London, 21 November 2013
EMA/CHMP/710310/2013
Committee for Medicinal Products for Human Use (CHMP)

# Withdrawal assessment report

## ISSARLOS

### International non-proprietary name: strontium ranelate / colecalciferol

### Procedure No. EMEA/H/C/002756/0000

## Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# ADMINISTRATIVE INFORMATION

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|---|---|
| **Invented name of the medicinal product:** | **Ditelos/ Issarlos** |
| **INN (or common name) of the active substance(s):** | Strontium ranelate and cholecalciferol |
| **Applicant:** | Les Laboratoires Servier, France |
| **Applied Indication(s):** | Treatment of severe osteoporosis in postmenopausal women at risk of vitamin D insufficiency and at risk for fracture to reduce the risk of vertebral and hip fractures.<br>Treatment of severe osteoporosis in adult men at risk of vitamin D insufficiency and at increased risk of fracture.<br>The decision to prescribe <Product name> should be based on an assessment of the individual patient's overall risks (see sections 4.3 and 4.4). |
| **Pharmaco-therapeutic group (ATC Code):** | M05BX53 |
| **Pharmaceutical form(s) and strength(s):** | Granules for oral suspension; 2 g strontium ranelate + 25 µg (1000 IU) cholecalciferol |

# 1. RECOMMENDATION

Based on the review of the data and the Applicant's response to the CHMP LoQ on quality, safety and efficacy, the CHMP considers that the application for Ditelos/Issarlos in the treatment of:

- *Severe osteoporosis in postmenopausal women at risk of vitamin D insufficiency and at high risk for fracture to reduce the risk of vertebral and hip fractures.*
- *Severe osteoporosis in adult men at risk of vitamin D insufficiency and at increased risk of fracture.*

*The decision to prescribe DITELOS/ISSARLOS should be based on an assessment of the individual patient's overall risks (see sections 4.3 and 4.4).*

is not approvable since "major objections" still remain, which preclude a recommendation for marketing authorisation at the present time.

The major objections precluding a recommendation of marketing authorisation pertain to the following principal deficiency:

**Quality:**

***Drug substance Cholecalciferol-cyclodextrin complex***

1. The applicant's approach regarding the inclusion of data on a cyclodextrin and the cholecalciferol-cyclodextrin complex is not acceptable. This complex should not be regarded as API but as an intermediate product with all due related requirements: i.e. the information on the complex should be removed from 3.2.S and transferred to the relevant paragraphs of Module 3.2.P. and the manufacturers of the mixture, should be regarded as manufacturers of the finished product, as they perform the first step of the DP production. The appropriate manufacturing authorisations and GMP certificates should be provided for those manufacturers. For the pure cholecalciferol new QP declarations are required for each manufacturing site listed in the referenced CEPs and a complete Module 3.2.S should be presented. For 3.2.S.1 to 3.2.S.5 reference can be made to CEPs. Along with a CEP, the applicant should supply results of batch analysis demonstrating compliance with the Ph.Eur. monograph and additional requirements mentioned on the CEP. As the CEPs provided do not state the packaging materials and re-test period, all details should be provided on packaging materials and stability by the applicant in sections 3.2.S.6 and 3.2.S.7 regarding the pure cholecalciferol. As alternative to stability data the applicant may also declare that the substance complies with the complete Ph.Eur. monograph immediately before use (Guideline on summary of requirements for active substances in the quality part of the dossier CHMP/QWP/297/97 Rev1 corr.).

## Questions to be posed to additional experts

N/A

## Inspection issues

N/A

# 2. EXECUTIVE SUMMARY

## 2.1. Problem statement

The applicant Les Laboratoires Servier submitted applications for a European Marketing Authorisation through the Centralised Procedure for their product Ditelos 2 g/1000 IU granules for oral suspension and its duplicate Issarlos, a fixed dose combination containing strontium ranelate and cholecalciferol. It is intended to provide an efficient anti-osteoporotic treatment and an adequate level of vitamin D supplementation for patients with severe osteoporosis. The targeted indication is:

- *Treatment of severe osteoporosis in menopausal women at risk of vitamin D insufficiency and at high risk of fracture to reduce the risk of vertebral and hip fractures,*
- *Treatment of severe osteoporosis in adult men at risk of vitamin D insufficiency and at increased risk of fracture,*

*The decision to prescribe <Product name> should be based on an assessment of the individual patient's overall risks (see sections 4.3 and 4.4).*

Osteoporosis is a systemic skeletal disorder characterised by reduction of bone mass and microarchitectural deterioration of bone tissue due to an imbalance between bone resorption and formation, leading to enhanced bone fragility. The clinical consequences of osteoporosis are vertebral and peripheral fractures. Vitamin D deficiency is one of the main risk factors for osteoporosis and ensuring sufficient intake of vitamin D is therefore a fundamental part of all prevention and treatment programs of osteoporosis. By combining the already registered active ingredients strontium ranelate and cholecalciferol into a single fixed combination product the applicant aims to provide a convenient way to treat severe osteoporosis while simultaneously ensuring sufficient intake of vitamin D. Strontium ranelate and cholecalciferol have not yet been registered in the EU as fixed dose combination.

## 2.2. About the product

The applicant Les Laboratoires Servier submitted applications for a European Marketing Authorisation through the Centralised Procedure for their product Ditelos and its duplicate Issarlos, 2 g/1000 IU granules for oral suspension, which are fixed dose combinations containing strontium ranelate and cholecalciferol. Strontium ranelate and cholecalciferol have not yet been registered in the EU as fixed dose combination.

Strontium ranelate (S12911) is made up of 2 atoms of stable strontium and 1 molecule of ranelic acid, the organic part permitting the best comprise in terms of molecular weight, pharmacokinetics and acceptability of the medicinal product. It increases bone formation in bone tissue culture as well as osteoblast precursor replication and collagen synthesis in bone cell culture and reduces bone resorption by decreasing osteoclast differentiation and resorbing activity, resulting in a rebalance of bone turnover in favour of bone formation. Strontium ranelate is approved as Protelos and its duplicate Osseor (powder for oral suspension), which are registered since 21 September 2004 and which marketing authorisation is held by Les Laboratoires Servier, also the applicant for Issarlos/Ditelos.

The indication of Protelos/Osseor was recently changed due to identified cardiovascular risks associated to strontium ranelate use from 'treatment of osteoporosis in postmenopausal women to reduce the risk of vertebral and hip fractures and in men at increased risk of fracture' to:

- *Treatment of severe osteoporosis in postmenopausal women at high risk for fracture to reduce the risk of vertebral and hip fractures.*
- *Treatment of severe osteoporosis in adult men at increased risk of fracture.*

*The decision to prescribe <Product name> should be based on an assessment of the individual patient's overall risk (see sections 4.3 and 4.4).*

The recommended daily dose of Protelos/Osseor is one sachet of 2 g strontium ranelate once daily. The SmPC for Protelos/Osseor further states that patients treated with strontium ranelate should receive vitamin D and calcium supplements if dietary intake is inadequate.

During assessment of the 13th PSUR for Protelos/Osseor it was concluded that, aside from the known VTE risk, there are additional cardiovascular risks associated to its use. Consequently, the indication was changed as indicated above and contra-indications and warnings were added to restrict use to severe osteoporosis and to exclude patients with or at risk of cardiovascular disease. Additionally, it was concluded that further assessment of the B/R is required and therefore an Art.20 referral (EMEA/H/A-20/1371) was started after finalisation of the PSUR, the outcome of which will have implications on Issarlos/Ditelos.

Cholecalciferol is an inactive pro-hormone derived from either 7-dehydrocholesterol conversion in the skin by solar ultraviolet B radiation or from food. Conversion to its active form 1,25-dihydroxyvitamin D3 in the kidney is regulated by blood parathyroid hormone (PTH), calcium and phosphorus levels. Vitamin D3 increases intestinal absorption of both calcium and phosphate and regulates serum calcium, renal calcium and phosphate excretion, bone formation and bone resorption. Vitamin D3 is required for normal bone formation and bone mineralisation. Vitamin D3 is thus a fundamental part of the prevention and treatment of osteoporosis.

Strontium ranelate/Cholecalciferol FDC (S06911): The applied indication for the new fixed dose combination Issarlos/Ditelos is:

- *Treatment of severe osteoporosis in postmenopausal women at risk of vitamin D insufficiency an at high risk for fracture to reduce the risk of vertebral and hip fractures.*
- *Treatment of severe osteoporosis in adult men at risk of vitamin D insufficiency and at increased risk of fracture.*

*The decision to prescribe <Product name> should be based on an assessment of the individual patient's overall risk (see sections 4.3 and 4.4).*

The rationale for the development of this FDC is that treatment of osteoporosis with any anti-osteoporotic drug requires additional vitamin D intake. It should be noted that concomitant intake of calcium may reduce the bioavailability of strontium ranelate by approximately 60-70%, excluding the feasibility of adding calcium to the strontium ranelate-vitamin D combination.

The ATC-code for strontium ranelate/cholecalciferol FDC is M05BX53, the pharmacotherapeutic group is still pending.

The finished product is a powder for oral suspension. The excipients are the same as contained in Protelos/Osseor except for a cyclodextrin, which is not present in Protelos/Osseor.

The recommended daily dose for Issarlos/Ditelos is one sachet, containing 2 g strontium ranelate and 25 µg cholecalciferol (1000 IU vitamin D3), taken orally once daily. Issarlos/Ditelos is intended for long-term use. In view of the recommended daily doses in current guidelines and its high safety margin, the applicant considers daily supplementation of 1000 IU of vitamin D appropriate to correct

the insufficiency in vitamin D commonly observed in the elderly osteoporotic population with no need for dose adaptation according to gender, age and population.

No dose adjustment is recommended in relation to age. However, no dose recommendations are given for children and adolescents below 18 years of age as no data are available on safety and efficacy in this age group. No dose adjustment is required in patients with hepatic impairment and in patients with mild-to-moderate renal impairment (30-70 ml/min creatinine clearance). Issarlos/Ditelos is not recommended in patients with severe renal impairment (creatinine clearance < 30 ml/min).

Issarlos/Ditelos should be taken at bedtime at least two hours after eating, since the absorption of strontium ranelate is affected by food, milk and milk derivative products.

Dose recommendations and method of administration are similar to those approved for Protelos/Osseor.

Since cholecalciferol is sensitive to many physiochemical agents (air, temperature, light, etc.) a cyclodextrin was added to the finished product Issarlos/Ditelos as stabilizer.

## *2.3. The development programme/compliance with CHMP guidance/ scientific advice*

The clinical development of S06911 is based on the Guideline on clinical development of fixed combination medicinal products (CHMP/EWP/240/95 Rev. 1).

The applicant has provided:

- a pharmacokinetic study to evaluate an interaction between the monocomponents .
- a Phase 3 study to demonstrate efficacy and safety.

The development of S06911 includes a pivotal Phase 3 study to evaluate the efficacy of S06911 on vitamin D insufficiency correction (i.e. to achieve a 25-OH vitamin D level superior or equal to 50 nmol/L) and safety of S06911 in osteoporotic postmenopausal women and men. This development was considered adequate during the National Scientific Advice of April 29, 2009 (Sweden, Uppsala).

## *2.4. General comments on compliance with GMP, GLP, GCP*

Quality

The cholecalciferol-cyclodextrin complex is an intermediate drug product instead of active substance; the appropriate manufacturing authorisations and GMP certificates should be provided for the manufacturers of the mixture. Reference is made to the Quality Assessment report. For the pure cholecalciferol new QP declarations are required for each manufacturing site listed in the referenced CEPs.

Clinical

According to the applicant the clinical development program of S06911 was conducted in full compliance with Good Clinical practice regulations and with regulatory requirements in force in Europe at the time the studies were set up (CHMP/EWP/240/95 Rev. 1, 2008). No violation of GCP regulations was encountered by the Assessor during assessment of the S06911 program.

## 2.5. Type of application and other comments on the submitted dossier

- Legal basis: Les Laboratoires Servier submitted Marketing Authorisation applications for Ditelos and its duplicate Issarlos, 2 g/1000 IU (strontium ranelate and cholecalciferol), granules for oral suspension, in accordance with article 10b fixed combination application of Directive 2011/83/EC as amended and via the optional scope (new FDC) of the centralized procedure in accordance with the Council Regulation (EC) no.726/2004. The applications are filed through the centralised procedure with the Netherlands acting as Rapporteur and Austria as Co-Rapporteur.
- Accelerated procedure: N/A
- Conditional approval: N/A
- Exceptional circumstances: N/A
- Biosimilar application: N/A
- 1 year data exclusivity: N/A
- Significance of paediatric studies: The European Medicines Agency has waived the obligation to submit the results of studies with Ditelos/Issarlos in all subsets of the paediatric population in osteoporosis.

# 3. SCIENTIFIC OVERVIEW AND DISCUSSION

## 3.1. Quality aspects

### Drug substance

**Drug substance strontium ranelate**

The active substance strontium ranelate (nonahydrate) is an achiral non-hygroscopic substance, which is produced as a well-characterised single morphological form. Due to the higher solubility of ranelic acid as compared to strontium ranelate, the active substance is freely soluble in aqueous media of low pH (< pH 2) but only slightly soluble in neutral aqueous media. Strontium ranelate is practically insoluble in organic solvents.

The detailed description of the strontium ranelate synthesis has been provided. Critical process conditions have been discussed. Acceptable specifications have been included for the substances used. No information has been included on any residues of reagents and solvents which may be present in the key raw material. The applicant should provide this information and discuss how it is prevented that any of these residues will be carried over the final DS.

The suppliers of the Sr starting material have been laid down. With regard to addition of a starting material supplier it is noted that the variation regulation should be followed.

Sufficient information has been provided on the upstream production and potential impurities. As a specific test is included in the DS specification for class 1C metals, they do not need to be specifically controlled in the starting material. For one of the potential impurities, a suitable limit & test method should be set in the quality requirements for the corresponding starting material.

The active substance specification included tests for identity, LOD, related substances, heavy metals, pH, strontium content, particle size, and assay. Limits are also set for each other impurity (nmt 0.05

%) and sum of impurities (nmt 2.0 %) in the specification. The limits for organic impurities are basically acceptable based on the levels observed in toxicological and clinical batches for Protelos drug product (EU/1/04/288/001-006 and EU/1/04/287/001-006), marketing authorization granted in 2004. However, based on provided batch data and complete stability data (including supplementary data in the responses), limits above the qualified level should be further reduced to the maximum found values.

Since the solvent levels in the batches are consistently low and water is the only solvent used in the last synthesis step, it is acceptable to omit a routine test for solvents. The solvent that is formed in the chemical reaction of the last step, was shown to be sufficiently removed.

The active substance has been subjected to stress testing, photostability testing, and stability studies under long-term, intermediate and accelerated conditions. The results from the ICH stability studies indicate that the active substance strontium ranelate (nonahydrate) is a stable compound stored in the commercial package. No clear changes are observed for the batches packed in both proposed packagings. The proposed re-test period of 3 years in the two packagings with no special storage conditions is justified.

**Drug substance cholecalciferol-cyclodextrin**

The applicant's approach regarding the cyclodextrin is not acceptable. The applicant has acknowledged that this cyclodextrin is an excipient but discussed it in Module 3.2.S. Furthermore, cholecalciferol is available as pure active substance and does not require stabilisation if appropriately packaged and stored (see CEPs). The concentrate should therefore not be regarded as API but as an intermediate product with all due related requirements: i.e. the information on the complex should be transferred to the relevant paragraphs of Module 3.2.P and appropriate manufacturing authorisations and GMP certificates should be provided. For the pure cholecalciferol new QP declarations are required for each manufacturing site listed in the referenced CEPs.

For the pure cholecalciferol a complete Module 3.2.S should be presented. For 3.2.S.1 to 3.2.S.5 reference can be made to CEPs supplied by the two different ASMs. Along with a CEP, the applicant should supply results of batch analysis demonstrating compliance with the Ph.Eur. monograph and additional requirements mentioned on the CEP. As the CEPs provided do not state the packaging materials and re-test period, all details should be provided on packaging materials and stability by the applicant in sections 3.2.S.6 and 3.2.S.7 regarding the pure cholecalciferol. As alternative to stability data the applicant may also declare that the substance complies with the complete Ph.Eur. monograph immediately before use (Guideline on summary of requirements for active substances in the quality part of the dossier CHMP/QWP/297/97 Rev1 corr.).

The applicant is requested to present a LoA for the safety data provided for the cyclodextrin used for the complex with cholecalciferol in the MA-dossier of another product in support of the current application. Otherwise the safety studies performed for this cyclodextrin provided for the application of another DP should also be included in the current application file.

The information presented on the production of this cyclodextrin is not deemed sufficient; it should be regarded as a novel excipient and details of the synthesis should be included. The applicant refers to a US DMF, however this DMF is not available for the CHMP and can therefore not be taken into account.

The preparation of the complex has been presented in sufficient details. The evaluation of the process was performed on three industrial batches of cholecalciferol-cyclodextrin complex. All batches comply with the specifications.

The intermediate product specification included tests for identity (cholecalciferol & cyclodextrin), water content, related substances, heavy metals, sulphated ash, cyclodextrin and cholecalciferol content, and particle size. The limits proposed are qualified and acceptable. Method descriptions are acceptable.

The intermediate product has been subjected to stress testing and stability studies under long-term, intermediate and accelerated conditions. The results from the ICH stability studies indicate no significant change under long term as well as accelerated conditions. A 2-year re-test period is proposed for the active substance complex, stored in the industrial bulk packaging. As the stability batches have a batch size < 10kg, the applicant is requested to reduce the maximum batch size (max. 100 kg production batch size would be acceptable) or to initiate new stability studies on adequate batches to support the bulk holding time/shelf life for the proposed batch size of intermediate product.

## *Drug Product*

The product is presented as granulate for oral suspension containing 2 g of strontium ranelate and 1000 IU of vitamin D3 (corresponding to 25 µg of cholecalciferol), packaged in sachets. It is intended as a daily treatment: the granules contained in the sachets must be taken as a suspension in a glass of water. The composition of the product applied for is identical to the composition of the centrally registered product Protelos/Osseor (EU/1/04/288/001-006 and EU/1/04/287/001-006), except that the product currently applied for contains an additional active substance.

From a quality point of view, the pharmaceutical development of this product is acceptable. The manufacturing process has been described sufficiently.

The manufacture of the granule is identical to the process used for Protelos. For the manufacture of the proposed product an additional step of mixing is introduced.

The quality of cyclodextrin is sufficiently justified. All other excipients used are of Ph.Eur. quality and of synthetic or vegetable origin.

The specification for the finished product at release and shelf-life includes tests for appearance, average mass, uniformity of dosage units for cholecalciferol and strontium, pH of suspension, microbial quality, identity of the active substance (cholecalciferol, ranelate part and strontium), assay (strontium ranelate and cholecalciferol) by HPLC, and strontium by AAS, degradation products and dissolution of strontium ranelate. The specification is not yet satisfactory. Batch and stability data provided do not justify the limits set for the impurities: all limits of the specified impurities should be revised.

The lower shelf life limit for cholecalciferol should be set at 85%, to allow some degradation. The limit should be re-evaluated when more data are available.

The information and specifications presented for the finished product packaging material (sachets) are satisfactory. Confirmation that the primary packaging material complies with the Ph.Eur. and the Community legislation for materials intended to come in contact with foodstuffs is provided.

Stability study data are presented for three full scale batches in the commercial package, in compliance with ICH requirements. In addition, one batch was subjected to stress testing.

No significant changes can be observed during long-term and accelerated storage. Based on these results, the applicant proposes a shelf-life period of 36 months without any special storage condition. This is acceptable.

The product shows an acceptable stability of the drug product as reconstituted solution in water over the time of 24h at room temperature.

## *Discussion on chemical, pharmaceutical and biological aspects*

Module 3 is mostly based on Module 3 accepted for Protelos/Osseor drug product (EMEA/H/C/000560 and EMEA/H/C/000561), marketing authorization granted in 2004. Quality reports for that procedure have been taken into account for the current assessment. There is, however, one major issue with regard to the quality dossier concerning the addition of a cyclodextrin to the formulation. The need for inclusion of a stabiliser and the subsequent selection of this cyclodextrin as such is sufficiently justified.

With regard to the designation of cholecalciferol-cyclodextrin stabilising complex/concentrate as active substance described in Module 3.2.S of the application dossier, advice was sought from CHMP's QWP. In view of the large excess of the cyclodextrin in the cholecalciferol-cyclodextrin mixture; it was concluded that, the cholecalciferol-cyclodextrin mixture can be regarded as conventional API-excipient mixture rather than a real complex or co-crystal. In line with the Q&A on quality for ASMFs, a mixture of an active substance with an excipient cannot be regarded as active substance. The only exceptions can be made where the active substance cannot exist on its own, and this is not the case for cholecalciferol. Reference to Ph.Eur. monographs for concentrates of cholecalciferol and to the EPAR of Fosavance are not deemed a valid justification for the applicant's approach. The blending of an active substance and an excipient is considered as the first step in the manufacture of the medicinal product, and therefore does not fall under the definition of an active substance. As a consequence relevant information should be included in module 3.2.P and be removed from section 3.2.S, and relevant manufacturing authorisations and GMP certificates as well as new QP declarations should be provided.

The cyclodextrin is regarded as a novel excipient. Appropriate data should be provided or referred to.

## *Conclusions on the chemical, pharmaceutical and biological aspects*

Module 3 is mostly based on Module 3 accepted for Protelos/Osseor drug product (EMEA/H/C/000560 and EMEA/H/C/000561). The need for inclusion of a stabiliser and the subsequent selection of this cyclodextrin is sufficiently justified.

With regard to the cholecalciferol-cyclodextrin complex, the MO remains: The complex should be regarded as an intermediate product. As a consequence relevant information should be included in module 3.2.P and removed from section 3.2.S and the appropriate manufacturing authorisations and GMP certificates should be provided. For the pure cholecalciferol new PQ declarations are required and a complete Module 3.2.S should be presented. For 3.2.S.1 to 3.2.S.5 reference can be made to CEPs.

This cyclodextrin is regarded as a novel excipient. Appropriate data should be provided or referred to.

With regard to the redefinition of starting material for the strontium ranelate DS 2 other concerns remain. Most of the OCs formulated in the D120 LoQ have been solved, however some OCs remain. They mainly concern limits for impurities. The remaining MOs and OCs need to be solved adequately, before a positive advice from a quality point of view can be given.

According to the decision tree of the "Note for guidance on evaluation of stability data" a 36-month shelf-life period can be proposed, for S 6911 (granules for oral suspension, packed in sachets containing 2 g of S 12911-2 and 1000 IU of colecalciferol.

However, from the SmPC it appears the applicant wishes to apply a shelf life of 24 months, this is no objection. According to the "Guideline on declaration of storage conditions: A: in the product information of medicinal products, B: for active substances", CPMP/QWP/609/96/Rev 2, the drug product does not require any special storage conditions.

## 3.2. Non clinical aspects

## Pharmacology

As no primary pharmacology studies with the fixed combination were provided with the preclinical dossier, the submitted data on the individual components are discussed and summarised.

Strontium ranelate

Strontium ranelate is a well-known active substance and the applicant refers to the nonclinical dossier of PROTELOS/OSSEOR®. In short, strontium ranelate has a dual effect on bone metabolism. The in vitro studies show that strontium ranelate stimulates the osteoblast precursor's replication and the bone matrix protein synthesis, and that it decreases osteoclasts differentiation and their resorption activity. Strontium ranelate has the ability to increase bone formation and to decrease bone resorption at strontium ranelate plasma exposure in rats, mice and monkeys similar to that obtained in postmenopausal women receiving the therapeutic dose of 2 g/d. These effects vary with the exposure to treatment, skeletal site and level of bone turnover. Strontium ranelate was safe at the bone tissue level. Only long-term treatment at doses equal to or higher than 38 times the oral dose in humans (corresponding to 2-4 times the therapeutic plasma exposure and 3.4 times the bone strontium concentration) induced fully reversible defective bone mineralization in rats and monkeys. At lower doses, the treatment was not associated with any detrimental effect on bone quality regardless of the duration applied.

No additional preclinical studies on the primary pharmacodynamic with strontium ranelate were performed.

The design of the safety pharmacology studies for strontium ranelate was based on the pharmacodynamic and pharmacokinetic characteristics of the substance. In vivo studies were conducted on female animals (rats and dogs) and functional evaluations were performed after repeated oral daily treatment (14 to 28 days), in order to reach exposures close to the pharmacokinetic steady state and, mimic more closely the human exposure. The cardiovascular, respiratory and central nervous system safety pharmacology evaluations were extended to other major functions such as renal and gastro-intestinal, which are of interest for a therapeutic long-term oral treatment. The data collected during the safety pharmacology program for PROTELOS/OSSEOR® show that strontium ranelate has no functional effect on the vital functions, in particular cardiovascular, as well as on all the other explored functions and systems.

Vitamin D3

Cholecalciferol is the well-known endogenous metabolite acting as a provitamin of the active 1-25 (OH)2 vitamin D3. Preclinical data describing the primary pharmacodynamics of vitamin D3 have been presented in the form of references to published literature.

Vitamin D3 is essential for skeletal development and health. Available literature shows that vitamin D3 enhances intestinal calcium absorption and renal calcium reabsorption, controls bone remodelling and has shown to be effective in preventing bone loss induced by estrogen deficiency in animals. The beneficial effect of vitamin D on the skeleton in intact animals occurs independently of calcium levels. Along with parathyroid hormone and calcitonin, it regulates serum calcium concentrations by increasing serum calcium and phosphate concentrations as needed.

No separate studies on the pharmacodynamics, but an extensive review of the literature of non-clinical studies of vitamin D3 and its metabolites was provided. Because of the provided preclinical literature

data and the available human data based on extensive use of vitamin D3 over many years in clinical trials, additional animal safety data are not considered necessary.

## *Pharmacokinetics*

No pharmacokinetic studies have been conducted for the non-clinical dossier of Ditelos/Issarlos. The individual components are discussed and summarized.

Strontium ranelate

In order to measure calcium, strontium and ranelate in biological samples, specific analytical methods were developed and validated. These data were originally collected and made available for the initial approved CTD for strontium ranelate ("Treatment of osteoporosis in postmenopausal women to reduce the risk of vertebral and hip fractures" (September 21st, 2004)).

The pharmacokinetics of strontium ranelate are similar in animals and in humans. Due to the contribution of an active saturable process, the gastrointestinal absorption of strontium is dose-dependent and decreases when dose increases, while the gastrointestinal absorption of ranelic acid remains low due to its high polarity. The extra vascular distribution of strontium is characterised by its affinity for bone-related tissues. Due to its high polarity, the extra vascular distribution of ranelic acid remains poor. Both strontium and ranelic acid are not metabolised. The binding of both strontium and ranelic acid to plasma proteins is low. The excretion of strontium is partly renal and partly intestinal, while ranelic acid is essentially excreted in urine. Higher concentrations of strontium are found in milk than in plasma.

Vitamin D3

The pharmacokinetics of vitamin D3 are well-known. An overview based on literature data is thus appropriate. These data indicate that after oral intake, vitamin D3 is almost completely absorbed in the intestine. Circulating vitamin D3 binds to the vitamin D-binding protein (DBP) and is transported to the liver where it is hydroxylated as 25-OH vitamin D3, the major circulating metabolite of vitamin D3. The 25-OH vitamin D3 is the storage form of vitamin D3 and the indicator of vitamin D3 status. The final activation step of vitamin D3 occurs in the kidney and corresponds to an 1α-hydroxylation forming calcitriol, i.e. 1,25-(OH)2 vitamin D3, the hormonal active form of vitamin D3. Calcitriol is then metabolically inactivated by 24-hydroxylase and undergoes oxidative cleavage. Vitamin D3 and its metabolites are mainly excreted in the bile.

Cyclodextrin

For the pharmacokinetics of the cyclodextrin, the applicant refers to a non-clinical dossier submitted for another registered drug product. These data show that the absorption of this cyclodextrin is low after oral administration (less than 10% of the administered dose). Since in Ditelos/Issarlos this cyclodextrin is in complex with vitamin D3, its low absorption could lead to lower gastrointestinal absorption and lower serum levels of vitamin D3 as compared to the intake of vitamin D3 separately, whether or not in combination with strontium ranelate. However, clinically the interaction between this cyclodextrin and Vitamin D was within the acceptance range and considered not significant (see the Clinical part of this Overview AR).

## *Toxicology*

As no toxicological studies with the fixed combination were provided with the preclinical dossier, the submitted data on the individual components are discussed and summarised.

Strontium ranelate

The toxicological profile of strontium ranelate has already been evaluated in the course of a marketing authorization procedure in 2004 of PROTELOS/OSSEOR®. The relevant studies were re-submitted with the Ditelos/Issarlos Dossier.

Single-dose toxicity in two rodent species (mice, rats) and in two non-rodent species (dogs, monkeys) by oral and IV route at very high doses. These data show that strontium ranelate has a low acute toxicity. Repeat-dose toxicity studies by the oral and IV routes were carried out over 2-week to 1-year periods, in three animal species (rat, dog, monkey). These data show that chronic oral administration of strontium ranelate at high doses in rodents induced bone and tooth abnormalities, mainly consisting of spontaneous fractures and delayed mineralisation. These effects were reported at bone strontium levels 2-3 times higher than long-term clinical bone strontium levels and were reversible after cessation of treatment.

The Genotoxicity studies-battery and Carcinogenicity studies showed that strontium ranelate has neither genotoxic nor carcinogenic potential.

Reproductive and developmental toxicity studies were performed in rats and rabbits. The NOAEL was determined as 1000 mg/kg/day for the toxicity and fertility in the F0 generation, for teratogenicity, post-natal development and fertility of the F1 generation and for pre- and post-natal development in the F2 generation. Due to the effects on bone, the NOAEL in the embryo-foetal development was determined to be less than 500 mg/kg/day. As a consequence, strontium ranelate should not be administered during pregnancy or during lactation.

During the post approval period, new studies of toxicology (i.e. local tolerance) were performed as well as a new assessment of the impurities in agreement with the guidelines on the limits of genotoxic impurities. All studies related to skin and eye tolerance, as well as the study detecting a potential to induce delayed contact hypersensitivity were negative. An up-to-date re-examination of the impurity profile did not reveal a cause of concern.

Vitamin D3

Literature data on preclinical toxicology studies with vitamin D3/calcitriol were presented

A single oral dose of calcitriol (1000, 2000 and 4000 µg/kg) in mice caused at the highest dose level respiratory depression, tremors, lower motor activity, ptosis and abnormal gait.

Vitamin D doses administered to animals during the toxicological studies have an acceptable safety margin regarding the expected vitamin D serum levels in human treated with a daily dose of strontium ranelate 2g/vitamin D3 1000 IU.

Repeated doses studies in rats and dogs reflected the well-known hypercalcemic effect at oral dose levels up to 5 times the human dose proposed in the fixed combination (i.e. strontium ranelate 2g/vitamin D3 1000 IU). In a 26-week oral study in rats, (5000, 10 000 or 20 000 IU (i.e. 125, 250 and 500 µg)/kg/d of vitamin D3), lower body weight gain at 10 000 and 20 000 IU/kg/d, higher serum calcium and phosphorus levels and elevated urinary calcium/creatinine ratios were observed at all dose levels. Renal tubule mineralization was reported at 5000 and 10 000 IU/kg/d, as well as nephrocalcinosis at 10 000 and 20 000 IU/kg/d and proliferative changes in adrenal medulla in the

majority of animals. At higher oral doses (i.e. up to 20 times) than the intended human dose level, reproductive toxicity of vitamin D was observed.

Cyclodextrin

The recommended dose of Ditelos/Issarlos is one sachet once daily by oral administration. Cyclodextrins are considered to be virtually nontoxic after oral administration. This cyclodextrin is a known excipient. For the registration of another product, safety studies were performed at that time for this cyclodextrin: single and repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and development toxicity and local tolerance. Two routes of administration were evaluated: intravenous and oral. These data show that the cyclodextrinis well tolerated after repeated oral dose up to the NOAEL values of 100 mg/kg/day in rats and 500 mg/kg/day in dogs in the 26 week studies. At higher exposures, the main target organ is the kidney which changes are due to osmotic nephrosis. This effect was observed after oral and IV dosing in the rat and after IV dosing only in the dog. Osmotic nephrosis was not observed in dogs after oral dosing in the tested dose range (maximal 500 mg/kg/day).

The (oral) reproduction toxicity studies (rats, rabbits), the genotoxicity tests, the carcinogenicity studies and the local tolerance studies did not lead to concerns.

The local tolerance of the cyclodextrin, in particular concerning the eye and the skin, was analysed throughout the preclinical development. No evidence of sensitization, ocular irritation or corrosion, and no irritation or corrosion to the skin were observed.

## *Ecotoxicity / environmental risk assessment*

The Applicant submitted an environmental risk assessment based on the EMEA/CHMP/SWP/4447/00 guideline (EMEA, 2006).

The drug is proposed for treatment of severe osteoporosis in men and post-menopausal women at risk of vitamin D insufficiency and fracture. The two active substances present in the drug are vitamin D3 and strontium ranelate.

Vitamin D3: According to the current environmental risk assessment guideline no ERA is necessary for vitamins.

The environmental risk assessment of strontium ranelate has been provided.

In conclusion, it is considered that the risk for aquatic organisms from exposure to the products "Ditelos" and "Issarlos" is acceptable according to the intended use.

No precautionary and safety measures for administration, disposal and labelling are required.

## *Discussion on non-clinical aspects*

A comprehensive non-clinical program of efficacy, pharmacokinetic and safety studies was performed for strontium ranelate. These studies are described in detail in the Non-Clinical Overview of the initial dossier of PROTELOS/OSSEOR. For vitamin D3, the second substance present in the fixed combination, an extensive review of the literature of non-clinical studies of vitamin D3 or its metabolites was provided.

The Applicant provided exclusively a pharmacological/toxicological summary of each individual substance. This approach is agreed, since the efficacy of the combined treatment strontium ranelate and vitamin D3 is clinically known.

The environmental risk assessment is performed for strontium ranelate based on the EMEA/CHMP/SWP/4447/00 guideline (EMEA, 2006). As strontium ranelate does not present a safety concern for the environment, specific wording in the product information is not considered necessary.: According present guideline no environmental risk assessment is not needed for vitamin D3.

## Conclusion on non-clinical aspects

Taken together, the submitted preclinical data support the MAA of Ditelos/Issarlos human use. All outstanding issues have been solved.

## *3.3. Clinical aspects*

## *Pharmacokinetics*

The pharmacokinetics of strontium are well described by the population pharmacokinetic models developed by the applicant. As could be expected, the pharmacokinetic parameters of the model of strontium do not differ after repeat administration of strontium ranelate alone or as the combination product with Vitamin D3. Taken into account the pharmacokinetic properties of strontium with main clearance by the renal route, the predicted decrease of excretion of strontium with decreased creatinine clearance is confirmed by the population pharmacokinetic analysis.

In an interaction study 42 healthy young men (volunteers) were included in an open, randomised, 3x cross-over study (6 groups of treatment sequences)) and were administered with a single oral dose of strontium ranelate 2 g/vitamin D3 1000 IU sachet, strontium ranelate 2 g sachet and vitamin D3 1000 IU tablet. The vitamin D3 formulation contained cyclodextrin. This study showed that after administration of a fixed dose combination of strontium ranelate and vitamin D3 the pharmacokinetic profiles of strontium and vitamin D3 did not change in a clinically significant way as compared with administration of the two components separately.

*Table PK01: Geometric mean ratios (test treatment / reference treatment) and 90% Confidence Intervals for baseline-corrected pharmacokinetic parameters of strontium and vitamin D3*

| Parameter | **Strontium** (n=39) | **Vitamin $D_3$** (n=38) |
|---|---|---|
| | Ratio test / reference (90 % CI) | Ratio test / reference (90 % CI) |
| $AUC_{72}$ | 99.62 % (93.16 %,106.53 %) | not applicable# |
| $AUC_{last}$ | not applicable* | 94.56 % (77.51 %,115.37 %) |
| $C_{max}$ | 98.99 % (92.82 %,105.55 %) | 83.56 % (78.59 %,88.84 %) |

**: $t_{last} \geq 72$ h for all subjects*
*#: $t_{last}$ not $\geq 72$h for all subjects*
*test: S06911, fixed combination of strontium ranelate 2 g/vitamin D3 1000 IU (one sachet)*
*reference for strontium: S12911, strontium ranelate 2 g (one sachet)*
*reference for vitamin $D_3$: vitamin $D_3$ 1000 IU (one sachet)*

Another interaction study was conducted to assess and compare (in a descriptive way) the pharmacokinetics of vitamin D3 obtained after a single oral dose of 2 tablets of 1000 IU of vitamin D3 each (without cyclodextrin) with those after single oral administration of 1 combination sachet of 2 g strontium ranelate and 2000 IU vitamin D3 stabilized by cyclodextrin in healthy young male volunteers.

This study was conducted as a parallel design (wash-out period between the treatments of 7 days) with 12 healthy young male volunteers. The products were administered under fasting conditions.

The results of this study showed that addition of cyclodextrin to the vitamin D3 formulation decreased the rate and extent of exposure in a significant way by 50% (see table PK02).

*Table PK02: Mean ± SD (median) vitamin D3 pharmacokinetic parameters (baseline corrected) (n=12 subjects/treatment)*

| Parameter (unit) | 2 tablets of 1000 IU of vitamin $D_3$ (without cyclodextrin) i.e. 2000 IU | 1 sachet of combination strontium ranelate 2 g/vitamin $D_3$ 2000 IU (complexed with cyclodextrin) |
|---|---|---|
| $C_{max}$ (ng/mL) | 3.6 ± 0.70 (3.6) | 2.1 ± 0.37 (2.2) |
| $t_{max}$ * (h) | 12 [7.0-24] | 12 [7.0-24] |
| $AUC_{last}$ (ng.h/mL) | 184 ± 43 (185) | 100 ± 42 (103) |
| $AUC_{0-72\ h}$ (ng.h/mL) | 152 ±29 (152) | 83 ± 26 (89) |
| $t_{last}$ (h) | 120 [72 – 120] | 108 [24 – 120] |
| *$R_{Cmax\ S6911/vitD}$ | 0.58 | |
| *$R_{AUClast\ S6911/vitD}$ | 0.50 | |

*$t_{max}$ and $t_{last}$ are expressed as median [min-max]*
**Ratios are calculated with geometric means*

In a second study this interaction of Vitamin D3 and cyclodextrin was further investigated. This study is comparable with the study discussed above but was better designed to minimize the variability with a much higher number of volunteers included.

This second study was performed with 54 healthy subjects (male and female) with a standardized basal Vitamin $D_3$ level (having a Fitzpatrick skin type II or III, 25-OH vitamin D serum concentrations ≥40 nmol/L with an inter-subject difference between the minimum and the maximum concentrations ≤40 nmol/L at selection, and no new and/or no accentuation of visible traces of sun exposure on the entire body at inclusion compared to selection). The study was conducted as a two-way, two sequence cross-over design with a wash-out period of 7 days. The reference product was Vitamin $D_3$ 100 IU (25 µg) without cyclodextrin (actual content 1058 IU) and the test formulation was Vitamin $D_3$ with cyclodextrin (actual content 927 IU).

The 25-OH vitamin D at baseline, mean ± SD value was 51.3 ± 9.4 nmol/L, with similar mean value in each treatment sequence. No participant had a value ≤40 nmol/L according to inclusion criteria required.

The results of the study show that the ratio's of the mean pharmacokinetic variables are within the acceptance range as used for bioequivalence and therefore an interaction between Vitamin D and cyclodextrin can be considered as not clinically significant.

Overall, it can be concluded that the applicant provided sufficient proof that cyclodextrin has no significant influence on the bioavailability of Vitamin D. The conclusions are limited with respect to the bioavailability of Vitamin D from the product to be marketed as it tested unequal amounts of vitamin D3 packed in a formulation differing from the actual product to be licenced.

## *Pharmacodynamics*

No new specific pharmacodynamic studies have been conducted for this application.

The applicant describes the extensive documentation on the pharmacodynamics properties of both monocomponents. Moreover, markers of bone turnover have been incorporated into the main clinical study CL3-06911-002.

## *Conclusions on clinical pharmacology*

The pharmacokinetics of strontium are not affected by co-administration of vitamin D with cyclodextrin, nor did strontium affect the exposure of vitamin D in a significant way.

The interaction between cyclodextrin and Vitamin D was within the acceptance range and considered not clinically significant.

## *Clinical efficacy*

Two phase III studies on clinical efficacy and safety have been submitted.

1. **CL3-06911-002 (M0-M6); extended (M0-M12) with a 6-month open-label for a subgroup**
   This study was designed to evaluate the efficacy of S06911 on vitamin D insufficiency (< 50 nmol/L (20 ng/ml) correction and its safety in 518 osteoporotic men and postmenopausal women over 6 months. This study included a 6-month open-label extension for a subgroup of patients belonging to 5 predefined countries to assess safety of a daily oral administration of S06911.
2. **CL3-06911-003**
   This additional one-group study was conducted in parallel to the study 1 to evaluate the efficacy of S06911 on the correction of vitamin D deficiency [≤ 22.5 nmol/L (9 ng/ml)].

The study objectives, the study design and further details of the studies CL3-06911-002 and CL3-06911-003 are summarised in Table 1.

*Table 1: Tabular listing of submitted Clinical Safety and Efficacy Studies*

| Study ID | Number of study centres location(s) | Study start Enrol. Status, date total/target | Design Control type Duration | Study & Control drugs Dose, Route & Regimen | Study objectives | Subjects entered/ completed the study | Gender M/F Mean Age ± SD (Range) | Diagnosis Inclusion criteria | Efficacy Primary Endpoint(s) |
|---|---|---|---|---|---|---|---|---|---|
| | **Main period** | | | | | | | | |
| **CL3-06911-002** | 55 centres in 13 countries | 28 January 2010 Completed 14 January 2011 518/500 | multi-centre, international phase III clinical study with a 6-month randomised, double blind, unbalanced (4:1) and parallel group period | S 06911 p.o. o.d<br>S 12911 p.o. o.d | -To demonstrate the efficacy of a 3-month daily oral administration of S 06911 (strontium ranelate 2 g + cholecalciferol 1000 IU), on the correction of vitamin D insufficiency (< 50 nmol/L).<br>-To demonstrate the efficacy of a 3-month daily oral administration of S 06911: on the treatment of vitamin D relative insufficiency (< 75 nmol/L) and on the absolute and relative change in 25-OH vitamin D from baseline to End (last post-baseline value over M0-M3).<br>-To demonstrate the efficacy of a 6-month daily oral administration of S 06911: on the correction of vitamin D insufficiency (< 50 nmol/L), on the treatment of vitamin D relative insufficiency (< 75 nmol/L) and on the absolute and relative change in 25-OH vitamin D to M3 and M6.<br>-To evaluate the safety and tolerability of a 3-month and a 6-month daily oral administration of S 06911 as compared to S 12911 (strontium ranelate 2 g).<br>-To assess the pharmacokinetics of strontium at steady state, after a repeated daily oral administration of S 06911 or S 12911. | 413/346<br>105/92 | 49/469<br>66.8±8.3<br>50 - 89 | Caucasian male and postmenopausal female patients aged ≥ 50 years with primary osteoporosis characterised by a BMD T-score ≤ -2.5 SD at the lumbar spine or femoral neck or total hip.<br>All patients were to have 25-OH vitamin D serum concentration > 22.5 nmol/L and 80% of patients were to have 25-OH vitamin D concentration between 22.5 nmol/L (exclusive) and 50 nmol/L and 20% of patients were to have 25-OH vitamin D concentration ≥ 50 nmol/L. | 25-OH vitamin D concentration |
| | **Extension period** | | | | | | | | |
| | 22 centres in 5 countries | Completed 01 July 2011 257/306 | 6-month open-labelled extension period in a subgroup of patients | S 06911 p.o. o.d. | -To evaluate the efficacy of a 12-month daily oral administration of S 06911 on the change of BMD in a subgroup of patients from selected countries.<br>-To describe the effect of a 12-month daily oral administration of S 06911 in a subgroup of patients from selected countries on the correction of vitamin D insufficiency (< 50 nmol/L) and on the treatment of vitamin D relative insufficiency (< 75 nmol/L).<br>-To evaluate the safety and tolerability of a 12-month daily oral administration of S 06911 in a subgroup of patients from selected countries. | 257/242 | 22/235<br>65.6±7.8<br>50 - 88 | patients participating for the main period in the countries which were determined in the study protocol to participate also in the open-label extension period | BMD |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **CL3-06911-003** | 12 centres in 5 countries | 2 March 2010 Completed 22 June 2011 19/60 | multi-centre, international phase III clinical study with a 12-month open-label, one treatment group period | S 06911 p.o. o.d. | -To evaluate the efficacy of a 12-month daily oral administration of S 06911 (strontium ranelate 2 g + cholecalciferol 1000 IU) on the correction of vitamin D insufficiency (*i.e.* to increase the serum 25-OH vitamin D level to a value ≥ 50 nmol/L) in patients with a baseline deficient vitamin D level (*i.e.* ≤ 22.5 nmol/L).<br>-To evaluate the efficacy of a 12-month daily oral administration of S 06911 on the correction of vitamin D deficiency (*i.e.* to increase 25-OH vitamin D to >22.5 nmol/L).<br>-To evaluate the efficacy of a 12-month daily oral administration of S 06911 on the absolute change in 25-OH vitamin D.<br>-To evaluate the safety and tolerability of a 12-month daily oral administration of S 06911. | 19/16 | 1/18<br>65.5±8.5<br>54 - 84 | Caucasian male and postmenopausal female patients aged ≥ 50 years with primary osteoporosis characterised by a BMD T-score ≤ -2.5 SD at the lumbar spine or femoral neck or total hip.<br>All patients were to have 25-OH vitamin D serum concentration ≤ 22.5 nmol/L. | 25-OH vitamin D concentration |

## *Dose-response studies and main clinical studies*

No specific dose-response studies were performed. However, the rationale for strontium, calcium and vitamin D dosing was presented.

**Strontium**

The dose of 2 g strontium ranelate daily is in accordance with the previously approved treatment of preventing osteoporosis.

**Calcium**

The dose of 1000 mg of calcium in the studies CL3-06911-002 and CL3-06911-003 was chosen according to the international osteoporosis treatment guidelines.

In view of reduced bioavailability of strontium ranelate by concomitant intake of calcium a fixed combination with calcium is contraindicated. Intake of calcium is indicated, but at another time of the day. In the pivotal phase 3 studies CL3-06911-002 and CL3-06911-003 Calcium (1000 mg) was administered at lunchtime, whereas the proposed Issarlos/Ditelos (Protelos plus vitamin D) was taken at bedtime in these studies.

**Vitamin D**

Concerning vitamin D status (as assessed according to 25-OHD level): according to the applicant in this application deficiency is defined as ≤ 22.5 nmol/L (9 ng/ml), insufficiency as < 50 nmol/L (20ng/ml), inadequacy as < 75 nmol/L (30 ng/ml) and toxicity as > 375 nmol/L (150 ng/ml).

The dose given should ensure 25-OHD levels of 50 nmol/L (minimal requirement), and the IOF recommendation 2010 is: 800-1000 IU/day. Up to 35% of the elderly people screened for studies in osteoporosis have levels < 50 nmol/L. The rationale for 1000 IU vitamin D3 in Issarlos/Ditelos is that 1000 IU (= 25 µg) would result in an increase of 25 OH levels by 18-25 nmol/L. The 1000 IU vitamin D3 dose is chosen to ensure 50 nmol/L and to have a chance to reach the optimal level.

There is a large safety margin for Vitamin D3. EU has determined a level of 2000 IU/day and doses of up to 4000 IU/day for up to 5 months do not cause toxicity. According to Heany (2003) doses up to 10,000 IU vitamin D3 per day for 5 months do not cause toxicity. Doses up to 10,000 IU per day are considered safe ("Council for Responsible Nutrition, Washington, Risk assessment for vitamin D, 2007").

It is clear that vitamin D3 is registered worldwide with a large range of doses and dosing regimen for the prevention and treatment of vitamin D insufficiency and deficiency and as an adjuvant treatment of osteoporosis.

**Choice of the vitamin D subtype**

Both vitamin D2 and vitamin D3 are metabolised to 1,25 dihydroxyvitamin D. Vitamin D3 has been shown to have a higher efficacy and longer duration of action than vitamin D2. Although this was challenged by another trial showing similar potency of both forms, it is the currently recommended form. Therefore, vitamin D3 was chosen by the applicant for the fixed combination S06911.

### Study CL3-06911-002

***Description***

Study CL3-06911-002 was a prospective, phase III study with a 6-month double-blind period to assess the efficacy and safety of a daily oral administration of S06911 versus S12911 (strontium

ranelate 2g) and a 6-month open-labelled extension for a subgroup of patients to assess safety of a daily oral administration of S06911.

***Inclusion criteria***

For the main period 500 patients were planned, for the extension period 200 patients . Main inclusion criteria were Caucasian male (at least 10% of the entire study population) and postmenopausal female patients aged ≥ 50 years with primary osteoporosis characterised by a BMD T-score ≤ -2.5 SD at the lumbar spine or femoral neck or total hip. The targeted population was defined according to the currently agreed cut-off for vitamin D insufficiency, i.e. 50 nmol/L. In addition to this main population, a subgroup of 20% of patients with adequate levels of vitamin D (≥ 50 nmol/L) was included to further assess the effect and particularly the safety of the vitamin D supplementation.

***Treatments***

During the 6-month double-blind period, patients received S12911 (=strontium ranelate 2 g sachet) or S06911 (=strontium ranelate 2g/vitamin D3 1000 IU sachet) (randomly assigned at inclusion with unbalanced ratio 4:1).

The patients participating in the extension period were from 5 pre-defined countries and received only S06911 during M6-M12 period. For this extension period, 2 groups of patients are therefore considered according to treatment received at inclusion: group S12911/S06911 and group S06911/S06911. The study design is presented in Figure 1. The selection criteria for the five countries were mostly based on their capacity to recruit at least 200 patients altogether, to rather carry on a 12-month versus a 6-month study, and to conduct in parallel the CL3-06911-003 study which recruited patients deficient in vitamin D.

***Rescue medication***

If at M1 or M3 a patient had a 25-OH vitamin D value below or equal 22.5 nmol/L, one vial of vitamin D3 200,000 IU was administered as an oral single dose (rescue medication). In these cases of vitamin D rescue, 25-OH vitamin D values following the rescue administration were not taken into account in the efficacy analysis. These excluded values were substituted by the last recorded value preceding the rescue.

***Primary and secondary parameters***

Primary efficacy criterion was the proportion of patients having a level of serum 25-OH vitamin D ≥ 50 nmol/L over the M0-M3 period.

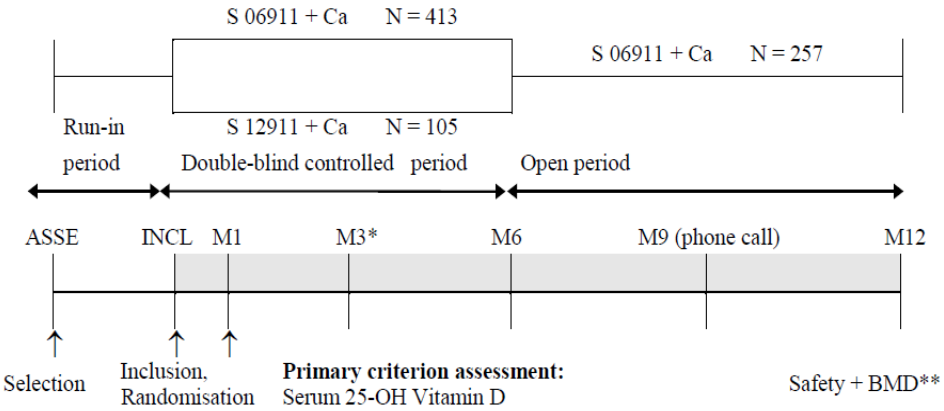
Secondary efficacy criteria were serum 25-OH vitamin D levels over 6 and 12 months, Falls, Short Physical Performance Battery (SPPB), Bone Mineral Density (BMD). Safety criteria were AEs, laboratory parameters (serum and urine biochemistry, haematology, endocrinology) and vital signs (weight, height, systolic blood pressure, diastolic blood pressure, pulse rate).

***Study design***

S06911 (=strontium ranelate 2g/vitamin D3 1000 IU sachet); S12911 (=strontium ranelate 2 g sachet).

In parallel to S06911 and S12911 (without vit. D), calcium (1000 mg) was taken for daily supplementation, administered as tablets around lunchtime.

*Figure 1: CL3-06911-002 Study design*




* *Main efficacy analysis*

** Additional 6-month open-labelled period in: Belgium, Poland, Russia, Spain and Switzerland.

***Statistical Methods***

- *Analysis sets*

The Randomised Set (RS) was defined as all included patients to whom a therapeutic unit was randomly assigned using Interactive Voice Response System. The Full Analysis Set (FAS) was defined as all patients of the RS who had taken at least one dose of study treatment and who had at least one post-baseline value of 25-OH vitamin D over the M0-M3 period. The Per Protocol Set (PPS) was defined as all patients of the FAS without relevant deviation(s) that could affect the effect of the study drug on the level of 25-OH vitamin D.

At inclusion, 20% of patients had a vitamin D level > 50 nmol/L. The treatment groups were thus also compared in the SubFAS defined as all patients of the FAS with a 25-OH vitamin D serum concentration < 50 nmol/L at baseline, i.e. patients with vitamin D insufficiency.

The *main efficacy analysis* was based on intention-to-treat principle.

The S06911 and S12911 (without vit. D) groups were compared on the proportion of patients having a 25-OH vitamin D concentration ≥ 50 nmol/L over 3 months (Last Observation Carried Forward (LOCF) approach) using a logistic regression model including treatment, country and classes of baseline vitamin D levels as factor.

- *Sensitivity analyses*

The same analysis was also performed in the PPS and the SubFAS (without adjusting on classes of baseline vitamin D levels). An analysis without adjustment, including only treatment effect was also performed to confirm the results of the adjusted analysis.

***Results***

- *Baseline characteristics*

Baseline characteristics are summarized in Table 2. Overall at baseline in the **CL3-06911-002 study – main period**, mean age was 66.8 years; most were women (90.5%) who were all postmenopausal (time since last menses from 2 to 49 years); 9.5% of the patients were men and all patients were ambulatory. The overall mean duration of osteoporosis from diagnosis was 41.8 ± 54.5 months with a median of 14.5 months.

The **CL3-06911-002 study – extension period** was performed in a subset of patients from 5 pre-defined countries, mean age was 65.6 years, most were women (91.4%) who were all postmenopausal

(time since last menses from 2 to 43 years); 8.6% of the patients were men and all patients were ambulatory.

In the **CL3-06911-002 study main period**, more than half of patients (53.7%) took previously at least one treatment for osteoporosis and/or interfering with bone metabolism, including 37.5% of the patients taking treatments containing vitamin D. A majority of patients (81.7%) reported at least one concomitant treatment at inclusion. The most frequently reported pharmacological classes of concomitant treatments taken by at least 20.0% of patients in either group were: agents acting on the renin-angiotensin system, beta-blocking and lipid modifying agents.

In the **CL3-06911-002 study extension period**, more than half of the patients (57.6%) took previously at least one treatment for osteoporosis and/or interfering with bone metabolism and treatments containing vitamin D. Other baseline characteristics were similar to these described for the main period as well as results for medical history other than osteoporosis and for concomitant treatments at inclusion.

*Table 2: Baseline characteristics of studies **CL-06911-002 (first six columns)** [and of CL-06911-003 (last column)].*

| | | Randomised Set of CL3-06911-002 study – Main period | | | Randomised Set extension of CL3-06911-002 study – Extension period | | | Included Set of CL3-06911-003 study |
|---|---|---|---|---|---|---|---|---|
| | | S 06911 (N = 413) | S 12911 (N = 105) | All (N = 518) | S 06911 / S 06911 (N = 204) | S 12911 / S 06911 (N = 53) | All (N = 257) | (N = 19) |
| **Age** (years) | Mean ± SD | 66.9 ± 8.3 | 66.6 ± 8.0 | 66.8 ± 8.3 | 65.7 ± 8.0 | 65.5 ± 6.9 | 65.6 ± 7.8 | 65.5 ± 8.5 |
| | Min ; Max | 50 ; 89 | 54 ; 86 | 50 ; 89 | 50 - 88 | 54 - 82 | 50 - 88 | 54 - 84 |
| **Sex** | Men | 41 (9.9) | 8 (7.6) | 49 (9.5) | 19 (9.3) | 3 (5.7) | 22 (8.6) | 1 (5.3) |
| | Women | 372 (90.1) | 97 (92.4) | 469 (90.5) | 185 (90.7) | 50 (94.3) | 235 (91.4) | 18 (94.7) |
| **BMI** ($kg/m^2$) | Mean ± SD | 25.3 ± 3.3 | 25.0 ± 3.0 | 25.3 ± 3.2 | 25.5 ± 3.2 | 24.6 ± 3.2 | 25.3 ± 3.2 | 25.9 ± 2.8 |
| | Min ; Max | 15 ; 32.5 | 17.8 ; 29.9 | 15.3 ; 32.5 | 16.6 - 30.6 | 17.8 - 29.7 | 15.3 - 32.5 | 19.6-29.7 |
| **Lumbar L1-L4** BMD ($g/cm^2$) | Mean ± SD | 0.736 ± 0.094 | 0.743 ± 0.105 | 0.738 ± 0.096 | 0.730 ± 0.076 | 0.716 ± 0.075 | 0.727 ± 0.076 | 0.745 ± 0.122 |
| | Min ; Max | 0.455 ; 1.310 | 0.526 ; 1.209 | 0.455 ; 1.310 | 0.46 - 0.94 | 0.53 - 0.92 | 0.46 - 0.94 | 0.48 - 1.14 |
| T-score≤-2.5 | n (%)' | 301 (73.8) | 80 (77.7) | 381 (74.6) | 153 (75.4) | 45 (84.9) | 198 (77.3) | - |
| **25-OH vitamin D (nmol/L)** | Mean ± SD | 44.0 ± 14.9 | 44.4 ± 13.3 | 44.1 ± 14.6 | 44.4 ± 14.6 | 44.9 ± 13.4 | 44.5 ± 14.4 | 18.8 ± 1.9 |
| | Min ; Max | 22.6 ; 115.6 | 25.4 ; 84.1 | 22.6 ; 115.6 | 22.8 - 115.6 | 25.4 - 84.1 | 22.8 - 115.6 | 15.4 - 22.4 |
| ≤ 22.5 | n (%) | - | - | - | - | - | - | 18 (100) |
| ]22.5 ; 50[ | n (%) | 333 (80.6) | 85 (81.0) | 418 (80.7) | 161 (78.9) | 41 (77.4) | 202 (78.6) | - |
| ≥ 50 | n (%) | 80 (19.4) | 20 (19.1) | 100 (19.3) | 43 (21.1) | 12 (22.6) | 55 (21.4) | - |
| **SPPB Total score** | Mean ± SD | 9.9 ± 1.8 | 9.7 ± 2.1 | 9.9 ± 1.9 | - | - | - | 9.1 ± 1.8 |
| | Min ; Max | 4 ; 12 | 1 ; 12 | 1 ; 12 | - | - | - | 6 - 12 |

*%': (n/n')*100*

- *Participant flow*

Of the 518 included patients, 438 completed the study. Overall, 80 patients (15.4%) were withdrawn from the study: 45 due to adverse event, 30 for non-medical reason and 5 due to protocol deviation. The rate of withdrawals was 16.2% of the patients in the S06911 group and 12.4% in the S12911 (without vit. D) group. The disposition of patients and the definition of the analysis sets are described in Table 3.

*Table 3: Patients disposition and efficacy analysis sets CL 06911-002*

| **Patients disposition** | | | | |
|---|---|---|---|---|
| **Main period** | | **S 06911** | **S 12911** | **All** |
| **Included** | N | 413 | 105 | 518 |
| **Withdrawn** | n (%) | 67 (16.2) | 13 (12.4) | 80 (15.4) |
| Adverse event | n (%) | 38 (9.2) | 7 (6.7) | 45 (8.7) |
| Non-medical reason | n (%) | 25 (6.1) | 5 (4.8) | 30 (5.8) |
| Protocol deviation | n (%) | 4 (1.0) | 1 (1.0) | 5 (1.0) |
| **Completed** | n (%) | 346 (83.8) | 92 (87.6) | 438 (84.6) |
| **Extension period** | n (%) | **S 06911/ S 06911** | **S 12911/ S 06911** | **All** |
| **Participated in the extension study** | n (%) | 204 | 53 | 257 |
| **Withdrawn** | n (%) | 12 (5.9) | 3 (5.7) | 15 (5.8) |
| Adverse event | n (%) | 9 (2.9) | 2 (3.8) | 11 (4.3) |
| Non-medical reason | n (%) | 3 (1.5) | 1 (1.9) | 4 (1.6) |
| **Completed** | n (%) | 192 (94.1) | 50 (94.3) | 242 (94.2) |
| **Efficacy analysis sets** | | | | |
| Main period | - FAS: all randomised patients who had taken at least one dose of study treatment and who had at least one post baseline value of 25-OH vitamin D over the M0-M3 period, | | | N = 498 |
| | - SubFAS: all patients of the FAS with a 25-OH vitamin D serum concentration < 50 nmol/L at baseline, *i.e.* patients with vitamin D insufficiency, | | | N = 400 |
| | - PPS: all patients of the FAS without relevant deviation(s) that could affect the effect of the study drug on the level of 25-OH vitamin D. | | | N = 425 |
| Extension period | - FAS extension: all randomised patients who had taken at least one dose of S 06911 on the M0-M12 period and who had at least one baseline and one post baseline value of BMD over M0-M12 (each patient should have a baseline and a post-baseline value on at least one site: Lumbar L1-L4, Femoral Neck or Total Hip), | | | N = 250 |
| | - PPS extension: all patients of the FAS extension without relevant deviation that could affect the evaluation of BMD. | | | N = 224 |

*Some analyses were not planned in the objectives of the study but were included in the changes in the statistical analysis planned before breaking the blind:*
*- analysis on the relative change at M3,*
*- analysis on the effect of a 12-month S 06911 administration on the correction of vitamin D insufficiency,*
*- analysis on the absolute and relative changes at M6.*

- *25-OH vitamin D – 3-month results*

Please refer to Table 4, Figure 4 and Figure 5, in which the profile of 25-OH vitamin D mean concentration during the study in the FAS, the Sub-FAS and FAS extension is shown.

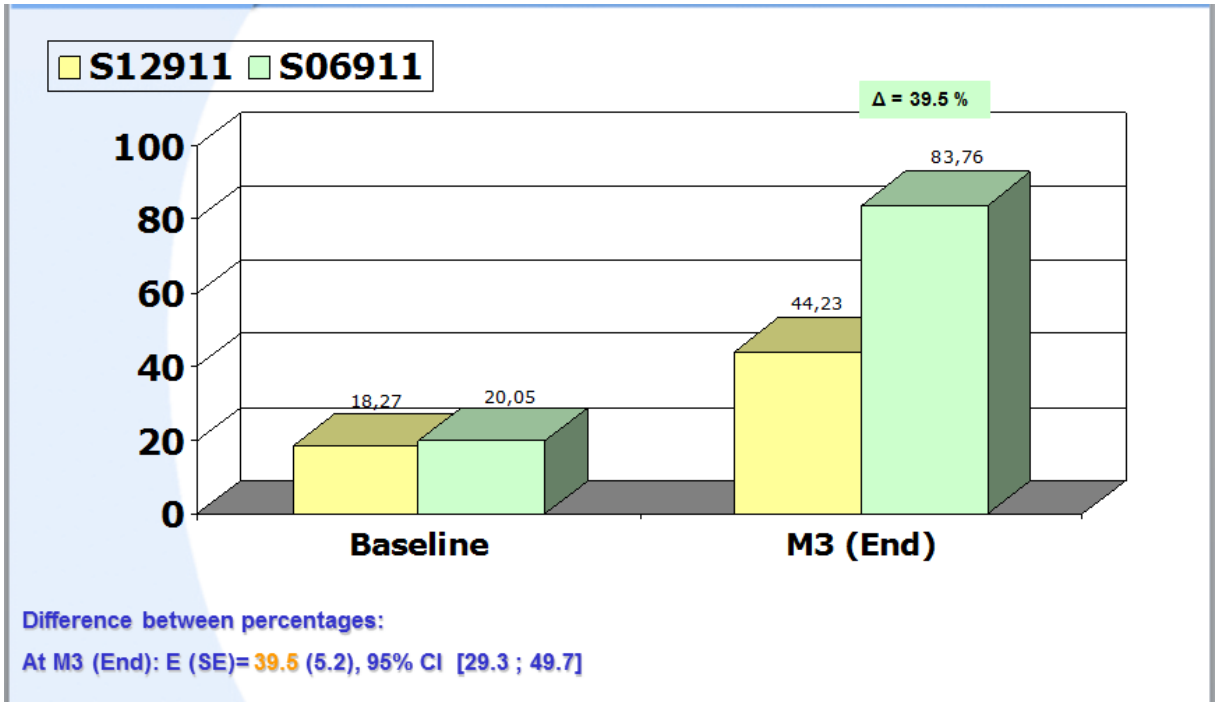
*Table 4: 25-OH vitamin D level ≥ 50 nmol/L at END over **M0-M3 period**- FAS CL 06911-002*

| **25-OH vitamin D concentration** | | **S 06911 (N = 394)** | **S 12911 (N = 104)** |
|---|---|---|---|
| **≥ 50 nmol/L** | n (%) | 330 (83.8) | 46 (44.2) |
| **< 50 nmol/L** | n (%) | 64 (16.2) | 58 (55.8) |
| ***Main analysis:*** | | | |
| **Logistic regression model** | E (SE) (1.1) | 6.7 (1.6) | |
| | 95% CI (2) | [4.2 ; 10.9] | |
| | p-value (3.1) | < 0.001 | |
| ***Unadjusted analysis*** | | | |
| **Logistic regression model** | E (SE) (1.2) | 6.5 (1.6) | |
| | 95% CI (2) | [4.1 ; 10.4] | |
| | p-value (3.2) | < 0.001 | |
| **Difference between percentages** | E (SE) (1.3) | 39.5 (5.2) | |
| | 95% CI (2) | [29.3 ; 49.7] | |

*%: (n/N)*100*
*(1.1): estimate (standard error) of the adjusted odds ratio between groups for 25-OH vit D ≥ 50 nmol/L: S 06911 / S 12911*
*(2): 95% confidence interval of the estimate*
*(3.1): difference test between S 06911 and S 12911, logistic regression model with country and baseline vitamin D levels as factor: ratio likelihood test*
*(1.2): estimate (standard error) of the unadjusted odds ratio between groups for 25-OH vit D ≥ 50 nmol/L: S 06911 / S 12911*
*(3.2): difference test between S 06911 and S 12911, chi-square test: ratio likelihood test (corresponding to logistic regression in this analysis)*
*(1.3): estimate (standard error) of the difference between groups percentages for 25-OH vit D ≥ 50 nmol/L: S 06911 - S 12911*
*Note: 25-OH vitamin D values reported after a vitamin D rescue were substituted with the last value preceding the rescue (3 patients in the S 06911 and 7 patients in the S 12911).*

In the FAS, the proportion of patients with a 25-OH vitamin D level ≥ 50 nmol/L at END over M0-M3 period was higher in the S06911 group (83.8%) than in the S12911 (without vit. D) group (44.2%).
Figure 2 illustrates the correction of vitamin D insufficiency, 25-OH vit. D≥ 50 nmol/L at M3 (FAS).
Please note: 83.8 minus 44.2: **Δ=39.5%**;
Difference between percentages: At M3 (End): E (SE)=39.5 (5.2), 95% CI [29.3; 49.7]

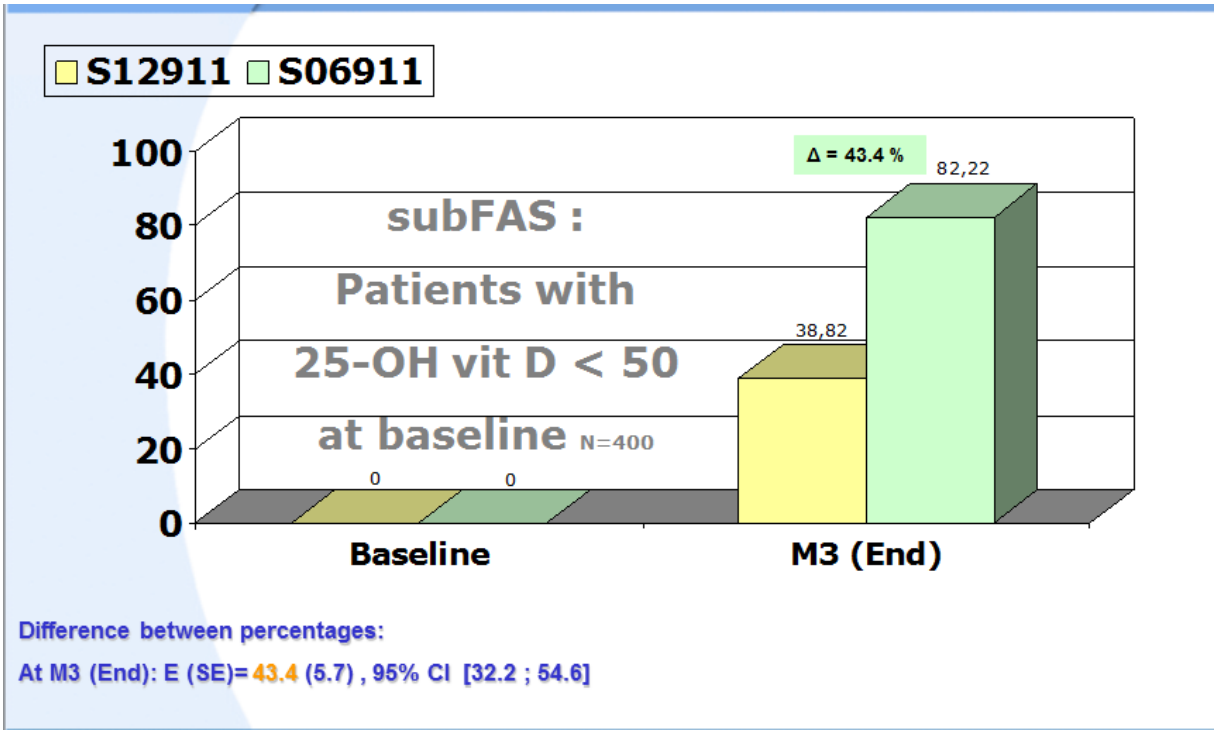
*Figure 2: Correction of vitamin D insufficiency, 25-OH vit. D≥ 50 nmol/L at M3 (FAS).*



In the Sub-FAS, where all patients had a 25-OH vitamin D level < 50 nmol/L at baseline, similar results for vitamin D insufficiency correction to those in the FAS were observed at END over the M0-M3 period: the proportion of patients with a 25-OH vitamin D level ≥ 50 nmol/L at END over M0-M3 period was higher in the S 06911 group (82.2%) than in the S 12911 (without vit. D) group (38.8%).

Correction of vitamin D insufficiency, 25-OH vit. D≥ 50 nmol/L at M3 (subFAS) is illustrated in Figure 3.
Please note: 82.2 minus 38.8: **Δ=43.4%**;
Difference between percentages: At M3 (End): E (SE)= 43.4 (6.72), 95% CI [32.2; 54.6]

*Figure 3: Correction of vitamin D insufficiency, 25-OH vit D≥ 50 nmol/L at M3 (subFAS).*
*subFAS: Patients with 25-OH vit D < 50 at baseline*




It is concluded that correction of vitamin D insufficiency to levels ≥ 50 nmol/L is demonstrated with Issarlos/Ditelos as compared with Protelos with a statistically significant between-group difference of 39.5% at M3.

- *25-OH vitamin D – 6- and 12-month results*

As shown in Figure 4 and Figure 5 the efficacy of S06911 on the correction of vitamin D is maintained until 12 months of administration. At M3, 78% of patients are responders with a level of 25-OH vitamin D≥ 50 nmol/L; at visit M12, 67% remain responder with level of ≥ 50 nmol/L.

*Figure 4: 25-OH vitamin D- Mean concentration during the M0-M6 study period in the FAS and Sub-FAS CL 06911-002*

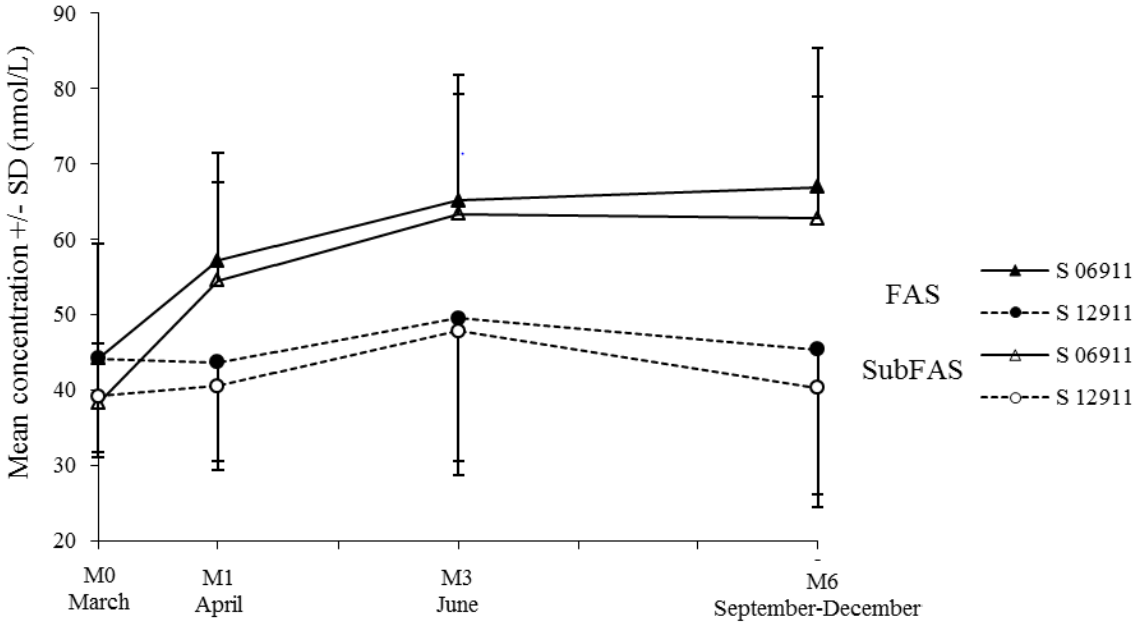
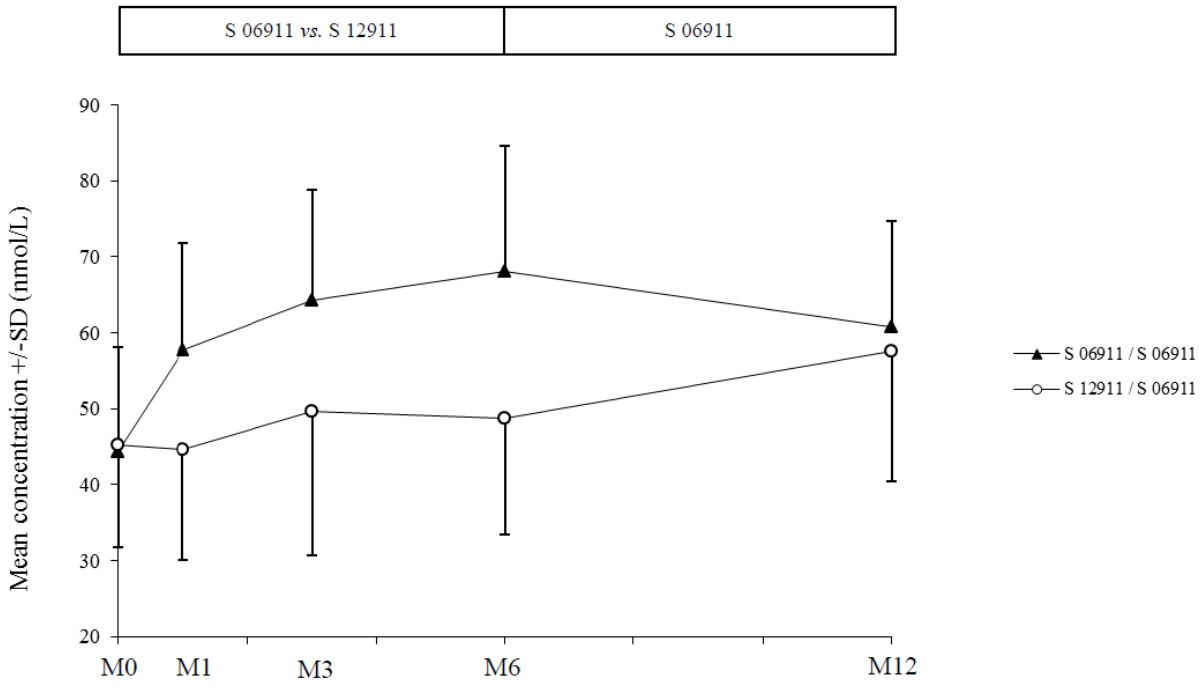



*Figure 5: 25-OH vitamin D- Mean concentration during the M0-M12 study period in the FAS extension CL 06911-002*




- *Rescue medication*

If at M1 or M3 a patient had a 25-OH vitamin D value below or equal 22.5 nmol/L, one vial of vitamin D3 200,000 IU was administered as an oral single dose (rescue medication). In these cases of vitamin D rescue, 25-OH vitamin D values following the rescue administration were not taken into account in the efficacy analysis. These excluded values were substituted by the last recorded value preceding the rescue. Three patients in the S06911 group and 7 patients in the S12911 (without vit. D) group needed a vitamin D rescue. The analysis without the substitution of post-rescue values showed that in the S12911 (without vit. D) group, the rate of patients with a 25-OH vitamin D level ≥ 50 nmol/L was

slightly higher than that in the analysis with the substitution of post-rescues values (47.4% versus 40.0%), the rate being similar in the S06911 group in the 2 analyses (86.6% versus 86.0%).

- *Secondary criteria*

*Falls and SPPB*

In the FAS, over the M0-M6 period, 16.5% of patients in the S06911 group and 20.2% of patients in the S12911 (without vit. D) group experienced one post-baseline fall. About 3% of patients in both treatment groups experienced at least 2 falls. No statistically significant between-group differences were observed on this secondary criterion.

In FAS, the SPPB score improved in both treatment groups from baseline to M3 and from baseline to M6. The relative change in SPPB score from baseline to M6 was of 3.9 ± 16.9 % in the S06911 group and 4.5 ± 16.4 % in the S12911 (without vit. D) group. No statistically significant between-group difference was observed on this secondary criterion.

According to the applicant results are interpreted as a trend to an improvement of the scores with vitamin D supplementation.

*BMD*

BMD was measured after one year of treatment in patients that participated in the extension period. Results were compared to results of the SOTI trial, a 5-year trial in postmenopausal women treated with strontium ranelate plus vitamin D suppletion.

*Table 5: BMD absolute and relative changes after 1 year of treatment with S06911 in the CL3-06911-002 study and with S 12911 (without vit. D) in the SOTI study*

| | | CL3-06911-002 (FAS extension) | | SOTI (FAS M48) |
|---|---|---|---|---|
| | | S 06911/S 06911 N=198 | S 12911/S 06911 N=52 | N=719 |
| **Lumbar spine (L1-L4)** | Baseline BMD values, g/cm$^2$ | 0.728 ± 0.075 | 0.716 ± 0.076 | 0.728 ± 0.123 |
| | 1-year BMD values, g/cm$^2$ | 0.768 ± 0.083 | 0.761 ± 0.098 | 0.772 ± 0.132 |
| | absolute change, g/cm$^2$ | 0.039 ± 0.042 | 0.045 ± 0.048 | 0.041 ± 0.061 |
| | relative change, % | 5.5 ± 5.8 | 6.2 ± 6.8 | 5.9 ± 7.4 |
| **Total hip** | Baseline BMD values, g/cm$^2$ | 0.743 ± 0.106 | 0.704 ± 0.096 | 0.686 ± 0.108 |
| | 1-year BMD values, g/cm$^2$ | 0.768 ± 0.109 | 0.741 ± 0.096 | 0.711± 0.109 |
| | absolute change, g/cm$^2$ | 0.024 ± 0.031 | 0.037 ± 0.035 | 0.021 ± 0.029 |
| | relative change, % | 3.4 ± 4.4 | 5.5 ± 5.4 | 3.2 ± 4.7 |
| **Femoral neck** | Baseline BMD values, g/cm$^2$ | 0.613 ± 0.084 | 0.584 ± 0.067 | 0.594 ± 0.087 |
| | 1-year BMD values, g/cm$^2$ | 0.637 ± 0.084 | 0.609 ± 0.071 | 0.607 ± 0.086 |
| | absolute change g/cm$^2$ | 0.024 ± 0.030 | 0.024 ± 0.023 | 0.011 ± 0.026 |
| | relative change, % | 4.1 ± 5.4 | 4.2 ± 4.0 | 2.0 ± 4.5 |

The absolute changes and relative changes in BMD from baseline value to M12 in patients of the FAS extension randomised at inclusion to S06911 (S06911/S06911) or to S12911 (without vit. D) (S12911/ S06911) were analysed. For the SOTI trial data at 48 months were used.

In both groups (S06911/S06911 and S12911/S06911) a significant increase was seen at Lumbar spine, Total hip and Femoral neck.

According to the applicant these BMD changes are comparable to those observed in the SOTI study after one year of treatment with strontium ranelate (FAS M48).

**Study CL3-06911-003**

***Description***

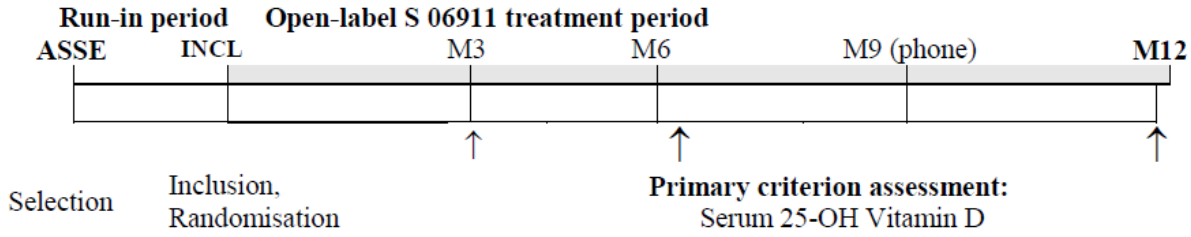
Patients with vitamin D deficiency (defined, according to many experts, as those with a 25-OH vitamin D serum level < 22.5 nmol/L) could not participate in the comparative CL3-06911-002 study for ethical reasons, as they would require vitamin D supplement. An additional one-group study (CL3-06911-003) was thus conducted in parallel to the pivotal CL3-06911-002 study to evaluate the efficacy of S06911 (strontium ranelate 2 g + cholecalciferol 1000 IU fixed combination) on the correction of vitamin D insufficiency (i.e. to achieve a 25-OH vitamin D level superior to 50 nmol/L) (see Table 1). The study design is presented in Figure 6.

In addition to S06911, calcium (1000 mg) was taken for daily supplementation, administered as 2 tablets around lunchtime.

It should be noted that if at M3 or M6 a patient had a 25-OH vitamin D value below or equal 22.5 nmol/L, rescue medication was administered as one oral single dose of vitamin D3. However, it appeared that no patient needed rescue medication.

Primary efficacy criterion is the proportion of patients having a level of serum 25-OH vitamin D ≥ 50 nmol/L over the M0-M12 period.

*Figure 6: CL3-06911-003 Study design. S 06911 (=strontium ranelate 2 g/vitamin D3 1000 IU sachet).*




***Results***

Only 19 patients were selected and included instead of the 60 patients planned. This was due to difficulties in recruitment. On protocol requirement, all patients had baseline 25-OH vitamin D concentration ≤ 22.5 nmol/L.

All patients were osteoporotic (BMD T-score ≤ 2.5 at at least one site). One man and 18 postmenopausal women were included. Baseline characteristics as compared with study CL3-06911-002 are summarized in Table 2.

At baseline in the CL3-06911-003 study, mean age was 65.5 years, on the 19 patients included, 18 were women who were all postmenopausal (time since last menses from 2 to 34 years) and all patients were ambulatory. 42.1% of the patients had taken previously at least one treatment for osteoporosis and/or interfering with bone metabolism. Among those patients, 5 were taking treatments containing vitamin D.

The disposition of patients and the definition of the analysis sets are described in Table 6.

*Table 6: Disposition of patients and definition of the analysis sets in CL3-06911-003*

| Patients disposition | |
|---|---|
| | **All** |
| **Randomised** | 19 |
| **Withdrawn** | 3 |
| Adverse event | 1 |
| Non-medical reason | 2 |
| **Completed** | 16 |
| **Efficacy analysis sets** | |
| FAS: based on intention-to-treat principle, all included patients who had taken at least one dose of study treatment and who had at least one post-baseline (M3 or M6 or M12) value of 25-OH vitamin D [N = 18]. | |

- *Efficacy*

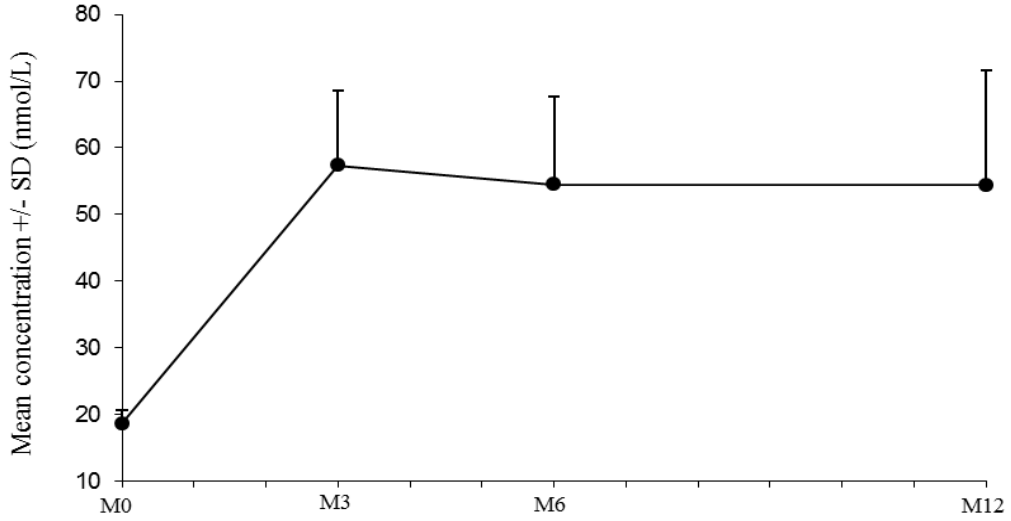
In this study, no patient required a vitamin D rescue.

- *25-OH vitamin D*

Out of the 18 patients of the FAS, 14, 11 and 11 patients had a serum 25-OH vitamin D ≥ 50 nmol/L at M3, M6 and M12, respectively. In the FAS, the proportion of patients with a 25-OH vitamin D level ≥ 50 nmol/L at END over M0-M12 period was of 66.7% (95% CI [0.41; 0.87]).
The mean increase in 25-OH vitamin D serum concentration from baseline to END was 35.7 ± 16.7 nmol/L.

Figure 7 shows the profile of 25-OH vitamin D mean concentration during the study in the FAS.

*Figure 7: 25-OH vitamin D- Mean concentration during the M0-M12 period-FAS CL3-06911-003*




Please note: 18 patients at baseline and M3, 16 patients at M6 and M12

- *Falls and SPPB*

Out of the 18 assessed patients over M3-M12, 6 patients experienced at least one emergent fall (including 2 patients with 2 falls).

There was only a trend to improvement in SPPB total score from baseline to last post-baseline value over M0-M12

## *Clinical studies in special populations*

N/A

## *Analysis performed across trials (pooled analyses AND meta-analysis)*

N/A

## *Supportive study(ies)*

N/A

## *Discussion on clinical efficacy*

**Design and conduct of clinical studies**

The applicant has provided the data from two multi-centre international phase III clinical studies to support the indication of treatment of osteoporosis in men and postmenopausal women at risk of vitamin D insufficiency.

The claimed indication is “first line”.

Study CL3-06911-002 was conducted in 413 patients with osteoporosis and vitamin D insufficiency (i.e. > 22.5 mmol/L and < 50 nmol/L). The inclusion of ~20% of subjects with baseline serum vitamin D ≥50 nmol/L is not supported from an efficacy perspective in light of the intended primary endpoint. However, this mainly renders the SubFAS being considered the most relevant analysis set for assessment, and the majority of relevant analyses on the SubFAS is already available. Patients with a BMI ≥30 kg/m2 were not included. However, the Applicant’s reference to the SmPC, already stating that “additional supplementation with Vitamin D should be considered on an individual basis” is considered valid and it is agreed that no exclusion of obese patients from the target population is necessary.

The study consisted of a main period of 6 months and an extension period to 12 months. In the main period patients were treated with S06911 (strontium + vit. D3) or S12911 (without vit. D) (strontium alone), while in the extension period all patients received S06911. The extension was conducted in a subgroup of patients belonging to 5 predefined countries. The selection criteria for these countries are acceptable.

There is a large discrepancy in gender: 90% was female. However it does not seem very probable that these differences would have impact on the study outcome.

Study CL3-06911-003 was conducted in patients with osteoporosis and vitamin D deficiency (i e ≤ 22.5 nmol/L). The intended number of participants was 60, whereas due to difficulties in recruitment only 19 were included. The applicant was requested to explain the difficulties in recruitment and the effect on study outcome. In response the applicant proposed to update section 5.1 of the SmPC to indicate that these results are insufficient to establish the efficacy of Ditelos/Issarlos in the correction of vitamin D deficiency (25-hydroxyvitamin D serum level ≤ 22.5 nmol/l).

The FDC contains 2 g strontium ranelate and 1000 IU vitamin D3. The dose of 2 g strontium ranelate daily is in accordance with the previously approved treatment of preventing osteoporosis (Protelos). The adequacy of dose of vitamin D was very recently specifically addressed (Bischoff-Ferrari. NEJM 2012; 367: 40-49). It was concluded that fracture risk was reduced only among persons who were assigned to receive doses of 800 IU per day or higher. Such an intake is consistent with the guidelines

for adults that have been issued by the Endocrine Society (1500 to 2000 IU per day)[1]. Given the congruence of the findings of the meta-analysis of Bischoff- Ferrari et al. with the guidelines from the Endocrine Society the dose of 1000 IU is at the lower end of up to date dosing recommendations for the concerned population.

It is assumed that for patients with baseline levels below 50nmol/L, surpassing this sufficiency threshold will convey clinical benefit. It cannot be excluded, however, that an optimal target range lies beyond that concentration, particularly for a population at increased risk for fracture. In the current situation, with regards to the initial concern raised, 50nmol/L can be accepted as a conservative, yet clinically relevant threshold for distinguishing responders from non-responders to Ditelos treatment.

The rationale for the chosen dosing (1000 mg) of calcium is acceptable. However, in order to prevent misunderstanding the (required) intake of calcium at another time of the day than the intake of strontium ranelate should be more explicitly indicated in the SmPC.

The Applicant proposes to update section 4.2 of the SmPC of Ditelos/Issarlos to be in line with that of Protelos/Osseor for calcium supplementation (see sections 4.5. and 5.2).

**Efficacy data and additional analyses**

In study CL3-06911-002 correction of vitamin D insufficiency to levels ≥ 50 nmol/L has been demonstrated with S06911 as compared with S12911 (without vit. D) with a statistically significant between-group difference of 39.5% at M3. The efficacy of S06911 is maintained until 12 months of administration. At M3, 78% of patients are responders with a level of 25-OH vitamin D≥ 50 nmol/L; at visit M12, 67% remain responder with level of ≥ 50 nmol/L. This implicates that 22% and 33% are non-responders at M3 and M12 respectively.

A rather high percentage of patients was withdrawn (15.4%).The applicant has discussed the possible consequences for the outcome of the study and additional analyses confirm the efficacy of S06911 over S12911.

Comparing M0 to M12 values, vitamin D levels in patients with baseline levels ≥50 nmol/L remained roughly stable in both S06911/S06911 and S12911/S06911 cohorts. Patients with higher 25-OH vitamin D baseline levels (i.e. ≥50nmol/L in this case) are likely to show less response to additional vitamin D intake than patients with lower levels. This is acknowledged as a likely explanation for the modest increase in vitamin D concentration over the observation period in these patients.

Regarding clinical relevance of these findings, the uncertainties surrounding the 50 nmol/L threshold have already been discussed above. For the alternative threshold of 75 nmol/L (secondary analysis) no data were provided for the SubFAS and the applicant was asked to provide these. The logistic regression analyses show a statistically significant and pronounced treatment effect. The effects are quite comparable to those observed in the FAS. The treatment effect is shown to be robust, though slightly lower in the SubFAS.

For matters of generalizability and in light of the impact of age on the vitamin D household, the applicant was asked to perform analyses for the primary efficacy variable in study participants ≥65 and ≥75 years of age from the pivotal trial. The obtained differences between S06911 and S12911 responder rates did not show a consistent age-related pattern (most likely due to a very high placebo effect in the ≥65 subgroup) which does not support the clinical relevance of the investigated subgroups.

[1] Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011;96:1911-30. [Erratum, J Clin Endocrinol Metab 2011;96:3908.]

A sensitivity analysis has been provided for absolute change from baseline in terms of serum 25-OH vitamin D levels including season/calendar month of inclusion (M0 visit) as an additional covariable in the ANCOVA. The additional results provided show that the previous estimate for the treatment effect was not biased by season/month of inclusion/assessment.

A primary logistic regression analysis has been provided including all patients treated, i.e. where patients with no post-baseline value are treated as failures. This was done for the SubFAS, as well as for the FAS. The additional analyses confirm significance of the treatment effect.

After inclusion in study CL3-06911-002 10 patients had at least one vitamin D rescue treatment. Substitution of post-rescue values with the pre-rescue value will lower the proportion of patients with a 25-OH vitamin D value ≥ 50 nmol/l. Most of the rescue treatment was used in the S12911 (without vit D) group, 7 patients (out of 104; 6.7%) versus 3 patients (out of 394; 0.7%) in the S06911 group. Therefore, this procedure favours the outcome for the study drug. In a secondary analysis, not substituting post-rescue values, the proportion of patients with 25-OH vitamin D value ≥ 50 nmol/l was higher in the S12911 (without vit. D) group (47.4% versus 40.0% with substitution), while the proportion in the S06911 group was similar (86.6% versus 86.0%). This means that most, if not all, patients with rescue medication had post-rescue values ≥ 50 nmol/l. These two analyses constitute a worst-case (i.e. rescue means treatment failure) and a best-case (rescue means treatment success) scenario. In both scenarios correction of vitamin D insufficiency is demonstrated in the S 06911 group, compared with the S12911 (without vit. D) group. The use of rescue medication does not have a major influence on the results. This is considered acceptable.

In the CL3-06911-002, BMD was measured after the extension period. In both groups there was a positive effect on BMD. According to the applicant, results were comparable with the SOTI trial. However, during the study main period 37.5% of the patients previously took treatments containing vitamin D. In the CL3-06911-002 study extension period, more than half of the patients (57.6%) took previously at least one treatment for osteoporosis and/or interfering with bone metabolism and treatments containing vitamin D. However, randomization guarantees comparable groups at inclusion. The potential effect of the possibly confounding factors is unlikely to have interfered significantly with study outcomes.

The claimed indication for Issarlos/Ditelos is in line with the indication of Protelos/Osseor, as was requested at D120. It should however be realised that as a result of identified cardiovascular risks related to the use of strontium ranelate currently an Art.20 referral for Protelos/Osseor (EMEA/H/A-20/1371). The outcome of this referral will have implications for this FDC.

In study CL3-06911-003, the absolute increase in serum vitamin D is considerably higher than observed in the pivotal trial CL3-06911-002. The difference is noteworthy in light of the concerns regarding the absolute effect size and the applicant was asked to discuss the results of the two trials in comparison. Non-linearity of cholecalciferol dose-response has been documented in the literature (Heaney et al. 2012). The Applicant's explanation that the differing plasma levels at inclusion have resulted in differing steepness and thus magnitude of 25-OH Vit. D increase between the two studies is accepted.

## *Conclusions on clinical efficacy*

A correction of vitamin D insufficiency (levels < 50 nmol/L) to levels ≥50 nmol/L has been demonstrated with Issarlos/Ditelos (S06911) as compared with Protelos (S12911 (without vit. D)) and was maintained until M12. However, 22% and 33% are non-responders at M3 and M12 respectively.

Correction of vitamin D deficiency (levels ≤ 22.5 nmol/L) has not been demonstrated due to the limited size of the study.

## *Clinical safety*

## *Patient exposure*

The clinical safety assessment in this application focuses on the CL3-06911-002 and the CL-06911-003 studies.

Table 7 indicates the analysis sets (i e the number of patients in the different sets for the safety analyses), treatment duration in the different sets and the compliance.

*Table 7: analysis sets, treatment duration and compliance.*

| Study | Studied period | Analysis sets | S 06911 | S 12911 | All | Treatment duration (days) | Compliance (%) |
|---|---|---|---|---|---|---|---|
| | | | n | n | n | Mean ± SD | Mean ± SD |
| CL3-002 | M0-M6 | Safety Set | 407 | 105 | 512 | 164.3 ± 45.9 | 90.4 ± 17.4 |
| CL3-002 | M0-12 | Safety Set 1 extension | 240 | - | 240 | 318.6 ± 109.2 | 87.2 ± 19.1 |
| | *M6-M12* | *Safety Set 2 extension* | *203+53** | - | *256* | *179.6 ± 22.8* | *92.1 ± 14.3* |
| CL3-003 | M0-12 | Safety Set | 19 | | | 331.4 ± 81.3 | 85.8 ± 15.5 |

**: S 06911/S 06911 + S 12911 /S 06911 groups: all patients had switched to S 06911 at M6*

The CL3-06911-002 study population comprised 518 randomised patients (recruited in 13 countries), of whom 6 failed to take any study treatment and were thus excluded from the Safety Set (SS), which consisted of 512 patients: 407 patients in the S06911 group and 105 in the S12911 (without vit. D) group.

The safety analysis of the M0-M12 period of the CL3-06911-002 study was performed in the Safety Set 1 (SS1), which consisted of the 240 patients, who had taken at least one dose of S06911 over M0-M12. Four of the 244 patients included in participating countries in the S06911 group did not take any study treatment and were thus excluded from the SS1. Among the 240 patients of the SS1, 37 withdrew before M6, thus only 203 actually participated in the extension period.

In addition, the safety analysis over the extension period M6-M12 is described in the Safety Set 2 (SS2). However only data of 53 patients from the S12911/S 06911 group are presented.

In the CL3-06911-002 study, the mean overall treatment duration was 164.3 ± 45.9 days (about 5.5 months) over M0-M6 and 318.6 ± 109.2 days (about 11 months) over M0-M12. In the CL3-06911-003 study, the mean treatment duration was 331.4 ± 81.3 days (about 11 months, as for the CL3-06911-002 study).

## *Adverse events*

The overall summary of safety results over M0-M6 and M0-12 are given in Table 8 and Table 9. It can be concluded that the safety results were globally similar in the two treatment groups.

*Table 8: Safety results M0-M6 CL3-06911-002 study*

| | | S 06911 (N = 407) | S 12911 (N = 105) |
|---|---|---|---|
| **Patients having reported :** | | | |
| at least one **EAE** | n (%) | 275 (67.6) | 73 (69.5) |
| at least one severe **EAE** | n (%) | 27 (6.6) | 7 (6.7) |
| at least one **treatment-related EAE** | n (%) | 59 (14.5) | 16 (15.2) |
| at least one **serious EAE** (including death) | n (%) | 21 (5.2) | 9 (8.6) |
| at least one **treatment-related serious** EAE | n (%) | - | 1 (1.0) |
| Patients **withdrawn** from treatment **due to an adverse event** | n (%) | 39 (9.6) | 7 (6.7) |
| Patients who **died** | n (%) | 1 (0.2) | - |

*N: total number of exposed patients in the considered treatment group; n: number of patients affected; %: n/N x 100*

*Table 9: Safety results M0-M12 in CL3-06911-002 (SS 1) and CL3-06911-003 studies*

| | | CL3-06911-002 S 06911/S 06911 (N = 240) | CL3-06911-003 S 06911 (N = 19) |
|---|---|---|---|
| **Patients having reported :** | | | |
| at least one **EAE** | n (%) | 196 (81.7) | 15 (78.9) |
| at least one severe **EAE** | n (%) | 24 (10.0) | 1 (5.3) |
| at least one **treatment-related EAE** | n (%) | 49 (20.4) | 2 (10.5) |
| at least one **serious EAE** (including death) | n (%) | 21 (8.8) | 1 (5.3) |
| at least one **treatment-related serious** EAE | n (%) | - | - |
| Patients **withdrawn** from treatment **due to an adverse event** | n (%) | 34 (14.2) | 1 (5.3) |
| Patients who **died** | n (%) | - | - |

*N: total number of exposed patients in the considered treatment group; n: number of patients affected; %: n/N x 100*

In addition, safety data of the 53 patients from S 06911/S 06911+ S 12911/S 06911 groups were presented: all patients had switched to S 06911 at M6, 30 patients reported at least one EAE (56.6%) including 2 patients with a treatment-related EAE, 2 with a serious EAE, of which one was a severe EAE, and one patient with an EAE leading to study withdrawal.

**Analysis of Emergent Adverse Events by System Organ Class**

For the main period (M0-M6) EAEs by system organ class (SOC) are presented in Table 10.

The most frequently affected SOC were:

- Gastrointestinal disorders (18.2% in the S 06911 group and 21.9% in the S 12911 (without vit. D) group);
- Injury, poisoning and procedural complications (17.2% and 22.9%, respectively;
- Infections and infestations (16.5% versus 9.5%, respectively). However, unbalanced incidence rates must be interpreted with caution given the small sample size in the S 12911 (without vit. D) group.
- Musculoskeletal and connective tissue disorders (16.2% and 21.0%, respectively).
- Blood and lymphatic disorders were more numerous in the S 06911 group than in the S 12911 (without vit. D) group: 13 patients were affected (3.2%) versus one patient i.e. 1.0% (who reported monocytopenia), respectively.

Overall analysis by system organ classes showed a comparable safety profile/pattern in patients treated with S 06911 and those treated with S 12911 (without vit. D).

Over M6-M12 in study CL3-06911-002, the main SOCs were similar as those described over M0-M6. The main SOC affected over M0-M12 in the CL3-06911-003 study were similar to those of the CL3-06911-002 study. Also in the 53 patients of SS2 the SOCs affected were similar.

*Table 10: Emergent adverse events over M0-M6 in the CL3-06911-002 study by System Organ Classes- Safety Set*

| System organ class | S 06911 (N = 407) | | | S 12911 (N = 105) | | |
|---|---|---|---|---|---|---|
| | NEAE | n | % | NEAE | n | % |
| Gastrointestinal disorders | 86 | 74 | 18.2 | 31 | 23 | 21.9 |
| Injury, poisoning and procedural complications | 114 | 70 | 17.2 | 39 | 24 | 22.9 |
| Infections and infestations | 86 | 67 | 16.5 | 13 | 10 | 9.5 |
| Musculoskeletal and connective tissue disorders | 78 | 66 | 16.2 | 24 | 22 | 21.0 |
| Nervous system disorders | 50 | 39 | 9.6 | 11 | 8 | 7.6 |
| Renal and urinary disorders | 35 | 34 | 8.4 | 8 | 8 | 7.6 |
| Skin and subcutaneous tissue disorders | 34 | 32 | 7.9 | 6 | 6 | 5.7 |
| Vascular disorders | 35 | 32 | 7.9 | 7 | 6 | 5.7 |
| Investigations | 30 | 28 | 6.9 | 19 | 15 | 14.3 |
| General disorders and administration site conditions | 18 | 15 | 3.7 | 4 | 3 | 2.9 |
| Respiratory, thoracic and mediastinal disorders | 15 | 15 | 3.7 | 3 | 3 | 2.9 |
| Ear and labyrinth disorders | 14 | 13 | 3.2 | 3 | 3 | 2.9 |
| Blood and lymphatic system disorders | 14 | 13 | 3.2 | 1 | 1 | 1.0 |
| Cardiac disorders | 14 | 12 | 2.9 | 3 | 2 | 1.9 |
| Eye disorders | 12 | 10 | 2.5 | 4 | 4 | 3.8 |
| Metabolism and nutrition disorders | 9 | 9 | 2.2 | 5 | 5 | 4.8 |
| Hepatobiliary disorders | 7 | 7 | 1.7 | 3 | 3 | 2.9 |
| Psychiatric disorders | 7 | 6 | 1.5 | 2 | 2 | 1.9 |
| Surgical and medical procedures | 4 | 4 | 1.0 | 0 | 0 | 0.0 |
| Endocrine disorders | 3 | 3 | 0.7 | 1 | 1 | 1.0 |
| Reproductive system and breast disorders | 3 | 3 | 0.7 | 1 | 1 | 1.0 |
| Neoplasms benign. malignant and unspecified (incl cysts and polyps) | 2 | 2 | 0.5 | 1 | 1 | 1.0 |
| **ALL** | **670** | **275** | **67.6** | **189** | **73** | **69.5** |

*NEAE: number of emergent adverse events*
*N: total number of exposed patients in the considered treatment group*
*n: number of patients affected*
*%: n/N x 100*

**Analysis of most frequent emergent Adverse Events**

Most frequently reported emergent adverse events in at least 1% of the patients in the S 06911 group over the M0-M6 period are presented in Table 11.

*Table 11: Most frequently reported emergent adverse events (at least 1% of patients in the S 06911 group) during the 6-month study period*

| Adverse event (Preferred Term) | S 06911 (N = 407) | | S 12911 (N = 105) | |
|---|---|---|---|---|
| | n | % | n | % |
| **ALL** | **275** | **67.6** | **73** | **69.5** |
| Fall | 57 | 14.0 | 21 | 20.0 |
| Hypercalciuria | 28 | 6.9 | 3 | 2.9 |
| Diarrhoea | 19 | 4.7 | 7 | 6.7 |
| Hypertension | 18 | 4.4 | 4 | 3.8 |
| Arthralgia | 14 | 3.4 | 2 | 1.9 |
| Nausea | 11 | 2.7 | 3 | 2.9 |
| Headache | 11 | 2.7 | 1 | 1.0 |
| Bronchitis | 10 | 2.5 | - | - |
| Vertigo | 10 | 2.5 | 2 | 1.9 |
| Nasopharyngitis | 9 | 2.2 | 4 | 3.8 |
| Back pain | 9 | 2.2 | 4 | 3.8 |
| Contusion | 9 | 2.2 | - | - |
| Osteoarthritis | 8 | 2.0 | 4 | 3.8 |
| Muscle spasms | 8 | 2.0 | 3 | 2.9 |
| Dyspepsia | 7 | 1.7 | 3 | 2.9 |
| Pain in extremity | 7 | 1.7 | 1 | 1.0 |
| Musculoskeletal pain | 7 | 1.7 | - | - |
| Blood CPK increased | 6 | 1.5 | 3 | 2.9 |
| Abdominal pain upper | 6 | 1.5 | 1 | 1.0 |
| Joint sprain | 6 | 1.5 | 1 | 1.0 |
| Pruritus | 6 | 1.5 | 1 | 1.0 |
| Abdominal pain | 5 | 1.2 | 2 | 1.9 |
| Respiratory tract infection viral | 5 | 1.2 | - | - |
| Oedema peripheral | 5 | 1.2 | 3 | 2.9 |
| Dizziness | 5 | 1.2 | 1 | 1.0 |
| Upper respiratory tract infection | 5 | 1.2 | 1 | 1.0 |
| Gamma-glutamyltransferase increased | 4 | 1.0 | 3 | 2.9 |
| Constipation | 4 | 1.0 | 1 | 1.0 |
| Gastritis | 4 | 1.0 | 1 | 1.0 |
| Cystitis | 4 | 1.0 | - | - |
| Asthma | 4 | 1.0 | - | - |
| Dry mouth | 4 | 1.0 | - | - |
| Sciatica | 4 | 1.0 | - | - |
| Transient ischaemic attack | 4 | 1.0 | - | - |
| Urinary tract infection | 4 | 1.0 | - | - |

*NEAE: number of emergent adverse events*
*N: total number of exposed patients in the considered treatment group*
*n: number of affected patients*
*%: n/N x 100*

The most commonly reported emergent adverse events (> 3% of the patients in either group for each event) were:

- Fall (15.2%): 14.0% of the patients in the S 06911 group and 20.0% in the S 12911 (without vit. D) group.
- Hypercalciuria (6.1%): 6.9% of the patients and 2.9%, respectively.
- Diarrhoea (5.1%): 4.7% of the patients and 6.7%, respectively.

- Hypertension (4.3%): 4.4% of the patients and 3.8%, respectively.
- Arthralgia (3.1%): 3.4% of the patients and 1.9%, respectively.

An excess of hypercalciuria was reported in the S 06911 group (28 patients: 6.9%) compared to the S 12911 (without vit. D) group in which 3 patients (2.9%) were affected. In addition, urine calcium increased was reported in 3 patients (0.7%) in the S 06911 group versus one patient in the S 12911 (without vit. D) group (1.0%).

Most frequently reported emergent adverse events over M0-M12 in the CL3-06911-002 (SS1) and the CL3-06911-003 studies were similar to those of M0-M6.

## *Serious adverse events and deaths*

One patient died during the CL3-06911-002 study in the S 06911 group. The death of this 78-year-old patient was due to a fatal congestive heart failure. The patient's medical history included a cardiac medical history for more than 32 years with arterial hypertension, atrial fibrillation, coronary heart disease, mitral valve replacement, aortic valve replacement and heart failure. This death was considered as not related to the study drug by the investigator.

During M0-M6 severe emergent adverse events were reported with a similar frequency in the two treatment groups: 27 patients (6.6%) in the S 06911 group and 7 patients (6.7%) in the S 12911 (without vit. D) group. Main SOCs affected were nervous system disorders (1.5% versus 1.9%, respectively) mainly transient ischaemic attack, and injury poisoning and procedural complications (1.0% versus none, respectively), mainly fall. The severe events reported in more than one patient were: Transient ischaemic attack (4 patients (1%) in the S 06911 group only); Fall (4 patients (1%) only in the S 06911 group); Hypertension (3 patients (0.7%) only in the S 06911 group) and Vertigo (2 patients (0.5%) in the S 06911 group and 1 patient (1.0%) in the S 12911 (without vit. D) group).

The nature and rate of severe events was similar over 6 months and 12 months of treatment in patients treated with S 06911 and in those treated with S 12911 (without vit. D).

## *Laboratory findings*

No clinically relevant changes over times or differences between groups were observed for vital signs, i.e. weight, heart rate and blood pressure over the 6 months double blind treatment period of the CL3-06911-002 study and the 12-month open period of the CL3-06911-002 and 003 studies.

The changes in laboratory findings (increase in CPK and creatinine, decrease in eGFR) were similar in patients treated with S06911 and those treated with S 12911 (without vit. D). Haematology and biochemistry markers did not show relevant changes in time between groups, except for phosphocalcic parameters.

***Phosphocalcic parameters***

In the 6-month double-blind period a decrease in mean blood calcium: -0.12 ± 0.10 mmol/L in the S 06911 group and -0.13 ± 0.09 mmol/L in the S 12911 (without vit. D) group, and an increase in blood phosphorus: 0.14 ± 0.18 mmol/L and 0.10 ± 0.18 mmol/L, respectively, were measured (Figure 8).

Low values for blood calcium (<2.23 mmol/L) were seen in 20.0% in the S 06911 group and 24.8% in the S 12911 (without vit. D) group.

High values for blood phosphorus were measured in 45.3% and 53.5%, respectively. High emergent PCSA values were reported in 9.5% and 3.0%, respectively.

High emergent PCSA values for blood calcium were reported in 3 patients (0.8%) in the S 06911 group and 1 patient (1.0%) in the S 12911 (without vit. D) group.

A similar pattern was observed in the 12 month open period of the CL3-06911-002 and CL3-06911-003 studies.

It is concluded that a decrease in mean blood calcium and an increase in mean blood phosphorus were observed similarly with S 06911 and S 12911 (without vit. D).

The urinary calcium/creatinine ratio increased in the S 06911 group from 0.43 ± 0.26 to 0.64 ± 0.39. The mean increase was higher in the S 06911 group than in the S 12911 (without vit. D) group (+0.2 ± 0.3 and +0.1 ± 0.1, respectively).

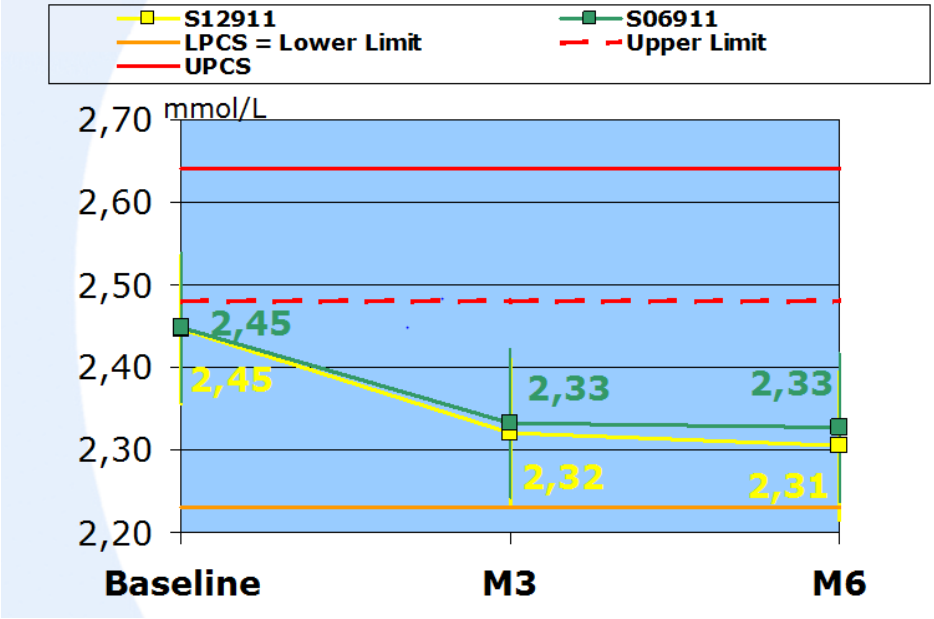
High emergent out-of-reference range values for urinary calcium/creatinine ratio were detected in 44 patients (11.6%) in the S 06911 group and 9 patients (9.0%) in the S 12911 (without vit. D) group.

High emergent out-of-reference range values for urinary spot calcium affected 109 patients (28.7%) and 22 patients (22.0%), respectively.

It is concluded that an increase in urinary calcium excretion (reflected by urinary calcium/creatine ratio and spot urinary calcium) was observed with S 06911 treatment. Potentially clinically significant values were sparse and were not associated with any symptoms potentially related to vitamin D toxicity.

None of the high urinary calcium levels were associated with any concomitant symptoms of vitamin D intoxication, in particular no concomitant hypercalcaemia was reported as adverse event or as abnormal laboratory value, and no renal lithiasis or nephrocalcinosis was reported on S06911.

*Figure 8: Mean serum calcium levels over time CL3-06911-002*




***Endocrinology parameters***

25-OH Vitamin D, 1.25(OH)2 vitamin D and intact parathyroid hormone (iPTH): as expected with S 06911, 1,25 (OH)2 vitamin D increased and PTH decreased. Only few patients reached a value of 25-OH vitamin D ≥ 125 nmol/L, considered for some experts as the upper limit that is likely to pose no risk. No clinical signs or symptoms linked to hypervitaminosis D were reported in these patients.

***Haematology***

In the 6-month double blind period of the CL3-06911-002 study, nor in the 12-month open period of the CL3-06911-002 study, nor in the CL3-06911-003 study relevant changes in haematology parameters were observed with S 06911.

## *Safety in special populations*

N/A

### *Immunological events*

N/A

### *Safety related to drug-drug interactions and other interactions*

N/A

### *Discontinuation due to AES*

In the 6-month double-blind period premature discontinuation due to emergent adverse events affected 39 patients (9.6%) in the S 06911 group and 7 patients (6.7%) in the S 12911 (without vit. D) group: mainly gastrointestinal disorders (2.9% and 1.0%, respectively) and skin and subcutaneous disorders (2.0% and 1.0%, respectively).

Overall it may be concluded that all emergent adverse events leading to premature treatment discontinuation were mostly non-serious adverse events listed with strontium ranelate and no withdrawal linked to a vitamin D-related event was reported.

### *Post marketing experience*

N/A

### *Discussion on clinical safety*

In the 6-month double-blind period of the CL3-002 study, the overall incidence of emergent adverse events was similar in patients treated with S06911 and in those treated with S12911 (without vit. D). Serious adverse events were similarly reported in 5.2% in the S06911 versus 8.6% in the S12911 (without vit. D) group.

No VTE or hypersensitivity syndromes were reported. One patient died while on S06911 from fatal congestive heart failure, 3 weeks after the first study drug intake. The patient had a history of coronary heart disease.

The most frequent biochemical abnormalities concerned increase in CPK without clinical relevance, and changes in phosphocalcic homeostasis parameters: decrease in blood calcium and increase in blood phosphorus. These changes are attributable to the mechanism of action of strontium ranelate and were observed in previous studies. They occurred with a similar or even lower frequency with S06911 than with S12911 (without vit. D).

Slight between-group differences were observed for high emergent out-of the reference range values of urinary calcium/creatinine ratio, which were reported with a higher incidence with S06911 (11.6%) than with S12911 (9.0%). The analysis of the urinary calcium/creatinine ratio with the Upper PCSA limit used in SOTI and TROPOS studies (i.e. > 3.36) shows that one patient in the S 06911 group had a high PCSA value at M6 (4.4). No other urinary calcium/creatinine ratio above 3.36 was reported in studies with S 06911. High emergent out-of the reference range values for blood calcium were similarly reported in both groups: 3.2% and 3.0%, respectively. None of these biochemical abnormalities were associated with any clinical symptoms. The applicant proposes to include ‘hypercalciuria’ in section 4.8 of the SmPC, this is endorsed.

Safety results obtained over a 12-month treatment period with S 06911 were comparable to those observed over the first 6 months.

The proportion of patients treated with analgesics at inclusion was 8% in the S06911 and 11.4% in the S12911 group. Both groups showed an increase in treatment with analgesics during the study, namely 15% and 18% respectively. The MAH has provided a detailed listing of the indications leading to analgesic treatment. Types and frequencies of the events requiring an analgesic treatment match the events expected in this study population. No unexpected new events requiring analgesic treatment were detected.

### *Conclusions on clinical safety*

The safety profile of strontium ranelate combined to vitamin D3 (S 06911) was in accordance with that expected with strontium ranelate alone (S 12911 (without vit. D)).

A decrease in mean blood calcium and an increase in mean blood phosphorus were observed similarly with S 6911 and S 12911 (without vit. D). These changes are expected according to the mechanism of action of strontium ranelate through its effect via the calcium-sensing receptor.

A higher incidence of hypercalciuria as adverse event was observed in patients treated with strontium ranelate/cholecalciferol compared to strontium ranelate alone. This has been adequately reflected in the SmPC.

### *Pharmacovigilance system*

The applicant has provided documents that set out a detailed description of the system of pharmacovigilance for Les Laboratoires Servier version 2 dated 10 April 2012. The Rapporteur considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

### *Risk management plan*

The applicant submitted an updated Risk Management Plan according to GVP Module V for strontium ranelate/vitamin D3 (version 01.1, dated 21 August 2013) in response to the D120 LoQ.

The MAH added serious cardiac disorders including myocardial infarction, as requested. Furthermore, the study protocols have been updated to study this safety concern.

A prescription survey and a new drug utilization study are proposed to assess the effectiveness of risk minimisation measures for VTE, DRESS and serious cardiac effects. These studies should be included in the RMP as pharmacovigilance activities rather than additional risk minimisation measures. The relevant sections of the RMP should be updated.

Further reference is made to the separate PRAC RMP assessment report.

## 4. ORPHAN MEDICINAL PRODUCTS

N/A

# 5. BENEFIT RISK ASSESSMENT

## *Benefits*

## *Beneficial effects*

S06911 is a fixed combination of strontium ranelate 2 g with a dose of 1000 IU of cholecalciferol. It is intended to provide -as a single oral intake (sachet) per day- an efficient anti-osteoporotic treatment and an adequate level of vitamin D supplementation for osteoporotic patients. Strontium ranelate has a marketing authorization for the treatment of osteoporosis in men and postmenopausal women.

In a pharmacokinetic study it had been shown that after administration of a fixed dose combination of strontium ranelate and vitamin D3 the pharmacokinetic profiles of strontium and vitamin D3 did not change in a clinically significant way as compared with administration of the two components separately.

The applicant has provided the data from two multi-centre international phase III clinical studies to support the indication of treatment of osteoporosis in men and postmenopausal women at risk of vitamin D insufficiency.

**Study CL3-06911-002** was conducted in 413 patients with osteoporosis and vitamin D insufficiency (i.e. < 50 nmol/L). This study consisted of a main period of 6 months and an extension period to 12 months. In the main period patients were treated with S06911 (Strontium + vit D3) or S12911 (Strontium alone), while in the extension period all patients received S06911. A correction of vitamin D insufficiency to levels ≥ 50 nmol/L has been demonstrated with a statistically significant between group difference of 39.5% at M3. The efficacy was maintained until 12 months of administration. At M3, 78% of patients were responders with a level of 25-OH vitamin D ≥ 50 nmol/L; at visit M12, 67% remained responder with level of ≥ 50 nmol/L.

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

A descriptive pharmacokinetic study in twelve subjects suggested that addition of a cyclodextrin used as a stabilizer agent for cholecalciferol, decreased the rate and extent of exposure of this compound in a significant way by 50%. In response to a major objection, this interaction of Vitamin D3 and cyclodextrin was further investigated with a new study in more volunteers that was adequately designed to minimize the variability; the study was performed in 54 subjects and its design was considered more adequate. The results of this second study showed that the ratios of the mean pharmacokinetic variables are within the acceptance range as used for bioequivalence and therefore an interaction between Vitamin D and cyclodextrin was not considered clinically significant.

No new specific pharmacodynamic studies have been conducted for this application. However, the applicant has described the extensive documentation on the pharmacodynamic properties of both monocomponents.

At the moment, there is no scientific consensus on optimal serum vitamin D levels or on the optimal vitamin D substitution dose with regard to fracture prevention. Recent literature suggests that even higher target levels than those chosen by the company to define vitamin D-deficiency, -insufficiency and -sufficiency and higher dosing recommendations for vitamin D substitution may be of greater benefit. Therefore, it is unclear if the thresholds applied to classify subjects and define responder variables in the clinical trials are the clinically most relevant ones.

In **Study CL3-06911-003** the intended number of participants was 60, whereas due to difficulties in recruitment only 19 were included. Due to the limited number of patients included the available data

are insufficient to establish the efficacy of Issarlos/Ditelos in the correction of vitamin D deficiency (25-hydroxyvitamin D serum level ≤ 22.5 nmol/l).

## *Risks*

## *Unfavourable effects*

In the 6-month double-blind period of the **CL3-06911-002 study**, the overall incidence of emergent adverse events was similar in patients treated with S06911 and in those treated with S12911 (without vit. D). Serious adverse events were similarly reported in 5.2% in the S06911 versus 8.6% in the S12911 (without vit. D) group.

The most commonly reported emergent adverse events (> 3% of the patients in either group for each event, S06911 vs S12911 (without vit. D)) were Fall (14.0% vs 20.0%), Hypercalciuria (6.9% vs 2.9%), Diarrhoea (4.7% vs 6.7%), Hypertension (4.4% vs 3.8%), and Arthralgia (3.4% vs 1.9%).

Most frequently reported emergent adverse events over M0-M12 in the CL3-06911-002 and the CL3-06911-003 studies were similar to those of M0-M6.

No VTE or hypersensitivity syndromes were reported. One patient died while on S06911 from fatal congestive heart failure, 3 weeks after the first study drug intake. The patient had a history of coronary heart disease.

The most frequent biochemical abnormalities concerned changes in phosphocalcic homeostasis parameters: decrease in blood calcium (-0.12 ± 0.10 mmol/L in the S 06911 group and -0.13 ± 0.09 mmol/L in the S 12911 (without vit. D) group), and an increase in blood phosphorus (0.14 ± 0.18 mmol/L and 0.10 ± 0.18 mmol/L, respectively). Similar changes were observed in previous studies. They occurred with a similar frequency with S06911 as with S12911 (without vit. D). There were no clinically relevant differences in the nature of emergent adverse events reported, except for a slight excess of hypercalciuria in the S06911 group (28 patients, 6.9%) compared to the S12911 group (3 patients, 2.9%).

Safety results obtained over a 12-month treatment period with S06911 were comparable to those observed over the first 6 months.

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

A higher incidence of hypercalciuria in the S06911 cohort compared to the S12911 cohort was observed.

## *Balance*

## *Importance of favourable and unfavourable effects*

An FDC might increase patients' compliance. The development of an FDC with the aim to improve patient compliance is in line with the FDC GL. In the context of osteoporosis therapy especially in the elderly compliance is a critical issue.

The FDC of strontium ranelate + vitamin D as compared with strontium ranelate alone can correct vitamin D insufficiency (i.e. > 22.5 nmol/L and < 50 nmol/L) to levels ≥ 50 nmol/L in 78% of patients. However, it has not been proven that this FDC is sufficiently effective in patients with vitamin D deficiency (levels below 22.5 nmol/L).

No PK interaction between strontium and Vitamin D3 has been demonstrated. A signal that addition of a cyclodextrin used as a stabilizing agent for cholecalciferol, would decrease the rate and extent of Vitamin D3 was not confirmed in a second, larger and better designed PK study in volunteers.

The safety profile of strontium ranelate combined to vitamin D3 (S 06911) was in accordance with that expected with strontium ranelate alone. A higher incidence of hypercalciuria as adverse event was observed in patients treated with strontium ranelate/cholecalciferol compared to strontium ranelate alone. This is a known side effect and has been adequately reflected in the SmPC.

## *Benefit-risk balance*

Strontium ranelate as well as vitamin D are known substances.

## *Discussion on the benefit-risk assessment*

There is an ongoing debate in the scientific community about optimal target levels of 25-OH vitamin D as regards its effect on bone health and, more specifically, on the reduction of fracture risk. E.g., Rizzoli et al. 2013, Dawson-Hughes 2013, Hanley et al. 2010, Holick et al. 2011, Bischoff-Ferrari et al. 2012 all recommend 25-OH vitamin D target levels above 50 nmol/L for the purpose of fracture prevention. Brouwer-Brolsma et al. 2013 and Ross et al. 2011, among others, recommend maintaining 50 nmol/L as a minimum target level. A daily supplementation of 1000 IU vitamin D covers the vitamin D requirement for most of the adult and elderly population with osteoporosis to achieve the recommended > 50 nmol/L 25(OH) vitamin D level. It can be concluded that the thresholds/dosing chosen by the applicant are of clinical value.

Due to the limited number of patients included the available data are insufficient to establish the efficacy of Issarlos/Ditelos in the correction of vitamin D deficiency (25-hydroxyvitamin D serum level ≤ 22.5 nmol/l). However, the applicant does not apply for an indication in patients with vitamin D deficiency.

## *5.1. Conclusions*

The most important issues with regard to pharmacokinetics and clinical requirements are considered solved. However, the overall B/R of Issarlos/Ditelos is still negative in view of the major objection on quality related to the cholecalciferol-cyclodextrin mixture, which should be regarded as intermediate drug product instead of drug substance.

**References**


- Holick MF, Binkley NC, Bischoff-Ferrari HA, et al.(2011) Evaluation, treatment and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab ; 96: 1911-30. [Erratum, J Clin Endocrinol Metab 2011; 96: 3908]
- Bischoff-Ferrari HA, WC Willett, PH Endel, et al. (2012) A pooled analysis of vitamin D dose requirements for fracture prevention N Engl J Med 367: 40-9.
- Editorial: Heany RP (2012) Vitamin D Baseline status and effective dose. N Engl J Med 367, 77.
- Dawson-Hughes B, Mithal A, Bonjour JP,.et al.(2010) IOF position statement: vitamin D recommendations for older adults Osteoporos Int 21:1151–1154