A response by Servier to the Decision Support Unit report on strontium ranelate

Servier gratefully acknowledges the report from the DSU on the appraisal of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women, and is pleased to provide further comments to assist NICE in their appraisal.

Summary

The efficacy of strontium ranelate in the prevention of peripheral fractures has been demonstrated in the pivotal Phase III study, TROPOS. This study demonstrated significant reductions in the risk of all peripheral and major osteoporotic fractures, compared to placebo. Strontium ranelate therefore represents a valuable treatment option for post-menopausal women at risk of osteoporotic fracture.

Since TROPOS was conducted, there has been increased emphasis on hip fracture as a key measure of efficacy for osteoporosis. As the incidence of hip fracture in the TROPOS study population was low, evaluation of hip fractures across the whole study population had insufficient statistical power to provide valid and meaningful results. Consequently, and at the request of the EMA, a *post hoc* subgroup analysis was performed to evaluate the efficacy of strontium ranelate in preventing hip fractures. Therefore, a subgroup was identified, by screening the placebo arm for known risk factors, in which the risk of hip fracture was sufficiently high as to confirm efficacy at the hip level. Women aged ≥74 years with a BMD T-score ≤-3 were found to have an increased risk of hip fracture, and that strontium ranelate gave rise to a significant reduction in the risk of hip fracture, compared to placebo, for this population. The *post hoc* subgroup analysis of strontium ranelate in women aged ≥74 years with osteoporosis therefore provides a valuable and robust assessment of the efficacy of strontium ranelate in preventing hip fractures.

The findings from TROPOS as a whole and the *post hoc* subgroup analysis provide a comprehensive evaluation of the efficacy of strontium ranelate for the treatment of

osteoporosis. These two analyses provide different and complementary information; Servier encourage NICE to consider both evaluations when assessing the respective aspects of osteoporosis treatment. A response to each of the three questions posed to the DSU is presented below.

Response

1). How scientifically valid is the proposition put forward by Servier related to the use of data derived from the TROPOS study subgroup analysis?

Servier believes that the methodology employed to evaluate the efficacy of strontium ranelate in the prevention of hip fractures is scientifically sound. The TROPOS trial was not powered to evaluate hip fracture data; however, the selected subgroup data robustly demonstrates the efficacy of strontium ranelate for this indication, based on sound statistical methodology.

The subgroup was identified by screening the placebo arm of the study for the effects of known risk factors on fracture incidence. This approach ensured that the subgroup selection was not influenced by the efficacy of strontium ranelate, and allowed a single analysis to be performed, based on accepted epidemiological risk factors, without the need for multiple exploratory analyses.

The selection criteria for the analysed subgroup were both biologically and statistically justified:

Age ≥74 years
- Age is a known risk factor for osteoporosis, and the risk of fracture increases exponentially after the age of 74 years.[1]
- The age cut-off of 74 years was selected as it is consistent with the inclusion criteria of the study, and is in line with established evidence on fracture risk.
- In the placebo arm of TROPOS, women aged ≥74 years had a significantly higher risk of hip fracture than younger women.

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[1] Donaldson *et al. J Epidemiol Community Health* 1990;44:241-5

BMD T-score ≤-3

- BMD T-score is significantly associated with fracture risk.
- The selected BMD score cut-off value of ≤-3, based on the local normative data, is equivalent to a T-score of ≤-2.4 using the NHANES III normative data. NHANES data was used as the reference values in the major osteoporosis outcome trials for bisphosphonates and in TA160/161. Hence a ≤-3 T-score in the TROPOS study is closely aligned with the internationally accepted criteria for osteoporosis (i.e. NHANES III ≤-2.5).
- In the placebo arm of TROPOS, a T-score ≤-3 was associated with a significantly higher risk of hip fracture than a T-score >-3.

The *post hoc* subgroup analysis of strontium ranelate in women aged ≥74 years with osteoporosis therefore provides a valuable and robust assessment of the efficacy of strontium ranelate in preventing hip fractures.

This efficacy on hip fractures is further demonstrated in analyses of the per protocol set (PPS) and in subsequent sensitivity analyses performed at the request of the EMA. For example, in women who were adherent to the strontium ranelate regimen, there was a significant 41% reduction in the risk of hip fractures. Furthermore, analysis of the 4-year data for the subgroup demonstrated a 31% reduction in the risk of hip fracture, further supporting the findings of the primary analysis. Taken together (points estimates ranging from 31% to 41% reduction in risk of hip fracture), these findings demonstrate the efficacy of strontium ranelate in the prevention of hip fracture, and that the evaluation of this efficacy is robust.

2). From a statistical viewpoint, what is the most appropriate approach to the use of data from the whole data set of the TROPOS study and the subgroup data set in relation to determining the relative effectiveness of strontium ranelate?

The DSU identified two separate components to this question: (i) for which population is the relative effectiveness required, and (ii) dependent on the relevant population, what is the most appropriate statistical analysis for estimating the pertinent RR.

Servier maintains that the presented analysis of the TROPOS data is a valid assessment of the efficacy of strontium ranelate. TROPOS successfully demonstrated that strontium ranelate significantly reduced the risk of all peripheral fractures in women with osteoporosis. Furthermore, even though the trial was not designed or powered to detect changes in the incidence of hip fractures, a 15% reduction in risk, across the full trial population, was observed with strontium ranelate therapy. The subgroup population was selected to more clearly evaluate the effect of strontium ranelate on the risk of hip fracture, based on screening the placebo arm for the effects of three of the main risk factors for hip fracture. The selected subgroup is biologically and clinically justified, and represents a more robust evaluation of the efficacy of strontium ranelate than the full trial data.

3). Given the data reviewed what, in their expert view, is the most plausible relative risk for strontium ranelate to use in making recommendations for the population covered by the marketing authorisation for strontium ranelate?

The initial evaluation of the cost-utility of strontium ranelate for TA160/161 used a value of 0.85 for the risk of hip fracture with strontium ranelate therapy:

"Where confidence intervals for RRs spanned unity, it was assumed that there was no effect of treatment, except in the case of strontium ranelate in a subgroup of older women. In this case, an RR of 0.85 for hip fracture was used to acknowledge an effect reported in a subgroup of the study."

The different point estimates obtained in the PPS and in the sub-population (RR ranging from 0.59 to 0.69) robustly corroborates the proposed relative risk of 0.64 obtained in the subgroup of women ≥74 years with osteoporosis followed-up over 3 years as being a more likely figure to use. However, Servier acknowledge, as stated by the DSU, that the true value may be intermediate between 0.64 and 0.85. It could also be argued that the real value lies between 0.59 and 0.69 and that a relative risk of 0.64 constitutes a reasonable value to estimate efficacy of strontium ranelate on hip fractures among women with post-menopausal osteoporosis.

One possible approach to aid such extrapolation would be to perform further, complementary subgroup analyses in the remaining population. Indeed, the supportive analyses performed to date show a consistent trend in favour of strontium ranelate over placebo for the prevention of hip fractures. However, applying this approach to the population excluded from the subgroup analysis would not be appropriate, as the incidence of hip fracture is substantially reduced in this population. Based on both the limited population size and reduced hip fracture incidence, such an analysis would be substantially underpowered.

Conclusion

In summary, the TROPOS data confirm that strontium ranelate therapy reduces the risk of peripheral fractures in women with osteoporosis. Servier believes that the subgroup analysis performed to evaluate the efficacy of strontium ranelate in the prevention of hip fractures is based on sound scientific principles and valid statistical methodology.