



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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Human Medicines Development and Evaluation

## Withdrawal Assessment report

Protelos

Strontium ranelate

EMA/H/C/000560/II/0035

This withdrawal Assessment Report is based on the 2<sup>nd</sup> Request for Supplementary Information as adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still on-going at the time of the withdrawal of the application.



# 1. Recommendation

Based on the review of the non-clinical data and the clinical data on safety and efficacy, the CHMP considers that the variation application EMEA/H/C/00560/II/35 for Protelos (strontium ranelate), as a disease modifying drug in the treatment of osteoarthritis of the knee and hip to reduce the progression of the cartilage damage,

is not approvable since "major objections" still remain, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided below and should be addressed in writing. In addition, satisfactory answers must be given to the "other concerns" as detailed below.

# 2. Benefit Risk Assessment

## Benefits

### Beneficial effects

Osteoarthritis is characterized by a progressive destruction of cartilage combined with pain and stiffness of joints. There is an unmet need for medical treatment that slow or prevent structural damage of the cartilage.

Strontium ranelate 1g and 2g retarded the progression of joint space narrowing (JSN) compared to placebo by 0.14 mm (SE=0.04 mm) and 0.10 mm (SE=0.04mm), respectively, at the last post-baseline visit with an average of 29.3±10.5 months follow-up (Full Analysis Set = 1371 patients).

Strontium ranelate treatment decreased the number of patients with radiological progression defined as reduction of JSW≥0.5mm (SrRan 1g, SrRan2g and placebo, 22%, 26% and 33%, respectively). The differences were statistically significant for SrRan 1g and SrRan 2g compared to placebo (p<0.001 and p=0.012, respectively).

### Uncertainty in the knowledge about the beneficial effects

The possible clinical relevance of the JSW findings is only weakly supported by the secondary endpoints where substantial symptomatic reduction was noted also in the placebo group, creating none or weak statistically significant differences in secondary endpoints as WOMAC (sub-)scores, pain score (VAS), and health related quality of life questionnaires. Whereas the average improvement in symptomatic scores with 2g SrRan treatment over placebo has to be considered very modest and does not bear "clinical importance" itself, a positive trend could be assumed for this dose.

The concomitant OA medication did not decrease in patients with active treatment. It was not possible to detect a prevention of surgery due to the fact that there were only 8 patients subjected to surgical intervention and these were evenly distributed between treatment arms (3, 3 and 2 patients in the SrRan 1g, SrRan 2g and placebo groups, respectively).

In addition, subgroup analysis data seem to indicate that SrRan may have reduced efficacy in relevant patient groups (i.e. patients with severely affected knee joint structure). It seems very difficult in a clinical situation to identify patients who would actually benefit from the treatment. Furthermore, SrRan efficacy on joint structure appears to diminish after two years of treatment.

There are concerns about methodology/the way the single pivotal study was carried out: individual patient observation period was prolonged and a sample size re-estimation was carried out without sufficient documentation. The lack of such documentation is viewed as a deficiency, not only from a formal viewpoint, but also from a methodological point of view. In addition, there are still unanswered questions regarding the raw data (values obtained for JSW/JSN).

## **Risks**

### **Unfavourable effects**

General symptoms from the gastrointestinal tract such as abdominal pain and diarrhea had higher occurrence in SrRan treated subjects than in the placebo cohort. More SrRan treated patients experienced SAE regarding VTE (5, 3 and 1, SrRan 1g, SrRan 2g and placebo, respectively, despite of exclusion of high-risk individuals at baseline) and ischemic cardiac disease (3, 10 and 1, SrRan 1g, SrRan 2g and placebo, respectively) compared to the placebo group. It is also expected that SrRan treatment in the osteoarthritis population will create a similar risk of adverse events as SrRan treatment does in the osteoporosis population, for example, hypersensitivity reactions and more unusual risks such as DRESS.

There were more patients with serious knee OA EAEs in the placebo group than in the treatment groups: 5, 9 and 13, SrRan 1g, SrRan 2g placebo, respectively. For serious hip OA EAEs, in contrast, there were fewer cases in the placebo group: 7, 9 and 4 in the SrRan 1g, SrRan 2g and placebo.

### **Uncertainty in the knowledge about the unfavourable effects**

Strontium ranelate has been approved since 2004 in treatment of osteoporosis. Several actions for safety reasons have been taken recently because of VTE events, serious skin reactions and possible increased risk of ischaemic cardiac events. The strontium ranelate safety database is large when patients with osteoporosis are included. However, rare adverse events that are specific for the population with osteoarthritis are unlikely to be detected among the 1000 individuals. For example, patients with osteoarthritis might due to the conditions of the disease generally not be fully mobile and might be less mobile than the osteoporosis population, which may have consequences as "temporary or permanent immobilisation" has been added as a contraindication for strontium ranelate because of increased VTE risk.

## **Balance**

### **Importance of favourable and unfavourable effects**

The uncertainties regarding the magnitude of clinical benefit on joint structure, the weak symptomatic effects, as well as robustness of overall treatment effect are of major concern. The proposed indication is novel and supported by only one pivotal study. There are also important methodological issues that need to be clarified.

Serious adverse events as DRESS and VTE are life-threatening conditions that need immediate treatment. Recently an article 20 procedure regarding DRESS and VTE has been finalized and the product information has been updated with new warnings and contraindications. The final results from new studies concerning increased risk of ischemic cardiac events are awaited.

### **Benefit-risk balance**

The magnitude of SrRan 2g effects on knee joint structure and OA symptoms is considered very modest. Whether the observed difference of 0.1 mm in JSN over three years between SrRan 2g and placebo conveys a clinically relevant benefit (i.e. by a reduced joint replacement frequency or

prolonged time to replacement) remains uncertain. Only a trend towards improvement in symptomatic outcomes was observed. For a disease modification claim this is considered insufficient. The risk of side effects, (although the majority of them non-serious; some of them life-threatening), is recognized and it cannot be considered justified to expose patients to that level of risk.

### **Discussion on the benefit-risk assessment**

The possible overall clinical benefit of the effect of strontium ranelate on JSW has been questioned in view of the size of demonstrated effects, the weak support from secondary endpoints, safety concerns and methodological issues.

### **Conclusions**

The overall B/R of Protelos/Osseor in the proposed indication is negative.

## **3. Major objections**

### **Clinical aspects**

#### **1. Clinical Efficacy/Benefit-Risk**

The magnitude of SrRan 2g effects on knee joint structure and OA symptoms is considered only modest. Whether the observed difference of 0.1mm in JSN over three years between SrRan 2g and placebo conveys a clinically relevant benefit (i.e. by a reduced joint replacement frequency or prolonged time to replacement) remains uncertain. Only a trend towards improvement in symptomatic outcomes was observed. However, this did not translate into a reduction of concomitant OA therapy (i.e. analgesics/anti-inflammatory medication) in the SrRan cohort. In light of the safety profile of SrRan, (i.e. several serious identified risks and serious potential risks) the benefit/risk balance is considered negative in the proposed indication.

#### **2. Clinical Efficacy**

The benefit of long-term SrRan treatment in a broad OA population is questioned. The Applicant is asked to further comment on the unclear finding that the effect size in terms of JSN for the SrRan 2g group was found to be substantially smaller after amendment 9 (broadened inclusion criteria). The provided subgroup analyses seem to indicate that SrRan may have reduced efficacy in patients with highly progressed OA. Further, the responder analyses indicate that a large proportion of patients do not have any radiological response to the treatment, especially after M24. In addition, the rate of cartilage decrease in the actively treated group was similar to placebo, questioning long-term effect. Consequently, it seems very difficult in a clinical situation to identify patients who would actually benefit from the treatment, especially as a substantial placebo-effect is demonstrated on symptoms. The Applicant should further discuss maintenance of efficacy, whether an optimal target population could be identified and should specify stopping criteria in patients where benefit is not obtained.

#### **3. Methodology**

- a) Based on variance estimates from the blinded interim analysis of pooled 1-year data for JSN, individual patient observation period was prolonged and a sample size re-estimation was carried out. The Applicant states in their reply, respective thought processes describing the outcome and consequences of the interim analysis were not made explicit in documents such as meeting minutes nor amendments. The lack of such documentation is viewed as a deficiency, not only from a formal viewpoint, but also from a methodological point of view.

b) General concern persists with regard to the quality of JSW raw data. The impact of the following unexplained phenomena remains unknown:

- For the whole data distribution, accumulation of raw data points to certain particular values on the range of possible values with a precision of 1/1000 mm;
- For individual patient data, the frequently occurring 'replication' of exactly the same value of JSW on subsequent visits with a precision of 1/1000 mm.

At the moment, a bias in favour of one of the study arms cannot be convincingly excluded. The description by the Applicant that the described phenomena were observed in all treatment arms is not considered sufficient. The Applicant is asked to explore the reasons for these two phenomena.

## 4. Other concerns

### Clinical aspects

#### Clinical Efficacy

1. SrRan 1g and SrRan 2g have demonstrated a statistically significant effect versus placebo in reducing joint space narrowing (JSN) over 3 years: 0.14 mm and 0.10 mm, respectively. In observational studies, the JSN is likely to be a result of cartilage loss. Strontium ranelate, however, is known to be distributed in bone and increase X-ray absorption as compared to calcium. It is unclear, how this increase in X-ray absorption affects the measurement of JSN. Theoretically, a statistically significant reduction of JSN in X-ray could be due to passive presence of strontium in the tissues. The Applicant is invited to comment.
2. In knee MRI parameters, the Applicant states that there were no significant differences in the global cartilage volume changes over time. These data should be presented in detail.
3. Concerning concomitant OA-related medication: The similar increases in these medications in both active treatment and placebo groups do not support a clinically relevant benefit from the treatment. The Applicant ought to specify "concomitant OA medication at inclusion" and "concomitant OA medication during the study" as it is yet unclear which time span is referred to in the former and whether one-time intake at/around inclusion and during the study has been included in the calculations. Comparisons between concomitant medications at the beginning and during the study would only be meaningful if it referred to repeat/chronic use.
4. Concerning the reading process of X-rays: The term 'knowledge of time sequence' may however generally imply that more patient images (from previous visits) than just the selection image were available for the reader. The Applicant is asked to explain the meaning of 'knowledge of time sequence' in the context of the reading setup described where only (always) the patient's corresponding selection image was used to facilitate reading.
5. After issues in relation to JSW reading raw data (MO 2 above) are clarified, the analyses of inter-rater agreement will require corresponding interpretation. Altman & Bland plots (from Appendix 6.3.19) seem to reveal the raw data problem in a graphical manner, as inter-rater differences appear in horizontal clusters in all charts where JSW data are presented per visit. For example, looking at the chart for JSW for visit M12, the arithmetically derived estimate for the mean difference between raters (red line) does not seem to be a representative measure for central tendency for the distribution of inter-rater-differences.

6. The Applicant is asked to calculate and present the Number (%) of patients that had a JSW loss of more than 0.3 mm between M24 and M36 in different treatment groups. Also, a M24-M36 responder analysis of the main secondary end-point criteria for symptoms: WOMAC global score, VAS for the target knee pain or quality of life, should be presented by the Applicant.
7. The Applicant is invited to further comment on possible confounding as statin use was around 8% more frequent in the SrRan 2g group as compared to placebo.

### **Clinical Safety**

8. Despite of the exclusion of high-risk individuals in the present study, there was a numerically higher number of patients that experienced VTE in both strontium ranelate treated groups as compared to placebo. Patients with osteoarthritis are due to the disease condition generally considered not fully mobile and are less mobile than patients with osteoporosis. The MAH should further discuss the consequences of the contraindication "temporary or permanent immobilization" in the new target patient group. A strict interpretation of this contraindication might exclude a large part of patients with osteoarthritis.
9. Concerning the higher rate of serious cardiac events, the MAH should present a table with the important baseline cardiovascular risk factors in each treatment group: age, gender, blood pressure, serum cholesterol, smoking, BMI, diabetes, medical history of different heart diseases. The mean values or percentages of each variable should be presented - instead of cut-off variables or combined summary variables.