3 December 2012
EMA/774827/2012
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment report for Jenzyl

International non-proprietary name: Ridaforolimus

Procedure no EMEA/H/C/2259

Note

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

This withdrawal Assessment Report is based on the latest assessment report adopted by the CHMP with all information of a commercially confidential nature deleted.

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

1. RECOMMENDATION

Based on the CHMP 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 Jenzyl, an orphan medicinal product, in the treatment metastatic soft tissue sarcoma or bone sarcoma as maintenance therapy for patients who have completed at least 4 cycles of chemotherapy without evidence of disease progression in adult and paediatric patients aged 13 through 17 years with weight over 100 pounds or 45.4 kilograms). is not approvable since "major objections" still remain, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the List of Outstanding Issues (see section 6).

Questions to be posed to additional experts

None proposed.

Inspection issues

A request for routine GCP inspection of Study P011 (SUCCEED) was adopted by the CHMP by decision at the September 2011 meeting. The study was selected due to the indication of the product.

The following sites were selected for inspection:

Centre Leon Berard, Lyon, France
Sarcoma Center, Boston, US
Sarcoma Oncology Center, Santa Monica, US

The Integrated Inspection Report (IIR), dated 27 February 2012, concludes with the recommendation for the use of the inspected data and procedures:

"Subject to observation described in section C.7.2 which is left to the CHMP evaluation, it is the recommendation of the inspectors that the results from the 3 sites can be used for evaluation of the application." The information in section C.7.2. concerned the quality of efficacy data, a major deviation in site 746:"Date of PD reported by the investigator for 4 reviewed patients (...) was 2 to 3 months posterior to date of PD according to RECIST guideline."

New active Substance status

Based on the review of the data the CHMP consider that the active substance status of ridaforolimus contained in the medicinal product Jenzyl cannot be determined (see list of outstanding issues, Section 6).

2. EXECUTIVE SUMMARY

2.1. Problem statement

Patients with metastatic soft-tissue or bone sarcoma face a poor prognosis, with a 5 year survival rate of 15-22%. Existing treatment options for patients with metastatic disease consist of cytotoxic chemotherapy, which has limited activity and considerable toxicity. Patients with metastatic sarcoma typically receive multiple lines of chemotherapy until achievement of maximal therapeutic benefit or failure of tolerance. Once a response or disease stabilisation is achieved, no further treatment is

administered until the patient progresses or become symptomatic. This strategy of “watchful waiting” spares the patient from cumulative toxicity associated with administration of chemotherapy. There is no established therapy to delay disease progression.

Once disease recurs, the options are limited. Trabectedin (Yondelis) is licensed under exceptional circumstances for the treatment of leiomyosarcoma and liposarcoma and recently pazopanib (Votrient) was licensed for the treatment of “selective subtypes of advanced Soft Tissue Sarcoma”.

Ridaforolimus was developed to provide sarcoma patients with at least stable disease after chemotherapy with an option to delay disease progression and to fill an unmet medical need.

2.2. About the product

Ridaforolimus (formerly referred to as AP23573 and deforolimus) is a non prodrug of rapamycin (sirolimus) that inhibits the mammalian Target of Rapamycin (mTOR). The molecular mechanism of ridaforolimus-induced anti-tumour activity is by inhibition of the activity of the mTOR protein and thereby of the multiple downstream effects of mTOR’s activity, which consequently leads to inhibition of the growth and proliferation of tumour cells. The mTOR inhibitory effect of ridaforolimus is thus mainly cytostatic. Some anti-angiogenic activity is also theoretically possible considering ridaforolimus’ ability to decrease VEGF production and inhibit the proliferation of normal endothelial cells, but no relationship between plasma VEGF levels and clinical outcome was seen in the phase II study P018. Anti tumour activity in sarcoma patients has been indicated by the achievement of partial responses in the pivotal study P011, as well as in the supportive dose finding phase I study P016 and the phase II study P018.

2.3. The development programme/Compliance with CHMP Guidance/Scientific Advice

CHMP Scientific Advice on the design of the Phase III study was sought twice. The initial advice was issued by the CHMP in November 2005. Further to this advice, the proposed study design was modified and presented for concurrence by the CHMP through a follow-up scientific advice in March 2007. The Applicant has addressed the heterogeneity of the patient population of the proposed study by incorporating stratification by histology in the study design. The need for relevant data on OS was expressed.

FDA advice was also sought in a Special Protocol Assessment procedure, where a hazard ratio of 0.75 in PFS was believed by the FDA to be consistent with therapy associated clinical benefit.

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

A specific GMP inspection is not required in support of this submission. The CHMP has been assured that acceptable standards of GMP are in place for this product type at all sites responsible for the manufacture and assembly of this product.

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

- Legal basis

This application was submitted in accordance with Article 8.3 of Directive 2001/83/EC, as amended (i.e. complete dossier with administrative quality, pre-clinical and clinical data).

- Conditional approval

Not requested by the applicant.

- Approval under exceptional circumstances

Not requested by the applicant.

- Accelerated procedure

Not requested by the applicant.

- Biosimilarity

Not applicable

- 1 year data exclusivity

Not applicable

- Significance of paediatric studies

As per EMA decision 25 January 2010,

- A Paediatric Investigational Plan (PIP) for ridaforolimus in solid tumours was agreed to,
- A deferral was granted,
- A waiver was refused.

PIP Decision Number(s): EMEA-000458-PIP01-08.

PDCO finalised on 17 June 2011 a partially completed compliance procedure and confirmed the compliance of all those studies contained in the agreed paediatric investigation plan that were to be completed until that date.

PIP COMPLIANCE VERIFICATION: PDCO compliance Opinion Number: EMEA-C1-000458-PIP01-08. National competent authority/EMEA document reference: EMA/345826/2011.

3. SCIENTIFIC OVERVIEW AND DISCUSSION

3.1. Quality aspects

Drug substance

Starting material

For the quality documentation of the rapamycin, the applicant refers to the Active Substance Master Files (ASMF) from two different manufacturers In addition, the Module 2.3 and Module 3 open portions of these ASMFs are included in the submission as Module 3 References. The Letters of Authorization to reference the manufacturer's Active Substance Master Files (ASMF) are included in Module 1.

Rapamycin/Sirolimus is obtained, by fermentation and subsequent purifications processes. The producing strain is obtained from Streptomyces hygroscopicus through chemical-physical mutagenesis (it is not a genetically modified organism). The actual strain is traceable to the origin strain. The manufacturing process concerns the following steps:

Fermentation steps

- Preparation of the Master Cell Bank (MCB)
- Preparation of the Working Cell Bank (WCB)
- Preparation of the inocula on commercial (industrial) scale

Purification steps

- Preparation of Crude Rapamycin/Sirolimus
- Preparation of Purification Rapamycin/Sirolimus

Information included in the restricted part:

- The characterisation of the producer micro-organism
- The fermentation process including raw materials used
- Downstream processing
- Purity of the final product
- In-process controls during fermentation and purification

A clear description of the fermentation process has been provided as well as flow diagram and a list of the raw material. Operating parameters such as temperature, culture time, aeration and agitation have been described for both stages.

Active Drug Substance

General information

The active substance is described as a white to off-white amorphous solid, chiral and hygroscopic compound. Ridaforolimus is sensitive to acid and base (exhibits optimum stability at pH 5.0). The substance shows extremely low solubility in water according to the Biopharmaceutical Classification System (BCS IV) but is freely soluble in ethanol, and it is dissolved along with the antioxidant Butyl Hydroxytoluene (BHT) in dehydrated ethanol for the wet granulation process used in the manufacture of ridaforolimus tablets. BHT is also added during the purification and isolation of the drug substance. It is stated by the applicant that without the addition of BHT ridaforolimus exhibits instability when stored at -20 ºC for six months. However, with the addition of 0.05-0.2% w/w BHT, the drug substance is stable up to 24 months at -20 ºC. According to the Q&A on quality of the EMA, the blending of an active substance and an excipient is considered as the first step in the manufacture of the medicinal product. The only exceptions can be made where the active substance cannot exist on its own. The necessity of the addition of BHT has been justified by the applicant and supported by stability data with and without the addition of BHT.

The potential degradation products of ridaforolimus are described in the dossier. Rapamycin produced by the applicant/ASM is in the amorphous form.

GMP certificate is provided from the Competent Authority of the Swiss confederation (swissmedic) certifying that the manufacture of ridaforolimus, complies with Good Manufacturing Practice.

A declaration signed by the QP has been provided from Merck Sharp & Dohme, NL the batch release site, confirming that the manufacturing of the drug substance, is performed in compliance with EU GMP.

Synthesis process

The synthesis processes for the drug substances have been described in flow charts and narratives. Proven acceptable ranges (PARs) are proposed for different unit operations. A thorough development work has been carried out where the parameters affecting the quality of the final drug substance have been evaluated. The development work addresses the development history including the development of the synthetic routes and process optimization. Proven acceptable ranges (PARs) are proposed for different unit operations. These ranges have been established based on univariate and multivariate experiments, mechanistic understanding and existing knowledge of the manufacturing process. The impact of the various processing parameters and in-process controls on the quality of the drug substance has been studied. Key risks that will impact the quality attributes for the ridaforolimus process are discussed and summarized. A defined control strategy has been provided for the manufacturing process. The specified boundaries seem reasonable given the information that has been provided. The manufacturer seems to have good control of the manufacturing process. No critical process parameters (CPPs) are identified and none of the in-process (IPC) tests are identified as critical attributes (CQAs).

Characterisation of drug substance

The structure of the drug substances is supported by the routes of synthesis and has been investigated and verified by spectroscopic methods. Ridaforolimus is a chiral molecule with 15 stereogenic centers; all of them are derived from the starting material rapamycin. The impurity profile of the active substance has been thoroughly evaluated: the applicant has provided information about their origin, how they are formed and the amount found in different batches. There are sixteen impurities in total for which the structures, methods of formation, and levels observed have been described. The acceptance criteria for each impurity has been justified considering the historical ranges and control limits in the rapamycin, crude ridaforolimus and ridaforolimus drug substance with process enrichment and other process contributions for impurities. Calculations have been provided. Additionally, the proposed acceptance criteria for the specified impurities have been qualified.

The impurities have undergone a structure alert screening. The process related impurity 28-chloro-29-desmethyl-ridaforolimus has been identified potential genotoxic impurity in one in silico model (DEREK) but was not alerted in two other in silico models, namely MCASE and Leadscope. The specification for 28-chloro-29-desmethyl-ridaforolimus impurity is controlled at a maximum of 0.15 area% in ridaforolimus drug substance. The applicant has justified the specification limit by referring to ICH S9 Guideline. This is considered acceptable.

Control of drug substance

The active substance specification is adequate to control the quality of the active substance. The analytical procedures are appropriately described, and analytical validation has been performed in line with ICH guidelines. Batch analytical data provided demonstrates compliance with the specification and shows the active to be of good quality.

The reference standard has been sufficiently characterised (by, IR, NMR, mass spectrometry, X-ray powder diffraction, HPLC, and elemental analysis). According to the applicant the impurities used in the spiking experiment for the validation of the HPLC methods have been isolated by HPLC and characterized by LC, GC (residual solvents), NMR, LC/MS and LC/MS/MS. *However, no chromatograms or spectra have been provided by the applicant.* The % purity of the impurities used in the spiking experiments is provided in Module 3 (see Sec. 3.2.S.4.3.1.9). The molar response factors for each of the impurities have been determined. According to the applicant authentic impurity reference standards are not required for quantification of the impurities in the ridaforolimus drug substance since molar response factor corrections are used for reporting levels of the impurities on a wt-% basis (see Sec. 3.2.S.4.2.1 Analytical Procedures - Assay and Impurities by RP HPLC). A system suitability impurity reference ridaforolimus drug substance lot containing known levels of the impurities is run in the analysis of ridaforolimus drug substance rather than the authentic impurities reference samples to assist in impurity identification. The COA for the ridaforolimus drug substance system suitability impurity reference sample is provided. *This is considered acceptable.*

Specification of the container closure system, which includes requirements for identification (a copy of the corresponding IR) and physical/dimensional characteristics has been provided.

Stability of drug substance

The active substance has been subjected to stress testing, photostability testing, and stability studies under long-term, intermediate and accelerated conditions. Stress testing shows that the drug substance is photo sensitive and should be stored protected from light. In addition, it was found that ridaforolimus is sensitive to thermal, oxidative, acidic and caustic stress conditions as demonstrated by elevated levels of known and unknown impurities at the end of each test condition.

Stability studies at accelerated (5 ºC) and long-term conditions (-20 ºC) of ridaforolimus drug substance were conducted using five batches production batches (24 months at -20 ºC). However, since the stability studies have been performed with batches produced by the former synthetic process C1 the applicant was requested to submit stability data with batches produced by the proposed commercial manufacturing route, process C2. Stability data of additional 4 batches at long-term conditions (3 x 12 months and 1 x 3 months at -20 ºC) and at accelerated conditions (3 x 12 months and 1 x 3 months at 5 ºC) produced by the commercial manufacturing process C2 have now been provided by the applicant, all batches comply with proposed specification.

The stability studies have been performed in accordance with the storage recommendation of the ICH guidelines. The data submitted justifies a retest period of 24 months when stored at – 20 ºC in the suggested packaging material. Additional long term stability data may be evaluated to support possible extension to the proposed retest date.

Drug Product

Pharmaceutical development and Manufacture of drug product

Ridaforolimus tablets are manufactured using conventional processes of wet granulation, drying, milling, blending, tableting, coating, and printing. The product is supplied as a gastro-resistant (delayed release) enteric coated tablet. Each tablet contains 10 mg of ridaforolimus. The tablets are packaged in aluminium/aluminium blisters. Tablet formulation can be separated into three main components: (i) a tablet core that provides immediate release of ridaforolimus (ii) a polymer sub coat smoothes any tablet imperfections to provide greater ease of application of the enteric coating (iii) an enteric coat provides pH sensitive release (e.g. gastro-resistant or delayed release) of ridaforolimus drug substance from the tablet core.

An extensive pharmaceutical development has been made where the parameters affecting the quality of the final film-coated tablets have been evaluated. Proven acceptable ranges have been established. The impact of various processing parameters and in-process controls on critical quality attributes (CQAs) has been characterized. Granulation parameters like solution step, granulation fluid level and wet massing time and their impact on tablet dissolution, tablet uniformity of content, and on tablet tensile strength have been studied. Other parameters like fluid bed drying, milling, blending and lubrication, compression and sub and enteric coating have also been thoroughly investigated. A summary and control strategy of the optimisation of the manufacturing process has also been included. The optimization of the dissolution methods used has been discussed. The critical attributes identified is tablet water activity at the end of enteric coating and residual ethanol in the final product. The impact of the upper limit for water and residual solvent on the potential seco-ridaforolimus degradation level is discussed in ref 3.3:9 in the dossier (Module 3).

The applicant has demonstrated the discriminatory power and robustness (i.e. with DoE experiments) of the final selected method. Also an overview of the dissolution comparability of the clinical, stability and proposed commercial batches are provided.

GMP certificate is provided from the Competent Authority of the Netherlands (Health Care Inpsectorate) certifying that the manufacture of Ridaforolimus, complies with Good Manufacturing Practice.

The manufacturing process has been described both in a flow scheme and in a narrative. The cumulative hold time of ridaforolimus process intermediates (unmilled granulation, milled granulation, granulation blend, core tablets, film coated tablets and unprinted enteric coated tablets) is restricted to 30 days at refrigerated conditions (2-8 °C/ambient humidity) in an HDPE drum with desiccant. A formal validation of the process in the production facilities will be completed prior to release of

Ridaforolimus Tablet to the market. This is considered acceptable since the process is a standard process and the batches produced for the stability studies are of commercial scale and by the fact that commercial volumes of this product are relatively small and clinical production proved useful in characterizing the commercial process. Five commercial scale clinical lots have been produced with all unit operations using similar processes and equipment as the proposed commercial process. Satisfactory control of the excipients is described.

Control of drug product

The drug product specification is considered acceptable. The description of applied analytical procedures is adequate and the validation of the analytical methods is acceptable. Representative batch analysis data for 21 batches of Ridaforolimus Tablet from the proposed production site used in clinical and stability studies are presented in the application. The batch analysis results show that the finished product meet the specifications proposed.

The components chosen for the proposed container closure systems are common for this type of dosage form and seem suitable for its purpose and it is stated that the packaging materials used comply with the EC Directive 2002/72/EC. Since both manufacturers are responsible for the primary packaging of the product detailed information about container closure system for bulk storage of the final product for transportation have been presented by the applicant.

Stability of drug product

Three batches of Ridaforolimus Tablet were prepared for the formal stability studies (FSS). Batch size selection for the FSS was consistent with the ICH Q1A guideline. Two of the three batches were prepared in the final market batch size. All three formal stability batches were manufactured at equal to or greater than 1/10th the commercial batch size.

An 18 months expiration period is proposed for the Jenzyl gastro-resistant tablets packed in the blister packs proposed for marketing. This is acceptable based on the stability data received. No out of specifications (OOS) results are seen at long-term (5 °C at ambient humidity) or accelerated storage conditions 25 ±2°C/60 ± 5% RH in Aluminium/Aluminium blister. Also a patient in-use period of up to 13 weeks (3 months) at room temperatures (≤ 30°C/≤ 86°F) after dispensing from the pharmacy is supported by acceptable stability data. The coldform aluminum blister package for this product is impenetrable to light, as demonstrated by a photostability study, and the packaged tablets are labelled to "Store tablets in the original package". Therefore, photostability is not considered a risk to the packaged product meeting proposed specifications during shelf life.

Since MSD in the Netherlands is also responsible for the primary packaging of the product and the product is sensitive to heat, moisture and oxygen the applicant has presented information regarding the control of the environment during storage and shipment to prevent temperature excursion and maintain the physical properties of ridaforolimus in the product. A thermally protective container (Merck Thermal Container TC391) used during shipment of bulk Ridaforolimus Tablets has been described. The container has been qualified for shipment of one 17 L bulk container with a load of 1 kg (minimum load) to 7 kg (maximum load) of bulk tablets while maintaining product temperatures between -20°C and +8°C under different conditions such as maximum shipment duration of 120 hours and summer, normal and winter ambient temperature conditions and shipping orientation and palletized for shipping.

Bulk hold study results for Ridaforolimus Tablet batch 09JM-249 (pilot batch, 96,000 tablets) at 5°C/ambient humidity for 52 weeks in simulated bulk container. The product was observed to be chemically and physically stable for the duration of the study. There were no out specifications results of the parameters studied. *The applicant has made a commitment to place 1-2 additional batches on*

bulk study. The same batches used in the bulk study should be packaged in the primary packaging material and tested under long-term and accelerated conditions.

The applicant has confirmed that the shelf-life of the finished product will be determined in accordance with the NfG on Start of Shelf-life of the Finished Dosage Form.

The post-approval stability protocol and stability commitment are considered acceptable.

The drug product part is generally of good quality. There is just one point for consideration remaining regarding the product. The stability data submitted justifies a shelf-life of 18 months when stored refrigerated in the original package. Also a patient in-use stability of 3 months when stored unopened at room temperature in the in the original package is considered acceptable.

Discussion on chemical, pharmaceutical and biological aspects

Details of the discussion are in drug substance and drug product sections.

Conclusions on the chemical, pharmaceutical and biological aspects

The major objection (MO) raised in relation to the definition of the active substance has been resolved. The issue was about weather it was acceptable to stabilize the active substance ridaforolimus with BHT and not consider this as a first step in the manufacturing of this product (Jenzyl). According to the QWP Quality of medicines Q&A (question 1) and the Guideline on Summary of Requirements for Active Substances in the Quality Part of the Dossier (CHMP/QWP/297/97 Rev 1 corr.), the blending of an active substance and an excipient is considered as the first step in the manufacture of the medicinal product. The only exceptions can be made where the active substance cannot exist on its own. Data have been submitted that support the instability of ridaforolimus. The applicant has provided information on the failure of other strategies to stabilise ridaforolimus by ways different of addition of antioxidants (as obtention of different crystalline forms). The amorphous drug substance stability data with and without BHT have demonstrated the need for including BHT in the drug substance process. Based on the above information, ridaforolimus stabilized with BHT is considered acceptable for this product. Since the use of BHT has been considered acceptable in stabilizing the active substance for this product, the current location for the information on the addition of BHT would also be acceptable. Likewise, it is acceptable to establish the drug product expiry date based on the date of the granulating solution preparation step of the drug product manufacturing process.

All points for clarification raised during the procedure are considered resolved.

In conclusion, from a quality point of view, the product is considered approvable.

3.2. Non clinical aspects

Pharmacology

In vitro proof-of-concept studies

Ridaforolimus is an inhibitor of the mTOR kinase activity in vitro and functions by an FKBP12-dependent mechanism with potency equivalent to that of rapamycin. In cellular assays, ridaforolimus was shown to inhibit the activity of mTOR, as reflected by a decrease in phosphorylation of multiple downstream signaling proteins, with kinetics and potency similar to those of rapamycin. Of the three markers examined, S6K1, 4E-BP1 and S6, phosphorylation of S6 was inhibited most completely. Exposure of cells to ridaforolimus had an effect on all mTOR-dependent activities examined; cells accumulated in the G1 phase of the cell cycle and cell size, VEGF production (EC50 ~0.1 nM) and

glucose uptake (EC50 0.1 - 1 nM) were all decreased. Evidence of G1 cell cycle accumulation without any detectable induction of apoptosis under the conditions examined indicates a predominant cytostatic mechanism of action in vitro. Ridaforolimus was shown to inhibit proliferation of all 36 cell lines examined, including 13 sarcoma lines. In a majority of the cell lines (27) proliferation was inhibited with an EC50 between 0.1 - 1.0 nM. Consistent with a cytostatic mechanism of action, ridaforolimus induced a decrease in the rate of proliferation of all cell lines examined (by 7 to 63%), but did not result in a net killing of cells. The concordance between the concentrations required to inhibit mTOR signaling and the cellular activities studied suggests that these activities are inhibited as a direct result of the effects of ridaforolimus on mTOR. Studies to identify molecular correlates of sensitivity of cell lines to ridaforolimus in vitro have not identified robust, universal predictors of sensitivity (data not shown).

In vivo proof-of-concept studies

Ridaforolimus exhibited antitumor activity in all cell line-derived xenograft models tested, including models derived from sarcoma, endometrial, prostate, colon, breast, pancreatic and lung cancers. Antitumor activity was also demonstrated in eight patient-derived NSCLC models and in genetically engineered mouse models of NSCLC and breast cancer. In all cases ridaforolimus inhibited tumor growth, but did not induce tumor regressions, which is consistent with a cytostatic mechanism of action. In all studies, intermittent dosing regimens were used, demonstrating that daily dosing regimens are not required for antitumor activity. In the most commonly used regimen, QDx5 every week, statistically significant inhibition of tumor growth was observed when administered i.p. at doses of 1.0 mg/kg or higher. Pharmacodynamic studies also demonstrated an association between inhibition of mTOR signaling and inhibition of tumor growth. Also, ridaforolimus decreased VEGF production and had antiproliferative effect on normal endothelial cells, these results indicate that some of the antitumor activity observed in vivo may be due to effects on angiogenesis.

In conclusion, the in vitro effects of ridaforolimus show inhibition of proliferation by 7-63% in the cancer cell lines tested. In vivo data from a xenogenic endometrial cancer model indicates cancer progression during dosing free periods. Together the data supports a clinical program of continuous treatment.

Secondary pharmacodynamics

When dosed daily at 10mg/kg ridaforolimus slightly extend time to graft rejection in a skin transplantation model. However, when using intermittent dosing regiments this effect was not observed. This could suggest that intermittent administration reduces the immunosuppressive effect.

Safety pharmacology

Ridaforolimus did not inhibit hERG current at a maximal testable concentration of 50 μM. However, at concentrations above 2 μM the solubility of Ridaforolimus is questionable and thus the hERG inhibition at 0.5-50 μM is uncertain. There were no test article-related cardiovascular effects in conscious dogs at 3 mg/kg iv (maximum dose tested due to mortality, no exposure data available) and conscious monkeys at ≤ 45 mg/kg (Blood Cmax = 316 ng/mL and Plasma Cmax = 155 ng/mL). In conscious mice, ridaforolimus decreased spontaneous motor activity at 20 mg/kg only and had no effect on nervous system function and motor coordination up to 20 mg/kg. Ridaforolimus had no test article-related effects on pulmonary function in anesthetized guinea pigs up to 20 mg/kg and the NOEL for renal effects was < 5 mg/kg.

Cardiac disorders were reported in 21.6% of patients receiving ridaforolimus and 10% of patients receiving placebo in the clinical study P011. The most common adverse event in the cardiac disorders was tachycardia (not otherwise specified). Cardiac toxicity was also observed in the repeat-dose studies assessed in section 4.2. The combination of data from the safety pharmacology studies,

repeat-dose studies and the clinical cardiac disorder signal indicates that the cardiac effects is of toxic origin rather than a direct pharmacological effect.

Pharmacokinetics

Absorption

Ridaforolimus was readily absorbed after oral dosing as a suspension with a Tmax of 0.5 to 1 hour in the rat and monkey. The terminal half-life of ridaforolimus in whole blood after an intravenous dose was long (19.6 and 29.7 hours in rats and monkeys, respectively). In general, the elimination of ridaforolimus from whole blood was biphasic, initially rapid, followed by a slow terminal elimination phase. The oral bioavailability in rats and monkeys, calculated from dose normalized $AUC_{(0 \text{ to inf})}$ values, was 23.5% and 11.2%, respectively. Although enteric coating of the ridaforolimus tablets caused a delay in absorption in monkeys, it led to 1.30- and 1.39- fold increases in Cmax and AUC, respectively, compared to film-coated tablets.

Distribution

Ridaforolimus was highly protein bound in plasma and, the binding was constant across the concentration range of 0.5 to 5 microM in each species. The differences in plasma protein binding in mouse compared to rat/monkey/human indicate that the data generated in mouse might of less relevance when it comes to addressing safety parameters.

Ridaforolimus was highly bound to red blood cells and the binding displayed saturable kinetics. The extent of binding of ridaforolimus to RBCs and the resulting blood/plasma concentration ratios were dependent on the concentration in whole blood and the species.

The highest amounts of [14C]ridaforolimus, expressed as percent of the administered dose in the male albino rats, was measured at 2 hours post-dose in the following tissues: liver (24.01%), kidney (1.59%), lung (0.65%), myocardium (0.63%), spleen (0.35%), brain (0.12%), and adrenal gland (0.07%). The highest percent of dose of administered [14C]ridaforolimus in male pigmented rats was measured at 2 hours post-dose in the following tissues: liver (18.01%), kidney (0.75%), myocardium (0.28%), lung (0.27%), spleen (0.18%), brain (0.04%), and adrenal gland (0.03%).

Overall, the distribution of drug-derived radioactivity in pigmented rats was similar to that found in albino rats. Concentrations in pigmented tissues of Long-Evans rats, such as uveal tract in the eye, and pigmented skin, were similar to the non-pigmented tissues of the albino rats, and radioactivity was eliminated in a similar pattern from these tissues. These data thus suggest that there was no specific association of [14C]ridaforolimus related radioactivity with melanin.

Metabolism

The major metabolic pathways of ridaforolimus in liver microsomes and hepatocytes were di-hydroxylation, mono-hydroxylation, and demethylation. Ring-opened metabolites have been observed in vitro and in vivo studies. Ridaforolimus undergoes ring-opening by two distinct mechanisms. Under basic conditions, the hydrogen at C23 can be abstracted leading to β-elimination of the carboxylate, resulting in ring-opening with a double bond at C22-C23 (M17, seco-ridaforolimus). Another mechanism is simple ester hydrolysis under basic conditions resulting in a ring-opened hydroxy-ester derivative (M12, 22- hydroxy ridaforolimus).

Following oral administration to rats, ridaforolimus was eliminated predominantly either by biliary excretion or as unabsorbed drug in faeces. Renal excretion was insignificant. Whole blood Cmax was observed at 4 hour post-dose and the mean blood-to-plasma radioactivity ratio was 0.63. In summary, ridaforolimus was the major drug component (68.3%) in circulation in whole blood of rats. Biliary

metabolites in rats were mainly due to hydroxylation and demethylation. In rat faeces, a large fraction of the metabolism was associated with ring-opened seco-ridaforolimus metabolites. Overall, biotransformation of ridaforolimus in rats was mostly through hydroxylation and demethylation.

Following oral administration to monkeys, ridaforolimus was eliminated predominantly in feces. Renal excretion was insignificant. Ridaforolimus was the major drug component (44.6%) in circulation in whole blood of monkeys. In monkey faeces, a large fraction of the radioactivity was unidentified polar degradants. Identified radioactive components in feces were ridaforolimus and ring-opened metabolites. Biotransformation of ridaforolimus in monkeys was mostly through hydroxylation, demethylation and ring-opened seco-ridaforolimus related metabolites.

In humans 88.2% of the dose was excreted in feces and 1.84% was excreted in urine through the last collection interval. The primary radioactive components circulating in whole blood were the parent compound along with metabolites M3, M8/M8A, M10, and M16. These components comprised 53.4, 8.8, 9.6, 4.8, and 4.1%, of the total radioactivity, respectively. The majority of the drug-related radioactivity in faeces eluted as chromatographically undifferentiated polar metabolites. Minor components included MK-8669 (<2%), as well as seco MK-8669 (M17a ring opened form of MK-8669), along with ester hydrolysis or seco-related products (M32, M33, and M34). The identity of the fecal radioactive components is thus largely unknown.

Metabolites in the blood of rats and monkeys were similar to the metabolites in the blood of humans. All the in vitro metabolites of ridaforolimus in human liver microsomes and hepatocytes were also formed in either rat or monkey liver microsomes or hepatocytes.

Excretion

After an oral dose, ridaforolimus was mainly excreted in feces with very little of the dose (~2%) being recovered in the urine of rats, monkeys, and humans.

Toxicology

Single-dose toxicity studies

Ridaforolimus was well tolerated by CD-1 mice and Spargue-Dawley rats when administered orally at single doses up to and including 1000 mg/kg and based on clinical observations.

Repeat-dose toxicity studies

As is the case for many drugs used in cancer therapy ridaforolimus is very potent with an extensive toxicity profile. Ridaforolimus is lethal in all species tested and major toxic effects are related to, food consumption, weight gain, haematological alterations, cardiomyopathy, heart weight, bone, kidneys, infections, reproductive organ effects, eye disorders, liver, lung, pancreas and skin. In pivotal studies none of the tested doses were free of toxicity. A toxicokinetic comparison of the doses used in the repeat dose studies does not generate any, or small, exposure margins to humans.

In the pivotal study in rats, the findings were consistent with the antiproliferative (gastrointestinal, and male and female reproductive systems) and immunosuppressive effects (lymphoid tissues), along with those commonly observed with other marketed mTOR inhibitors (hyperglycemia, myocardial degeneration, cataract, alveolar histiocytosis, pancreatic islet cell vacoulation, bone fractures, etc.) Lameness was observed around 1 month into the study and the fractures occurred after approximately 3 to 6 months of daily dosing, at all dose levels. Histomorphologically, reduced trabecular bone was present in rats at all dose levels, but the bone changes were reversible. The absence of limb disuse, fractures or histological findings in bone in the 3-month or 6-month studies in non-human primates with ridaforolimus is consistent with the available information for other mTOR inhibitors, suggesting that the occurrence of bone changes is a rat-specific effect. Vacuolation of pancreatic islet cells in rats

has been reported for other marketed mTOR inhibitors. Pancreatic islet cell vacuolation has not been observed in monkeys treated with ridaforolimus. Therefore, the weight of evidence suggests that pancreatic islet cell vacuolation is a rat-specific effect for mTOR inhibitors. Myocardial degeneration/necrosis/fibrosis has been observed in rats treated with ridaforolimus (oral and IV studies) at all dose levels. This observation is consistent with what has been reported with other mTOR inhibitors. The myocardial degeneration in rats is likely an exacerbation of the species-specific spontaneous cardiomyopathy.

In oral and IV toxicity studies in cynomolgus monkeys, findings were generally similar to the ones caused by other marketed mTOR inhibitors. Mortality secondary to diarrhea and related complications (e.g., dehydration, weakness) were observed in multiple studies. Antiproliferative and immunosuppressive properties of ridaforolimus, with secondary protozoal infection, likely contributed to the gastrointestinal effects. Additionally, changes in the one-month, 13-week, and six-month oral toxicity studies in monkeys included decreased food consumption and body weight, increased neutrophils, alterations in hematocrit, serum chemistry changes very similar to those detected in the studies in rats, and decreased serum levels of testosterone. Histomorphologic observations included findings related to antiproliferative effects in the reproductive tract tissues and the gastrointestinal tract, or related to immunosuppressive effects such as lymphoid depletion, myocardial degeneration, skin lesions and anterior uveitis. The NOAEL in the 6- month oral toxicity study in monkeys was <0.5 mg.kg.day (6 mg/m2/day; AUC0-24 hr 219-178 ng•hr/mL; ~0.09x clinical AUC0-24 hr; 0.25x clinical dose based on BSA).

Toxicokinetics

The toxicokinetic parameters in one-month and six-month monkey studies were generally similar. In whole blood and plasma, there were no substantial gender-related differences in the mean systemic exposure (AUC0-24 hr) or mean Cmax. Ridaforolimus appeared rapidly in whole blood and plasma at all doses, with mean maximum whole blood or plasma concentrations occurring between 1.0 hour and 4.0-hour postdose. Whole blood and plasma ridaforolimus elimination was generally rapid. In the six-month study, the mean whole blood and plasma systemic exposure steady state was attained within the first day of dosing and was maintained until Study Week 26.

Genotoxicity

The genotoxic potential of ridaforolimus was evaluated in three separate assays. The potential for reverse mutations in S. typhimurium and E. coli strains was assessed in vitro in the standard Ames assay. Human lymphocytes were used to evaluate in vitro the potential to induce chromosomal aberrations. Lastly, the potential clastogenic and aneugenic effects of ridaforolimus were determined in vivo using the Mouse Micronucleus Test. Ridaforolimus was not genotoxic in these studies. The plasma protein binding of Ridaforolimus in mouse is high (99.7%), but the pharmacokinetic data provided by the applicant show that the exposure of the bone marrow of the mice in the bone marrow micronuclei test is expected to result in much higher Cmax and AUC values compared to the human exposure, considering the high plasma protein binding of ridaforolimus in mice.

Embryo-foetal toxicity

The maternal NOAEL of ridaforolimus is 0.5 mg/kg/day. The 2 mg/kg/day dosage of ridaforolimus was associated with significant reductions in body weight gain and body weights. Developmental toxicity, evident as reduced fetal weights and increased postimplantation loss coupled with reduced litter sizes, occurred in the 2 mg/kg/day dosage group (embryo-foetal NOAEL is 0.5 mg/kg/day). The 2 mg/kg/day dosage of ridaforolimus was also associated with increased incidences of fetal skeletal alterations and delays in skeletal ossification. Since this study give evidence for embryo-foetal toxicity the applicants

argues that a second confirmatory study in a non-rodent species is not considered necessary, this is agreed. Also, similar embryo-foetal toxicity has been reported by other mTOR inhibitors.

Local tolerance

Once daily administration of 10 mg strength film-coated or entericcoated ridaforolimus tablets to mini pigs for seven consecutive days did not result in grossly observable gastrointestinal irritation.

Impurities

With the exception of ridaforolimus diene-one isomer, each of the specified impurities has been qualified by virtue of being a metabolite (seco-ridaforolimus, 29-desmethyl-ridaforolimus, and 7-S-desmethyl ridaforolimus), a fermentation or semi-synthetic product (28-chloro-29- desmethyl-ridaforolimus), or having been present in lots tested in subchronic or chronic toxicity studies in rats and/or monkeys at levels higher than the expected levels in humans (mg/kg basis) and having not caused any unique toxicities relative to ridaforolimus alone or being present at levels below the qualification thresholds as allowable under ICH Threshold Guidelines for Impurities in Drug Substances. Given the intended patient population, clean genetic toxicity profile of ridaforolimus, and lack of genotoxicity structural alerts for the diene-one isomer, it is considered acceptable to exceed the level of this impurity qualified in a 6-month toxicity study in monkeys.

Phototoxicity

Ridaforolimus do not induce phototoxic reactions when administered orally to pigmented rats at 75 mg/kg/day for three days before light exposure. In addition, there is no difference in tissue distribution between pigmented and non-pigmented rats indicating no specific ridaforolimus association with melanin (see section 3.3.4 above). Combined, these findings exclude light from being the inducer of the skin and eye findings in the rat and monkey repeat-dose toxicity studies.

ERA

The Phase I assessment indicated a potential for bioaccumulation based on a log Kow of 4.68. A subsequent bioconcentration study (OECD 305) showed no bioaccumulation. Therefore it can be concluded that ridaforolimus is not a PBT compound.

The Phase I PECsw was calculated using a refined Fpen of 0.0005 based on prevalence calculations and is acceptable. The PECsw obtained was 0.01 µg/L, and a Phase II assessment was conducted. The outcome of the Phase II Tier A assessment indicated that ridaforolimus may pose a risk to the aquatic environment and to ground water organisms. Ridaforolimus is unlikely to represent a risk to microorganisms.

Because a significant shift to sediments was detected, a sediment toxicity study per OECD 218 was conducted. The results indicated a low toxicity of ridaforolimus to sediment dwelling organisms. Ridaforolimus is therefore unlikely to pose a risk to the sediment environment.

A Phase II Tier B assessment was then conducted. The PECsw was further refined based on human ADME data in which the applicant claims that only 4 % of the excreted compounds were identified as unchanged ridaforolimus and a Fexcreta of 4 % (0.04). Also, the applicant claims that no single metabolite exceeded 10 % of the amount excreted. By doing so the applicant refines the PECsw as 4 x 10-4 µg/L and all RQs were now below 1.

Discussion on non-clinical aspects

There were no indications for an arrhythmic effect of ridafirolimus in the nonclinical studies. However, the results from the hERG study are uncertain due to solubility problems at concentrations ≥2.5 µM.

An in vivo study in dogs showed no adverse ECG changes at an iv dose of 3 mg/kg but no exposure data are available. The applicant has performed an allometric scaling to calculate a Cmax but the value of this calculation is uncertain. Lastly, in monkeys no adverse ECG effects were seen in repeat dose toxicity studies, but no exposure multiples to clinical exposure were achieved in these studies.

As is the case for many drugs used in cancer therapy ridaforolimus is very potent with an extensive toxicity profile. Ridaforolimus is lethal in all species tested and major toxic effects are related to, food consumption, weight gain, haematological alterations, cardiomyopathy, heart weight, bone, kidneys, infections, reproductive organ effects, eye disorders, liver, lung, pancreas and skin. In general, the toxicity profile of Ridaforolimus is not very different from other mTOR inhibitors already on the market. In pivotal studies none of the tested doses were free of toxicity. A toxicokinetic comparison of the doses used in the repeat dose studies does not generate any, or small, exposure margins to humans. Ridaforolimus is not regarded as genotoxic. Dosing of ridaforolimus to pregnant rats induced both maternal and embryo-foetal toxicity.

Conclusion on non-clinical aspects

Excluding the QT issue discussed above, there are no unresolved non-clinical issues.

3.3. Clinical aspects

- **Tabular overview of clinical studies**

Study ID	No. of study centres / locations	Design	Study Posology	Study Objectives	Subjs by arm Gender M/F Median age	Duration	Diagnosis Incl. criteria	Endpoints
P011 Pivotal	23 countries and 186 sites world-wide including the US, Europe, and Asia	Phase 3 rando-mised, Placebo-controlled, double-blind trial	Oral ridaforolimus 40 mg QD x 5 days/week as 10 mg enteric-coated tablets.	Comparison of ridaforolimus vs. placebo as maintenance therapy with regard to: 1': PFS 2'a: OS 2'b: best target lesion response 2'c: changes in cancer-related symptoms.	Ridaforolimus: 347 Placebo: 364 M: 314 F : 397 Age range: 14-92	Until PD or intolerable toxicity	Patients aged ≥13 with metastatic soft tissue sarcoma or bone sarcoma, who had achieved response or stable disease after completion of at least 4 cycles of chemotherapy given in 1st -3rd line.	Primary: PFS 2nd-ary: OS, best target lesion response, change in cancer-related symptoms
P016	3 sites in the US	Phase 1* non-rando-mised, multi-center, 3+3 design, dose-escalation study	Oral ridaforolimus as 10 mg enteric-coated tablets. Dose range 10-70 mg in 7 different dosing regimens.	To determine/ examine: 1': safety, tolerability, and MTD of ridaforolimus. 2'a: PK and PD of ridaforolimus. 2'b: anti-tumour activity of different dosing regimens. 2'c': experimental potential response predictive parameters.*	Total n: 147 N given 40 mg QD x 5 d/w: 24 M: 65 F: 82 Age range: 23-84	Until PD or intolerable toxicity	Patients aged ≥18 with advanced/ refractory solid tumours.	MTD, -> dose and regimen for phase III study
P018	17 sites: 14 in the US, 2 in France, 1 in Belgium	Phase 2 open-label, un-controlled, fixed-dose trial	I.V. ridaforolimus 12.5 mg QDx5 days every 2 weeks.	1': Efficacy	N= 216, treated: 212 M: 105 F: 107 Age range: 16-78	Minimum 2 cycles (8 weeks). Until PD or intolerable toxicity	Patients aged ≥15 with metastatic/ unresectable sarcoma.	Primary: CBR 2nd-ary: Safety. TTP, PFS, OS, DoR, QoL, experimental

CBR: Clinical benefit response (defined as complete or partial response or prolonged stable disease ≥ 16 weeks); DoR: duration of response, MTD: maximum tolerated dose, OS: Overall Survival, PD: pharmacodynamics, PFS: Progression-free Survival, PK: pharmacokinetic, QoL: quality of life assessment, TTP: time to disease progression.

* An intended Phase IIa segment of this trial (per Protocol Amendment #2, 27-Jul-2005) was to assess the antitumour activity of orally administered ridaforolimus in patients with advanced sarcoma. The planned Phase IIa segment was not executed because sufficient numbers of sarcoma patients had been enrolled in the Phase I segment of the trial.

Additionally 33 studies were conducted with ridaforolimus (including the clinical pharmacology studies). These also include studies that are either ongoing or have been completed but have limited relevance from a safety perspective to the sarcoma indication based upon the tumour type being treated, the wide range of dosages administered, the route of administration, or co-administration of other anti-cancer therapeutics.

Pharmacokinetics

Clinical pharmacology studies of ridaforolimus have been performed in healthy male subjects (single-dose studies) and in patients with advanced cancer (multiple-dose studies).

In most studies, ridaforolimus was administered as the enteric-coated tablet (ECT) intended for market. In the interaction study with ketoconazole and in the mass-balance study a dry-filled capsule, potentially with lower bioavailability, was used.

Bioanalysis of ridaforolimus in whole blood and plasma was made using validated HLPC-MS/MS methods. Due to the preferential binding of ridaforolimus to erythrocytes, primarily whole blood concentrations of ridaforolimus, and not plasma concentrations, were reported in the pharmacokinetic studies.

When interpreting the pharmacokinetic data, the Applicant has used a (limited) PK/PD analysis. This analysis suggests that at “typical exposure” after the 40 mg dose, about 30% of patients will need to down-regulate the dose due to dose-limiting grade 2 stomatitis, while at a 2-fold increase in exposure, about 50% of patients will need to dose adjust. The Applicant proposes that an increased risk for dose-limiting toxicity from 30% to 50% is acceptable. Thus, for intrinsic and extrinsic factors leading to up to 2-fold increase in exposure, no adjustment of the starting dose is suggested to be necessary. The analysis is discussed in more detail below under Relationship between Plasma Concentration and Effect.

Absorption

Ridaforolimus is essentially insoluble in water. *In vitro* permeability was intermediate, but the data are inconclusive. *In vivo* data indicate that ridaforolimus has moderate to high permeability and, thus, may be a BCS class II substance.

Using dose-normalised data from two studies with intravenous single-dose administration (doses of 3-12.5 mg) and one study with oral administration (doses 10-40 mg), the absolute bioavailability of ridaforolimus was estimated to be 13-19%. A mean value of 16% is proposed for the SPC. Due to non-linear pharmacokinetics of ridaforolimus, with AUC increasing less than dose-proportionally, oral bioavailability might have been somewhat overestimated when comparing oral exposure with the much higher IV exposure. Nevertheless, it may be concluded that bioavailability is low, possibly due to a high first-pass metabolism and active efflux.

In the pivotal study, administration of ridaforolimus with a light meal was permitted. A single-dose, food effect study has been performed at the 40 mg dose using the ECT formulation. When administered with a low-fat meal, ridaforolimus C_{max} and AUC increased by 15% and 6% respectively. After a high-fat meal, C_{max} and AUC increased by 12% and 46%, respectively. The Applicant suggests that a 46% increase in AUC will not lead to a non-acceptable increase in the risk for dose-limiting toxicity. However, the effect of a high-fat meal is not negligible, and the CHMP of the opinion that

patients should be instructed to take the tablet fasting or with a light meal, as in the pivotal efficacy/safety study.

Distribution

The volume of distribution with respect to blood concentrations ranged from 148 L to 523 L between the 6.25 mg and 100 mg dose levels in a single-dose IV study.

Plasma protein binding of ridaforolimus as determined using an ultrafiltration method was 93.8%. The average binding of ridaforolimus to human liver microsomal protein was 53.8%.

Ridaforolimus binds to the FK506 binding protein (FKBP), present in erythrocytes. The blood/plasma (B/P) ratio is dependent on the concentration of ridaforolimus in whole blood, remaining high until the saturation levels are and decreasing with increasing ridaforolimus concentrations. In human whole blood, the mean B/P ratio was 9.1 until the total ridaforolimus whole blood concentration was approximately 300 ng/ml and then the ratio continually dropped to 0.7 at 3000 ng/ml. The saturable binding to red blood cells (RBCs) is suggested to be the reason for the non-linear whole-blood pharmacokinetics of ridaforolimus.

Ridaforolimus was shown to be a Pgp substrate in MDR1-transfected cells, with higher efflux ratios (26.6, 47.0 and 53.9 at 0.5 µM, 1 µM and 5 µM, respectively) than the control substrate digoxin (5.0).

The apparent permeability data for ridaforolimus obtained from parental LLC-PL1 cannot be readily translated into passive permeability due to the presence of endogenous transporters. However, *in vivo* mass-balance data indicate that ridaforolimus may be almost completely absorbed but subject to a high first-pass metabolism, thus indicating high permeability.

Elimination

In summary, available data indicate that ridaforolimus is eliminated via metabolism mediated almost entirely via CYP3A4. Excretion of metabolites is primarily in the faeces. The *in vitro* clearance was high, while estimates of total blood clearance (CL_B) following IV administration were about 2-8 L/hr and indicate that ridaforolimus is a low-extraction ratio compound. The elimination was relatively slow, with reported mean $t_{1/2}$ values around 40-70 hr across studies.

In vitro metabolism studies were performed with microsomes, hepatocytes and cDNA-expressed human CYP isozymes. In general, the metabolite profile in hepatocytes was similar to the metabolite profile in liver microsomes. The *in vitro* metabolism of ridaforolimus was extensive. Major biotransformation pathways in liver microsomes were hydroxylation (M3, M6, M8, M11, and M13), dihydroxylation (M1, M2) and demethylation (M10, M16/M18, and M19) of ridaforolimus. Other minor pathways were dehydrogenation (M7, M20), dehydrogenation/ demethylation (M15), dehydrogenation-hydroxylation (M4), reduction (M9, M22), and didemethylation (M5, M14).

In buffer only and in no-NADPH incubations, non-enzymatic chemical degradation of ridaforolimus to ring opened products were observed (about 6-11% seco-ridaforolimus and ring-opened hydroxy ridaforolimus, M17 and M12). In total, about 20% of the ridaforolimus underwent non-enzymatic chemical degradation.

In studies with recombinant human CYP enzymes, ridaforolimus was mainly metabolised by CYP3A4 and to a much lesser extent by CYP3A5, 2C8 and 2D6 in that order. The metabolism of ridaforolimus by recombinant CYP3A4/5 was qualitatively identical to the metabolism by human liver microsomes and hepatocytes. Ridaforolimus was not metabolised by CYP1A2, 2C9, or 2C19. In microsomes, quercetin at 30 µM (CYP2C8 inhibitor) and quinidine at 10 µM (CYP2D6 inhibitor) did not inhibit the metabolism of ridaforolimus. At 3 µM and 10µM, ketoconazole (CYP3A4/5 inhibitor) inhibited the metabolism of ridaforolimus by 92% and 95.5%, respectively. Anti-CYP2D6 and anti-CYP2C8/9

monoclonal antibodies did not inhibit the formation of any ridaforolimus metabolite, while anti-CYP3A4/5 monoclonal antibody inhibited >85% of the metabolism of ridaforolimus. These results indicate that ridaforolimus is metabolised almost exclusively by CYP3A4/5.

A mass-balance study has been performed with administration of a single 40 mg oral dose of [14C]-ridaforolimus (as 10 mg dry-filled capsules, DFC) to six male, healthy volunteers in the fasted state. Total recovery of radioactivity was approximately 90%, with 1.84% recovered in urine and 88.2% in faeces during a 360-hr period. The majority of the dose was excreted within 192 hr.

The major radioactive components in faeces eluted as undifferentiated polar radioactivity (>90% of radioactivity in faeces). Thus, only <10% of the radioactivity in faeces could be structurally identified. Of the identified material, unchanged ridaforolimus accounted for <2% of the radioactivity. Of the remaining identified material, seco-ridaforolimus (M17, a ring opened form of ridaforolimus), ester-hydrolysis or seco-related products (M32, M33, and M34) and two minor unidentified components with m/z 1000 and 1014 each accounted for <1% of the radioactivity. The identity of the unresolved polar metabolites, accounting for the majority of radioactivity in faeces, was further analysed and although their structures could not be finally determined, they were suggested to be the result of metabolism and not chemical degradation.

As permeability data are inconclusive, mass-balance data alone are not sufficient to conclude whether ridaforolimus is largely absorbed but subject to a high first-pass metabolism in the enterocytes, or whether the large bulk of polar metabolites are formed in the intestinal fluid from unabsorbed ridaforolimus. However, the 8.5-fold increase in ridaforolimus at co-administration of the CYP3A4/Pgp inhibitor ketoconazole (see below) despite the fact that ridaforolimus is a low-extraction ratio substance indicate inhibition of a large first-pass effect. As ridaforolimus is a good substrate to Pgp, the high first-pass metabolism could possibly be due to enzyme-transporter interplay in the enterocyte leading to repeated presentations of the substance to CYP3A4 in the enterocyte. The large effect of ketoconazole may therefore be a combination of inhibition of CYP3A4 and Pgp in the enterocyte.

In whole blood, 81% of the radioactivity was structurally identified. Ridaforolimus was the major circulating compound in whole blood, accounting for on average 53% of the total radioactivity. The metabolites found in blood were M3, M8, M10 and M16, with none of them contributing to more than 10% of the total radioactivity. Thus, there appears to be no major metabolites in blood.

Ridaforolimus has 15 chiral centers, and a specific assessment of *in vivo* chiral inversion was not scientifically feasible. The Applicant suggests that any major chiral inversion would have been detected during metabolism studies, as inversion at any single center would result in the formation of a diasteromer, which can be separated from parent under achiral conditions. As no such metabolite was detected, significant *in vivo* chiral inversion is not likely.

Dose-proportionality and time dependency

Dose proportionality was evaluated from three dose-finding studies, two with intravenous administration and one with oral administration. Based on these data ridaforolimus whole-blood Cmax and AUC increased less than proportionally with dose. In the intravenous studies, the model-predicted whole-blood CL increased from about 2 L/hr to about 9 L/hr when doses increased from 6.25 mg to 100 mg. In the study with oral administration, whole-blood AUC increased 1.8 times between the 10 and 20 mg doses, 2.6 times between the 10 m and 30 mg doses and 1.7 times between the 20 mg and 40 mg doses. Thus, although the deviation from linearity was not large in the oral dose range 10-40 mg, there was a clear trend.

The non-linearity is suggested to be due to saturation of binding of ridaforolimus to red blood cells (RBCs). However, based on the *in vitro* data indicating that blood/plasma ratio is constant up to whole-blood concentrations of 300 ng/ml, and the reported C_{max} values after the 40 mg dose of around

180 ng/ml, binding would not be expected to be saturated at oral doses of 10-40 mg, with which most of the clinical pharmacology studies were made. Nevertheless, less than dose proportional increases in AUC were seen already at these doses. Furthermore, the non-linearity appeared to be somewhat more pronounced after oral than after IV dosing, which might indicate that there are also other, possibly absorption-related, reasons for the non-linearity that would also affect plasma concentrations and not only whole-blood concentrations. Observed data, however, indicate that plasma concentrations increase more with dose than whole-blood concentrations (although strict linearity in plasma concentrations cannot be concluded) and a model with saturated distribution reasonably well explains the pharmacokinetics of ridaforolimus. Therefore, saturated RBC binding may be assumed to be the predominating non-linearity. However, presence of other non-linearities, affecting also plasma concentrations, cannot be completely excluded.

Based on model-predicted data, the accumulation in AUC_{0-24hr} from day 1 to day 5 in the first week is estimated to be 1.9-fold at dosing qd for 5 consecutive days per week with no relevant further increases in blood levels during subsequent dosing weeks. Non-compartmental data (n=6) indicate an accumulation ratio of 1.44 for AUC_{0-24hr}. These data indicate no change in ridaforolimus pharmacokinetics over time.

Variability

In single-dose, oral studies in healthy subjects and patients with advanced cancer, the inter-individual variability (CV%) for AUC was 53-71%. The variability appeared to be higher in the fasted state. The intra-individual variability (determined in healthy subjects only) was fairly high, around 37%.

Special populations

Renal clearance appears to be of minor importance for the elimination of ridaforolimus as well as its metabolites, and no study in renal impairment was performed. In patients with severe renal impairment but not on dialysis, urinary toxins might affect hepatic clearance and thereby affect bioavailability and metabolism of ridaforolimus. As this can possibly be handled by dose reductions in subsequent treatment weeks, lack of a study to evaluate such an effect is acceptable, but a warning is included in the SPC regarding severe renal impairment.

In a specific study in 10 non-cancer patients with moderate hepatic impairment, there was a mean 2-fold increase in AUC as compared with matched healthy controls, and the Applicant suggests that the starting dose should be halved at moderate hepatic impairment. When interpreting the data from this study, it should be kept in mind that the study was performed with a single, 10 mg dose of ridaforolimus, and due to the non-linearity in ridaforolimus pharmacokinetics, the magnitude of the effect in unbound concentrations at the 40 mg dose might be difficult to predict. Moreover, from individual data it can be seen that about half of the subjects with hepatic impairment did not have increased exposure to ridaforolimus. Therefore, there might be a risk that halving the dose will lead to inadequate exposure in some individuals, while in others the reduction might not be sufficient to avoid toxicity. There was no apparent relationship between Child-Pugh score or other hepatic markers and AUC in this study, so there are currently no means to predict which patients will need dose reductions. The SmPC clarifies that the 2-fold dose reduction is an initial dose that might need to be further reduced or possibly increased based on tolerability.

Due to lack of data the Applicant suggests that treatment with ridaforolimus should not be recommended to patients with *severe* hepatic impairment, which is appropriate given the palliative setting currently proposed for ridaforolimus.

A co-variate analysis on data from altogether 44 cancer patients in a dose-finding study (P016) and a study in Japanese patients (P003; n=6) had some drawbacks, including dose-normalisation of pharmacokinetic data and limited data for some co-variates. The analysis is still considered sufficient

to suggest that there are no clinically relevant effects of gender, weight, BMI or hematocrit on ridaforolimus pharmacokinetics. Data were insufficient to draw conclusions on the effect of race or age above 70 years. There are currently no data in children.

Interactions

Effects of other substances on ridaforolimus

Ridaforolimus is almost exclusively metabolised by CYP3A4 and is a substrate for the efflux transporter Pgp. The effects of continuous treatment with a moderate CYP3A4/Pgp inhibitor (diltiazem), a potent CYP3A4/Pgp inhibitor (ketoconazole) and a potent CYP/transport inducer (rifampicin) on ridaforolimus exposure after a single dose were therefore performed. In order to avoid high exposure levels in healthy volunteers, the inhibitor studies were performed with lower doses of ridaforolimus than the clinically relevant 40 mg dose, which might have some implications on the interpretation of the results due to the non-linearity in ridaforolimus pharmacokinetics. It is, however, agreed that use of a lower dose was appropriate from a safety point of view.

With a moderate CYP3A4/Pgp inhibitor, diltiazem, the mean increase in ridaforolimus whole blood AUC was 2.3-fold. The Applicant therefore suggests that the dose should be halved at concomitant treatment with a moderate CYP3A4 inhibitor. However, individual AUC ratios ranged from about 0.8 – 8.0, i.e. there was a large variability in the effect. The variability would likely be even higher if different moderate inhibitors had been tested. In addition, the effect on plasma AUC is not known. A dose reduction by half could therefore lead to inadequate exposure in some subjects, while in others it would not reduce the exposure sufficiently to avoid dose-limiting toxicity. Thus, a reduction of the initial dose by half based on PK data followed by potential further dose adjustments based on tolerability is a reasonable approach.

With a potent CYP3A4/Pgp inhibitor, there was a substantial increase in ridaforolimus AUC, with a mean AUC ratio of 8.5. Exact quantification of the effect at the clinical dose may be somewhat uncertain, given that a lower dose was administered, and the formulation used was a dry-filled capsule with possibly lower bioavailability than the enteric-coated tablet intended for market. However, this is acceptable as such a large effect (which is also highly variable between individuals) can hardly be handled by dose reductions, and the Applicant therefore suggests that concomitant treatment with potent CYP3A4/Pgp inhibitors should be avoided, which is adequate. The Applicant does not want to add a contra-indication for potent CYP3A4/Pgp inhibitors, as this is not the case for other mTOR inhibitors that are affected by inhibitors to a similar extent.

The potent inducer rifampicin decreased ridaforolimus whole blood exposure by on average 43%, but the effect varied from between a 5-fold decrease in exposure to a 10% increase. The Applicant suggests that the primary recommendation should be to avoid concomitant treatment with potent inducers, but that if such treatment cannot be avoided, the ridaforolimus dose should be increased by 50%, to 60 mg qdx5. However, for individual patients, this dose increase will not be sufficient to compensate for the decrease in AUC. The SmPC clarifies that individual patients might need further dose adjustments upwards (to a maximum of 70 mg) or downwards based on tolerability, which is possibly the best option if concomitant administration of an inducer cannot be avoided. Another problem is that rifampicin, although being an inducer of CYPs via PXR, is an inhibitor of OATP1B1. Indeed, the mean effect of rifampicin was unexpectedly small given the large effect of a CYP3A4 inhibtor, and more in the range that would be expected for a moderate inducer, which might indicate that ridaforolimus is a substrate for OATP1B1, and that the induction effect was therefore counteracted by OATP1B1 inhibition. If this is the case, the effect of other inducers, not inhibiting OATP1B1, might be larger. Until data on whether ridaforolimus is a substrate to OATP1B1 are available, firm conclusions on the effect of other potent inducers cannot be drawn.

Effects of ridaforolimus on other substances

In vitro CYP inhibition

The inhibition potential of ridaforolimus against CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 was investigated in human liver microsomes. The concentration range of ridaforolimus (0.03-30 µM, 7 concentration levels) was suitable in order to detect any interactions of clinical relevance. At steady state with the 40 mg qd x 5 days/week dosing, mean C_{max} is about 190 ng/ml, or 0.2 µM. Given the B/P ratio of 9 and a plasma protein binding of about 94%), unbound C_{max} is in the range of 0.001 µM. Ridaforolimus was a direct inhibitor of CYP2C9, CYP2D6 and CYP3A4/5 (as measured by both testosterone 6β–hydroxylation and midazolam 1´-hydroxylation) with (nominal) IC50 values of 21, 16, 21 and 1.4 µM, respectively. There was also some inhibition of CYP2B6 and CYP2C8, but no IC50 value could be determined (>30 µM).

There was substantial degradation of ridaforolimus in the *in vitro* incubations. Within the 5 minutes incubation used in these experiments, there was an approximately 40% loss of the investigational drug. The majority of substrate loss was likely caused by NADPH-dependent metabolism. Thus, the IC50 values determined in the inhibition assay may be overestimated and the actual IC50 values may be only 60% of the nominal value. The margin to unbound C_{max} (0.001 µM) at the clinical dose is still wide, and inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP2D6 at clinically relevant concentrations is not expected.

However, in another *in vitro* study, some time-dependent inhibition of CYP3A4 was observed. After 30 minutes pre-incubation, the IC50 value for inhibition of testosterone 6β–hydroxylation shifted from 21 µM to 2.8 µM and for inhibition of midazolam 1´-hydroxylation from 1.4 µM to 0.94 µM. This was only observed when a NADPH-generating system was present, which might indicate that the effect was metabolism dependent. Therefore, an *in vivo* interaction study with midazolam (CYP3A4 substrate) was performed.

In vitro CYP induction:

The potential of ridaforolimus to induce enzymes and transporters via activation of the aryl hydrocarbon receptor (Ah-receptor) and the pregnane X receptor (PXR) was investigated with CYP1A2 and CYP3A4 as marker for the regulatory pathways, respectively. Ridaforolimus was incubated in human hepatocytes (three donors) for three days treated once daily with vehicle (0.1% v/v DMSO), one of three concentrations of ridaforolimus (0.1, 1 or 10 µM) or one of two known inducers serving as positive controls (50 µM omeprazole, CYP1A2; 10 µM rifampin, CYP3A4). The concentration of ridaforolimus was not determined during the 3-day hepatocyte incubation. Given the observation of degradation of ridaforolimus in the inhibition experiments, the actual drug exposure surrounding the hepatocytes is uncertain, and margins to clinical exposure may not be readily calculated.

Ridaforolimus slightly reduced CYP1A2 activity at the lower concentrations. The decrease was on average 14%, 22% and 25% at 0.1 µM 1 µM and 10 µM, respectively. The decrease in CYP1A2 activity was accompanied with a reduction in CYP1A2 mRNA levels. The Applicant suggests that ridaforolimus could be an inhibitor/suppressor of CYP1A2. Even though the *in vivo* consequences of the findings remain unclear, information on the effect needs to be included in the SmPC.

Ridaforolimus reduced CYP3A4 activity in a concentration-dependent manner: the decrease was on average 12%, 33% and 53% in the 0.1 µM, 1 µM and 10 µM incubations, respectively. In contrast to the activity data, ridaforolimus caused a concentration-dependent increase in the CYP3A4 mRNA levels. In one of the hepatocyte preparations, substantial increase in CYP3A4 mRNA levels was observed also at the lower concentrations: the increase was 39% and 33% of the positive control at 0.1 µM and 1 µM, respectively. Based on the increase in CYP3A4 mRNA levels in this specific hepatocyte preparation (that may serve as “worst-case”) and the uncertainty in the actual drug exposure surrounding the

hepatocyte, it cannot be excluded that ridaforolimus may be an inducer via PXR *in vivo*. The interaction study with midazolam suggested that the net effect on CYP3A of repeated use of ridaforolimus in vivo is inhibition and not induction of the enzyme (see below). However, CYP3A4 serves only as a marker for PXR-mediated induction and it cannot be excluded that for other co-regulated enzymes that are not also inhibited the net effect of ridaforolimus in vivo might be induction. Hence, the SmPC should include information that *in vitro* data suggest that ridaforolimus may induce CYP2C8, CYP2C9, CYP2C19 and CYP2B6, but that the clinical relevance of this result is unknown.

In vitro Pgp inhibition:

The inhibitory effect of ridaforolimus (at 1, 5, 10, 25 and 50 µM) on Pgp was investigated in wildtype LLC-PK1 (control) and LLC-PK1 cells stably transfected with MDR1 (Pgp), using [^{3}H]digoxin as marker substrate.

At the highest incubation concentration of ridaforolimus (50 µM) the mean digoxin efflux ratio was reduced from 5.0 to 1.1 in the LLC-MDR1 cells. Ridaforolimus inhibited MDR1-mediated digoxin transport with an IC50 of 13.4 µM. The ratio of the total Cmax at steady state to IC50 is 0.015, and the margin for unbound concentrations is considerably wider. Therefore, at the clinical dose a systemic *in vivo* interaction is not likely. Regarding inhibition of intestinal Pgp, additional data provided by the Applicant in response to questions indicates that there was no problem with non-specific binding in the LLC-PK1 *in vitro* assay. The chemical stability data provided shows minor degradation during 60 min in microsome and hepatocyte incubation buffer (6-7% degradation). Also if assuming a somewhat greater degradation in the 3-hr Pgp assay, the ratio between the worst-case concentration of ridaforolimus in the gut (I_2=dose/250=161 µM) and the estimated IC50 value (13.4 µM) is close to 10, which is the limit for not excluding a risk for *in vivo* interaction (Agarwal et al, J Clin Pharmacol, 2012, Feb 7, Epub). As the I_2 is most likely overestimated by this formula given the poor solubility of ridaforolimus, the ratio is expected to be even smaller, and the risk for a clinically relevant *in vivo* interaction appears unlikely.

In vivo data:

An *in vivo* study with oral midazolam, a sensitive CYP3A4 substrate, was performed in healthy volunteers. Midazolam was administered on Day 5 in Cycle 1 of ridaforolimus dosing at 40 mg, i.e. when ridaforolimus blood concentrations are expected to be at its maximum with the normal clinical regimen of 40 mg qdx5 per week. The results of the study indicated that ridaforolimus is a mild CYP3A4 inhibitor *in vivo*. The midazolam AUC increased by on average 23%, with individual values ranging from a 43% *de*crease to an 80% increase. As it was unclear whether any time-dependent inhibition had reached its maximum effect after 5 days of dosing with ridaforolimus., the Applicant performed a simulation using Simcyp in order to estimate the effect on CYP3A34 after repeated cycles. The results indicated that the maximal inhibitory effects of ridaforolimus were reached following oral administration of 40 mg ridaforolimus once daily for 5 days and that longer term treatment of ridaforolimus would not have had additional inhibitory effects on CYP3A. However, the provided data lacked some important information, including a discussion of some of the assumptions made and sensitivity analyses. A short Kdeg was used (corresponding to an enzyme half-life of 23 hours), likely due to the fact that the Applicant mainly predicts inhibitory concentrations in the intestine. This may be true but some inhibition also in the hepatocyte cannot be excluded. The simulated $AUC_{0\text{-}24h}$ of ridaforolimus on day 15 is about 15% under-predicted and, thus, if there is some inhibition in the hepatocytes, this will lead to a slight under-prediction in the inhibitory effect. Adding to the under-prediction in this case will be the short kdeg used (fast turnover of enzyme), and the uncertainty of the *in vitro* IC50 value (which might be over-predicted due to degradation in the incubation). In conclusion, the SmPC text should inform that it may not be excluded that the inhibitory effect on

CYP3A4 substrates is somewhat higher after repeated cycles, than that observed in the midazolam study.

Potential, not studied interactions

The low bioavailability of ridaforolimus is likely due to first-pass metabolism via CYP3A4 and also to active efflux and transporter-enzyme interplay. BCRP has been identified as an important efflux transporter that may be involved in first-pass metabolism.

It is agreed that ridaforolimus does not possess the characteristics typical seen for substrates of uptake transporters OCT1, OAT1B1 and OATP1B3. However, since there are no firm conclusions to date regarding the relationship between the molecular structure of a compound and the potential of a compound being a substrate for a transport protein such reasoning remains speculative. Also the fact that ridaforolimus might be a high-permeability compound is not considered sufficient to exclude that active transport contributes to the movement across the membrane of hepatocytes. The relatively small induction effect of rifampicin on the plasma AUC of ridaforolimus (43% decrease, see below) could possibly be explained by rifampicin inhibiting liver uptake of ridaforolimus via OATP1B1/OATP1B3 and thereby counteracting the induction effect by limiting access to the hepatocytes. To avoid speculative arguments on whether ridaforolimus is a substrate for OATP1B1 and OATP1B3, and to clarify what the effect would be when co-administering ridaforolimus with an inducer of CYP3A with no inhibitory effects on hepatic uptake transporters, the Applicant should perform *in vitro* experiments investigating this issue.

Thus, additional *in vitro* studies should be performed to investigate whether ridaforolimus is a substrate to BCRP or OATP1B1/1B3.

Relationship between plasma concentration and effect

In order to determine the clinical relevance of a change in exposure due to intrinsic or extrinsic factors, the Applicant defined a 90% interval for the whole-blood AUC geometric ratio of the mean that is considered to indicate clinical comparability (clinical comparability bounds) of 0.65 to 2.0. These bounds were determined based on a PK-PD analysis of data from the dose-finding study P016.

The upper range of the therapeutic window was explored through the PK/AE relationship for the probability of occurrence of Grade 2 or greater stomatitis as a function of blood C_{avg}. The PK/AE model predicts that roughly half of patients at a 2.0-fold elevation in blood exposure will experience a Grade 2 or higher stomatitis event and thus will require a dose-adjustment. However, since a meaningful proportion (roughly half) of the patients are predicted to be able to tolerate the starting dose of 40 mg q.d. x 5 days/wk at the 2.0-fold upper bound, the Applicant suggests that it is clinically appropriate to use the full starting dose for patients with intrinsic/extrinsic factors with effects up to 2.0-fold. At greater elevations, the Applicant means that it is clinically appropriate to start patients at a reduced starting dose.

The lower range of the therapeutic window was explored through the PK/Efficacy relationship for the best percent change in target lesion measurement as a function of blood C_{avg}. Based on the PK-PD analysis, lowering the exposure to about 65% of the typical exposure (corresponding to about half the dose, due to the non-linearity in pharmacokinetics), would decrease the probability of the individual patient to achieve a reduction in target lesion measurement from 0.61 to about 0.54, i.e. a decrease by 12%, which by the Applicant is considered acceptable. Given the currently proposed palliative setting for ridaforolimus this might possibly be agreed. It should be noted that the estimates should be carefully interpreted in view of the limited data (n=59 patients from P016) and may not be applicable to different patient populations. The model-estimated residual error was high (i.e. SD 19.5%), suggesting that additional factors beyond PK substantially contribute to response in an individual patient. Thus, there are a number of drawbacks to the exploratory PK/PD assessments primarily due to

the small size of the available PK/tolerability/RECIST dataset for modelling, which limit the certainty to which the therapeutic window for ridaforolimus can be determined.

Pharmacodynamics

The mechanism of action is described in section 2.2. p.3.

For dose selection, please refer to **Dose response study – P016**.

Biomarkers were investigated in the phase II study P018. No relationships were found between clinical outcome and 9 tumour markers or with plasma VEGF levels.

Secondary Pharmacology

The potential for QTc prolongation was assessed in Study P037, please see p. 47.

Pharmacodynamic interactions

Pharmacodynamic interactions with other anti-cancer agents causing additive degrees of side effects such as myelosuppression and mucositis can be foreseen.

Discussion on clinical pharmacology

The Applicant has performed a number of relevant *in vivo* pharmacokinetic studies, and no additional *in vivo* data are considered necessary, while regarding *in vitro* data, a couple of additional investigations should be performed in order to predict the interaction risk on a transporter level.

When interpreting data from studies in special population and interactions studies, the non-linearity of ridaforolimus pharmacokinetics should be considered. Some of these studies were not performed at the clinical 40 mg dose, and the magnitude of e.g. an interaction effect at a lower dose might not be the same as at a higher dose. Moreover, as the non-linearity is likely primarily due to saturated binding to RBCs, changes in *plasma* AUC due to extrinsic/intrinsic factors might be similar regardless of dose level or blood concentration, while changes in whole-blood AUC will be greater at lower doses/lower concentrations than at higher doses/higher concentrations. An increase in whole-blood AUC due to e.g. an interaction will then be smaller than the increase in plasma AUC. For example, with a moderate CYP3A4-inhibitor (diltiazem), the AUC_{blood} increased by on average 2.3-fold, and a dose reduction from 40 mg to 20 mg QDx5 is proposed. By simulation using model-predicted plasma levels, the estimated change in AUC_{plasma} would be about 2.8-fold. However, it is currently unknown whether plasma pharmacokinetics of ridaforolimus are linear, and therefore whether the assumptions made in the simulation are correct.

Nevertheless, it is agreed that since dose adjustments will be limited to 10 mg increments or decrements, it might not be clinically feasible to take a potential difference between change in plasma and blood AUC into account, and the Applicants proposals for adjustment of the *initial* dose at moderated hepatic impairment, with a moderate CYP3A4 inhibitor and with an inducer, respectively, are accepted. However, the variability in the observed effects of extrinsic/intrinsic factors is a concern. The Applicant argues that the variability in AUC seen after the proposed dose adjustments in patients with moderate hepatic impairment, on a moderate CYP3A4 inhibitor or with a CYP3A4 inducer, respectively, is not predicted to be greater than that observed after a 40 mg single dose. This argument is not considered fully valid as the distribution of AUC values after a single dose does not say anything about safety or efficacy at the upper and lower ends of the AUC range, respectively. Thus, like in the “normal” patient population, also after dose adjustment for an intrinsic or extrinsic factor, overexposure will have to be handled by further dose reductions while underexposure will be more difficult to detect. In response to questions, the Applicant has amended the SmPC to clarify that also in

patients who have their starting dose adjusted due to intrinsic or extrinsic factors, additional dose adjustments, upwards as well as downwards, may be necessary. The recommendations for moderate hepatic impairment and a moderate CYP3A4 inhibitor are now considered acceptable. However, as it is uncertain whether the effect of the potent inducer rifampicin can be extrapolated to other potent inducers, due to the OATP1B1 inhibiting properties of rifampicin, some amendments of the wording for CYP3A4 inducers should be made.

The Applicant has defined a 90% confidence interval (clinical comparability bounds) within which a change in exposure from the typical is not considered clinically relevant. This attempt to determine the therapeutic window for ridaforolimus is interesting, but the PK/PD analysis is limited by the low number of patients included in the analysis, and the comparability bounds should be used with caution.

Conclusions on clinical pharmacology

Ridaforolimus pharmacokinetics have been sufficiently well characterised *in vivo*, but additional *in vitro* studies should be performed to investigate whether ridaforolimus is a substrate to BCRP or OATP1B1/1B3, in order to better predict the interaction risk. This should be added as missing information in the RMP.

In response to questions, the Applicant has adequately discussed some uncertainties in the available pharmacokinetic data and made improvements of the SmPC in terms of food effect, the information around the dosing adjustments for extrinsic or intrinsic factors and regarding interaction warnings. Apart from the recommendation for concomitant use of inducers, the SmPC is considered acceptable from a pharmacokinetic point of view.

The mTOR inhibitory effect of ridaforolimus is mainly cytostatic, by causing a decreased proliferation. Some anti-angiogenic activity is also theoretically possible, but no relationship between plasma VEGF levels and clinical outcome was seen in the phase II study P018. Anti tumour activity in sarcoma patients has been shown by the achievement of partial responses in the pivotal study P011, as well as in the supportive dose finding phase I study P016 and the phase II study P018.

The effect on QTc has not been thoroughly evaluated. A weak signal for an effect on QTc was observed at whole blood concentrations similar to those of the standard dosing regimen.

Pharmacodynamic interactions with other anti-cancer agents causing additive degrees of side effects such as myelosuppression and mucositis can be foreseen.

Clinical efficacy

Dose response study – P016

The dose and schedule selected for the pivotal sarcoma study (P011) was based upon achievement of the best balance between dose density (most doses administered in a dosing cycle), cumulative dose, cumulative exposure (AUC0-28days), and tolerability in the regimens tested in Study P016 (Protocol AP23573-05-106 / MK-8669-016). P016 is also a supportive study for efficacy in the present application.

Patients in this trial were assigned to receive one of seven different ridaforolimus dosing regimens, including two regimens with daily dosing. Treatment was continued until disease progression or intolerable toxicity. Dose-limiting toxicity (DLT) was determined on the basis of the severity, duration, and negative effect on daily activities. As a result, DLT was not necessarily related to the severity grade of the adverse event. The maximum tolerated dose (MTD) was defined as the dose below the

dose that produced dose-limiting toxicities in at least one-third of at least six patients treated within a dose cohort in Cycle 1.

The two daily dosing regimens both had early DLTs and MTDs at the 10-15 mg/day level. Based on the MTD identified for each of the tolerated schedules, two schedules had the highest cumulative dose (800 mg over the 28 day cycle). Of these, the 40 mg q.d. x 5 days/week regimen had the highest dose density over the 28 day cycle (20 doses) compared to 50 mg q.d. x 4 days/week (16 doses). The cumulative exposures appeared similar. Accordingly, the 40 mg q.d. x 5 schedule had the highest combination of cumulative dose, dose density, and cumulative exposure, and was chosen for the pivotal study.

Efficacy

After 26 weeks of treatment with ridaforolimus, 13.2% and 23.1% of the patients across histologies and with sarcoma, respectively, were progression-free. Two patients (both sarcoma patients) in the 40 mg q.d. x 5 days/wk cohort experienced partial response, but none in other cohorts. No conclusions can be drawn with regard to the relative efficacy in different cancer types due to the uncontrolled nature of the study, i.e. the longer PFS in sarcoma compared with other disease entities may be a reflection of underlying prognosis rather than a differential effect of ridaforolimus. The partial responses seen in two sarcoma patients in the 40 mg q.d. x 5 days/week cohort may be considered supportive of the pivotal study.

Main study – Pivotal Study P011

Design and Methods

The Pivotal study, Protocol 011 (P011), "SUCCEED", was a multicenter, randomized, Phase III placebo-controlled, double-blind trial that evaluated the efficacy and safety of ridaforolimus maintenance therapy in patients with metastatic soft tissue sarcoma (STS) or bone sarcoma who had achieved response or stable disease from immediately prior cytotoxic chemotherapy given for a minimum of 4 cycles as 1st, 2nd or 3rd line therapy.

This design was initially questioned on the grounds that observation may not be the most probable clinical option after four to six cycles of chemotherapy obtaining stabilisation. However, in the responses to questions the Applicant has convincingly shown that the median of 6 cycles of the preceding line of chemotherapy shown for both the ITT population and the 2nd/3rd line (2/3 L) population of Study P011 is in line with what is seen, or planned for, in other sarcoma studies (SABINE) and databases (Lyon database). It is agreed that watchful waiting is a standard strategy in this setting after stable disease is achieved and consolidated, which in relevant comparisons thus has occurred after a median of 6 chemotherapy cycles. The reaching of maximum cumulative doses of anthracyclines and ifosfamide is also a reason for not continuing therapy beyond 6 cycles in many cases, in current day treatment practice.

Eligible patients were stratified by geographical region, histological category (STS vs. bone sarcoma), and prior treatment (1st line vs. 2nd/3rd line) and were randomly assigned in a 1:1 ratio within strata to receive either ridaforolimus or placebo using an Interactive Voice Response System (IVRS). Regions (North America, EU, Rest of World [ROW]) were selected based on geographic and treatment practice considerations.

P011 was a double-blind trial. The unblinding occurred after database lock for the final PFS analysis. However, due to the characteristic toxicity profile of ridaforolimus, including mucositis/stomatitis, the treatments may have been unblinded to investigators and patients.

Tumour response assessments were made according to internationally accepted RECIST criteria version 1.0.

Treatments

Patients took four tablets once daily of ridaforolimus (10 mg each) or matching placebo, 5 days per week continuously, without interruption (40 mg qdx5/week of ridaforolimus).

Baseline characteristics

The study population was predominantly white (80%). Fifty percent were recruited in North America, 34% in the EU. The histology was STS in 90% and bone sarcoma in 10% of patients. Leiomyosarcoma was the largest histology subgroup of STS, composing 32% of both treatment arms. Prior surgery had been received by 90%, and prior radiotherapy by 50% of study patients. Sixty-three percent had received only one prior chemotherapy regimen. At initial diagnosis 35% had lung metastasis, 83% had liver metastasis and 89% had bone metastasis. These and other baseline characteristics, including response to prior therapy, were all well balanced between treatment arms.

Table 1. Key Baseline and Demographic Factors by Line of Therapy

	First Line		Second/Third Line	
	Ridaforolimus (n=212)	Placebo (n=224)	Ridaforolimus (n=135)	Placebo (n-140)
Age, Median (Years)	52.0	51.5	56.0	53.0
Male	49%	40%	41%	47%
ECOG 0	50%	54%	50%	45%
ECOG 1	50%	46%	49%	55%
Histological Category[a]				
Soft Tissue	89%	92%	90%	89%
Bone	**11%**	**8%**	**10%**	**11%**
Number of prior cytotoxic chemotherapy regimens[b]				
1	99%	100%	3%	6%
2	<1%	0	67%	68%
3	0	0	30%	24%
≥4	0	0	<1%	<1%
Number of chemotherapy cycles prior to enrollment (median)	6	6	6	6
Independent Pathologist Tumor Grade				
Low	4%	3%	4%	9%
High	71%	79%	**79%**	**64%**
Cannot be assessed	11%	5%	4%	13%
Not Applicable	2%	2%	3%	2%
Missing	12%	11%	10%	11%
Best response to most recent cytotoxic chemotherapy regimen[b]				
CR	6%	8%	**5%**	**1%**
PR	22%	25%	**13%**	**9%**
SD	71%	67%	80%	89%
Unknown	<1%	<1%	2%	<1%
Metastatic Sites [c]				
Lung	67%	63%	67%	66%
Liver	14%	17%	16%	22%
Bone	13%	12%	10%	9%

[a] From stratification. [b] For metastatic disease. [c] Based on presence of target or non-target lesions in these sites at baseline by IRC (Database Cutoff Date: 25OCT2010)

The key baseline and demographic factors were overall well balanced between the ridaforolimus and the placebo arm in the 2/3L subgroup, with the main exception of best response to most recent cytotoxic chemotherapy, where fewer responses (CR+PR) were seen in the placebo group (10%), compared with the ridaforolimus group (18%), causing potential bias in favour of the ridaforolimus arm.

The net effect of the difference in high grade tumours (64 vs. 79%; placebo vs. ridaforolimus) is difficult to predict, i.e. whether the higher proportion of high grade tumours would be reflected by a poorer prognosis or by better chemo-responsiveness in the ridaforolimus arm.

Primary endpoint - PFS

The primary endpoint and analysis was PFS in the ITT population by the IRC assessment. Alternative assessments (by Site) and populations (PP, and modified ITT) were also analysed. Additionally, exploratory alternative methods adjusting for the interval censored nature of the data (not shown, see Table 8 in Clinical Day 80 AR).

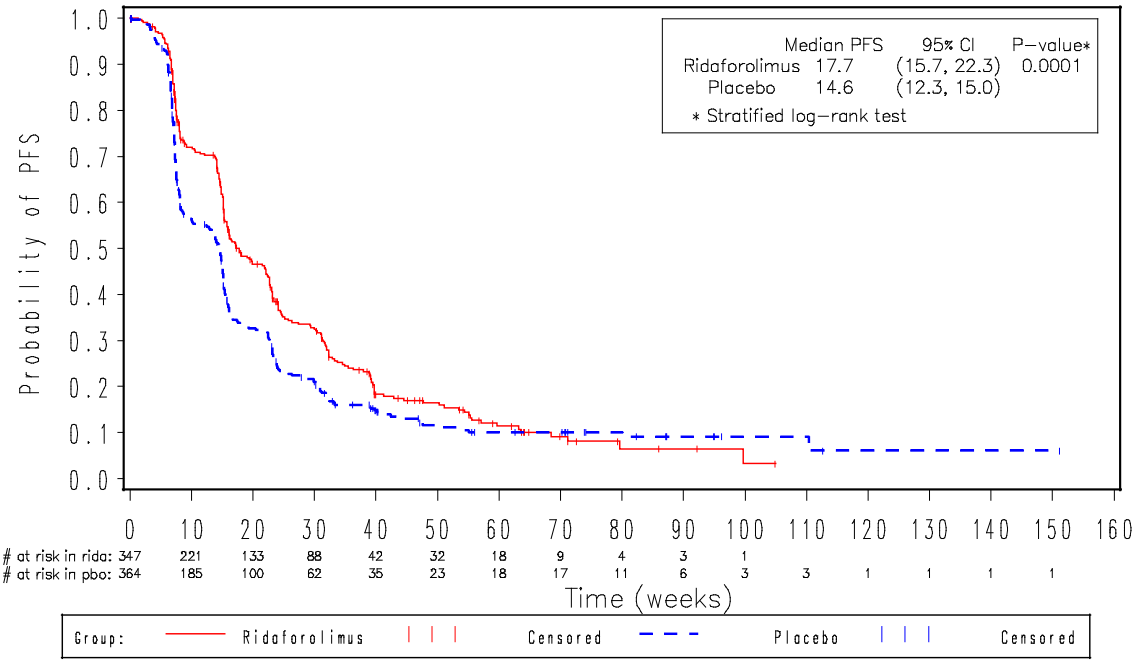
Table 2. Progression-Free Survival (ITT Population)

	N	Number of PFS Events	Number Censored	PFS (weeks) Median (95% CI)	Hazard Ratio§ (95% CI)	p-value†	p-value‡
IRC Assessment							
Ridaforolimus	347	261	86	17.7 (15.7, 22.3)	0.72 (0.61, 0.85)	0.0001	0.0012
Placebo	364	291	73	14.6 (12.3, 15.0)			
Total	711	552	159				
Site Assessment							
Ridaforolimus	347	278	69	22.4 (17.7, 23.4)	0.69 (0.58, 0.81)	<.0001	<.0001
Placebo	364	319	45	14.7 (12.9, 15.1)			
Total	711	597	114				

†: Log-rank test, stratified over histology (bone vs. soft-tissue sarcoma) and prior chemotherapy (lst line vs. 2nd/3rd line)
‡: Unstratified log-rank test
§: Based on a stratified[1] Cox Proportional Hazards Model with treatment as a covariate (Ridaforolimus relative to Placebo)
IRC= Independent Review Committee
PFS= Progression Free Survival
CI=Confidence Interval
(Database Cutoff Date: 25OCT2010)

Source: Study P011 CSR, Table 11-2.

Figure 1.Kaplan-Meier Plot of Progression-Free Survival by IRC Assessment (ITT Population)



(Database Cutoff Date: 25OCT2010)
Note: (Counts- E+C=N, N=Total, E=PFS Event, C=Censored Event):
(Ridaforolimus: 261+86=347, Placebo: 291+73=364, Overall: 552+159=711)

Source: Study P011 CSR, Figure 11-1 (Clinical Overview Figure 2.5: 1)

The stratified and unstratified IRC-based and site-based analyses of the ITT population showed statistically significantly longer PFS in the ridaforolimus arm compared with the placebo arm, with similar significant(stratified) HRs for the IRC (0.72) and site-based (0.69) analyses.

The 3.1 week difference in median PFS between the treatment arms is most likely an underestimation of the treatment effect, judging by the look of the Kaplan-Meier curves. A rough estimation based on the HR and median of the control arm perhaps gives a more relevant estimation of the treatment effect: $Median^{control}$ / HR = estimated $Median^{experimental}$, i.e. 14.6 / 0.72 = 20.3. This would indicate a difference in PFS medians of approximately 5.7 weeks (20.3 – 14.6 = 5.7).

The difference in medians of the site assessment-based analysis was 7.7 weeks (22.4-14.7 weeks). When the same formula as above is applied, the calculated median for the ridaforolimus arm is 21.3 weeks and the difference in medians 6.6 weeks.

PP and MITT populations

Apart from the ITT population, two additional efficacy populations were analysed.
The per protocol (PP) population included all patients who were randomised, treated, eligible, and without major protocol violations. The most frequent protocol violations were: patients deemed non-compliant with study medication (e.g. a dose delay of > 4 weeks in any cycle, or less than 75% compliant with study medication for all cycles while treated), less than 4 cycles of prior CT or last dose of prior CT being delivered outside the stipulated time frame, and patients not eligible based on histology. The Modified ITT (MITT) population was the ITT population excluding the patients who were not eligible based on pathology.

The IRC-based PFS analysis in the PP population generated the HR 0.71 (0.59, 0.86), p=0.0004, and the site-based analysis the HR 0.69 (0.58, 0.83), p<0.0001. The median PFS was 16.3 vs. 13.9 weeks in the IRC-based analysis (difference: 2.4 weeks), and 19.9 vs. 14.1 weeks in the site-based analysis (difference: 5.8 weeks).

The IRC-based PFS analysis in the MITT population generated the HR 0.72 (0.60, 0.85) 0.0002, and the site-based analysis the HR 0.68 (0.58, 0.81), p<0.0001. The median PFS was 17.3 vs. 14.6 weeks in the IRC-based analysis (difference: 2.7 weeks) and 22.4 vs. 14.7 weeks in the site-based analysis (difference: 7.7 weeks).

IRC vs. Site:

In the ITT analyses (including alternative methods), as well as in PP and MITT analyses, larger differences in median PFS are seen in the site assessment-based analyses compared with the IRC-based analyses. Since the investigators were in many cases likely to be unblinded with regard to study arm due to the toxicity of the active arm, a theoretical risk exists that this affected the assessment.

It was also noted as a major deviation with regard to quality of efficacy data at the inspection of site 746 that date of PD reported by the investigator for 4 reviewed patients was 2 to 3 months posterior to date of PD according to RECIST guideline.

A concordance analysis between IRC and Site assessments of PD and Non-PD was performed. This showed an overall high degree of concordance of 82%. There did however appear to be a certain degree of bias in the site assessments favouring the ridaforolimus arm. Given this tendency of bias in the Site assessment, it is suggested that most emphasis in the evaluation of results should be given to the IRC analysis. Fortunately, the pre-specified primary endpoint was IRC assessed PFS.

2nd/3rd line Subpopulation

As a response to CHMP opinion of a negative benefit/risk balance in the full study population, the proposed indication has been narrowed to comprise patients in the 2nd/ 3rd line setting only. Data for this subset is presented below.

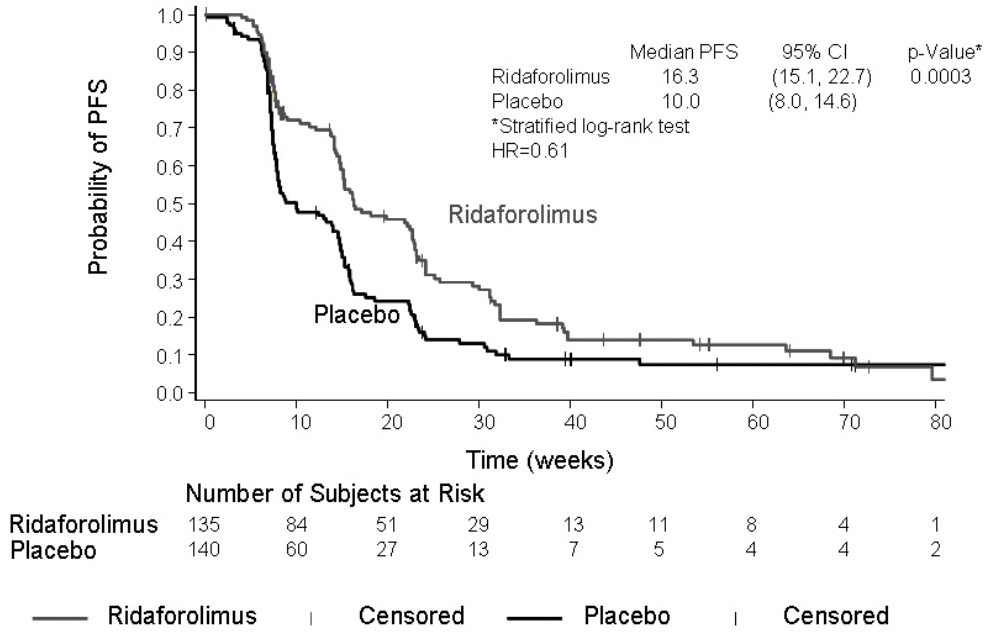
Table 3. Progression-Free Survival by Line of Therapy (ITT Population)

	N	Number of PFS Events	Number Censored	PFS (weeks) Median (95% CI)	Hazard Ratio§ (95% CI)	p-value†	p-value‡
1st Line of Therapy							
Ridaforolimus	212	158	54	17.7 (15.4, 23.0)	0.80 (0.64, 0.99)	0.043	0.0608
Placebo	224	179	45	15.0 (13.9, 15.6)			
Total	436	337	99				
2nd or 3rd Line of Therapy							
Ridaforolimus	135	103	32	16.3 (15.1, 22.7)	0.61 (0.46, 0.80)	0.0003	0.0011
Placebo	140	112	28	10.0 (8.0, 14.6)			
Total	275	215	60				

†: Log-rank test, stratified over histology (bone vs. soft-tissue sarcoma) and prior chemotherapy (1st line vs. 2nd/3rd line).
‡: Unstratified log-rank test
§: Based on a stratified[1] Cox Proportional Hazards Model with treatment as a covariate (Ridaforolimus relative to Placebo)
CI=Confidence Interval
PFS=Progression Free Survival
(Database Cutoff Date: 25OCT2010)

Source: Applicant's Clinical Response Document to Day 180 LoI, Table S-3.

Figure 2.Kaplan-Meier Plot of Progression-Free Survival by IRC Assessment in the 2nd/3rd line Subpopulation



Source: Applicant's Clinical Response Document to Day 180 LoI, Figure 1.

In the 2/3L subpopulation, the PFS HR is 0.61 (p = 0.0003), and the median PFS difference is 6.3 weeks by Kaplan-Meier estimate. In this case, if the median difference is "smoothed" and estimated based on the hazard ratio (1/HR x PFS in the control arm = PFS in the treatment arm, as above), the result is 6.4 weeks, in good agreement with the PFS estimate from the Kaplan-Meier curves.

Thus, the absolute effect of ridaforolimus on the primary endpoint in the 2/3L is similar to the effect in the total population, after simple smoothing has been applied based on the HR to correct for the shape of the curves (5.7 weeks).

Secondary endpoints

Overall survival

The original analysis of the secondary endpoint OS was based on 313 death events (44% of the ITT population) up to the data cut-off date 25-Oct-2010 (Table 4).The study was not powered to detect an OS difference. The stratified analysis is the primary analysis of this endpoint.

An updated OS analysis was performed based on 386 deaths (54% of the ITT population) as per the data cut-off on 30-Apr-2011 (Table 4, Figure 3). In this analysis there were altogether 386 deaths or 54% of the ITT population.

In response to questions an additional OS update was performed in January 2012 based on 478 deaths (67% event rate) that showed a median OS of 90.6 weeks (95% CI: 80.0, 102.3) for patients assigned to ridaforolimus and 85.3 weeks (95% CI: 76.3, 92.7) for patients assigned to placebo, a difference of 5.3 weeks, consistent with the difference observed in PFS of about 5-6 weeks (Table 4). The HR is 0.93, favouring ridaforolimus (95% CI: 0.78, 1.12; p-value=0.4561). The Kaplan-Meier plot of OS based on 21 January 2012 cut-off is shown in Figure 3.

Table 4. Overall Survival per original and updated analysis, respectively, Study P011 (ITT Population)

Analysis/ Cut-off date	Treatment arm /Total	N*	Number of OS Events	Number Censored	Median OS (weeks) (95% CI)	Hazard Ratio§ (95% CI)	p-value†	p-value‡
Original analysis, Data cut-off 25 Oct 2010	Ridaforolimus	347	147	200	88.0 (77.9, 102.3)	0.92 (0.74, 1.15)	0.4681	0.5429
	Placebo	364	166	198	78.7 (68.3, 89.9)			
	Total	711	313	398				
Updated analysis, Data cut-off 30 Apr 2011	Ridaforolimus	347	178	169	93.3 (80.0, 102.6)	0.88 (0.72, 1.08)	0.2256	0.315
	Placebo	364	208	156	83.4 (71.3, 91.7			
	Total	711	386	325				
Updated analysis, Data cut-off 21 Jan 2012	Ridaforolimus	329	228		90.6 (80.0, 102.3)	0.93 (0.78, 1.12)	0.4561	
	Placebo	354	250		85.3 (76.3, 92.7)			
	Total	683	478					

*For the 2012 updated analysis patients known to be dead or having a survival follow-up recorded within 90 days of the data cut-off were included in the analysis. Survival follow-up was incomplete on 28 (3.9%) patients (18 [5.2%] in the ridaforolimus arm, and 10 [2.7%] in the placebo arm).

§: Based on a stratified Cox Proportional Hazards Model with treatment as a covariate (Ridaforolimus relative to Placebo)

†: Log-rank test, stratified over histology (bone vs. soft-tissue sarcoma) and prior chemotherapy (1st line vs. 2nd/3rd line).

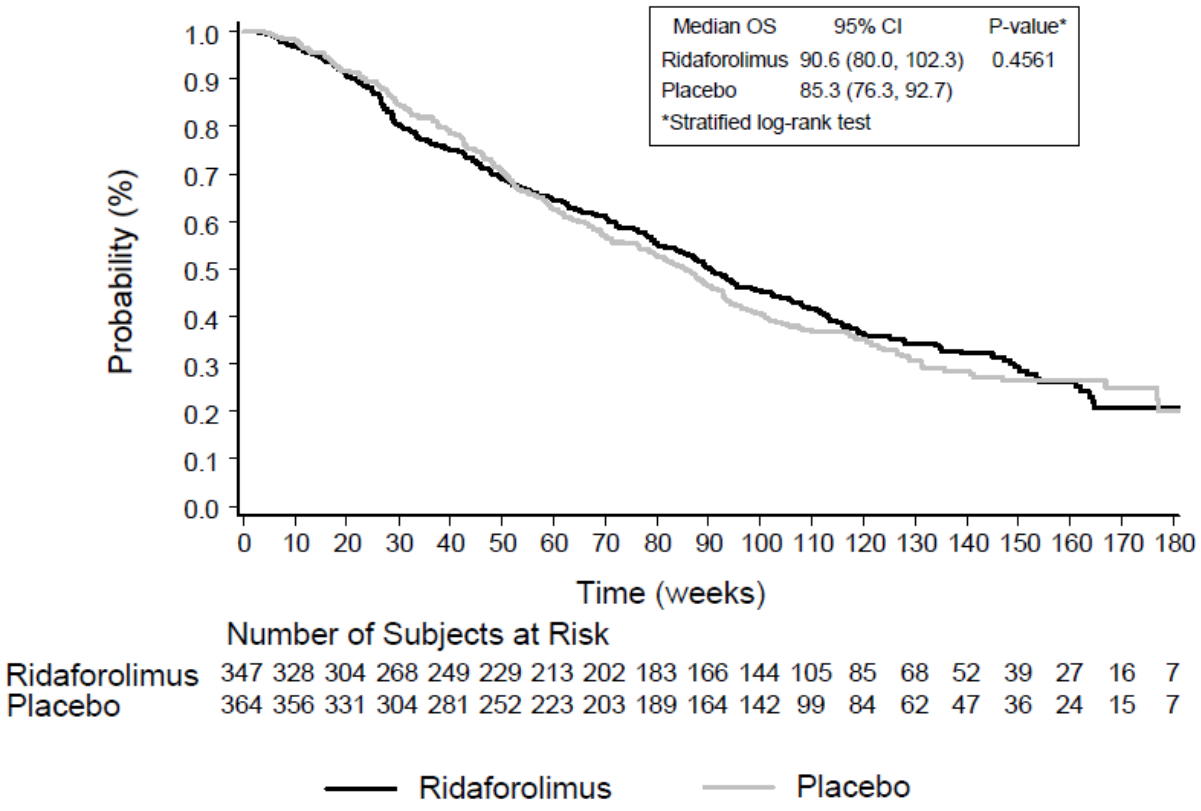
‡: Unstratified log-rank test

OS = Overall Survival

CI = Confidence Interval

Source: Study P011 CSR, Table 11-7; Updated OS Report (Reference 1047), Table 1; and Responses to CHMP Day 120 LoQ, Q 65.

Figure 3.Kaplan-Meier Plot of Overall Survival Update Protocol 011 (ITT Population)



Source: Responses to Day 120 list of Questions, Figure 1. (Database cut-off date: 21 January 2012)

Table 5 Overall Survival by Line of Therapy, 21-Jan-2012 Data Cutoff (ITT Population)

	N	Number of OS Events	Number Censored	OS (weeks) Median (95% CI)	Hazard Ratio@ (95% CI)	p-value[1]	p-value[2]
1st Line of Therapy							
Ridaforolimus	212	137	75	92.4 (79.6, 113.0)	1.02 (0.81, 1.29)	0.8728	0.7486
Placebo	224	146	78	92.7 (82.0, 102.9)			
Total	436	283	153				
2nd or 3rd Line of Therapy							
Ridaforolimus	135	91	44	85.3 (70.6, 99.0)	0.82 (0.62, 1.09)	0.173	0.1961
Placebo	140	104	36	67.6 (56.3, 86.7)			
Total	275	195	80				

[1]: Stratified log-rank test.

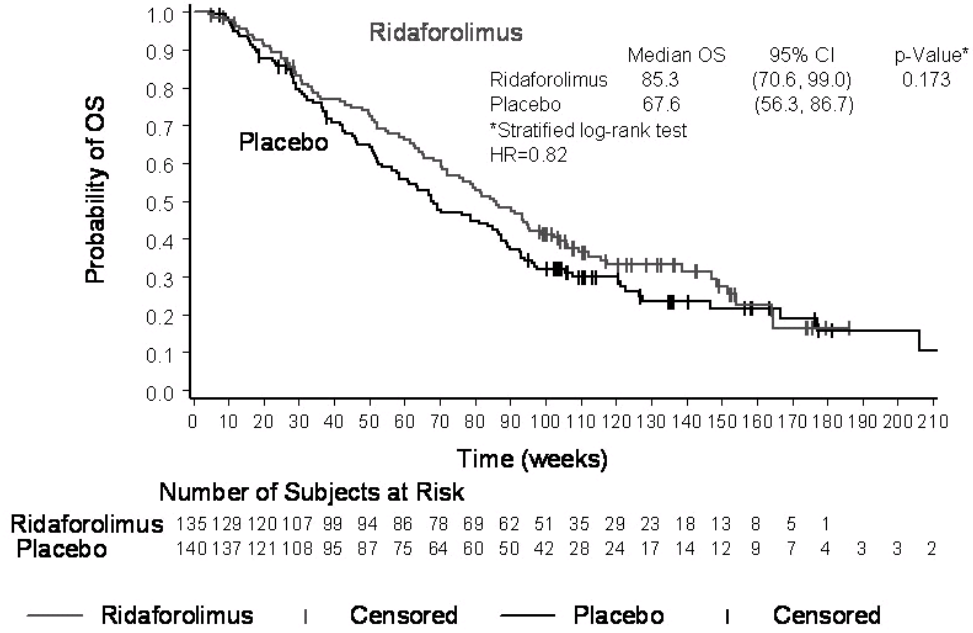
[2]: Unstratified log-rank test

@: Based on a stratified[1] Cox Proportional Hazards Model with treatment as a covariate (Ridaforolimus relative to Placebo)

(Database Cutoff Date: 21JAN2012)

Source: Applicant's Clinical Response Document to Day 180 LoI, Table S-4.

Figure 4 Kaplan-Meier Plot of Overall Survival (2nd/3rd line Subpopulation) 21-Jan-2012 Data Cutoff



Source: Applicant's Clinical Response Document to Day 180 LoI, Figure 2.

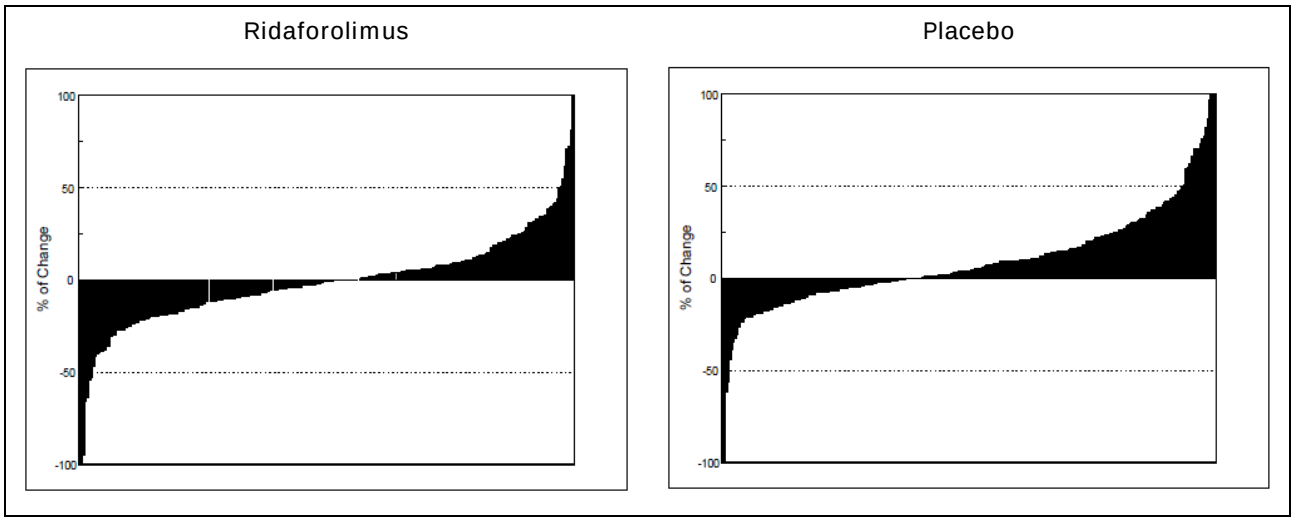
The estimated OS effect is larger in the 2/3L subgroup (4 months prolongations of OS; 3.5 months with HR-based smoothing) compared with the total population (1 month), and even more compared to the 1L subgroup where there was no difference between treatment arms. The results are not statistically significant, however. It is noted that the estimated OS effect is larger than expected, given the size of the statistically significant and consistent PFS effect, underlining the uncertainty in the estimate. It appears reasonable to conclude that a detrimental effect on OS is unlikely, however.

Best Target Lesion Response

Based on IRC assessment, the ridaforolimus group had a mean reduction of 1.3% (SD 24.7) and a median reduction of 1.0% in target lesion tumour size. The placebo group showed a mean increase of 10.3% (SD 36.8) and median increase of 4.0% in target lesion tumour size. The (two-sided) p-value based on Wilcoxon Rank Sum Test was <0.0001. The site assessment-based analysis supports the IRC based analysis. Thus, a larger proportion of patients in the ridaforolimus group achieved shrinkage of the target lesion compared with the placebo group. However, as seen in Figure 5, tumour reductions were also seen in the placebo group.

It should be noted that comparison of medians is more appropriate than means, since analysed using a non-parametric method.

Figure 5 Best Target Lesion Response (IRC Assessment) Maximum Percent Change From Baseline



Source: Study P011 CSR, Figure 11-9 and Figure 11-10.

The relative effect of ridaforolimus on Best Target Lesion Response compared with placebo is more prominent in the 2/3L subgroup compared with the 1L subgroup and the ITT population (Table 6).

Table 6 Best Target Lesion Response in First versus 2nd/3rd Line Subpopulations IRC Assessment (ITT Population)

	Ridaforolimus	Placebo	Overall	p-Value[1]
1st Line of Therapy				0.0155*
N	212	224	436	
n	148	161	309	
Mean (SD)	-2.1 (26.3)	4.3 (24.7)	1.2 (25.6)	
Median	-2.3	1.0	0.0	
Min - Max	-100.0 – 100.0	-100.0 - 70.5	-100.0 - 100.0	
2nd or 3rd Line of Therapy				<0.0001*
N	135	140	275	
n	107	113	220	
Mean (SD)	**-0.2 (22.5)**	**18.8 (48.1)**	9.5 (38.9)	
Median	**0.0**	**10.0**	4.0	
Min - Max	-100.0 - 61.5	-62.0 - 412.0	-100.0 - 412.0	

Note: Best Target Lesion Response is defined as the maximum percentage change in the sum of longest diameters from baseline

[1]: P-value comparing Ridaforolimus to Placebo is based on the Wilcoxon Rank Sum test

(Database Cutoff Date: 25OCT2010)

Source: Applicant's Clinical Response Document to Day 180 LoI, Table 3.

Overall response rate

ORR was not pre-specified as a secondary endpoint but is based on the same data as best target lesion response. As might be expected from the cytostatic mechanism of action, very few formal responses (PR only) were seen: 1.4 vs. 0.5 % in the ridaforolimus and placebo arms, respectively (IRC/ITT). By site assessments, there were more responses in the placebo compared with the ridaforolimus group, 16 (4.4%) vs. 12 (3.5%), including more CRs, but considerably more SD ≥4months in the ridaforolimus arm. There was a 12% (40.6 vs. 28.6%) absolute difference in the Clinical Benefit Response (CBR: CR+PR+ SD ≥4 months) in the IRC assessment (p=0.0009) favouring ridaforolimus,

and a 15.5% (48.7 vs. 33.2%) absolute difference in CBR according to the site assessment ($p<0.0001$).

Overall response rate was not reported for the 2/3L subgroup.

Changes in Cancer-Related Symptoms – Patient Reported Outcomes (PRO)

The evaluation and comparison of changes in cancer related symptoms was a protocol pre-specified secondary efficacy endpoint. A non-validated instrument was used, with questionnaires addressing three categories of cancer-related symptoms: pain, cough, and shortness of breath, which were chosen as symptoms that are attributable to the presence of tumours. Each symptom category had 4 severities: none, mild, moderate and severe. Questionnaires were completed by the patients every 4 weeks until Week 16 and every 8 weeks afterwards during treatment and at treatment discontinuation.

The results in the ITT population show a consistent trend throughout the first 32 weeks for all three symptom parameters, of the ridaforolimus treated patients having a lower percentage of no symptoms and higher percentages of moderate-severe symptoms compared with the placebo group. The percentage not completing the questionnaire at each time point is consistent over time very similar for the two treatment arms. Due to the earlier progressions in the placebo group, the numbers at risk at each time point is lower in the placebo group. The missing data is likely to be informative, in particular that due to progression; even so the impression is that patients on ridaforolimus experience more cancer related (or treatment related?) symptoms than patients receiving placebo. The excess of pulmonary symptoms in the ridaforolimus arm compared with the placebo arm are most likely treatment-related, but the trend is there also for Pain.

As an example, the percentage of patients with symptom score “moderate” or “severe” pain are summarised below (Table 7). It is noted that the ridaforolimus arm had a higher percentage at baseline, but also a larger increase on therapy than the placebo arm.

Table 7 Patient reported outcomes for Pain – percentage of patients with symptom score “moderate” or “severe” (ITT population)

	Baseline		Week 4		Week 8		Week12		Week 16	
	n	%	n	%	n	%	n	%	n	%
Ridaforolimus	347	14.4	334	23.1	298	21.1	225	20.0	204	20.1
Placebo	364	10.1	357	13.2	322	14.0	207	10.1	186	15.6

The findings of more symptoms in the ridaforolimus arm are contrary to the underlying hypothesis of this secondary objective, and as such it has failed.

2/3L

The Applicant has provided a subgroup analysis of the PRO data for the 2/3 and 1L subpopulations, respectively. In this analysis only the average (i.e. mean) cancer-related symptom scores at each time point are presented, indicating very small differences, if any, between ridaforolimus and placebo-treated patients in the 2/3L, whereas statistically significant differences are seen for 1L patients. Moreover, the Applicant points out, the differences between treatment arms are small, 0.35 points or less on a scale of 1-4. It should be noted, however, that the large proportion of non-symptomatic patients (60-40% at each time point) naturally lowers the mean, why the mean scores may give a somewhat misleading impression. Furthermore, as the instrument is not validated, the clinical relevance of a 0.35 point difference is not known.

It is important to note that the actual questionnaires specifically addressed cancer-related symptoms. I.e. the data generated cannot be used to make conclusions on overall health-related Quality of Life (QoL), or the impact of AEs on QoL, since the questionnaire instructed patients to only report symptoms that they perceived as caused by the disease (and not those caused by adverse drug reactions).

Exploratory analyses

Post-progression survival

There was no statistically relevant difference in post-progression survival between ridaforolimus and placebo treated patients (HR = 1.0). Thus, no detrimental effect on next-line therapies was observed.

Subgroup analyses

Subgroup analyses of PFS and OS by IRC assessment in the ITT population show an overall consistency in results, including for the two main histology subgroups, STS (PFS HR 0.72, OS HR 0.93) and bone sarcoma (PFS HR 0.70, OS HR 0.86). The CI is wide in the small bone subgroup, however, and of the HRs given above only STS PFS was statistically significant. The results by region show a falling HR for PFS from North America (HR 0.75) to EU (HR 0.68) to Rest of world (ROW, HR 0.55), all statistically significant. For OS the results were similar in the EU (HR 0.98) and North America (HR 0.97), but dissimilar in ROW (HR 0.69) (all non-significant).
The need for consistency in histology subgroups was addressed in CHMP advice. To the degree possible, this was shown.

2/3L subpopulation

The effect of ridaforolimus in the post-hoc 2/3L subpopulation is overall consistent across subgroups, with PFS HR point estimates below 1 (mostly between 0.4 and 0.7) for all subgroups tested, although all confidence intervals (CI) encompass 1.0.

The small histology subgroup bone (n=28) has a HR estimate of 0.89 with very wide CI. In the OS analysis the bone HR estimate is >1 (1.30). Similar estimates are seen for Adjuvant therapy (n=49) and it is likely that these subgroups to a relevant extent includes the same patients, given the standard use of neoadjuvant and adjuvant therapy in bone sarcoma. Similarly, in an analysis by independent pathology assessment in the 2/3L subpopulation, the osteosarcoma subgroup (n=22) has a wide CI with PFS HR estimate at 0.77, and OS HR >1 (1.18).

Liposarcomas (n=40), according to independent histology assessment, have a HR estimate above 1.0 for both PFS and OS.

The general impression, however, is consistency of the results, even in this analysis of subgroups of a subgroup.

Paediatric subpopulation

P011 enrolled patients 13 years of age and above, as long as their weight was at least 45.4 kg or 100 pounds. There were 12 patients 13 to 17 years of age enrolled in the study. Seven (7) of the patients were in the ridaforolimus treatment group, 4 with bone sarcoma and 3 with STS. The other 5 paediatric patients were in the placebo group, 4 with bone sarcoma and 1 with STS. Among the 7 patients treated with ridaforolimus, 1 with osteosarcoma had PR with tumour shrinkage of 64%, 4 had SD with PFS durations of 23, 20, 48, and 19 weeks, respectively, and 2 had PD. In contrast, among the 5 patients in the placebo group, 1 had SD with PFS duration of 20 weeks, and 4 had PD.

A Paediatric Investigation Plan has been agreed upon.

Clinical studies in special populations

A pharmacokinetic study in subjects with moderate hepatic impairment has been performed. Please, see Pharmacokinetics above.

Supportive studies

Two supportive studies were used for the present application:

- **P016** was a dose finding phase I (-IIa) study, which evaluated oral ridaforolimus in several different dosing regimens and included patients with solid tumours, of which 58% had metastatic sarcoma. Patients were age 18 or older, without limitation in prior lines of therapy. (The planned phase IIa segment was not performed.)
- **P018** was a single-arm phase II study, which evaluated an I.V. form of ridaforolimus in a dosing regimen different to the pivotal trial in patients with metastatic sarcoma, age 15 or older, also without limit in prior lines of therapy.

The two supporting trials thus included patients with more advanced stages of disease. In P018, 39% of patients had received ≥4 prior lines of therapy, i.e. more than the number allowed in the pivotal study.

Table 8 Key Supportive Efficacy Data from Protocols 016 and 018 (All Treated Patients)

	P016 (Sarcoma patients; N = 85)	P018 (N=212)
Progression-Free Survival (weeks) Median (95% CI)	17.1 (14-20)	15.3 (14.3, 16.3)
Clinical Benefit Rate	27.1%	28.8%
Overall Survival Median (weeks) (95% CI)	42.7 (29-88)	40.1 (32.1, 51.6)

Source: Summary of Clinical Efficacy, Table 2.7.3-sarcoma: 31.

The Clinical Benefit Rate, CBR (CR+PR+SD ≥ 4 months) achieved in the two supportive studies (around 28%) are similar to that observed in the placebo arm of the pivotal trial, and dissimilar to the CBR seen for ridaforolimus in the pivotal trial (40-50%, depending on assessment). This apparent difference in activity, as well as the much shorter median OS in the supportive studies (around 40 weeks) compared with the pivotal study (>80 weeks), can be explained by the selection of patients into the pivotal study who were in response or stable disease after prior CT and the use of ridaforolimus as a maintenance therapy, whereas in P016 and P018 it was a next line therapy in patients who presumably had failed prior therapy. There was also no limit in prior number of lines of therapy in the supportive studies.

Discussion on clinical efficacy

Design and conduct of clinical studies

The Pivotal study P011 was a multicenter Phase III randomized (1:1) placebo-controlled double-blind trial that evaluated ridaforolimus as maintenance therapy in patients with metastatic STS or bone sarcoma who had achieved response or stable disease from immediately prior cytotoxic chemotherapy. This design has been questioned on the grounds that observation may not be the most probable clinical option after four to six cycles of chemotherapy obtaining stabilisation. However, in the responses to questions the Applicant has convincingly shown that the median of 6 cycles of the preceding line of chemotherapy, shown for both the ITT population and the 2/3 L population of Study P011, is in line with what is seen, or planned for, in other sarcoma trials and studies. The design is therefore accepted.

Efficacy data and additional analyses

ITT population

In the ITT population, the primary objective of the study was met, with a statistically significant PFS HR of 0.72 in the primary analysis by IRC (Table 9, below), supported by similar statistically significant HRs in the alternative and sensitivity analyses of the primary endpoint, and can as such be considered robust. The difference in medians is small, however, only 3.1 weeks. Even when adjusted for the unfortunate location of the median (by simple smoothing based on the HR), the difference in median PFS between arms in most of the analyses is only between 5-7 weeks.

Two of the three pre-specified secondary endpoints offered some degree of support of the primary endpoint. Thus, a prolonged OS was seen in the ridaforolimus arm compared with placebo, however not statistically significant (Table 9). Best target lesion response showed small but statistically significant differences between arms, with a difference of 5% in median target lesion response (largest reduction or smallest increase in tumour size). Furthermore, there was a statistically significant absolute difference of 12% favouring ridaforolimus in Clinical benefit response (CR+PR+ SD ≥ 4 months). The third secondary efficacy endpoint, changes in cancer-related symptoms, failed to meet its objective since patients in the ridaforolimus arm had a consistent trend of more symptoms than the placebo-treated patients.

Due to the negative B/R balance in previous rounds, based on the results of the ITT-population, the Applicant has narrowed the proposed indication to include only adults, and only patients who have completed second or third line chemotherapy for metastatic bone or soft tissue sarcoma. Data for this subset is therefore discussed below.

2nd/3rd line Subpopulation

Please see summary of PFS and OS results in Table 9 below.

Table 9 Summary of PFS and OS in subgroups based on line of prior treatment compared to the overall study population

	2/3L subgroup	1L subgroup	Overall study population
PFS HR (95% CI) (p-value)	0.61 (0.46 – 0.80) (p = 0.0003)	0.80 (0.64 – 0.99) (p = 0.043)	0.72 (0.61 – 0.85) (p = 0.0001)
Median PFS in placebo arm	10 weeks	15 weeks	15 weeks
Median PFS in ridaforolimus arm	16 weeks	18 weeks	18 weeks
OS HR (95% CI) (p-value)	0.82 (0.62 – 1.09) (p = 0.173)	1.02 (0.81 – 1.29) (p = 0.8728)	0.93 (0.78 – 1.12) (p = 0.4561)
Median OS in the placebo arm	16 months	22 months	20 months
Median OS in the ridaforolimus arm	20 months	22 months	21 month

Source: Applicant's Clinical Response Document to Day 180 LoI, Table 2.

The absolute effect of ridaforolimus on the primary endpoint PFS is similar in the 2/3L and ITT populations, i.e. approximately 6 weeks (after HR-based smoothing in ITT).

In the 2/3L subgroup the difference in PFS medians between treatment arms is 6.3 weeks based on the Kaplan-Meier estimates (p=0.0003), and 6.4 weeks after HR smoothing.

The difference in median OS is 17.7 weeks, i.e. > 4months, however not statistically significant (p = 0.173).

The difference between arms in Best target lesion response was still small in the 2/3L subgroup (10%) but larger than in the ITT population and still statistically significant (p<0.0001). Clinical benefit response was not reported for the 2/3L subgroup.

Changes in cancer related symptoms, as assessed by a non-validated patient reported symptom instrument apparently did not capture any relevant differences between arms, and thus failed to meet its objective. The usefulness of these data with regard to the QoL and safety assessment is also low, since the actual questionnaires specifically addressed *cancer-related* symptoms, rather than all symptoms, why important toxicity may not be reflected in these data. (E.g. mucositis/stomatitis that patients are likely to identify as adverse drug reactions rather than disease-related.)

QoL was not assessed in the pivotal Study P011. In responses to questions the Applicant refers to the SABINE study, where patients with stable disease (SD) that were off chemotherapy treatment (n=36) were compared to patients with progressive disease (n=28). Not surprisingly the QoL, as assessed by both the EQ-5D instrument and the EORTC QLQ-C30 questionnaire, showed clinically relevant decreases for patients in disease progression (Reichardt et al 2012). The Applicant considers these data to support the need for a maintenance treatment that could be administered in an effort to delay disease progression in patients with metastatic sarcoma. However, the comparison in the SABINE study was made against a chemotherapy-free setting, with no new chemotherapy-related AEs occurring, whereas maintenance therapy with ridaforolimus is associated with some tolerability problems likely to affect the QoL, as well as possible psychological effects of still being on therapy. So given that there might be a therapeutic opening for largely non-toxic maintenance therapies in a post-chemotherapy SD setting, it is not convincingly shown that ridaforolimus fulfils the requirements.

The two supportive studies, Phase I dose finding P016 of oral ridaforolimus, and single-arm Phase II P018 of I.V. ridaforolimus, showed a few single cases of partial responses indicating activity. Apart from that, the supportive value of these studies is marginal.

Statistical considerations

1 L and 2/3 L were stratification factors based on the assumed prognostic value which also was confirmed by study results. Why these factors, however, should be predictive of the relative efficacy of ridaforolimus is less obvious and the proposed restriction in the indication must be regarded as data driven and without apparent external support. (Without knowing the results, the opposite hypothesis might appear just as likely, i.e. that 1L patients would respond better, e.g. since having had less prior lines of therapy, less (cross-) resistance mechanisms activated, fewer activated alternative growth signalling pathways etc.)

At this stage, plausibility is therefore questioned. The Applicant has undertaken some simulation exercises showing that it is highly unlikely that the statistical significance is a chance finding. This, however, is not the issue; it is rather to what extent the magnitude of the treatment effect is overestimated. Choosing the best out of a number of possible subgroups will automatically lead to an overestimation of the treatment effect even if the alpha level is protected by Bonferroni or other correction.

Furthermore, there is an unbalance in response frequency of the preceding chemotherapy between the treatment arms in the 2/3L subpopulation potentially favouring the ridaforolimus arm (18% vs. 10% in placebo arm). This unbalance was not present in the 1L subgroup, and could contribute to the improved relative efficacy seen in 2/3L compared with 1L patients.

Conclusions on clinical efficacy

The clinical benefit of ridaforolimus therapy in this therapeutic setting is small, and the effect size uncertain, despite achievement of formal statistical significance.

Clinical safety

There are currently two licensed mTOR inhibitors/rapamycin analogues: temsirolimus (Torisel) and everolimus (Afinitor) and pharmacology related safety issues are considered well established. With respect to important safety issues, ridaforolimus appears similar to temsirolimus.

Patient exposure

As of 30-Apr-2011, ridaforolimus has been evaluated in 36 clinical trials including more than 2000 patients with advanced malignancies or in healthy subjects, of whom more than 1600 were exposed to either the intravenous or oral dosage formulations.

From a safety perspective the most informative studies were study P011 and the supportive Phase I/II studies (P018 and P016) with a collective total of 359 treated patients, including 212 sarcoma patients from P018 and 85 sarcoma patients from P016. P016 was conducted as a dose-finding study, using the oral formulation, in patients with refractory or advanced malignancies, including patients with sarcoma. P018 was a Proof of Concept study using the IV formulation in patients with advanced sarcoma.

The dose limiting toxicity is stomatitis, mucositis and the recommended initial dose of ridaforolimus 40 mg daily for 5 days followed by 2 days rest. As expected for an anti-cancer drug the actual total dose

was lower, than the “expected” total dose, in study P011 about 75%. Most dose adjustments were undertaken early and after week 4 the dose intensity was essentially stable on a group level.

Adverse events

Study P011 was placebo controlled and it is of interest to note that in the placebo group there were 231 events considered treatment-related vs. 334 events in the test arm. With respect to grade 3 or more, however, there were 157 events in the ridaforolimus arm vs. 16 in the placebo arm.

Table 10 Patients with Adverse Events (Incidence ≥ 10% Patients in One or More Treatment Groups) (P011, Safety Population)

MedDRA System Organ Class Preferred Term	Ridaforolimus (N=343) Pts. n (%)	Placebo (N=359) Pts. n (%)	Difference in Percentages Ridaforolimus versus Placebo % (95% CI)
Number of Patients with at least One Adverse Event	343 (100.0)	336 (93.6)	6.4 (4.3, 9.4)
Gastrointestinal disorders	306 (89.2)	223 (62.1)	27.1 (21.0, 33.1)
Stomatitis	179 (52.2)	50 (13.9)	**38.3** (31.7, 44.5)
Nausea	93 (27.1)	90 (25.1)	2.0 (-4.5, 8.6)
Diarrhoea	108 (31.5)	66 (18.4)	**13.1** (6.7, 19.4)
Vomiting	63 (18.4)	36 (10.0)	8.3 (3.2, 13.6)
Constipation	55 (16.0)	38 (10.6)	5.5 (0.4, 10.6)
Abdominal pain	45 (13.1)	40 (11.1)	2.0 (-2.9, 6.9)
Dry mouth	38 (11.1)	24 (6.7)	4.4 (0.2, 8.8)
General disorders and administration site conditions	250 (72.9)	181 (50.4)	22.5 (15.4, 29.3)
Fatigue	122 (35.6)	80 (22.3)	**13.3** (6.6, 19.9)
Pyrexia	80 (23.3)	27 (7.5)	**15.8** (10.6, 21.2)
Asthenia	59 (17.2)	42 (11.7)	5.5 (0.3, 10.8)
Oedema peripheral	75 (21.9)	26 (7.2)	14.6 (9.6, 19.9)
Mucosal inflammation	57 (16.6)	16 (4.5)	**12.2** (7.8, 16.9)
Respiratory, thoracic and mediastinal disorders	213 (62.1)	119 (33.1)	29.0 (21.7, 35.9)
Cough	105 (30.6)	58 (16.2)	**14.5** (8.3, 20.7)
Dyspnoea	66 (19.2)	31 (8.6)	**10.6** (5.6, 15.8)
Oropharyngeal pain	58 (16.9)	14 (3.9)	13.0 (8.7, 17.7)
Epistaxis	59 (17.2)	4 (1.1)	16.1 (12.2, 20.5)
Musculoskeletal and connective tissue disorders	162 (47.2)	163 (45.4)	1.8 (-5.5, 9.2)
Back pain	42 (12.2)	52 (14.5)	-2.2 (-7.3, 2.8)
Pain in extremity	54 (15.7)	31 (8.6)	7.1 (2.3, 12.1)
Arthralgia	39 (11.4)	38 (10.6)	0.8 (-3.9, 5.5)
Metabolism and nutrition disorders	227 (66.2)	97 (27.0)	39.2 (32.2, 45.7)
Decreased appetite	92 (26.8)	35 (9.7)	**17.1** (11.5, 22.7)
Hypertriglyceridaemia	93 (27.1)	32 (8.9)	18.2 (12.7, 23.8)
Hypercholesterolaemia	73 (21.3)	16 (4.5)	16.8 (12.1, 21.8)
Hyperglycaemia	49 (14.3)	9 (2.5)	11.8 (7.9, 16.1)
Hypokalaemia	47 (13.7)	10 (2.8)	10.9 (7.1, 15.2)

MedDRA System Organ Class Preferred Term	Ridaforolimus (N=343) Pts. n (%)	Placebo (N=359) Pts. n (%)	Difference in Percentages Ridaforolimus versus Placebo % (95% CI)
Skin and subcutaneous tissue disorders	202 (58.9)	78 (21.7)	37.2 (30.3, 43.7)
Rash	97 (28.3)	22 (6.1)	**22.2** (16.8, 27.6)
Pruritus	38 (11.1)	14 (3.9)	7.2 (3.4, 11.3)
Nervous system disorders	166 (48.4)	111 (30.9)	17.5 (10.3, 24.5)
Headache	93 (27.1)	51 (14.2)	12.9 (7.0, 18.9)
Dysgeusia	55 (16.0)	13 (3.6)	**12.4** (8.2, 17.0)
Infections and infestations	177 (51.6)	92 (25.6)	26.0 (18.9, 32.8)
Blood and lymphatic system disorders	190 (55.4)	68 (18.9)	36.5 (29.7, 42.9)
Anaemia	95 (27.7)	35 (9.7)	17.9 (12.3, 23.7)
Thrombocytopenia	115 (33.5)	13 (3.6)	29.9 (24.6, 35.4)
Neutropenia	62 (18.1)	22 (6.1)	11.9 (7.3, 16.9)
Leukopenia	46 (13.4)	15 (4.2)	9.2 (5.2, 13.6)
Investigations	103 (30.0)	40 (11.1)	18.9 (13.1, 24.8)
Weight decreased	51 (14.9)	16 (4.5)	**10.4** (6.2, 15.0)
Psychiatric disorders	66 (19.2)	61 (17.0)	2.3 (-3.5, 8.0)
Cardiac disorders	74 (21.6)	36 (10.0)	11.5 (6.2, 17.0)
Tachycardia	43 (12.5)	16 (4.5)	8.1 (4.1, 12.4)
Vascular disorders	48 (14.0)	49 (13.6)	0.3 (-4.8, 5.5)
Renal and urinary disorders	55 (16.0)	26 (7.2)	8.8 (4.1, 13.7)
Injury, poisoning and procedural complications	39 (11.4)	27 (7.5)	3.8 (-0.5, 8.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	23 (6.7)	37 (10.3)	-3.6 (-7.8, 0.6)

Note: Percentages are based on the number of patients in each treatment group.
Only treatment-emergent adverse events with a start date on or after the first dose of study drug are reported.
Confidence Interval calculated using Mietinnen and Nurminen method.
(Database Cutoff Date: 25OCT2010)

The adverse event profile is what would be expected from a rapamycin analogue. In **bold** in the « difference column » some events where the difference between verum and placebo was considered large and where it is likely that these events would affect patients daily living if not only reported for a short period of time. Weight decrease is also highlighted as a possible summary measure of mucositis, dysgeusia, decreased appetite, etc.

With respect to grade 3 or higher, the reporting essentially reflects the overall pattern so that per MedDRA class: Gastrointestinal (18%), general disorder (12%), respiratory (11%), metabolism (18%, thereof hyperglycaemia 7%), infectious (6%), haematology (20%).

There were altogether 15% events leading to discontinuation in the ridaforolimus arm vs. 2.5% in the control. The leading cause was related to stomatitis/mucositis.

Serious adverse events and deaths

Deaths: Within 30 days after last dose, there were altogether 16/343 cases in the ridaforolimus arm vs. 13/359 in the control. In both arms 13 cases were not considered related to treatment.

In the more complete follow up, “AEs leading to death”, the event leading to death should have started on therapy but death could follow also more than 30 days after end of therapy. In this analysis there

were 21 and 16 events. The difference was caused by respiratory events (pneumonitis and related conditions), 6 vs. 0. There were also two events of death caused by cardiac events in the ridaforolimus arm vs. none in the placebo group.

Table 11 Serious Adverse Events (P011)

MedDRA System Organ Class Preferred Term	Ridaforolimus (N=343) Patients. n (%)	Placebo (N=359) Patients. n (%)	Difference in Percentages Ridaforolimus versus Placebo % (95% CI)
Number of Patients with at least One Adverse Event	**124 (36.2)**	**77 (21.4)**	**14.7 (8.0, 21.3)**
Gastrointestinal disorders	**23 (6.7)**	**16 (4.5)**	**2.2 (-1.2, 5.9)**
Nausea	4 (1.2)	1 (0.3)	0.9 (-0.5, 2.7)
Vomiting	4 (1.2)	1 (0.3)	0.9 (-0.5, 2.7)
Respiratory, thoracic and mediastinal disorders	**26 (7.6)**	**10 (2.8)**	**4.8 (1.6, 8.4)**
Pleural effusion	5 (1.5)	3 (0.8)	0.6 (-1.2, 2.6)
Pneumonitis	6 (1.7)	1 (0.3)	1.5 (-0.0, 3.5)
Dyspnoea	5 (1.5)	1 (0.3)	1.2 (-0.3, 3.1)
Pulmonary embolism	4 (1.2)	0 (0.0)	1.2 (0.1, 3.0)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**12 (3.5)**	**20 (5.6)**	**-2.1 (-5.3, 1.1)**
Malignant neoplasm progression	1 (0.3)	5 (1.4)	-1.1 (-3.0, 0.4)
Infections and infestations	**22 (6.4)**	**8 (2.2)**	**4.2 (1.3, 7.5)**
Pneumonia	8 (2.3)	2 (0.6)	1.8 (0.0, 4.0)
General disorders and administration site conditions	**14 (4.1)**	**14 (3.9)**	**0.2 (-2.8, 3.3)**
General physical health deterioration	3 (0.9)	4 (1.1)	-0.2 (-2.1, 1.6)
Blood and lymphatic system disorders	**14 (4.1)**	**5 (1.4)**	**2.7 (0.3, 5.5)**
Anaemia	7 (2.0)	3 (0.8)	1.2 (-0.6, 3.4)
Thrombocytopenia	6 (1.7)	1 (0.3)	1.5 (-0.0, 3.5)
Nervous system disorders	**12 (3.5)**	**5 (1.4)**	**2.1 (-0.2, 4.8)**
Cardiac disorders	**11 (3.2)**	**5 (1.4)**	**1.8 (-0.4, 4.4)**
Metabolism and nutrition disorders	**15 (4.4)**	**0 (0.0)**	**4.4 (2.7, 7.1)**
Dehydration	5 (1.5)	0 (0.0)	1.5 (0.4, 3.4)

MedDRA System Organ Class Preferred Term	Ridaforolimus (N=343) Patients. n (%)	Placebo (N=359) Patients. n (%)	Difference in Percentages Ridaforolimus versus Placebo % (95% CI)
Musculoskeletal and connective tissue disorders	**7 (2.0)**	**4 (1.1)**	**0.9 (-1.1, 3.2)**
Renal and urinary disorders	**9 (2.6)**	**1 (0.3)**	**2.3 (0.7, 4.7)**
Renal failure acute	5 (1.5)	0 (0.0)	1.5 (0.4, 3.4)
Skin and subcutaneous tissue disorders	**5 (1.5)**	**0 (0.0)**	**1.5 (0.4, 3.4)**

Note: Percentages are based on the number of patients in each treatment group.
Only serious treatment-emergent adverse events with a start date on or after the first dose of study treatment are reported.
CI=Confidence Interval, calculated using Mietinnen and Nurminen method.
(Database Cutoff Date: 25OCT2010)

Most serious events are “listed” and also part of the RMP. However, notice that “nervous system disorders” is listed only as headache and dysgeusia and “cardiac” only as tachycardia. Also notice pulmonary embolism.

Laboratory findings

Table 12 Summary of Grade 3 and 4 Laboratory Abnormalities (P011)

	P011 Ridaforolimus 40 mg daily x 5 days/week		P011 Placebo	
	n	(%)	n	(%)
Patients in population	343		359	
with one or more lab abnormalities	181	52.8	64	17.8
ABSOLUTE NEUTROPHIL COUNT - DECREASED	26	7.6	11	3.1
Grade 3	9	2.6	1	0.3
Grade 4	17	5.0	10	2.8
ALBUMIN - DECREASED	5	1.5	2	0.6
Grade 3	2	0.6	0	0.0
Grade 4	3	0.9	2	0.6
ALKALINE PHOSPHATASE - INCREASED	4	1.2	4	1.1
Grade 3	4	1.2	3	0.8
Grade 4	0	0.0	1	0.3
ALT (SGPT) - INCREASED	9	2.6	3	0.8
Grade 3	9	2.6	3	0.8
AST (SGOT) - INCREASED	2	0.6	0	0.0
Grade 3	2	0.6	0	0.0
BICARBONATE - DECREASED	0	0.0	2	0.6
Grade 3	0	0.0	1	0.3
Grade 4	0	0.0	1	0.3
CALCIUM - DECREASED	3	0.9	1	0.3
Grade 3	1	0.3	1	0.3
Grade 4	2	0.6	0	0.0
CREATININE - INCREASED	1	0.3	0	0.0
Grade 4	1	0.3	0	0.0
GLUCOSE - DECREASED	2	0.6	0	0.0
Grade 3	1	0.3	0	0.0
Grade 4	1	0.3	0	0.0
GLUCOSE - INCREASED	40	11.7	3	0.8
Grade 3	40	11.7	3	0.8
HEMOGLOBIN - DECREASED	13	3.8	1	0.3
Grade 3	9	2.6	1	0.3
Grade 4	4	1.2	0	0.0
LYMPHOCYTES - DECREASED	80	23.3	24	6.7
Grade 3	65	19.0	14	3.9
Grade 4	15	4.4	10	2.8
PHOSPHOROUS - DECREASED	43	12.5	5	1.4
Grade 3	43	12.5	5	1.4
PLATELETS - DECREASED	34	9.9	12	3.3
Grade 3	17	5.0	0	0.0
Grade 4	17	5.0	12	3.3
POTASSIUM - DECREASED	18	5.2	1	0.3
Grade 3	17	5.0	1	0.3
Grade 4	1	0.3	0	0.0
SERUM TRIGLYCERIDES - INCREASED	12	3.5	1	0.3
Grade 3	9	2.6	1	0.3
Grade 4	3	0.9	0	0.0
SODIUM - DECREASED	10	2.9	1	0.3
Grade 3	9	2.6	1	0.3
Grade 4	1	0.3	0	0.0
SODIUM - INCREASED	1	0.3	1	0.3
Grade 4	1	0.3	1	0.3
TOTAL CHOLESTEROL - INCREASED	5	1.5	0	0.0
Grade 3	5	1.5	0	0.0
WHITE BLOOD CELLS - DECREASED	18	5.2	1	0.3
Grade 3	17	5.0	1	0.3
Grade 4	1	0.3	0	0.0

Laboratory tests only appear when a Grade 3 or 4 event is present in a treatment group.

For an anticancer drug, the haematological events are considered moderate at most and manageable. Lymphocytopenia is in general less frequently encountered at the degree reported here, but is

expected for mTOR inhibitors. Lipid increase is also a class effect, but considered not to be of relevance in the target population in contrast to hyperglycaemia where one case of ketoacidosis has been reported and monitoring is warranted.

QTc

No signals for QTc prolongation were seen in the preclinical studies, but the relevance of those results are questioned on methodological grounds (please see Non-Clinical section).

A thorough QT study could not be performed due to the cytostatic effect of the substance and the advanced condition of the patients. No signs of QTc prolongation were seen from a supratherapeutic single oral dose of 100mg ridaforolimus achieving a C_{max} and AUC_{0-24} in whole blood similar to the standard dose in multiple dosing. Plasma exposure data are missing.

A weak relationship between exposure and QT prolongation was shown at therapeutic exposure levels.

It is concluded that the effect on QTc has not been thoroughly evaluated. The issue remains insufficiently addressed and further non-clinical and/or clinical studies are warranted..

Safety in the 2/3L subgroup and in special populations

2/3L patients

1L vs. 2/3L were stratification factors and within the groups, baseline factors were well balanced. As expected the tumour burden was higher in the 2/3L groups. Despite this, only treatment emergent AEs leading to death were more commonly reported in the placebo group (6.5% vs. 3.2%). There was also an apparent increase in dyspnoea comparing 2/3L with 1L. For most AEs, the pattern does not differ to a major degree between the 1L and 2/3L subgroups, but there are some signals, e.g. in relation to gastrointestinal events.

Probably reflecting prior cytotoxic therapy, thrombocytopenia was more commonly reported in the 2/3L subgroup.

Age, gender, ethnicity

Table 13 Summary of Grade ≥3 AEs (Safety population, P011)

	Ridaforolimus		Placebo		Difference in Percentages Ridaforolimus versus Placebo		
	n	m (%)	n	m (%)	% Difference	LCL	UCL
Male	155	96 (61.9)	153	37 (24.2)	37.8	27.1	47.5
Female	188	124 (66.0)	206	55 (26.7)	39.3	29.8	47.9
Age < 18 years	7	3 (42.9)	5	1 (20.0)	22.9	-33.1	64.8
Age 18 to 64	254	161 (63.4)	287	72 (25.1)	38.3	30.3	45.8
Age ≥ 65 years	82	56 (68.3)	67	19 (28.4)	39.9	24.2	53.6
Asian	43	28 (65.1)	43	9 (20.9)	44.2	23.8	60.9
Black	13	8 (61.5)	8	1 (12.5)	49.0	4.6	75.7
White	269	171 (63.6)	294	78 (26.5)	37.0	29.2	44.4
Other	18	13 (72.2)	14	4 (28.6)	43.7	8.3	69.2
North America	174	108 (62.1)	177	46 (26.0)	36.1	26.1	45.4
European Union	111	75 (67.6)	128	35 (27.3)	40.2	28.0	51.2
Rest of World	58	37 (63.8)	54	11 (20.4)	43.4	25.7	58.3

LCL and UCL are the Lower Confidence Limit and Upper Confidence Limit of the 95% CI.

Other refers to Races other than White, Black, or Asian.

Only treatment-emergent adverse events with a start date on or after the first dose of study drug are reported.

Confidence Interval calculated using Mietinnen and Nurminen method.

Treatment-Related: Considered by the investigator to be possibly, probably, or definitely related to study therapy.

(Database Cutoff Date: 25OCT2010)

There are no obvious differences related to age, gender etc., but the number of paediatric patients is small. The discontinuation rate due to AEs, however, was clearly higher in patients >65, 27% vs. 11% in those below. This is not surprising.

Hepatic Impairment

Moderate hepatic impairment results in an about two-fold increase in exposure. The clinical experience is limited but more hepatic adverse events might be expected in this likely to be more sensitive patient group. Dose reduction is recommended in the SPC.

Renal Impairment

From a PK perspective no dose adjustments is required in patients with moderate renal insufficiency, but intensified monitoring is required due to the increased risk for renal events.

Patients who are Pregnant or Lactating

In the dose-ranging portion of a developmental toxicity study performed in female rats, the incidence of early foetal resorption was 100% for all doses of ridaforolimus tested (i.e.10, 25, 50, and 100 mg/kg/day). Developmental toxicity was seen at 2 mg/kg in the form of reduced foetal weights and increased post-implantation loss with reduced litter sizes and an increased incidence of skeletal alterations and delays in skeletal ossification. No developmental toxicity was observed at 0.1 and 0.5 mg/kg dose levels. It is not known whether ridaforolimus is excreted in breast milk.

No pregnancies have been reported from clinical studies in patients treated with ridaforolimus, two, however, in the placebo group.

Immunological events

Hypersensitivity reactions

Anaphylaxis, urticaria and angioedema have been observed for ridaforolimus and other rapamycin derivates. In the clinical studies, patients with severe hypersensitivity reactions to lactone antibiotics were excluded due to structural similarity. This restriction in ridaforolimus use does not appear in the SPC. The Applicant should comment.

Safety related to drug-drug interactions and other interactions

Ridaforolimus is eliminated almost exclusively by metabolism via CYP3A4. It is also a sensitive substrate to Pgp, and active efflux by Pgp has likely a role in the low oral bioavailability of ridaforolimus. Therefore, ridaforolimus is prone to interactions with inhibitors of CYP3A4 and/or Pgp. In a clinical interaction study, concomitant administration with the potent CYP3A4/Pgp inhibitor ketoconazole increased ridaforolimus exposure by more than 8-fold (see Pharmacokinetics above)

Discontinuation due to AEs

A total of 50 (14.6%) ridaforolimus-treated patients discontinued in the confirmatory trial due to AEs compared to 9 (2.5%) in placebo. Data regarding discontinuations due to AEs has been presented broken down by age, gender and geographical location.

Table 2.7.4: 9

Adverse Event Summary
Protocols 011, 016, and 018
Safety Population

	P011 Ridaforolimus 40 mg daily x 5 days/week		P011 Placebo		P016 Ridaforolimus 40 mg daily x 5 days/week		P016 Ridaforolimus All Dose Levels		P018 Ridaforolimus 12.5 mg IV daily 5 days/2weeks	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients in population	343		359		24		147		212	
Any Treatment-Emergent Event	343	(100.0)	336	(93.6)	24	(100.0)	146	(99.3)	212	(100.0)
Severe (Grade ≥3) Treatment-Emergent AE	220	(64.1)	92	(25.6)	15	(62.5)	101	(68.7)	147	(69.3)
Serious Treatment-Emergent AE	124	(36.2)	77	(21.4)	9	(37.5)	77	(52.4)	96	(45.3)
Treatment-Emergent AE Leading to Death	21	(6.1)	16	(4.5)	4	(16.7)	28	(19.0)	29	(13.7)
Treatment-Emergent AE Leading to Withdrawal	50	(14.6)	9	(2.5)	5	(20.8)	24	(16.3)	45	(21.2)
Treatment-Emergent AE Leading to Dose Reduction or Dose Delay	270	(78.7)	45	(12.5)	18	(75.0)	101	(68.7)	82	(38.7)
Any Treatment-Emergent Treatment-Related Event	334	(97.4)	231	(64.3)	23	(95.8)	139	(94.6)	208	(98.1)
Severe (Grade ≥3) Treatment-Emergent Treatment-Related AE	157	(45.8)	16	(4.5)	9	(37.5)	51	(34.7)	81	(38.2)
Serious Treatment-Emergent Treatment-Related AE	46	(13.4)	7	(1.9)	4	(16.7)	18	(12.2)	20	(9.4)
Treatment-Emergent Treatment-Related AE Leading to Death	5	(1.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Treatment-Emergent Treatment-Related AE leading to Withdrawal	37	(10.8)	2	(0.6)	1	(4.2)	4	(2.7)	10	(4.7)
Treatment-Emergent Treatment-Related AE leading to Dose Reduction or Dose Delay	250	(72.9)	22	(6.1)	17	(70.8)	73	(49.7)	54	(25.5)

Dose Interrupted for P018 is included in Dose Delay.

[Ref. 5.3.3.2: P016] [Ref. 5.3.5.1: P011] [Ref. 5.3.5.2: P018]

Of note, whilst time to treatment discontinuation (TTD) shows an HR of 1.00, in the 1L subgroup, the HR 2/3L is 0.65, i.e. reflects well PFS. The perceived B/R thus appears better in the latter group of patients. This might partly reflect the situation when the study was conducted as there were no viable next-line treatment options.

Table 14 Time to Treatment Discontinuation (1st Line of Therapy)

	N	Number of Events	Number Censored	Median (weeks) (95% CI)	Hazard Ratio@ (95% CI)	p-value[1]	p-value[2]
Time to Discontinuation							
Ridaforolimus	210	193	17	15.6 (14.1, 18.7)	1.00 (0.82, 1.22)	0.9980	0.8940
Placebo	221	201	20	15.4 (14.6, 16.6)			
Total	431	394	37				

Note [1]: Log-rank test, stratified over histology (bone vs. soft-tissue sarcoma) and prior chemotherapy (1st line vs. 2nd/3rd line)

[2]: Unstratified log-rank test

@: Based on a stratified[1] Cox Proportional Hazards Model with treatment as a covariate (Ridaforolimus relative to Placebo)

(Database Cutoff Date: 25OCT2010)

Table 15 Time to Treatment Discontinuation (2nd or 3rd Line of Therapy)

	N	Number of Events	Number Censored	Median (weeks) (95% CI)	Hazard Ratio@ (95% CI)	p-Value[1]	p-Value[2]
Time to Discontinuation							
Ridaforolimus	133	123	10	17.1 (12.4, 22.9)	0.65 (0.51, 0.84)	0.0009	0.0019
Placebo	138	132	6	8.7 (7.7, 14.3)			
Total	271	255	16				

Note [1]: Log-rank test, stratified over histology (bone vs. soft-tissue sarcoma) and prior chemotherapy (1st line vs. 2nd/3rd line)

[2]: Unstratified log-rank test

@: Based on a stratified[1] Cox Proportional Hazards Model with treatment as a covariate (Ridaforolimus relative to Placebo)

(Database Cutoff Date: 25OCT2010)

Discussion on clinical safety

There are currently two rapamycin analogues licensed within EU and the tolerability and toxicity profiles of ridaforolimus appear similar. Thus from a tolerability perspective stomatitis, mucositis, diarrhoea are of major importance. These events are dose limiting, and duration is non-trivial; median from onset of grade 2 to resolution about one month despite dose reductions as appropriate. Fatigue and pyrexia is also increased about 10 to 15% compared with placebo. Despite this, the discontinuation rate is not more than about 15%, i.e. moderate severity as regards tolerability for an anti-cancer compound.

There are also serious events:

- Non-infectious pneumonitis and related events, all grades about 10%, ≥ grade 3 about 3%.
- Renal events, all grades 16%, ≥ grade 3 about 3%. To a large part caused by pre-renal and post-renal conditions.
- Infectious events, including opportunistic infections, all grades about 50% (vs. 25% in placebo control), ≥ grade 3 about 10% (vs. 3% on placebo).
- Hyperglycaemia, all grades 18%, ≥ grade 3 about 7%, including one case of ketoacidosis.

Cardiac, CNS events and pulmonary embolism merited further scrutiny, and cardiac failure has now been added as an important potential risk to the RMP.

In the 2/3L population there were fewer discontinuations due to AEs than in the 1L subgroup, 11% vs. 17%. Dose reductions were undertaken in similar, and high proportions, 76% vs. 81%.

Conclusions on clinical safety

Taking into account what is known about other rapamycin analogues, the tolerability and toxicity profiles are as expected and manageable and uncertainties are not a major issue.

Pharmacovigilance system

The CHMP 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

Table 14 Summary of Risk Management Plan

Safety Concern	Planned Action(s)
Important Identified Risks	
1) Non-infectious pneumonitis	a)Routine Pharmacovigilance: • Routine safety surveillance in the postmarketing environment • Product information b) Additional data from on-going SUCCEED trial (P011)
2) Stomatitis	a) Routine Pharmacovigilance: • Routine safety surveillance in the postmarketing environment • Product information b) Additional data from on-going SUCCEED trial (P011)
3) Hyperglycaemia	a) Routine Pharmacovigilance: • Routine safety surveillance in the postmarketing environment • Product information b) Additional data from on-going SUCCEED trial (P011)
4) Infections	a) Routine Pharmacovigilance: • Routine safety surveillance in the postmarketing environment • Product information b) Additional data from on-going SUCCEED trial (P011)
5) Renal function impairment	a) Routine Pharmacovigilance: • Routine safety surveillance in the postmarketing environment • Product information b) Additional data from on-going SUCCEED trial (P011)
6) Haematologic toxicity	a) Routine Pharmacovigilance: • Routine safety surveillance in the postmarketing environment • Product information b) Additional data from on-going SUCCEED trial (P011)
Important Potential Risks	
1) Drug interaction with	Routine Pharmacovigilance:

strong CYP3A inhibitors	• Routine safety surveillance in the postmarketing environment • Product information
Important Missing Information 1) Pediatric patients (less than 13 years of age)	a) Routine Pharmacovigilance: • Routine safety surveillance in the postmarketing environment • Product information b) Additional data from planned pediatric studies
2) Pregnant and lactating women	Routine Pharmacovigilance: • Routine safety surveillance in the postmarketing environment • Product information
3) Patients with renal impairment	Routine Pharmacovigilance: • Routine safety surveillance in the postmarketing environment • Product information
4) Patients with severe hepatic impairment	Routine Pharmacovigilance: • Routine safety surveillance in the postmarketing environment • Product information

Ridaforolimus' effect on QTc has not been adequately investigated, since supratherapeutic exposure was not achieved in the clinical study and convincing non-clinical data is missing. It is known that e.g. patients using a moderate CYP3A4 inhibitor may achieve concentrations outside the normal variability for the standard 40 mg dose. Recommendations for precautionary dose reductions are given in the SPC, however not all variability may be predicted and not all situations resulting in higher concentrations may be foreseen.

The RMP, relying on routine PhV activities, is well justified and the revised RMP is considered acceptable.

3.4. New active substance status

Ridaforolimus is made by phosphonilation of sirolimus and is considered as a derivative (phosphinate ester) of the active substance sirolimus. However, according to the applicant all of the metabolites identified retain the dimethylphosphinate functionality associated with ridaforolimus and there is no evidence, from in vitro and in vivo studies of the metabolites formed from ridaforolimus that any chemical substance previously authorized as an mTOR inhibitor in the EU (e.g. sirolimus, temsirolimus, and everolimus) plays an active role.

The fact that ridaforolimus is a derivative of sirolimus doesn't mean that it could not be considered as a New Active Substance (NAS), however, there are no head to head non-clinical or clinical sirolimus comparative studies.

The applicant should further justify that the derivative ridaforolimus differs significantly in properties with regard to safety and/or efficacy with sirolimus, taking into consideration clinically relevant safety and /or efficacy differences, non-clinical data as well as scientifically justified indirect non-comparative evidence.

4. ORPHAN MEDICINAL PRODUCTS

Ridaforolimus, or "(1R, 2R, 4S)-4-{(2R)-2-[(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R, 27R,34aS)-9,27-dihydroxy-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-1,5,11,28,29-pentaoxo-1,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-tetra-cosahydro-3H-23,27-epoxypyrido[2,1-c][1,4]oxazacyclohentriacontin-3-yl]propyl}-2-methoxycyclohexyldimethyl-phosphinate", is designated as an orphan medicinal product for the indication: Treatment of soft tissue sarcoma, and for the indication: Treatment of primary malignant bone tumours, as per the decisions of the Commission of The European Communities on 26 Aug 2005 and 28 Oct 2005, respectively, in accordance with Regulation (EC) No 141/2000.

Soft tissue sarcoma

According to the conclusion of the COMP (Opinion dated 13/07/05) the prevalence of the “condition” soft tissue sarcoma is 2 per 10000 individuals in the EU.

Primary malignant bone tumours

According to the conclusion of the COMP (Opinion dated 09/09/05) the prevalence of the “condition” primary malignant bone tumours is 1 per 10000 individuals in the EU.

5. BENEFIT RISK ASSESSMENT

Benefits

Beneficial effects

The Pivotal study P011 was a multicenter Phase III randomized (1:1) placebo-controlled double-blind trial that evaluated ridaforolimus as maintenance therapy in patients with metastatic STS or bone sarcoma who had achieved response or stable disease from immediately prior cytotoxic chemotherapy.

The B/R balance based on the full study population has been found negative, despite a statistically positive study with regard to the primary endpoint, progression-free survival (PFS), since the absolute benefit was small (3-6 weeks PFS) in relation to the side effects. The Applicant has therefore narrowed the indication to include only adult patients, and only patients with response or stable disease following second or third line (2/3L) chemotherapy.

For a comparison of PFS and overall survival (OS) results in the ITT population, the 2/3L and 1L subgroups, please refer to Table 9, p. 41.

The following results were seen in the **2/3L subgroup** of pivotal trial P011:

PFS (primary endpoint): HR 0.61 (95% CI 0.46 – 0.80, p = 0.0003), median PFS 16 vs. 10 weeks for ridaforolimus vs. placebo arms, respectively.

OS (key secondary endpoint), updated analysis January 2012 with 71% event rate in this subgroup: HR 0.82, (95% CI 0.62 – 1.09, p = 0.173). Median OS was 20 months (85 weeks; 95% CI: 71 – 99 weeks) vs. 16 months (68 weeks; 95% CI: 56 – 87 weeks) for ridaforolimus vs. placebo arms, respectively.

Best target lesion response (secondary endpoint), defined as the maximum percentage change in the sum of the longest diameters from baseline, showed median 0.0% change for ridaforolimus-treated patients compared with 10.0% increase in placebo-treated patients, p<0.0001.

No data on overall response rate was provided for the 2/3L subgroup. (In the ITT population a statistically significant 12% difference in clinical benefit rate (CR, PR, SD) favouring ridaforolimus was seen.)

Changes in cancer related symptoms (secondary endpoint): Using a non-validated instrument, no apparent relevant differences between arms were seen, and as an efficacy endpoint therefore failed.

The two supportive studies, Phase I dose finding P016 of oral ridaforolimus, and single-arm Phase II P018 of I.V. ridaforolimus, showed a few single cases of partial responses. Apart from that, the supportive value of these studies is marginal.

Uncertainty in the knowledge about the beneficial effects

The estimated magnitude of the beneficial effects of ridaforolimus with regard to median difference PFS in the 2/3L subpopulation is similar to the ITT population, i.e. approximately 6 weeks but at an HR of 0.6 instead of 0.7.

Since this is a data-driven post-hoc analysis, the magnitude of the treatment effect, irrespective of outcome measure, is likely to be overestimated. Furthermore, at the planning stage it would not have been unlikely to consider the opposite hypothesis, i.e. that the 1L subpopulation would be expected to do better than the 2/3L, e.g. since having received less prior therapy and therefore more likely to be responsive to therapy, as often seen in other malignant situations.

The (updated) OS results show a trend (p=0.17) for an OS effect in the 2/3L subpopulation that is not present in the 1L patients. No cross-over to active drug was allowed, thus no dilution of OS results are expected. There is an unbalance in response frequency (CR+PR) to the preceding chemotherapy between the treatment arms in the 2/3L subpopulation (ridaforolimus 18% vs. placebo 10%), causing potential bias in favour of the ridaforolimus arm. This unbalance was not present in the 1L subgroup, and could contribute to the improved relative efficacy seen in 2/3L compared with 1L patients. It is also noted that the point estimate difference for OS (4 months) is larger than expected, given the magnitude of the PFS effect (1½ months), further underlining the uncertainty in the OS estimate.

Data for the secondary efficacy endpoint, “Changes in cancer related symptoms”, were presented for the 2/3L subgroup as mean symptom score values over time. These showed a low level of symptoms (as expected in sarcoma patients) with a mean symptom score around “mild” for both control arms, and only minor differences between arms; whereas statistically significant differences (also around the “mild” level) were seen in the 1L subgroup. However, as the instrument is not validated, the clinical relevance of a these small differences is not known. Furthermore, the large proportion of asymptomatic patients can generate low mean values despite a relevant proportion experiencing moderate - severe symptoms. The Applicant should present data corresponding to those provided for the ITT population, where the percentage of patients experiencing different severities of symptoms is shown.

It is interesting to note that there is a clear trend in the ITT and 1L populations of poorer symptom scores for ridaforolimus compared with placebo, despite the fact that the actual patient questionnaires specifically addressed *cancer-related* symptoms and therefore aims to exclude symptoms generated by adverse drug reactions. For this reason, the relevance of these patient reported outcomes with regard to health-related QoL or the impact of AEs on QoL is low, since important toxicity may not be reflected

in these data. (E.g. mucositis/ stomatitis that patients are likely to identify as adverse drug reactions rather than disease-related.)

Most STS patients were leiomyosarcomas and liposarcomas, known to respond better than the rest of histotypes to other treatment options, compromising the validity of efficacy data for the general STS population.

Despite the likely overestimate of the treatment effect in the 2/3 L patient group, the reported treatment effect is considered modest at best.

The majority of patients in the pivotal study had soft tissue sarcoma. Bone sarcoma (in total 69 patients) constituted 10% of the patients in the ITT population, as well as in the 2/3L subgroup. The results in the bone sarcoma subgroup were not statistically significant, but otherwise consistent with the results in the full ITT populations.

Risks

Unfavourable effects

From a tolerability perspective, gastrointestinal AE were particularly relevant and the most commonly reported AE in the ridaforolimus treatment arm (89.2% versus 62.1%). All patients (100%) in P016 receiving the proposed full dose of 40 mg q.d. x 5 days/week experienced GI AEs. Of major importance are stomatitis, mucositis, and diarrhoea, which are dose limiting and of non-trivial duration, with a median from onset of grade 2 to resolution about one month despite dose reductions as appropriate.

The higher frequency of hematological toxicities and the frequent need to require supportive therapies to manage these toxicities support the impression that ridaforolimus is not well tolerated and further questions the role of this drug as a maintenance therapy.

Additionally, SAEs were reported more frequently in patients over the age of 65 than those between 18 and 64 years of age, which indicates that this group of older patients tolerated the study treatment worse, questioning the tolerability of the maintenance treatment in this age group.

The discontinuation rate is about 15%, i.e. compatible with moderate tolerability for anti-cancer medicinal products.

Of note, time to treatment discontinuation data and discontinuation rates due to AEs indicate that treatment is better accepted in the 2/3 L subgroup (11% vs. 17%). Otherwise there seems to be no major differences between the 1L and 2/3 L subgroups.

There are also well-defined serious and severe adverse reaction; pneumonitis, infectious and renal events. Hyperglycaemia and signs of dehydration should be monitored.

Uncertainty in the knowledge about the unfavourable effects

Most adverse reactions seem to be class-related, thus the safety experience may be regarded as rather extensive.

Ridaforolimus' effect on QTc has not been adequately investigated, since supratherapeutic exposure was not achieved in the clinical study and convincing non-clinical data are missing. It is known that e.g. patients using a moderate CYP3A4 inhibitor may achieve concentrations outside the normal variability for the standard 40 mg dose. Recommendations for precautionary dose reductions are given

in the SPC, however not all variability may be predicted and not all situations resulting in higher concentrations may be foreseen.

Further non-clinical and/or clinical studies investigating possible effect of ridaforolimus on QTc are warranted.

Balance

Importance of favourable and unfavourable effects

The cornerstone of a cancer maintenance treatment is its ability to stabilize the disease for a long period of time at a stage when tumour-related symptoms are still bearable, using a comfortable schedule, delaying toxic chemotherapeutic treatments and avoiding side effects as much as possible. In terms of clinical trial endpoints, this scenario translates into PFS and tolerability.

Patients with non-curable advanced sarcoma often have a relatively good performance status and moderate symptoms in relation to their tumour burden. Nevertheless, tumour progression eventually causes physical deterioration and increased symptoms. A major delay in tumour progression would therefore have been clearly clinically relevant, even if, due to expected long survival after progression (about 1½ year), statistically significant effects on survival would not have been documented.

In the present case, the observed PFS benefit of ridaforolimus maintenance therapy in STS/bone sarcoma following stable disease or better after 2nd /3rd line chemotherapy is a median increase of 6.4 weeks, from 10.0 weeks on placebo to 16.3 weeks in ridaforolimus-treated patients. Treatment is given continuously until progression or non-acceptable toxicity, i.e. in the ridaforolimus arm for a median of about 4 months. Thus, ridaforolimus therapy during 4 months with related adverse reactions gives 1½ months improvement of PFS compared with placebo, in patients with at least stable disease at study entry. To put in perspective, ridaforolimus is administered during about 20% (4/20 months) of the median survival time from study entry to achieve a prolonged progressions-free interval over placebo of <10% (1½/20) of the survival time from study entry. As there were no likely efficacious next-line therapies available at time of study conduct and as sarcoma patients become highly symptomatic late in life, the symptomatic benefit in the majority of patients is likely to be modest at best. The failed efficacy endpoint concerning patient-reported cancer-related symptoms should be considered in this context.

In the present setting, where treatment is given with mainly palliative aims and no major impact on the course of the underlying disease is demonstrated, “tolerability” is always an issue of major importance. The high frequency of treatment-emergent AEs and treatment-emergent treatment-related AEs leading to dose reduction or dose delay (76% and 71%, respectively) in the 2/3L subgroup is not indicative of a well-tolerated maintenance therapy. On the contrary, stomatitis/mucositis and related symptoms such as weight decrease constitute a major concern. On top of this, there is the increase of serious adverse events, from 21% on placebo to 36% in ridaforolimus-treated patients.

It is agreed that there is a strong need for new therapeutic options in sarcoma, not least in the 2/3L setting. However, the treatment effect of ridaforolimus maintenance therapy is only 6 weeks improvement in PFS, in patients who are in stable disease and as a group largely asymptomatic or with only mild symptoms of disease. The acceptance of toxicity affecting QoL is therefore low. When a product is given for progressive disease, more toxicity can be accepted.

Discussion on the benefit-risk assessment

In addition to making an assessment on the B/R balance based on the presented efficacy estimates and safety data for the 2/3L subgroup, there is in this case an additional level to consider, i.e. the likely overestimate of the treatment effect in the 2/3L post-hoc analysis *(see Section 5 Uncertainty in the knowledge about the beneficial effects, and Section 3.3 Discussion on clinical efficacy).*

Benefit-risk balance

Also if the indication is restricted to patients with 2 or 3 prior lines of therapy, the benefit of maintenance ridaforolimus by a 6 week improvement (potentially overestimated) in median PFS compared to placebo - when put in relation to the long expected OS, and with no other demonstrated benefits such as a improved symptom control – does not outweigh the risks in terms of side effects interfering with patients' wellbeing and uncommon, but potentially life threatening, events.

The subpopulation of bone sarcoma should be treated as an important subset with proper characteristics and clearly unpowered in this study. On the whole, the results from all study's population cannot be translated to this special subgroup. The sample size of bone sarcoma subjects is too limited to draw any conclusions.

5.1. Conclusions

The overall B/R of Jenzyl is negative.