



# **Osteoporosis Drug Development Moving Forward**

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# The Need for Fracture Trials

- The challenges for drug development
  - The conflict between the fracture trials needed to show benefit and the ethics of conducting these studies
  - Concern regarding the validity of non-inferiority trials
  - Active control trial sample sizes could be prohibitively large

# Definition

- A surrogate endpoint of a clinical trial is a biomarker used as a substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions or survives.
- Changes induced by a therapy on a surrogate endpoint are expected to reflect changes in a clinically meaningful endpoint (i.e. – fracture).

# The Role of Biomarkers/Surrogates

- As markers or correlates of risk permitting identification of target populations for study and/or treatment
- As endpoints for assessment of drug efficacy when the change in the marker predicts reduction or augmentation in clinical risk

# The Risk of Relying on Surrogates

- The risk/benefit assessment is much more difficult with surrogate endpoints in clinical trials and may not be as robust
- The relationship between biomarker/surrogate and clinical event may not be causal, but coincidental or co-related to a third factor
- The measured change-predicted benefit relationship may not hold up when tested

# Use of Surrogates in Osteoporosis Drug Development

- **Morphometric Vertebral Fractures**
  - Asymptomatic fractures diagnosed by imaging could be considered a surrogate marker of clinical fractures
- **Bone Mineral Density (DXA)**
  - A fracture risk correlate and used for identification of the population at risk for fracture
  - Primary efficacy endpoint in non-inferiority trials once fracture efficacy has been established
- **Biochemical Markers of Bone Turnover**
  - Supportive secondary efficacy endpoints

# BMD for Prediction of Fracture

- **1990 – Fluoride**
  - 35% increase in spine BMD
  - No vert fx reduction, Increase in nonvert fx
- **1991 – Etidronate**
  - 8% increase in spine BMD
  - Vert fx reduction Year 2, Increase in vert fx incidence in Year 3
  - ? Accrual of adverse effects on bone quality

# Calcitonin - PROOF

	Placebo NS	Calcitonin 100 IU	Calcitonin 200 IU	Calcitonin 400 IU
N	270	273	287	278
<b>Lumbar Spine BMD at 36 months</b>				
% change	0.40	1.03	1.04	1.54
<b>Morphometric Vertebral Fracture</b>				
% with $\geq 1$ new MVF	26%	22%	18%	22%
RRR	-	15%	33%	16%
ARR	-	4%	8%	4%

# Trial A2303

## New vertebral fractures

	SMC021	Placebo
N	2125	2064
<b>Lumbar Spine BMD at 36 months</b>		
LS BMD, % change	1.02	0.18
<b>Morphometric Vertebral Fracture at 36 months</b>		
% ≥ 1 new MVF	4.6%	4.7%

# Fracture Efficacy: Ibandronate

	Oral 2.5 mg qd	IV 1.0 mg q3m
<b>N</b>	977	961
<b>Lumbar spine BMD at 36 months, % change from baseline</b>		
<b>Ibandronate</b>	6.5	4.9
<b>Placebo</b>	1.3	1.0
<b>New vertebral fractures at 36 months, % of subjects</b>		
<b>Ibandronate</b>	4.7	9.2
<b>Placebo</b>	9.6	10.7
Clinical review NDA 021455, Drugs@fda		

# Questions to Consider

- Is BMD able to adequately predict fracture efficacy?
- Which BMD site should be used?
  - Lumbar spine?
  - Total hip?
  - Femoral neck?

# Questions to Consider

- What type of fracture should be used to qualify or validate a new surrogate?
  - Morphometric vertebral?
  - Clinical vertebral or other sites?
  - Major osteoporotic fractures?
  - Hip?



# Thank You



# Back-up Slides



## Fracture Trials, BMD and MVF results

	N		LS BMD % change		MVF % subjects			
	pla	drug	pla	drug	pla	drug	ARR	RRR
Alendronate1	397	597			6.2	3.2		
Alendronate2	965	981	1.7	7.9	15.0	7.9	7.1	
Raloxifene	1522	1490	0.2	2.9	4.3	1.9	2.4	55
Raloxifene2	770	769	1.1	2.2	20.2	14.1	6.1	30
Risedronate1	678	696	0.8	5.0	16.3	11.3	5.0	41
Risedronate2	346	344	1.0	6.6	29.0	18.1	10.9	49
Teriparatide **	544	541	1.1	9.7	14.3	5.0	9.3	65
Ibandronate, po	977	977	1.3	6.5	9.6	4.7	4.9	52
Ibandronate, iv	949	961	1.0	4.9	10.7	9.2		
Zoledronic Acid	3861	3875	0.2	7.0	10.9	3.3	7.6	70
Denosumab	3691	3702	0.6	9.4	7.2	2.3		

ARR = Absolute Risk Reduction, RRR = Relative Risk Reduction

\*\* 19 month data