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Dear [REDACTED],

The DSU and the technical team at NICE have carried out an initial review of your response to NICE's Statement of Reasons, and have the following clarification questions:

1. The Statement of Reasons (¶15) requests that NICE should to be provided with "*... a full account of dealings with the EMA on the question of subgroup analysis in the TROPOS study including, but not limited to, all original documentation bearing on this question; all communication relating to the subgroup analysis; the 'day 120' questions and responses and 'day 180' meeting notes, questions and responses.*"

Your response document (and appendices) contains a description of communications between Servier and the EMA, and we are grateful for this. However, we note that you have not provided copies of the original documentation, and we remain of the view that it is essential for the DSU and the Appraisal Committee to have access to this material. In some of Appendix A you quote, verbatim, some parts of letters from EMA. However, we cannot unequivocally establish what text is derived from the EMA and what originates from yourselves,

particularly as there is some repetition between the main Appendix A and the Annex 3 documents.

Therefore, we request that original documentation detailing Servier's communications with the EMA be provided. We expect this material to include (but not be limited to) full copies of day 120, day 150 and day 180 questions from EMA from which the above mentioned quotes are derived, along with any additional original correspondence between Servier and the EMA on the subject of the identification of, and derivation of results from, a subgroup of the TROPOS trial population deemed to be at elevated risk of hip fracture, and EMA's acceptance of your choice of subgroup. We are happy to receive scanned in photocopies of that correspondence, and undertake to preserve the confidentiality of the original correspondence.

Without this, it is not possible to arrive at a complete appreciation of the precise processes by which your subgroup analysis was produced and, by extension, to assess the appropriateness or otherwise of that analysis in the detail that is required in present circumstances.

2. Please would you provide copies of the documentation in which, you assert, a precedent is set for the regulatory approval of strontium ranelate on the basis of a post-hoc subgroup? Table 6, on p. 20 of Appendix 1 summarises data from major trials of risedronate and alendronate. This is, of course, material that is familiar to us. However, the particular regulatory decisions to which you say these data were relevant is not entirely clear. We note that the table caption refers to "French SPC"; do you wish to draw our attention to decision-making in that jurisdiction (we note that the initial authorisation of these products predates the centralised European system)? Please provide copies of all documentation that you consider relevant to this question (we are happy to receive copies of foreign-language material, if that is what is relied upon).

3. Please provide clarification regarding the number of people in the placebo arms of TROPOS and SOTI analysed for underlying risk of hip fracture. In Table 1 on p. 12 of Appendix A, the total number of participants analysed (for prevalence of hip fracture relative to T-score) sums to 3246 whereas, in Table 2 on p. 13, the total number of participants analysed (for prevalence of hip fracture relative to age) sums to 3256. This latter number also apparently corresponds to the population analysed according to prevalent fragility fracture (text on p. 12). These numbers are inconsistent and, moreover, do not correspond directly to the population sizes of the professed data-source: as far as we are aware, the numbers randomised in TROPOS + SOTI were $(2537+821=)$ 3358, and the FAS ("ITT") populations sum to $(2453+723=)$ 3176. Are you able to account for the apparent discrepancies?
4. Please provide more detailed information regarding the methods according to which the pooled placebo arm was "screened" for risk factors for hip fracture. In particular,
 - a. For age, how was the particular threshold of 74 arrived at and what other values were investigated? Please provide full incidence data for hip fracture by age in the pooled placebo population (i.e. numbers of participants experiencing events at each year of age).
 - b. Were any other baseline variables considered?
5. We note your comment at the foot of Table 3 (p. 33, Appendix A) that the 4-year dataset includes two participants who were not included in the 3-year analysis. Have you undertaken an updated analysis of relative risk at 3 years with these additional individuals included? If so, please provide the results.
6. Please provide basic data (numbers at risk & numbers of hip fractures per randomized group – SR vs placebo) and the estimate of the relative risk of hip fracture, and 95% Confidence interval, for the

remainder of the TROPOS population that are not included in the subgroup i.e. point 15 of the original request from NICE.

7. Please provide basic data (as defined in ¶6), estimate and 95% CI from the SOTI trial data for the relative risk of hip fracture for the same subgroup of patients as from the TROPOS trial (i.e. women aged ≥ 74 years with a BMD T-score equivalent to ≤ -2.4 according to NHANES III normative data) as well as for those not in the subgroup.
8. Please provide the following information (relative risk of hip fracture and CI, number of events and numbers at risk) for each of the following 6 patient subgroups:
 - a. Age ≥ 74 yrs
 - b. Femoral BMD T-score ≤ -3.0
 - c. Prior fragility fracture only
 - d. Femoral BMD T-score ≤ -3.0 and prior fragility fracture
 - e. Age ≥ 74 yrs and prior fragility fracture
 - f. Age ≥ 74 yrs and femoral BMD T-score ≤ -3.0 and prior fragility fracture
9. Please provide the individual patient level data from the TROPOS trial in order for the DSU to replicate your analyses.
10. Many thanks for sending amended and redacted versions of your submissions on Monday, 6 September with the revised marking of confidential information. We note that some of the information that is highlighted as being commercial in confidence has previously been made publicly available. For example the following pieces of information are all mentioned in the EPAR and can therefore not be confidential:

- page 6 of Appendix A “The EMA requested a post hoc analysis be performed in a subset of patients with established osteoporosis,”
- page 9, first 2 bullets (and elsewhere in App A), the RR for the additional subgroups of 0.69 and 0.7
- page 19 (and elsewhere in App A) the mention of ‘32 versus 51’

Where such data is indeed publicly available, we can refer to it, and will do so. However, all other items marked as commercial in confidence cannot be referred to in our published documentation and this means that the Appraisal Committee would not be able to make any major decisions based on that information. As you know we need to be transparent about the information that is used in the Committee’s decision making. In addition, you would not be able to see what the Committee’s conclusions are on the points highlighted by you as commercial in confidence. If you want to reconsider the confidentiality marking of your submission, please let us know.

Please may we request a response by **Wednesday 15 September 5 pm**?
However, as you are aware, timelines are fixed and pressing, so we would be grateful for anything you can do to expedite our receipt of this material.

Yours sincerely

Dr. Elisabeth George
Associate Director - Appraisals