bone remodeling. J Bone Miner Res 20:177–184
6. Committee for Medicinal Products for Human Use (CHMP) (2006) Guideline on the evaluation of new medical products in the treatment of primary osteoporosis. European Medicines Agency, London, UK, November 2006. Document CPMP/EWP/552/95, rev. 2
7. McClung MR, Grauer A, Boonen S, Bolognese MA, Brown JP, Diez-Perez A, Langdahl BL, Reginster JY, Zanchetta JR, Wasserman SM, Katz L, Maddox J, Yang YC, Libanati C, Bone HG (2014) Romosozumab in postmenopausal women with low bone mineral density. N Engl J Med 370:412–420
8. Becker CB (2014) Sclerostin inhibition for osteoporosis—a new approach [comment]. N Engl J Med 370:476–477
9. Kanis JA, McCloskey EV, Johansson H, Strom O, Borgstrom F, Oden A (2008) Case finding for the management of osteoporosis with FRAX—assessment and intervention thresholds for the UK. Osteoporos Int 19:1395–1408
10. Kanis JA, McCloskey E, Johansson H, Oden A, Leslie WD (2012) FRAX® with and without BMD. Calcif Tissue Int 90:1–13
11. Kanis JA, Odén A, McCloskey EV, Johansson H, Wahl D, Cyrus Cooper C, IOF Working Group on Epidemiology and Quality of Life (2012) A systematic review of hip fracture incidence and probability of fracture worldwide. Osteoporos Int 23:2239–2256
12. Bliuc D, Nguyen ND, Milch VE, Nguyen TV, Eisman JA, Center JR (2009) Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. JAMA 301:513–521
13. Gabriel SE, Tosteson AN, Leibson CL, Crowson CS, Pond GR, Hammond CS, Melton LJ 3rd (2002) Direct medical costs attributable to osteoporotic fractures. Osteoporos Int 13:323–330
14. Hasserius R, Karlsson MK, Nilsson BE, Redlund-Johnell I, Johnell O (2003) Prevalent vertebral deformities predict increased mortality and increased fracture rate in both men and women: a 10-year population-based study of 598 individuals from the Swedish cohort in the European Vertebral Osteoporosis Study. Osteoporos Int 14:61–68
15. Jalava T, Sarna S, Pylkkänen L, Mawer B, Kanis JA, Selby P, Davies M, Adams J, Francis RM, Robinson J, McCloskey E (2003) Association between vertebral fracture and increased mortality in osteoporotic patients. J Bone Miner Res 18:1254–1260
16. Johnell O, Kanis J, Gullberg G (2001) Mortality, morbidity, and assessment of fracture risk in male osteoporosis. Calcif Tissue Int 69:182–184
17. Kanis JA, Oden A, Johnell O, Jonsson B, de Laet C, Dawson A (2001) The burden of osteoporotic fractures: a method for setting intervention thresholds. Osteoporos Int 12:417–427
18. Committee for Medicinal Products for Human Use (CHMP) (2013) Guideline on clinical investigation of medicinal products for the treatment of systemic lupus erythematosus, cutaneous lupus and lupus nephritis. EMA/CHMP/51230/2013, draft 21, February 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/03/WC500139615.pdf