

Quantify Osteoporosis Clinical Outcomes Database

1. Summary Information

Drug therapies for osteoporosis include bisphosphonates (alendronate, ibandronate, risedronate, and zoledronic acid), hormone replacement therapy (estrogen), selective estrogen receptor modulator (raloxifene), calcitonin, and parathyroid hormone (teriparatide, PTH1-84). Several newer therapies (such as lasofoxifene, bazedoxifene, odanacatib, denosumab) are in development.

The current version of the database focuses on prevention and treatment of osteoporosis in postmenopausal woman. It extracts all relevant changes in bone mineral density, biochemical markers of bone turnover, fracture risk, and safety parameters after treatment with drug therapies listed above.

Table 1. Summary information

Parameter	Description
Format	Excel
Indications	Prevention and treatment of post menopausal osteoporosis
#Trials/References	78/95
# Patients	108,000
# Rows of Data	11,289
Last Updated	June 30 th , 2009
Compounds	Placebo, alendronate, bazedoxifene, calcitonin (salmon), denosumab, ibandronate, lasofoxifene, ospemifene, raloxifene, risedronate, zoledronic acid, HRT, PTH1-34, PTH1-84
Key efficacy end points	BMD endpoints, fractures, markers of bone turnover (24 key endpoints in total)
Key safety end points	Tolerability percentages, clinical lab safety outcomes (30 endpoints in total)

2. Features and benefits

Key Features:

- **Comprehensiveness:** includes information for marketed drugs as well as drugs in development; data source includes journal publications, conference posters, regulatory reviews, etc.

- **Ease of tracking:** all clinical trial publications are listed in a separated source database and linked to unique clinical trial names
- **Flexibility:** the database design allows for quick updates as well as expansions to include additional indications/drugs/endpoints/trials
- **Model-friendliness:** designed and reviewed by experienced modelers to ensure highest quality and usability for modeling and simulation to support drug development strategies
- **Customizability:** can be augmented with clinical trial data proprietary to the client (this information goes into a separate proprietary database and will be owned by the client)

Potential Applications:

Characterize relative (comparative) clinical safety and efficacy profile:

- What is the difference in magnitude of BMD changes across drugs and mechanisms of action?
- Is there a difference in speed of onset of BMD changes across drugs? Does this impact the time course of fracture risk benefit?
- What is the difference in magnitude of BMD changes between women with established osteoporosis or osteopenia? Does this impact the fracture risk benefit?

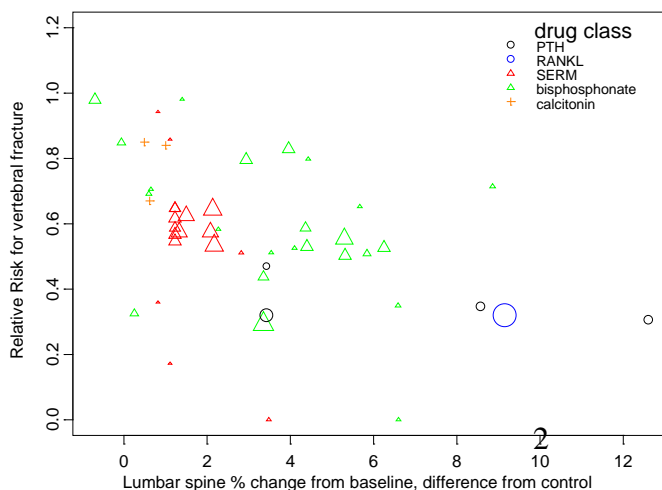
Characterize endpoint-to-endpoint relationships:

- Is there a relationship between markers of bone formation and resorption and BMD changes?
- Is there a difference in relative effect at different anatomical sites across drugs and mechanisms of action?

Ultimately, these analysis help drug companies to optimize trial design, improve trial outcomes, and strengthen product differentiation.

Example:

Question: what is the relationship between bone mineral density and fracture risk? Is this relationship similar across mechanisms of action? Does this relationship explain all treatment effect or is there an additional benefit of certain treatments? What anatomical site of BMD changes is most predictive for fracture risk? Is there a plateau on the benefit for fracture risk?



Approach: Use the BMD time course data to derive the relationship between BMD changes and fracture risk.

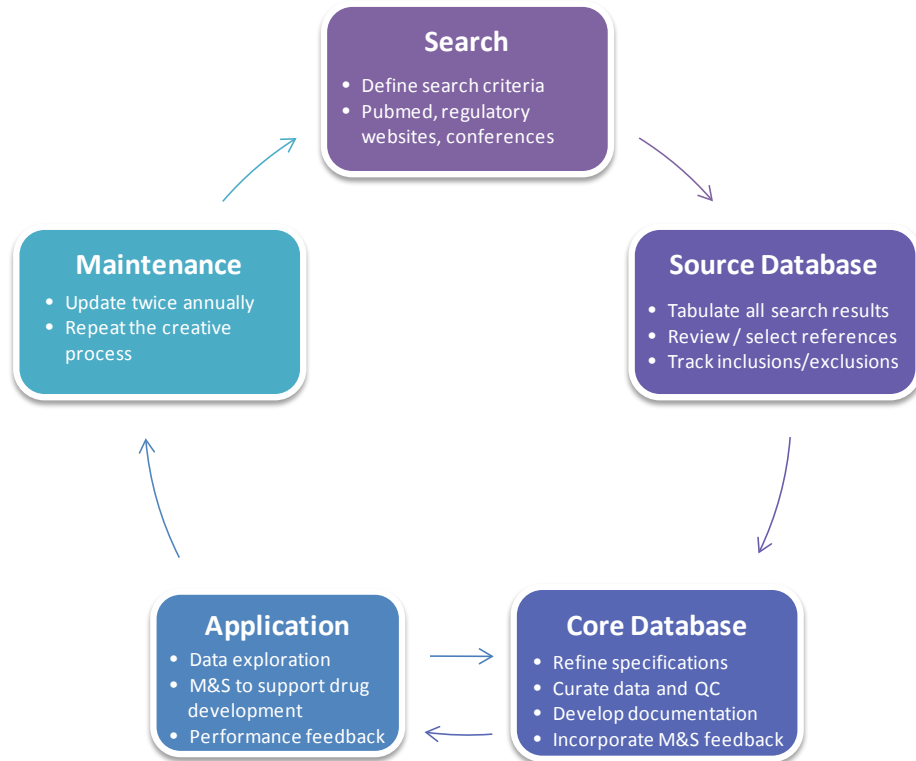
Why use our databases:

- Designed and managed by experienced modelers
- Provide most relevant data to support clients' needs for quantitative decision making
- Contain up-to-date and high quality data so that it is always readily available to provide timely analysis required to support critical clinical trial decisions
- Supported by additional services such as modeling and simulation consulting services and custom curation services (by our partner, GVK Bio)

3. Organization and Structure

This product consists of two databases, the *source database* and the *clinical outcomes database(core database)*, developed for RA. The *source database* is a database that maintains the sources of information identified by searches and reviewed for inclusion or exclusion from the database. The *clinical outcomes database* contains the information on trial, treatment and patients characteristics and safety and efficacy results of the trials identified for inclusion in the database.

The following is a flowchart showing the process with which databases are created, optimized and updated.



4. Overview of the Osteoporosis Source Database

The primary data sources were controlled clinical trials published in the medical literature or available through the FIA from the FDA. A secondary source of information was published abstracts or presentations of clinical trial data from conferences and corporate websites.

769 references were identified and documented in the source database, of which a total of 152 references were selected for inclusion in the database after careful review of the abstracts. The detailed reference information as well as reasons for exclusion is recorded to facilitate potential future expansion of the database. Of the selected references, 94 are included in the current database. They provided information on 77 unique trials.

5. Overview of the Osteoporosis Clinical Outcomes Database

The following randomized controlled trials provided information on safety and efficacy that was used for the registration with the FDA and EMEA as primary or supportive

evidence. The links to the FDA and EMEA reviews are provided in Appendix C. The publication for two trials, ALN038 and BMD-US was not found. Data from trial ALN038 was available from the SBA and included in the database bringing the total number of trials in the database to 78.

Table 2. List of registration trials in the database

Drug	Indication	Study
alendronate	prevention	ALN029
		ALN038
		ALN055/EPIC
	treatment	ALN026
		ALN035
		ALN037
		ALN072
		ALN097
		FIT1
		FIT2
ibandronate (oral)	treatment	MF4411/BONE
		MF4433
		MF4348
		M75003
	prevention	MF4499
		MF4500
		MF16549/MOBILE
ibandronate (iv)	treatment	MF4470/IRIS
		BM16550/DIVA
		MF4380
		MF4361
	prevention	MF4488
risedronate	treatment	RVN/VERT-US
		RVE/VERT-MN
		BMD-US
		ROE/BMD-MN
	prevention	RBL
		RPE
zoledronic acid	treatment	2301/HORIZON
		41

		2313
		2315
PTH1-34	treatment	GHAC
		GHAF
		GHAH
Raloxifene	prevention	GGGG
		GGGF
		GGGH
	treatment	GGGK/MORE

The clinical outcomes database contains information from 78 trials, representing 256 unique treatment arms and about 108,000 patients. There are a total of 11,289 rows in the database. Each row contains the information for an endpoint in one arm of a trial at a specific point in time. The table below provides an overview of the available data for certain randomized treatments.

Table 3. Number of trials, treatment arms and patients for each drug

Treatment	# trials	# arms	# patients
Placebo	55	55	32797
alendronate	31	57	13823
bazedoxifene	2	5	4720
calcitonin (salmon)	2	4	1019
denosumab	4	15	4424
ibandronate	14	40	10338
lasofoxifene	1	2	164
ospemifene	1	3	89
raloxifene	17	27	15892
risedronate	13	25	17315
zoledronic acid	4	8	3519
HRT	5	5	840
PTH1-34	4	5	1329
PTH1-84	2	4	1527
total	78	256	107971

Table 4. Overview of BMD endpoints

The table shows the most relevant BMD endpoints. There are a total of 31 different BMD endpoints

Endpoint	# trials	# arms	# patients	drugs
BMD_femoral neck	55	180	64635	/HRT/PTH1-34/PTH1-84/Placebo/alendronate/calcitonin (salmon)/denosumab/ibandronate/raloxifene/risedronate/zoledronic acid
BMD_femur	1	6	180	/Placebo/ibandronate
BMD_femur proximal	3	7	2918	/Placebo/risedronate
BMD_hip total	47	154	66121	/HRT/PTH1-34/PTH1-84/Placebo/alendronate/bazedoxifene/denosumab/ibandronate/lasofoxifene/raloxifene/risedronate/zoledronic acid
BMD_intertrochanter	6	21	10554	/HRT/PTH1-34/Placebo/alendronate/raloxifene
BMD_radius 1/3 distal	13	49	12554	/HRT/PTH1-34/Placebo/alendronate/denosumab/ibandronate/raloxifene
BMD_radius distal	9	30	15221	/HRT/PTH1-34/PTH1-84/Placebo/alendronate/ibandronate/raloxifene/risedronate/zoledronic acid
BMD_radius midshaft	2	5	1750	/HRT/Placebo/risedronate
BMD_radius total	1	3	520	/Placebo/ibandronate
BMD_radius ultra distal	12	40	13721	/HRT/PTH1-34/Placebo/alendronate/ibandronate/raloxifene
BMD_spine lumbar	71	228	86501	/HRT/PTH1-34/PTH1-84/Placebo/alendronate/alfacalcidol/bazedoxifene/calcitonin(salmon)/denosumab/ibandronate/lasofoxifene/raloxifene/risedronate/zoledronic acid
BMD_total body	22	79	22177	/HRT/PTH1-34/PTH1-84/Placebo/alendronate/denosumab/ibandronate/raloxifene
BMD_trochanter	45	144	46277	/HRT/PTH1-34/PTH1-84/Placebo/alendronate/calcitonin (salmon)/denosumab/ibandronate/raloxifene/risedronate

BMD_wards triangle	16	53	16228	/HRT/PTH1-34/Placebo/alendronate/calcitonin (salmon)/ibandronate/raloxifene
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6. Outcome fields

The following efficacy measurements are recorded in the database

Efficacy outcomes fields

- 1. Bone Mineral Density (BMD).** The method and machine (Lunar or Hologic) of BMD was recorded. The outcome in T-score, g/cm^2 , % change and proportion of patients with a predefined change was recorded for the following anatomical areas
 - Lumbar spine
 - Femoral neck
 - Femoral Trochanter
 - Total hip
 - Whole body
 - ultra distal radius
 - one-third distal radius
 - Ward's triangle
 - other areas if reported
- 2. Fractures.** The method and definition of fracture assessment was recorded. The incidence, hazard ratio, relative risk, and risk reduction was recorded for the anatomical areas listed below. Kaplan-Meier curves were digitized to capture the time course of cumulative incidence and relative risk.
 - new vertebral fractures
 - clinical vertebral fractures
 - non-vertebral fractures
 - hip fractures
 - wrist fractures
 - other relevant fractures
- 3. Markers of bone turnover**
 - makers of bone formation
 - Serum osteocalcin

- Serum Bone-Specific Alkaline Phosphatase (BSAP)
- Total Serum Alkaline Phosphatase
- C-terminal propeptide of type 1 procollagen (P1CP)
- N-terminal propeptide of type 1 procollagen (P1NP)
- markers of bone resorption
 - urinary deoxypyridinoline/ creatine ratio (d-pyr)
 - urinary pyridinoline/ creatinine ratio
 - urinary N-Telopeptide of type I collagen/ creatinine ratio (NTX)
 - urinary C-telopeptide of type I collagen/ creatinine ratio (CTX/creatinine)
 - Serum C-telopeptide of type I collagen (CTX)

Adverse events outcome fields: The following adverse events information were extracted:

- Total dropout (treatment discontinuation). This refers to all patients that did not complete the study (dropout).
- Dropout related to adverse events (dropout AE)
- any adverse events (AE any)
- serious adverse event (AE serious)
- any upper gastrointestinal symptom (GI upper any)
- abdominal pain
- dyspepsia
- esophagitis
- gastritis
- stomach ulcer
- esophageal ulcer
- hypocalcemia
- hypercalciuria
- nausea
- headache
- dizziness
- leg cramps
- cancer
- breast cancer
- vomiting
- palpitation

- hot flashes
- dyspnea
- inflammatory eye disease (conjunctivitis, uveitis, scleritis)
- musculoskeletal pain
- other AEs deemed relevant from each publication

Clinical laboratory safety outcome fields: The following laboratory safety variables will be extracted:

- Serum calcium
- Urinary calcium
- Phosphorus
- 25-Hydroxyvitamin D
- 1,25-Hydroxyvitamin D