COLLEGE
TER BEOORDELING VAN
GENEESMIDDELEN

CBG

MEB

MEDICINES
EVALUATION
BOARD
Surrogate endpoints for fractures ??

regulatory perspective

Dr. Frits Lekkerkerker
CHMP alternate member
Chairman Medicines Evaluation Board
in The Netherlands
*Time for an update?*

Surrogate Endpoints in Clinical Trials for osteoporosis:

- are they reliable?
  - is there any validation
- are we being misled?

better is to use the terminology (bio)markers only if validated - surrogates
Time for an update?

Guideline on the evaluation of medicinal products in the treatment of primary osteoporosis released November 2006

- For new products there is a need for demonstration of effect both on spinal and on non spinal fractures
- Biomarkers are not considered as an appropriate surrogates as endpoints in confirmatory studies
Biomarkers in clinical trials for osteoporosis can be used as tools when:

- understand the biology of the process
- understand the effect of a new medicine
- provide information on sub- or other populations that might respond?
Endpoints in studies

✓ fractures (vertebral /other)
✓ pharmacodynamic endpoints - biomarkers
  ▪ BMD
  ▪ bone turn-over parameters
    − osteocalcin, alk fosf
    − N- or C-telopeptide of type I collagen
  o two independent factors relating to efficacy treatment
  o two factors with different measurement accuracy
Time for an update?

Why there will be a need for surrogate endpoints
✓ fracture studies difficult to perform
✓ concerns about performing placebo controlled studies
✓ new formulations with same active substances
✓ dosage range
✓ new indications
Why there will be a need for surrogate endpoints

✓ fracture studies difficult to perform
  ▪ long follow up
  ▪ costly
  ▪ fracture is a relative rare event.

✓ concerns about performing placebo controlled studies
✓ new formulations with same active substances
✓ dosage range
✓ new indications
Time for an update?

Endpoints in studies

✓ fractures (vertebral /other)
✓ surrogate endpoints or pharmacodynamic endpoints
  ▪ BMD
    - BMD not // fracture reduction
Fractures with Risedronate

Reductions in New and Worsening Vertebral Fractures

- Year 0-1: 49%
- Year 0-3: 50% (PBO-NA), 33% (RIS-NA), 41% (PBO-MN, RIS-MN)
**Progressive Increases in Spine BMD over 7 yrs**

- 5 mg Alendronate
- 10 mg Alendronate
- 20mg/5 mg/Placebo 1 - 5 year
- 20mg/5 mg/Placebo 6 - 7 year

Mean Percent Change (± SE)

- 11.2%
- 9.0%
- 8.0%
Time for an update?

Reduction in fracture risk for bisfosfonates in relation to BMD

- after first year already on there maximum
- further increase in BMD doesn't relate to an increase in fracture reduction
Normalization of Bone Turnover Maintained

Bone Resorption

- 5 mg Alendronate
- 10 mg Alendronate
- 20mg/5 mg/Placebo 1 - 5 year
- 20mg/5 mg/Placebo 6 - 7 year

Change in Urine NTX (%)

Bone Formation

- 5 mg Alendronate
- 10 mg Alendronate
- 20mg/5 mg/Placebo 1 - 5 year
- 20mg/5 mg/Placebo 6 - 7 year

Change in Serum BSAP (%)
Time for an update?

Reduction in fracture risk in relation to BMD
✓ Bisphosphonates
✓ HRT
✓ SERM/raloxifene
✓ Calcitonin
✓ Fluor
✓ Strontium
✓ PTH
Time for an update?

Why there will be a need for surrogate endpoints
✓ fracture studies difficult to perform
✓ concerns about performing placebo controlled studies
✓ new formulations with same active substances
✓ dosage range
✓ new indications
  ▪ effect on non vertebral fractures
  ▪ effect on man
Why surrogate endpoints

✓ fracture studies difficult to perform
✓ concerns about performing placebo controlled studies
  ▪ easier / quicker to measure
  ▪ reduce trials size, duration size costs
  ▪ but should be measured accurately and reproducibly
  ▪ change in proportion to what it represents
  ▪ it is a misunderstanding that, if their outcome is correlated with true outcome for one product, it could be used as a validated surrogate endpoint when studying other products
Why surrogate endpoints

- fracture studies difficult to perform
- concerns about performing placebo controlled studies
- new formulations with same active substances
- dosage range
  - daily to weekly, monthly, 3 monthly
  - different effect on different biomarkers
  - bridging studies
- new indications
  - effect on non vertebral fractures
  - effect on man
Time for an update?

Why surrogate endpoints
✓ fracture studies difficult to perform
✓ concerns about performing placebo controlled studies
✓ new formulations with same active substances
✓ dosage range
✓ new indications
  ▪ effect on non vertebral fractures
  ▪ effect on man
Time for an update?

Why surrogate endpoints

✓ fracture studies difficult to perform
✓
✓ new indications
  ▪ effect on non vertebral fractures
  ▪ effect on man
    o duration one year
    o dosage justified
    o inclusion criteria the same
    o magnitude is the same
    o if mode of action is not gender specific
Fracture studies are required
However, biomarkers can be used
✓ dose finding studies
✓ if fracture reduction have been demonstrated
  ▪ new dose regime
    o both biomarkers
  ▪ new route of administration
  ▪ new indication in men if according guideline
COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

CBG

MEDICINES EVALUATION BOARD