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Dear Cathryn

Thank you for the opportunity to comment on the Assessment Report for Strontium Ranelate. We believe that the Assessment Report makes assumptions about the evidence base and draws conclusions on this evidence base that results in a serious under-estimation of the efficacy and cost effectiveness of strontium ranelate. For the Appraisal Committee to be effectively informed about the evidence supporting the use of strontium ranelate, NICE should consider requesting that the Assessment Group revise the report and present further analysis where needed.

The comments provided below are set out according to the page and paragraph number of the report.

Page 10/Para 5 – Efficacy in hip fracture prevention

The report states that efficacy in fracture prevention needs to be strengthened, particularly in hip fracture. A large amount of evidence is already available to establish the efficacy of strontium ranelate as efficacious in the prevention of hip fracture. Indeed, this evidence was sufficient to justify a license in the prevention of hip fracture. We request that the Appraisal Committee recognise the weight of the evidence in support of this approved claim and adjust their comment accordingly.

Page 18-23 – WHO Risk Algorithm and Economic Model

The failure of the Assessment Group and NICE to supply the methods used to estimate cost effectiveness to any consultee makes it impossible for consultees to review the methods of this technology appraisal. This lack of transparency is not consistent with previous NICE appraisals and we therefore request access to this algorithm and to the economic model.

Page 42/Para 2 – Additional Data

Additional supportive data were provided in-confidence to the Assessment Group. Analysis of these data should inform any decision made by the Appraisal Committee.

Page 43 – Choice of the Relative Risk of Fracture

The economic analysis produced by the Assessment Group made use of three basic rates of treatment effect: the risk of vertebral fracture, the risk of peripheral fracture and the risk of hip fracture. The assessment group took advice that relative risk was not related to absolute risk. The same degree of risk reduction was assumed no matter what the baseline risk of fracture.

This comment will focus in particular on the choice of relative risk of hip fracture. A relative risk of hip fracture is available for the entire TROPOS patient population. Another estimate of relative risk is available and was presented in the submission and is published as part of the published clinical paper and in the Summary of Product Characteristics. This estimate of relative risk was taken from the analysis of patients over or equal to 74 years of age and with a T-score$\leq$-2.4 according to NHANES normative values. This analysis was undertaken under the instruction of the EMEA as a method for testing the efficacy of strontium ranelate in the prevention of hip fractures. Both results were published in a peer-reviewed clinical journal[1] [Meunier PJ et al, NEJM, 2004, Reginster Y et al, JCEM 2005].

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[1] Meunier, P. J., Roux, C, Seeman, E, Sergio, O, Badurski, JE, Spector, TD, Cannata, J, Balogh, A, Lemmel, E-M, Pors-Nielsen, S, Rizzoli, R, Genant, HK, and Reginster, J-Y The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. New England Journal of Medicine 2004; 350 459-468;
J. Y. Reginster, E. Seeman, M. C. De Vernejoul, S. Adami, J. Compston, C. Phenekos, J. P. Devogelaer, M. Diaz Curiel, A. Sawicki, S. Goemaere, O. H. Sorensen, D. Felsenberg, and P. J. Meunier Strontium Ranelate Reduces the Risk of Nonvertebral Fractures in Postmenopausal Women

The Assessment Group justified this choice on the grounds that because patients were not randomised within the sub-group, the baseline risk of the patients in these groups could not be verified as being the same. Therefore, it was more scientifically correct to use the data from the fully randomised group, even if it did contain a large proportion of patients with low hip fracture risk.

Another justification that can be implied, although it is not specifically stated, is that all data were considered for the appraisal of bisphosphonates. The analysis proceeds to compare the data from the bisphosphonate data set to the strontium ranelate data and generate a prioritisation of treatments based on the outcome of the economic analysis of all drug efficacies.

There are a number of flaws in the analysis of the assessment group. These will be set out in turn.

Baseline Characteristics of the At-risk Sub Group

On a number of occasions in the Assessment Report, the authors refer to sub group data used as the basis for the economic analysis submitted as part of the Servier Laboratories submission. The Assessment Group judged that these data were not usable because patients were not randomised to treatment and placebo groups upon entry into the sub group. In fact, as outlined above, this post hoc analysis was requested by the EMEA after previous discussions on trial design had defined the non-vertebral fracture endpoint as being appropriate to measure efficacy for licensing purposes.

The approach taken by the Assessment Group was made without reference to the evidence establishing that the baseline risk of patients in the placebo and treatment groups in the sub-groups of concern could be verified as the same. This evidence was published in the TROPOS publication made available to the Assessment Group. It is disappointing that the Assessment Group chose not to correspond on this issue before the Assessment Report was finalised. We respectfully request that the Assessment Group take note that the EMEA endorsed the use of this endpoint and included it in the SPC and that the data

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with Osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) Study The Journal of Clinical Endocrinology & Metabolism 90(5):2816–2822

were published in an eminent peer-reviewed clinical journal as a guide that the relative risk from the sub-population was indeed a valid estimate of efficacy.

Data available and published show that patients in these sub-groups were well balanced for baseline characteristics. Please see the table below.

TABLE 1. Baseline characteristics of the ITT population and in high-risk fracture subgroup

Characteristics[a]	ITT		High-risk fracture subgroup	
	Strontium ranclate (n = 2479)	Placebo (n = 2453)	Strontium ranclate (n = 982)	Placebo (n = 995)
Age (yr)	76.7 ± 5.0	76.8 ± 5.0	79.7 ± 4.6	79.5 ± 4.4
Time since menopause (yr)	28.4 ± 7.3	28.5 ± 7.5	31.4 ± 7.0	31.6 ± 7.0
Any prevalent (vertebral or nonvertebral) osteoporotic fracture (%)	55.4	54.2	58.8	57.4
BMD T-score				
Femoral neck	−3.13 ± 0.59	−3.13 ± 0.60	−3.55 ± 0.48	−3.55 ± 0.48
Total hip	−2.70 ± 0.94	−2.70 ± 0.96	−3.24 ± 0.85	−3.28 ± 0.86
Lumbar spine	−2.83 ± 1.63	−2.84 ± 1.62	−3.16 ± 1.60	−3.24 ± 1.53

No significant difference between groups for all baseline characteristics.
[a] Plus-minus values are means ± SD.

The table shows that the baseline characteristics of the placebo and the treated groups were entirely consistent. Please be aware that the T-scores shown refer to the Slosman T-score levels for BMD. Using the NHANES III scale significantly increases these levels. In fact, mean BMD T score –3 according to Slosman corresponds to around –2.4 according to NHANES.

Again, discussions about this matter were at the core of the decision making process conducted by the EMEA which accepted that the sub-group was adequately balanced for baseline risk.

In summary, the sub group analysis of patients at risk of a fracture is an unbiased and appropriate measure of efficacy in hip fracture prevention. It is incumbent upon the Appraisal Committee to consider requesting an economic analysis inclusive of the use of these data in order for its decision to be fully informed by the facts.

Scientific Validity of the At-risk sub group

The at-risk sub-group from TROPOS was chosen by the EMEA as the group in which to test the efficacy of strontium ranelate for hip fracture prevention for two major reasons, both of which relate to the risk of fracture.

Firstly, it is this at-risk group that provides sufficient power to demonstrate a treatment effect. To elaborate, the TROPOS trial was set up in 1996, more than one year before the first CPMP guideline on osteoporosis, but still in line with this guideline and that issued by the FDA in 1994. Non-axial fractures including hip were documented separately, as requested in the CPMP guideline issued in 2001. A placebo-controlled study based on hip fractures as the primary endpoint would have led to exposing a much larger population to the test product: in the target population (with a 1% incidence per year of hip fracture, as observed in the placebo group in TROPOS, and with a 15-20 % theoretical difference between groups at 3 years) 24600 and 13600 patients per group, respectively, would have needed to be followed and analysed in a phase III study to ensure a 90% power to establish superiority (at the type one error rate of 5%). Under these circumstances it is not reasonable for regulatory authorities, or indeed for NICE, to demand such a study. Instead, the EMEA agreed to investigate the efficacy in a sub-group that had sufficient events and therefore the power to identify a stable treatment effect.

Secondly, and following on from the first point, it was in the at-risk populations that alternative bisphosphonate medications had been assessed. A comparison of these populations is made below.

The post-hoc analysis was specified by the EMEA external to Servier Laboratories Ltd[2]. In effect, the analysis was independently generated and did

[2] As detailed in the EPAR, page 18

not represent a data-mining exercise. Under these circumstances, NICE should consider the relative risk generated as an entirely legitimate estimate of treatment effect and instruct the Assessment Group to use it in the analysis of cost effectiveness.

Bias in Summarising of Data

The Assessment Group decision to use the entire TROPOS data set rather than the data in the at-risk sub-group to inform the estimate, significantly biased results against strontium ranelate because of the breadth of the data set in which the drug has been tested. By comparison, an alternative drug, risedronate, was tested in a population with a significantly higher risk of hip fracture. A comparison of the treatment effect of strontium ranelate and risedronate, where the drugs have been tested in populations of a similar baseline risk, shows that strontium ranelate is indeed more effective in hip fracture prevention.

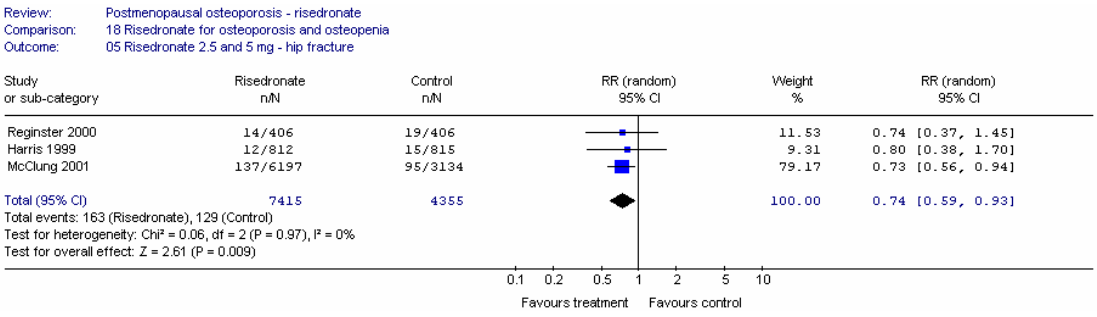
Underlying the choice of the Assessment Group to use the low risk group relative risk data from TROPOS is the assumption that relative risk of treatment would not vary with absolute risk at baseline. This assumption was not evidence-based. Rather it was based on the "wide knowledge of the vast published literature of members of the guideline development group". While there is evidence for this conclusion for vertebral fractures, there is evidence from bisphosphonate studies as well as strontium ranelate studies that baseline risk is very important in determining treatment effect for hip fracture. For example, there is substantial evidence within the trials of alendronate and risedronate that the relative risk reductions for vertebral fracture are consistent across study populations but the relative risk for hip fracture is dependent on underlying femoral neck BMD. This is illustrated by the wide discrepancy in the point estimates for the relative risk for hip fracture in the FIT studies and in the two randomised strata of the risedronate hip fracture study. The FIT1 study[3] recruited patients with a mean t-score of –2.4 (NHANES). It achieved a relative

[3] Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet 1996;348(9041):1535-1541.

risk of hip fracture of 0.49. However, the FIT 2 study[4] recruited a sample with a mean BMD of –2.2 and achieved a relative risk of hip fracture of 0.79. Indeed, the Cummings article makes extended reference to the relationship. In the case of risedronate, there is additional evidence for the importance of baseline risk. The McClung study[5] of this drug was split into two stratums. The stratums differed in baseline risk of hip fracture. Again the results were consistent with the hypothesis that testing hip fracture efficacy should rely on recruiting patients at risk of fracture. These observations are entirely consistent with and supported by the analysis of efficacy for strontium ranelate on hip fracture.

In the light of these facts, it is useful to consider the difference between the baseline risk of patients included in the meta-analysis of the risedronate data and the patients in the entire population and in the at-risk sub-group from TROPOS that was the basis for the license for hip fracture prevention.

In the meta-analysis that the Assessment Group used to generate the relative risk for risedronate, almost 80% of patients came from one study, McClung et al (2001). The meta analysis is presented below:



At entry into McClung (2001) study, patients T-scores were recorded at between –2.9 and –2.7 standard deviations (using NHANES III) below the mean for health adults lower than those observed in TROPOS study. The rest of the patients included in the meta-analysis of the risedronate data were in patients

[4] Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 1998;280(24):2077-2082.

[5] McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. New England Journal of Medicine 2001;344:333-40.

with a previous fracture and thus severely osteoporotic. Both the Reginster[6] (2000) and the Harris[7] (1999) study only included high-risk patients. T-scores were not reported in these publications. In the case of the Harris study, patients had to have at least 2 fractures at baseline or one fracture and low BMD. In fact, the mean number of fractures per patients was 2.3 in the placebo group and 2.7 in the group treated with 5mg of risedronate. In the Reginster study, patient had to have suffered at least two fractures before study entry. Mean BMD level was also recorded as very low at baseline. In the TROPOS study, only 55% of subject had suffered a previous fracture before study entry.

As reported above, the EMEA decided that, given the characteristics of patients at entry into TROPOS, consideration of efficacy in the sub group of patients at risk of fracture was an appropriate group in which to test efficacy in hip fracture. The baseline characteristics of the patients in the at-risk group are detailed above. A review of these characteristics shows that they are more in line with the risedronate data set.

To reiterate the point made above, TROPOS was not design to assess hip fracture prevention. If it had been, the study population would have been selected for its risk of such a fracture and would have had similar characteristics to the risedronate studies and to the at-risk sub-group within TROPOS. The method used by the Assessment Group in selecting data for the comparison of drug efficacy and cost effectiveness resulted in very significant disadvantage for strontium ranelate because it was tested in a patient group with a lower average risk than risedronate. All three risedronate trials imposed entry criteria that significantly increased patient risk. It was in part due to this fact that the EMEA decided that a sub-group of patients at a significantly elevated risk of hip fracture would be appropriate to test the efficacy of strontium ranelate. As stated above, the analysis in this group produced results comparable or better than

[6] Reginster J, Minne HW, Sorensen OH et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Osteoporosis International 2000;11(1):83-91.

[7] Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. JAMA 1999;282(14):1344-1352.

bisphosphonate alternatives. In these circumstances, the Appraisal Committee might consider asking the Assessment Group to provide an analysis of the cost effectiveness of strontium ranelate that includes the estimate of hip fracture reduction that fairly reflects the testing of that efficacy consistent with the testing applied to alternative medications.

Alternative Estimate Of Relative Risk of Hip Fracture

An alternative estimate of efficacy in the prevention of non-vertebral fracture is provided in the relative risk of major non-vertebral fractures, published in the TROPOS study. In this study, strontium ranelate treatment was associated with a 19% reduction in the risk of major non-vertebral osteoporotic fractures [RR = 0.81; 95% CI (0.66; 0.98), P = 0.031]. Compared to the estimate of 0.85 for hip fracture, this estimate has a narrower confidence interval and is thus a more stable estimate of non-vertebral fracture efficacy in the entire TROPOS population. As stated above, the TROPOS study was not powered to demonstrate an effect in rare fractures such as fractures to the hip. This estimate of efficacy is more efficient should efficacy in the entire population be required.

Page 49 Para 4 – Compliance Sensitivity Analysis

Comment was made in the Assessment Report that insufficient information is available on the method of compliance measurement. In fact, compliance was extensively measured as a part of the studies of efficacy and safety. Two methods were used to assess compliance. The principle method of measuring compliance to strontium ranelate treatment in TROPOS was the monitoring of the levels of strontium in the blood. In addition, compliance was measured by counting sachets returned to the investigator by the patient at each visit. The second measure of compliance is termed Global Compliance and is useful for both the placebo and treated patient groups.

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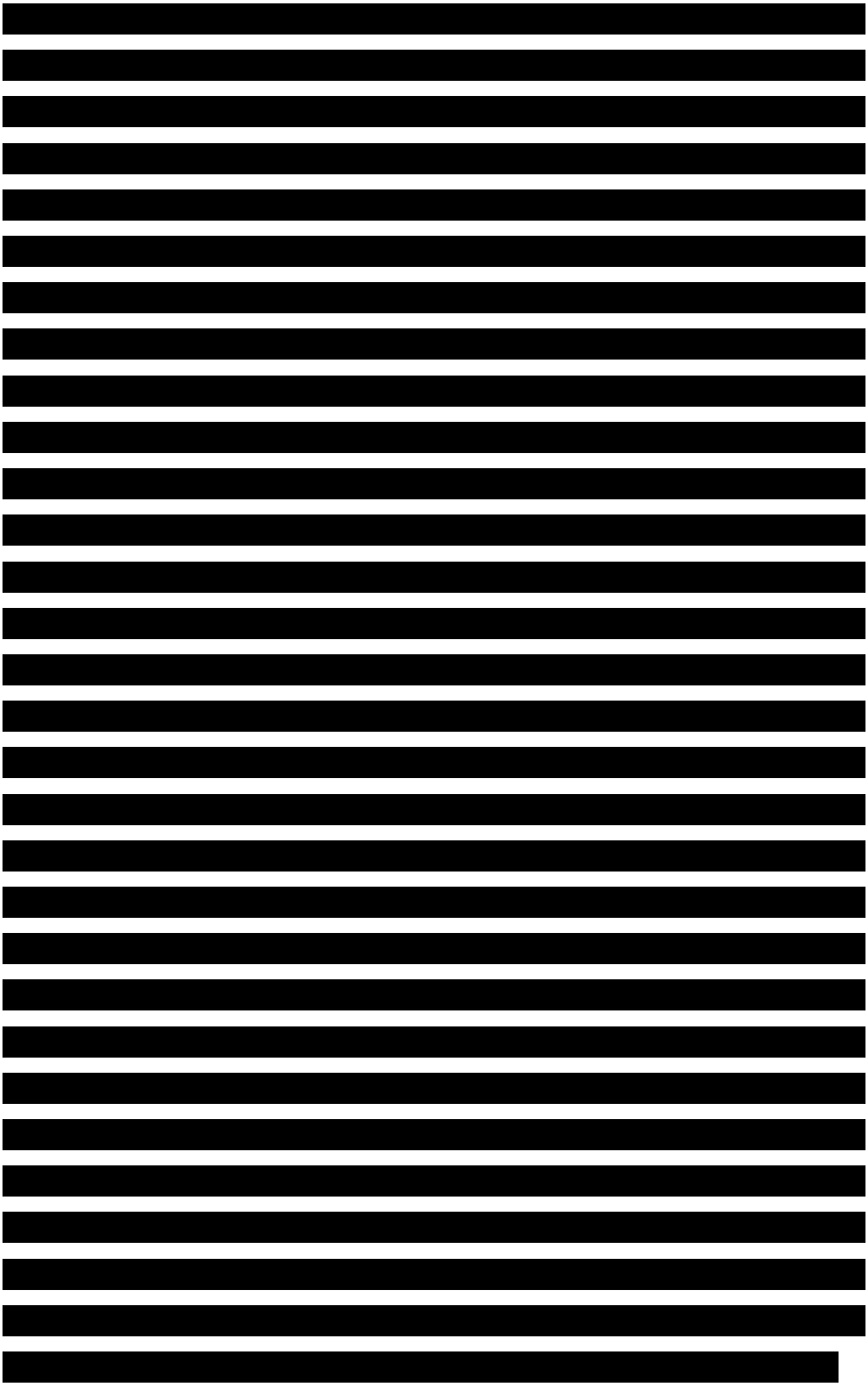

In conclusion, the Assessment Report recently distributed to consultees has a number of shortcomings that significantly hamper its usefulness to the Appraisal Committee in providing the basis for making a decision about the place in therapy of strontium

ranelate. Specifically, the Report misrepresents the core estimate of efficacy in hip fracture prevention by assuming the most pessimistic estimate of treatment effect. A treatment effect was demonstrated in a patient population at-risk of this fracture and consistent with the population in which bisphosphonates medications were tested. It was this estimate upon which the EMEA granted a license for the prevention of hip fracture. To better inform the Appraisal Committee of the cost effectiveness of strontium ranelate, an analysis could be supplied using the efficacy detailed. In addition, cost effectiveness could also be assessed using in-confidence data and data on major non-vertebral fracture supplied to the Assessment Group in the previous correspondence. Where compliance to medication can be monitored, specific data are available that could prove useful in estimates of cost effectiveness. To better insure that the process is fair, the Committee should also consider directing the release of the economic model and the WHO algorithm to consultees for review.

We value this opportunity to comment on the process and substance of the NICE appraisal. We trust that this response will prove useful in your consideration of the Assessment Report. I remain at your disposal should you wish to consult me on any matter regarding this or previous correspondence.

Yours truly

Trefor Jones