

Osteoporosis: Addressing the Unmet Need

Development trends, regulatory landscape, disease and operational approach considerations

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Despite numerous approved and available drugs, established risk assessment and diagnostic criteria, osteoporosis remains underdiagnosed and undertreated in at-risk populations. Clinical development in osteoporosis represents an excellent opportunity to bring new and more affordable medications to patients.

In this article we will provide a brief assessment of the trajectory of the osteoporosis landscape, an overview of the regulatory environment with assessments of the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidelines, and some critical considerations that address the unique components of osteoporosis clinical trials, including:

- Fracture risk assessment – Finding clinical outcomes that are scientifically sound and meaningful to patients
- Patient-focused study design – Addressing the needs of and managing elderly populations in a trial
- ePRO technology – Adapting interfaces to improve compliance and adherence in elderly patients

Worldwide Prevalence and Financial Burden of Disease

Globally, one in three women and one in five men are at risk of an osteoporotic fracture. Currently it is estimated that more than 200 million people worldwide suffer from this disease. Approximately 30% of all postmenopausal women in the United States and Europe have osteoporosis.¹

Despite the wide availability of several classes of approved osteoporosis medications, and, even after documented osteoporotic fractures occur, initiation of treatment rates has been observed to be quite low, ranging from 5% to 30%.²

According to a recent fact sheet³ from the International Osteoporosis Foundation, “the cost of osteoporosis is 37 billion euros per year in the EU, and \$19 billion USD per year in the USA.” Costs are projected to rise dramatically alongside osteoporosis prevalence in coming years.

Key Trends in Osteoporosis Development Landscape

Worldwide market sales of drugs for osteoporosis in 2017 were \$7.3 billion USD and are projected to grow at a CAGR of 1% to \$8.1 billion USD in 2024.⁴ This landscape is undergoing a change in treatment class.

By comparing estimated changes in 2017 to 2024 forecasts (Figure 1), what's striking is the increase in sales of RANKL MAb (Denosumab) from \$2.2 to \$3.5 billion USD, an increase of 61%. Only selective estrogen receptor modulators (SERM) are expected to perform better in terms of sales increase (+77%), even though it represents a much lower market share.

While RANKL MAb and SERM will expand their shares, other classes of medication will reduce their worldwide sales, as bisphosphonates have dropped more than 30% and calcitonin is down about 27%, the latter probably affected, at least in Europe, by the review and further re-examination in 2012 of risks and benefits by the EMA, confirming calcitonin not being used any longer in osteoporosis.⁵

Based on the growth of RANKL MAb, we can anticipate that biosimilars will be of keen interest with patent expiration pending between 2022 and 2025.

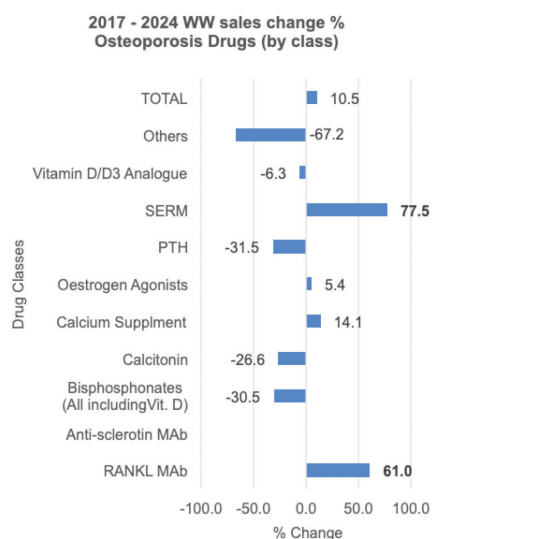


Figure 1. 2024 forecast of change in sales of leading osteoporosis treatments worldwide

Despite Denosumab Patent Expiration, New Opportunities on The Horizon

The patents on the originator product for Denosumab, Amgen’s Prolia, will expire in the U.S. in February 2025 and in Europe in June 2022, except for France, Italy, Spain and the U.K., which expire in 2025.

There are currently five drug companies⁶ reported with ongoing clinical development of Denosumab biosimilar. Two of those companies are in advanced Phase III trials (Aryogen Pharmed [Iran] and Intas Pharmaceuticals [India]), and it is likely their drug development is targeted for domestic markets. Three other companies are still in preclinical or pipeline phase.

It can be further assumed that other major biosimilars companies, even if not disclosed yet, have interests to take shares of this \$3.5 billion USD market in 2025, while more clinical development news around Denosumab biosimilars is expected in the next few years.

Regulatory Landscape

As stated in the FDA “Guidelines for the Clinical Evaluation of Drugs Used in the Treatment of Osteoporosis” the “difficulties in assessing the state of skeletal bone quantitatively *in vivo*, the relatively small changes that are usually encountered and the duration of studies necessary to show significant effects” present major challenges for clinical studies.⁷

Understanding these limitations, the FDA and EMA have established guidance documents on the conduct of osteoporosis clinical trials. An understanding of where the FDA and EMA align and where they differ on these trials is critical to any global market access strategy. The main objective of osteoporosis trials, commonly stated by the FDA and EMA guidelines for the development of drug treatments for osteoporosis, is to demonstrate a decrease in the incidence of fractures.⁸

For example, as outlined in the 1994 FDA guidance on osteoporosis trials, clarifications on requirements for approval included:

1. Normal bone quality in preclinical studies of two animal species.
2. Normal bone quality in a subset of clinical trial participants.
3. A statistically and clinically significant increase in bone mineral density (BMD).
4. At least a positive trend (i.e., $p < 0.2$) in three-year fracture data.

However, while the FDA guideline considers as requirements a statistically significant increase in BMD and a three-year positive trend in fracture data to demonstrate efficacy, the EMA guideline is exclusively focused on occurrence of new fractures to demonstrate efficacy of new drugs. Specifically, the EMA “Guideline on the Evaluation of Medicinal Products in the Treatment of Primary Osteoporosis”⁹ effective May 2007, clarifies in section 4.3.2 that bone mineral density “may be the primary endpoint in exploratory studies but it is not an appropriate surrogate for fracture reduction,” and the primary efficacy variable should be based on the occurrence of new axial and peripheral fractures (not on worsening of previous fractures).

Additional comparisons for critical requirements of FDA and EMA trials are noted in Table 1.

Considerations for Fracture Risk Assessment in Osteoporosis Clinical Development

Osteoporosis is operationally defined on the basis of BMD assessment. According to World Health Organization (WHO) criteria, osteoporosis is defined as a BMD that lies 2.5 standard deviations or more below the average value for young healthy women (a T-score of < -2.5 SD).^{10,11} This criterion has been widely accepted and provides both a diagnostic and intervention/treatment threshold. As such, BMD is considered to be the gold standard measurement for the diagnosis of osteoporosis and the assessment of fracture risk.²

However, the majority of fragility fractures (defined as a low-energy fracture due to a fall from no greater than standing height)² occurs in patients with a BMD in the osteopenic (less severe) rather than osteoporotic range. As such,

Table 1. FDA and EMA osteoporosis guidelines requirements – A comparison

Requirements	FDA 1994	EMA 2007
Phase II studies	Randomized, double-blind, placebo-controlled and at least 24 months in duration	Parallel-group, fixed-dose, double-blind, placebo-controlled study design should be used in Phase II The treatment duration required for evaluating significant effects may vary depending on the drug
Phase III studies	Expected to be continuations of the Phase II trials – no minimal duration of study suggested	Parallel-group, double-blind, placebo-controlled and/or comparator-controlled studies are necessary
Primary endpoint	Skeletal mass or fractures	The primary variable should be based on the occurrence of new axial and peripheral fractures
Normal bone quality in two animal species (Preclinical)	YES	YES
Normal bone quality in a subset of patients	YES	YES
Statistically and clinically significant increase in BMD	YES	NO May be the primary endpoint in exploratory studies but not an appropriate surrogate for fracture reduction
Positive trend (i.e., $p < 0.2$) in three-year fracture data	YES	NO Primary variable should be based on the occurrence of new axial and peripheral fractures
Use of placebo	YES Placebo-controlled trials are still appropriate/feasible in many circumstances	YES Placebo-controlled trials should be performed whenever possible

osteoporosis and bone health scientific guidelines agree that a systematic approach to assessing risk factors for fractures in addition to bone density should be included in the risk assessment for fractures that also contribute independently to the risk of fracture.

Because of the importance of BMD and fracture risk, the following are essential factors to consider when planning an osteoporosis trial.

Fracture Risk Assessment Tool

The fracture risk assessment tool (FRAX) was developed, released and validated in 2008 by the WHO's collaboration with Dr. John Kanis and other osteoporosis experts and organizations, including the American Society for Bone and Mineral Research, the National Osteoporosis Foundation, the International Society for Clinical Densitometry and the International Osteoporosis Foundation.¹² The FRAX model is a critical tool for assessment in clinical trials because it:

- Provides a tool for the prediction of fractures in men and women with use of clinical risk factors with or without femoral neck bone mineral density.
- Calculates the 10-year probability of a major osteoporotic fracture (in the proximal part of the humerus, wrist or hip or a clinical vertebral fracture) and of a hip fracture calibrated to the fracture and death hazard.

In addition to the clinical risk factors, the geographic area in which an individual resides should be considered in the fracture risk assessment because fracture probability varies markedly among different regions of the world.¹³

BMD with Dual Energy X-ray Absorptiometry

Dual energy X-ray absorptiometry (DXA) is the most commonly accepted technique for BMD assessment.¹⁴ Understanding BMD assessment parameters, guidelines and limitations can result in more efficient execution and a lower screen fail rate, when considering clinical trial design and operational elements.

BMD is expressed in absolute terms of grams of mineral per square centimeter scanned (g/cm^2) and as a relationship to two norms:

- Compared to the BMD of an age-, sex- and ethnicity-matched reference population (Z-score), or
- Compared to a young-adult reference population of the same sex (T-score).¹⁵

Osteoporosis definition is based on the BMD T-score at the femoral neck, which is considered the reference site, while most guidances favor the use of proximal femur and lumbar spine BMD T-scores. Osteoporosis is defined based on the lower of the two T-scores. As such, prediction of fracture risk is not improved by using T-scores from multiple sites. In clinical trials, BMD T-score assessments, therefore, should be limited to femoral neck and lumbar spine.

Most patients who sustain fragility fractures have a T-score above -2.52. However, by allowing patients to be eligible based on their history of fragility (osteoporotic) fracture with T-score ≤ -2.0 , or, current osteoporosis related fracture based on X-ray, will likely improve the screen failure rates due to BMD alone. Regardless of drug class being studied, most screen failures in published osteoporosis studies are due to BMD T-scores not being low enough (failing to meet the BMD T-score definition of osteoporosis).

In assessing BMD, DXA does present a few demographic and operational limitations. For example:

- Detectable changes in bone density due to treatment can take up to two years to become apparent. Therefore, the identification of non-responders to treatment is delayed.¹⁶

- BMD assessments by DXA are not consistently available in all countries and geographic regions, in part because of the high capital costs of DXA.¹⁵
- BMD tests are not always reimbursed despite the availability and approval of effective drug treatments.¹⁵

Quality Control Requirements for DXA

BMD measuring devices require higher precision than other medical devices, and strict precision is required for the follow-up of osteoporotic patients as the range of BMD change is very narrow in those patients. Frequent, precise calibrations and quality control (QC) checks of the DXA equipment are critical.¹⁷

For clinical trials:

- Not only are individual DXA machine calibrations required, but consistent cross-calibrations also are necessary for multiple machines across sites, countries and regions.
- Protocol-specific DXA training manuals are a useful resource for study sites to reference and to train and retrain staff throughout the study.
- QC and calibration specifications for a clinical trial should be consistent with scientific guidelines from organizations such as the American Society for Bone and Mineral Research (ASBMR) and the International Society for Clinical Densitometry (ISCD).
- Careful attention also should be given to selection of a DXA central reader vendor to ensure consistency of intra- and inter-subject study assessments.

Bone Turnover Markers

Bone turnover markers (BTM) can offer an alternative monitoring strategy. Studies have shown that bone turnover may be an independent predictor of fracture risk.²

Biochemical markers of bone turnover are used to monitor treatment response and may prove to be more useful than serial BMD measurements. They measure bone resorption or formation. BTMs have advantages over DXA as they are non-invasive, relatively inexpensive and able to detect changes in bone turnover rates – in some cases, detecting bone turnover as early as two weeks for some therapies and between three and six months for most. Additionally, there is an increased availability of auto-analyzers in clinical chemistry laboratories.¹²

There are also disadvantages to using BTM. For instance, there can be high intra- and inter-patient variability, although the ability of bone turnover markers to identify treatment non-responders and predict future fracture risk has yet to be established. The relationship between bone turnover and bone density and architecture means the rate of bone turnover may be an independent predictor of fracture risk.¹⁸

There is a complex association between changes in bone turnover and fracture risk that is influenced by the treatment–bone turnover marker combination. The observed change in bone turnover markers will depend upon the treatment (bisphosphonates, teriparatide, hormone replacement therapy, etc.) being administered. BTM can be measured by serum and/or urine collection, with most evaluations done at baseline, and then after three and six months of treatment.

Regardless of the methods used to assess fracture risk, bone density and treatment efficacy, the goal in a clinical trial setting is to determine clinical outcomes that reflect sound science and medicine and are meaningful to patients and clinical trial study subjects. Risk assessment algorithms, BMD testing with DXA and use of BTMs represent options that can successfully meet this goal in different settings and regions.

Patient-Focused Approach in Osteoporosis Drug Development

Osteoporosis drug development represents a unique opportunity for sponsors and CRO trial collaborators to apply patient-centric strategies to improve clinical trial design and patient outcomes. Regulatory agencies, clinical trial sponsors and patient advocacy organizations are increasingly intentional about including the “patient voice” across the full life cycle of the drug development process.

Increased patient involvement in setting research goals and objectives, including endpoint and biomarker identification, protocol design, key inclusion/exclusion criteria, recruitment, improved access, treatment adherence, patient-reported outcomes and post-study communications are priorities for clinical research stakeholders, such as sponsors, patients, investigators and regulators.

“There is an increasing need to draw on patient knowledge and experience to understand what it is like to live with a specific condition, how care is administered and the day-to-day use of medicines. This input helps to improve discovery, development and evaluation of new effective medicines.”

(EUPATI 2016)

While most osteoporosis patients are elderly, the participation of this population in clinical trials is known to be associated with problems of medication adherence, reduced mobility and multiple co-morbidities. Similarly, ethnic minorities as well as male patients are underrepresented in osteoporosis trials. Patient-focused strategies can address the barriers to inclusion of a representative, diverse patient cohort.

Virtual study visits, “patient concierge” care coordination teams, mobile research vans and home health visits are examples of offerings that bring trials closer to patients, reducing the patient burden and barriers of access to and participation in clinical trials.

The underlying goal for these strategies in osteoporosis trials is to improve recruitment, enhance study drug adherence, reduce the patient burden and mitigate dropouts, while offering solutions to improve quality of participation and the patient experience and, ultimately, quality of data and making trials more cost-effective.

Clinical Trials in the Aging Population

The elderly population is the fastest-growing portion of the population worldwide, consuming roughly one-third of all medications, while making up only 13% of the population.¹⁹

According to the National Council on Patient Information and Education (NCPIE), most older Americans (eight of 10) take at least one medication and many take three or more per day. This patient group accounts for not only 34% of all prescription medicine use, but also 30% of all over-the-counter medicine use.

Clinical trial participation, compliance and completion pose additional challenges in the older population. For example, they can lose interest in trials as their health declines because it becomes more difficult for them to attend study visits without assistance.²⁰ Trial sponsors and clinical providers should not underestimate the operational implications of including elderly participants. To address the specific needs of this population, strategy should focus on use of purposely designed ePRO devices and patient and site concierge services to promote compliance and retention in a study.

ePRO and Use of Technology in the Elderly Population

Professor Nicholas Bellamy of the University of Queensland, an authority in validated clinical assessments, commented that “[although] it might be assumed that cognitive and dexterity problems in elderly patients would preclude their use of mobile ePRO,” elderly populations are “using technology

regularly,” particularly mobile phones. “So long as the interface is designed appropriately and is user friendly,” Bellamy suggests, “then it should be implementable across a broad range of age groups, including the elderly.”²¹

In the last 10 years, electronic data collection of clinical outcome assessments (COA), including patient-reported outcomes (PRO), attained directly from the patients increased thanks to the integration with mobile technology.

Mobile technologies are now very familiar to the older population (compared to 10 years ago) and widely used in their day-to-day lives. However, in the scope of clinical trials, they should be designed and programmed to consider the specific needs of this population, rather than just pushing to implement what already is available. For example, use of wider screens, easy and short questionnaires, and properly programmed reminders can help improve compliance and retention rates.

Summary and Future Considerations

The aging of the global population is causing an increase in the prevalence of age-related chronic diseases, including osteoporosis. Despite numerous approved and available drugs, established risk assessment and diagnostic criteria, osteoporosis remains underdiagnosed and undertreated in at-risk populations. However, the market for osteoporosis treatments is expected to experience exponential growth in emerging treatments, such as RANKL-Mab, anti-sclerotin Mab and biosimilars.²²

Understanding the global osteoporosis regulatory framework, as well as the state of fracture risk assessment, will help sponsors properly identify and meet endpoints. Moreover, inclusion of patient-focused strategies in osteoporosis drug development represents an opportunity to improve trial design, patient recruitment and retention in trials, treatment adherence, and clinical outcomes.

Osteoporosis-focused medical and scientific organizations, advocacy groups, public health organizations and regulatory authorities agree that primary and secondary fracture prevention strategies, while well documented, have not adequately penetrated routine clinical practice.

Experts also have identified several areas that urgently require epidemiologic, clinical and economic research. They include:

- Primary prevention strategies for decreased bone mass in the young.
- Evaluation of optimal duration of antiresorptive treatment.
- Inclusion of diverse populations in osteoporosis clinical trials (racial/ethnic minorities, men, elderly).
- Increased focus on health services intervention and treatment trials to better address under-diagnosis and under-treatment.²³

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