Surrogate threshold effect: a novel approach for potential approval of new osteoporosis treatments using change in BMD. Study-level analysis from the FNIH Bone Quality Project

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For the FNIH Bone Quality Project

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Background

• Change in dual-energy X-ray absorptiometry (DXA) bone mineral density (BMD)
  o May be a useful surrogate for fracture endpoints
  o Could enable much smaller and shorter clinical trials for new drug approvals in osteoporosis
• The difference in the change in total hip BMD between active and placebo groups is strongly related to fracture risk reduction with osteoporosis treatments (1)
• What BMD increase would predict a fracture benefit?
  o Such knowledge could allow us to develop a new regulatory pathway for approval of new osteoporosis treatments

Change in BMD is related to vertebral fracture risk reduction

**Total Hip BMD**

\[ r^2 = 0.56, p = 0.0002 \]

**Femoral Neck BMD**

\[ r^2 = 0.54, p < 0.0001 \]

**Lumbar Spine BMD**

\[ r^2 = 0.63, p < 0.0001 \]
Surrogate Threshold Effect (STE)

- The level of the marker that would predict an improvement in a disease outcome with 95% certainty
- Example: systolic blood pressure change and stroke risk on treatment

Population

• Data from study participants
  o collected as part of the FNIH Bone Quality project
  o a public-private partnership, which compiled IPD from over 150,000 participants in all major clinical trials of osteoporosis therapies, including DXA BMD and fracture outcomes

• The current analyses reflect data from 61,415 study participants with 2-year BMD from 16 osteoporosis trials
  o 9 bisphosphonate; 4 SERM; 1 teriparatide; 1 denosumab; 1 odanacatib
Methods

• Meta-regression using
  o baseline and follow-up BMD results
  o incident fractures from each study
• Assessment of the relationship between
  o the treatment-related difference in total hip BMD changes (percent difference, active minus placebo at 24 months)
  o to the observed fracture risk reduction in each study
• We fit a linear regression to the logarithm of the relative risks and estimated the 95% confidence interval and prediction limits
• The surrogate threshold was defined as the point where the prediction limits crossed the relative risk of fracture of unity
Total Hip BMD difference and fracture reduction - 1

- Arrow indicates the minimum BMD difference predicting significant fracture reduction in a future trial
Total Hip BMD difference and fracture reduction - 2

- Arrow indicates the minimum BMD difference predicting significant fracture reduction in a future trial.
Total Hip BMD difference and fracture reduction - 3

- Arrow indicates the minimum BMD difference predicting significant fracture reduction in a future trial
- Application of thresholds to completed clinical trials

Trials sorted by 2-year difference in THBMD.

Fracture reduction ns, not significant N/A, not available
* p<0.05, ** p<0.01

<table>
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<tr>
<th>Study name</th>
<th>Study drug</th>
<th>THBMD</th>
<th>VFx</th>
<th>Hip Fx</th>
<th>NV Fx</th>
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VFx, 1.7%
Non-VFx, 3.2%
Hip Fx, 4.6%
Strengths and Limitations

• **Strengths**
  - Application of approach used for other surrogate endpoints
  - Large study
  - Access to individual patient data allows study of 2-year BMD and consistent fracture definition

• **Weaknesses**
  - The approach depends on the power of the underlying studies

• **Further analyses**
  - Use of clinically meaningful reduction (e.g. 20%)
  - Use of different time windows, different levels of confidence
Conclusions

• Conclusions
  o This analysis identifies the BMD increases that would predict a fracture benefit

• Discussion
  o The results may be helpful to regulatory agencies if they adopt total hip BMD as a surrogate for fracture risk reduction in clinical trials of new osteoporosis drugs
  o Why are the BMD increases not the same for all fracture types?
    ➢ The drugs may work preferentially on the trabecular bone of the spine
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**UCSF & FNIH colleagues**
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Reserve Slide: Total Hip, Femoral Neck, Lumbar Spine BMD difference and fracture reduction

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<th>Fracture type</th>
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<th>Femoral Neck</th>
<th>Lumbar Spine</th>
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