EDA Request	Relationship of early changes in bone resorption to the risk of incident fracture.
Internal Contact(s)	*Ian Barton*
External Contact(s)	*Prof. Richard Eastell*
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BUSINESS PURPOSE

Anti-fracture efficacy of antiresorptive therapy is only partially explained by increases in BMD. Early decreases in bone resorption markers (BRMs) may also play a role. Initial analysis, focusing on the relationship between changes in urine CTX and NTX and incident vertebral fracture, was undertaken on patients from the risedronate VERT programme (Eastell et al. ASBMR 2001).

This proposed analysis is intended to confirm the findings of the initial analysis in patients from the risedronate HIP programme.

OBJECTIVE(S)

The primary objective is to explore the relationship between changes in BRMs (urine CTX and NTX) and the incidence of new vertebral fracture.

Secondary objectives include:

- Estimate the proportion of treatment effect in vertebral fracture risk explained by changes in BRMs,
- Explore the relationship between changes in BRMs and the incidence of osteoporosis-related non-vertebral fracture. Estimate the proportion of treatment effect in osteoporosis-related non-vertebral fracture risk explained by changes in BRMs,
- Estimate the proportion of treatment effect in fracture risk explained by both changes in BMD and BRMs,
- Investigate the influence of pre-treatment BRMs on incident fracture *{we may want to keep this separate, and give it to Seibel or another global TL. What do people think?}*.

LIMITATIONS/POTENTIAL RISKS

It is known that not all patients enrolled in the HIP programme had confirmed osteoporosis (e.g. majority of group 2), and therefore the relationship between changes in BRMs and the incidence of fracture may not be as expected. As the inclusion criteria of the HIP and VERT programmes are different, the results observed in the initial analysis may not be replicated. Consequently, the primary populations of interest from the HIP programme are to be those with known osteoporosis (e.g. group 1, baseline femoral neck T-score ≤–2.5SD).

The observed cumulative incidence in osteoporosis-related non-vertebral fractures from the two clinical programmes is lower than that for new vertebral fractures. Consequently, the two programmes may have to be combined in order to investigate the true relationship between changes in BRMs and non-vertebral fractures.

POPULATIONS

The populations of primary interest will be patients with known osteoporosis:

- HIP programme: Two groups of patients will be individually investigated:
  - Group 1, and
  - Patients with baseline femoral neck T-score ≤–2.5SD).
- HIP and VERT programmes combined: Two groups of patients will be individually investigated:
  - VERT+HIP (Group 1), and
  - Patients with at least one prevalent vertebral fracture and/or baseline T-score ≤–2.5SD (at either the lumbar spine or femoral neck skeletal site).

Populations of secondary interest will comprise of the following:

- HIP programme: Group 2 and all patients.
- HIP and VERT programmes combined: All patients.

DATA ENDPOINT(S)

The primary endpoint will be time-to-first incident new vertebral fracture. Incident vertebral fracture status is based on both quantitative morphometry and semi-quantitative assessment, with discrepancies between such methods being resolved by adjudication.

The secondary endpoint will be time-to-first osteoporosis-related non-vertebral fracture (defined as all radiographically-verified fractures of the hip, wrist, humerus, pelvis, clavicle and leg). In order to investigate the relationship between changes in BRMs and different types of non-vertebral fracture, cancellous sites (e.g. humerus, pelvis and wrist) and cortical sites (e.g. clavicle, and leg) will be grouped separately. {note: in the VERT trials we didn't separate hip-trochanter and hip-femoral. I'm not sure what to do with the hip site. We only have a handful of hip fractures in the addendum centres. What do people think?}

Surrogate measures of fracture will be BRMs and BMD. BRMs (CTX and NTX) will come from morning second void samples collected at baseline, 3 months and 6 months (samples from each individual will be analysed in one batch). BMD data (lumbar spine and femoral neck) will come from dual-energy x-ray absorptiometry measurements collected at baseline and …{should we use the last post-baseline BMD value on or just prior to the patients incident fracture/last fracture status visit? I need clarification?}.

STATISTICAL METHODOLOGY

Patients with both baseline and follow-up urinary BRMs, from the HIP and VERT programmes, will be included in the analysis. Appendix 1 summarises the tables and figures which will be constructed for the different populations. Below, summarises the number of patients who have (VERT programme) and are expected to have (HIP programme) baseline BRMs:

Estimates Of Patients With Baseline BRMs

Clinical Programme	Placebo	Risedronate 2.5 mg	Risedronate 5mg
VERT	335	354	358
HIP (Group 1)	380	382	375
HIP (Group 2)	183	178	187
HIP (Femoral Neck ≤–2.5SD)	336	345	327
≥ 1 prev vert fxs &/or BMD ≤–2.5SD (VERT + HIP)	722	771	748

When analysing the HIP programme separately, both doses of risedronate will be investigated. As the 2.5mg risedronate treatment group from the VERT programme was discontinued, the following will be undertaken when combining both the HIP and VERT programmes: 0-1 year new vertebral fracture will include all three treatment groups, 0-3 year fracture will include placebo and risedronate 5mg only.

Demographic and baseline characteristics will be summarised across treatment groups using descriptive statistics. Baseline lumbar spine data using the gender-specific T-score for patients with all four vertebrae (L1-L4) deemed intact will be included.

Post-baseline data will be summarised within and between treatment groups. Mean of the 3 and 6 month percent change from baseline for BRMs will be summarised using non-parametric statistics (median, inter-quartile range, Wilcoxon Signed-Rank and Rank Sum tests) due to the data being non-normally distributed. The cumulative incidence of fracture (new vertebral and osteoporosis-related non-vertebral) will be estimated using time-to-first fracture methodology (e.g. Kaplan-Meier, Cox Regression, Stratified log-rank test), consistent with the prospectively planned analysis of both the HIP and VERT programmes.

To visualise the association between fracture incidence and early changes in bone turnover makers, the probability of sustaining a fracture will be plotted against the mean 3 to 6 month BRMs. Empirical displays of the incidence will be constructed using a smoothing curve, which allows for the possibility of a nonparametric trend to be modelled. Cox-regression polynomial models will be constructed to compare the fit of the data when using linear and non-linear functions. These models will be statistically compared using the likelihood-ratio chi-square test.

To understand how the treatment effect varies across the observed distribution of BRMs, the relative risk and 95% confidence interval will be plotted. This will be obtained by using the estimates of the fitted Cox regression model, including treatment group (placebo, risedronate 2.5mg or 5mg), mean 3-6 month BRM (continuous covariate) and the treatment-by-BRM interaction {Zhengqing, I will talk to you about obtaining the 95% CIs}.

A method based on the Cox-regression model proposed by Li et al. (Statistics in Medicine, 2001) will be used to estimate the overall treatment fracture effect and the effect explained by BRM within 1 model. Adjustment for prognostically important baseline risk factors (e.g., age, baseline BMD and prevalent vertebral fractures) will be performed and compared to the unadjusted model. In addition, a model including both post-baseline BRM and BMD data will be constructed to understand the impact of including post-baseline BMD {Zhengqing, I will need to talk to you about this model}.

Appendix 1 – Proposed Tables and Figures

Baseline Characteristics
Patients for Whom Bone Resorption Markers Were Available

	Placebo (n=??)	Risedronate 2.5 mg (n=??)	Risedronate 5mg (n=??)
Age-y			
N	??	??	??
Mean (SD)	?? (?.?)	?? (?.?)	?? (?.?)
Vertebral Fractures			
N	??	??	??
Median	?	?	?
Mean (SD)	?.? (?.??)	?.? (?.??)	?.? (?.??)
N Patients with Fracture	?? (??%)	?? (??%)	?? (??%)
FN BMD T-Score*			
N	??	??	??
Mean (SD)	-?.?? (?.???)	-?.?? (?.???)	-?.?? (?.???)
LS BMD T-Score†			
N	??	??	??
Mean (SD)	-?.?? (?.???)	-?.?? (?.???)	-?.?? (?.???)
NTX (nmol BCE/mmol)			
N	??	??	??
Median	??.?	??.?	??.?
Inter-Quartile Range	??.?, ??.?	??.?, ??.?	??.?, ??.?
CTX (nmol/nmol)			
N	??	??	??
Median	?.??	?.??	?.??
Inter-Quartile Range	?.??, ?.??	?.??, ?.??	?.??, ?.??

* National Health and Nutrition Examination Survey III
† Gender-specific T-score, calculated using manufacturer's normative data if all 4 baseline vertebrae were deemed intact.

Mean 3-6 Month Percent Change From Baseline In BRMs

	Placebo (n=??)	Risedronate 2.5 mg (n=??)	Risedronate 5mg (n=??)
NTX (nmol BCE/mmol)			
N	??	??	??
Median	??.?	??.?	??.?
Inter-Quartile Range	??.?, ??.?	??.?, ??.?	??.?, ??.?
Wilcoxon Signed Rank Test	p=0.???	p=0.???	p=0.???
Wilcoxon Rank Sum Test	–	p=0.???	p=0.???
CTX (nmol/nmol)			
N	??	??	??
Median	??.?	??.?	??.?
Inter-Quartile Range	??.?, ??.?	??.?, ??.?	??.?, ??.?
Wilcoxon Signed Rank Test	p=0.???	p=0.???	p=0.???
Wilcoxon Rank Sum Test	–	p=0.???	p=0.???

Cumulative Fracture Incidence

	Placebo (n=??)	Risedronate 2.5 mg (n=??)	Risedronate 5mg (n=??)
New Vertebral Fracture			
0-1 Years			
n/N	??/??	??/??	??/??
Percent‡	??.?%	??.?%	??.?%
Risk Reduction (95% CI) §	??% (??, ??%)	??% (??, ??%)	??% (??, ??%)
P-value¶	–	p=0.???	p=0.???
0-3 Years			
n/N	??/??	??/??	??/??
Percent‡	??.?%	??.?%	??.?%
Risk Reduction (95% CI) §	??% (??, ??%)	??% (??, ??%)	??% (??, ??%)
P-value¶	–	p=0.???	p=0.???
Osteoporosis-Related Non-Vertebral Fracture			
0-3 Years			
n/N	??/??	??/??	??/??
Percent‡	??.?%	??.?%	??.?%
Risk Reduction (95% CI) §	??% (??, ??%)	??% (??, ??%)	??% (??, ??%)
P-value¶	–	p=0.???	p=0.???

n/N Patient with incident fracture / Patients included in fracture analysis

‡ Cumulative proportion of patients having an incident fracture based on Kaplan-Meier estimate

§ Based on Cox regression, stratified for trial

¶ Based on stratified log-rank test (stratified for trial)

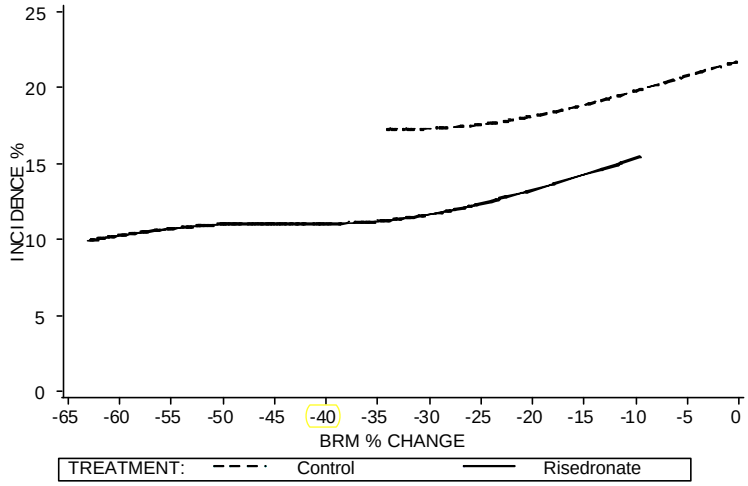
Proportion Of Fracture Treatment Effect (Risedronate 5mg vs. Placebo) Explained By Surrogate

	New Vertebral Fracture		Osteoporosis-Related Non-Vertebral Fracture
	0-1 Years	0-3 Years	0-3 Years
Mean 3-6 Month BRMs			
NTX	??% (??, ??%)	??% (??, ??%)	??% (??, ??%)
CTX	??% (??, ??%)	??% (??, ??%)	??% (??, ??%)
Mean 3-6 Month BRMs (Adjusted By Post Baseline BMD)			
NTX	??% (??, ??%)	??% (??, ??%)	??% (??, ??%)
CTX	??% (??, ??%)	??% (??, ??%)	??% (??, ??%)

Statistical model based on Li et al. Statistics In Medicine 2001
Estimate (95% confidence interval)

Fictitious Figures

Fracture Incidence
vs. Mean 3-6 Month BRM % Change From Baseline



Fracture Treatment Effect
vs. Mean 3-6 Month BRM % Change From Baseline