LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Certican
(everolimus)

SE/H/356/01-06/E02

This module reflects the scientific discussion for the approval of Certican. The procedure was finalised at 2014-10-08. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Novartis Sverige AB has applied for a marketing authorisation for Certican, tablet, 0.25 mg, 0.5 mg, 0.75 mg, 1.0 mg and dispersible tablet, 0.1 mg, 0.25 mg. The active substance is everolimus, a macrolide immunosuppressant used in kidney, heart and liver transplantation, derived from rapamycin (sirolimus, SRL), and is claimed to have the same mechanisms of action as SRL, i.e. inhibition of the proliferation of T and B lymphocytes, as well as of proliferation of a variety of transformed cell lines, including smooth muscle cells in vivo.

For approved indications, see the Summary of Product Characteristics.

Certican was authorized through the Mutual recognition procedure (MRP) on 18-Jul-2003 in the European Union (except in the UK and Ireland), with Sweden acting as RMS. Unlimited renewal of the marketing authorization was granted in 2009 by the RMS and all Concerned Member States (CMSs).

This application is a Repeat Use MRP (RU-MRP) for Certican to include the UK, Ireland, Bulgaria, Croatia, Romania, Poland and Tjeckia.

II. QUALITY ASPECTS

II.1 Introduction

Certican is presented in the form of dispersible tablets containing 0.1 mg and 0.25 mg and tablets containing 0.5 mg, 0.75 mg, and 1.0 mg of everolimus.

The excipients are butylhydroxytoluene, crospovidone, hypromellose, lactose monohydrate, lactose anhydrous, and magnesium stearate. The tablets are packed in/filled in blister.

II.2 Drug Substance

Everolimus does not have a monograph in the Ph Eur.

Everolimus is a white to faintly yellow powder, crystalline powder which is slightly soluble in water. The structure of everolimus has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism and chirality, is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Certican dispersible tablets and tablets are formulated using excipients described in the current Ph Eur. All raw materials used in the product has demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

The product development has taken into consideration the physico-chemical characteristics of the active substance, such as poor aqueous solubility and stability.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

Everolimus is a macrolide, related to but structurally somewhat different from sirolimus (rapamycin) and with potent immunosuppressive and anti-proliferative activities. Everolimus in association with its binding protein, FKBP, binds to the intracellular regulatory protein mTOR (mammalian Target Of Rapamycin) and inhibits its action. mTOR has a protein kinase function and appears to be involved in translational control. The inhibition of mTOR suppresses the cytokine-driven (IL-2, 4, 7 and 15) T-cell proliferation by inhibiting the progression from G_1 to S phase of cell cycle. It has been shown that everolimus unlike the CNIs acts as a proliferation signal inhibitor of the growth factor-dependent stimulation of vascular smooth muscle cells and hematopoietic cell lines. These activities are complementary to those of cyclosporine and provide a rationale for the addition of everolimus to cyclosporine-based immunosuppression. In preclinical models, everolimus has shown the potential to prevent acute and chronic rejection and acts synergistically with CsA, with graft survival being significantly prolonged in rat models of kidney and heart allotransplantation. Everolimus inhibited growth factor-stimulated cell proliferation in a variety of cellular assays. The IC_{50} values for everolimus were consistently in the range of 0.5 – 2.0 nM, regardless of the cell type studied or the type of *in vitro* system used. In all instances, everolimus was consistently 2- to 3-times less active when compared side-by-side to rapamycin. A possible explanation for this slightly lower *in vitro* activity could be the slightly lower affinity of everolimus for FKBP-12, as compared to rapamycin, which results from the introduction of the 2-hydroxyethyl group in position 40 of the molecule.

The results from *in vivo* studies demonstrate that everolimus is an orally active immunosuppressant, which efficiently prevents acute allograft rejection in rat and non-human primate allotransplantation models, in particular when used in combination with CsA. CsA and FK506 inhibit T cell immune responses at an early stage by preventing the activation of antigen-specific T cells while everolimus acts later, achieving its immunosuppressive effect by inhibiting the IL-2-induced proliferation and clonal expansion of activated T cells. Further, the

ability of everolimus to inhibit vascular smooth muscle cell proliferation (a key process leading to vascular remodelling and eventually late graft loss) suggests a potential of everolimus for prevention of late graft loss. With respect to rapamycin, although everolimus has a slightly lower *in vitro* activity, both compounds were found to be equipotent in animal models at comparable exposures to the compounds.

In conclusion, in the preclinical models, the combination of everolimus and CsA has shown the potential to prevent acute and chronic rejection. No statistically significant differences in median survival times between sirolimus and everolimus were reported in an allogenic kidney transplant model in monkey. However, there is a broad spectrum of factors which lead and contribute to the development of late graft loss and therefore, prediction of the impact of everolimus on the long term outcome in clinical transplantation is not possible.

III.2 Pharmacokinetics

Everolimus has a low and variable bioavailability due to limited absorption, but also due to metabolism and secretion of metabolites into bile. The plasma protein binding of everolimus was 99.9% in mice, 92% in rat, 84% in monkey and 75% in human. Volume of distribution at steady state was 44 L/kg in rats, 4.3 L/kg in monkeys, 0.42 L/kg in mice. An apparent volume of distribution in man was calculated to be 1.4 L/kg, comparable with that of monkey. Despite the high affinity of everolimus to erythrocytes the tissue/blood ratios were high with highest concentrations being found in the heart, lung, liver, kidney, spleen, thyroid and adrenal glands after both i.v. and oral administration of everolimus in rats. Everolimus is extensively metabolized mainly by CYP3A4 in human and all animal species tested (mice, rats, monkeys), giving rise to 5 major metabolites found both in human and animal species tested. Upon testing in the mixed lymphocyte reaction (MLR) assay, these major metabolites showed significantly lower activity compared to everolimus and are considered as biologically irrelevant. Systemic clearance consists mainly of metabolic clearance with majority of the drug recovered in the feces. The terminal half-life of everolimus was 9 hours in mice after i.v. dose, 47 to 61 hours after i.v. and oral doses in rats and 27 and 18 hours after i.v. and oral doses in monkeys. Taken together, from the pharmacokinetic point of view including the metabolite pattern, the monkey can be the considered most similar to human of the species used in toxicity studies.

III.3 Toxicology

The pivotal studies were conducted in accordance to GLP principles.

General toxicology

Everolimus had low acute toxicity in the mouse and rat. The repeat dose toxicity studies were extensive and included oral and intravenous administration routes. Decreased food consumption and reduced body weight gain were observed at higher doses in all species. Changes in clinical chemistry parameters were increased neutrophils at ≥1.5 mg/kg in rats, mini-pigs and monkeys. Decreased platelets were noted in all species except for monkeys at ≥0.5mg/kg and increased fibrinogen in mini-pigs and monkeys at ≥1.5mg/kg. Cholesterol was increased in most species at ≥0.5mg/kg and triglycerides in rats and monkeys. There was a slight increase in low-density lipoproteins and a slight decrease in high-density lipoproteins in the 4-week minipig study.

Target tissues/organs for toxicity were male and female reproductive organs, lungs, bone, exocrine pancreas, thymus, spleen, lymph nodes, eye, heart, GI, and skin.

Male and female reproductive organs (atrophy at ≥0.5mg/kg): males exhibited depletion of germ cells and vacuolation of the germinal epithelium in testes, reduced sperm content and germ cells in the epididymides. Females had reduced ovarian follicular development and uterine atrophy at ≥1.5 mg/kg. Similar findings in reproductive organ have been reported in rats treated with rapamycin. Lungs: (alveolar macrophages at ≥1.5 mg/kg): apparently a rodent specific target organ in rats and mice. These findings showed evidence of phospholipidosis. Cortical bone: a rat specific target organ: slight depletion of the cortical bone was evident in the 4 weeks rat study at doses ≥1.5mg/kg. However, the lifetime carcinogenicity study in rats, at doses up to 0.9 mg/kg were not associated with any adverse bone effects. Exocrine pancreas: a potential target organ in monkeys and minipigs. Degranulation (monkeys) and vacuolization (minipigs) of the pancreatic cells possibly secondary to inflammation was observed. In addition, atrophy of thymus, spleen, lymph nodes (associated with decrease in circulating lymphoid as well as total white blood cells), lens opacities in rats, myocardial degeneration of heart and adverse GI-tract changes were reported. Skin lesions (ulcerations, scabs and inflammation) were reported at higher doses. Toxic effects were observed at systemic exposure levels not much higher or even lower than the therapeutic level, especially in the rat. Rat appears to be more sensitive to adverse effects than other species, which may be due to the greater tissue distribution of the compound. In monkey studies, systemic exposure at the no observed effect level was over the range of similar to or up to 10-fold the clinical exposure.

Most findings in toxicology studies can be related to the pharmacology of the substance. Effects secondary to immunosuppression, e.g. such as skin lesions and changes in myocardial tissue in the rat and monkey were evident at higher doses in all species. Similar findings reported for rapamycin have been attributed to pre-existing parvovirus. Inflammatory changes in the gastrointestinal tract were probably secondary to immunosuppression as well, causing poor health condition of the animals.

Kidney lesions as reported for calcineurin inhibitors were not observed with everolimus. However, renal tubular degeneration in a 13 week mouse study at ≥5 mg/kg was possibly a consequence of immunosuppression and related to the aggravation of pre-existing interstitial inflammation. An exacerbation of renal effects of CsA was demonstrated after the combination treatment of CsA with everolimus and rapamycin and therefore, when CsA and everolimus or rapamycin are used in combination, CsA doses should be kept at minimum required for the pharmacological activity in order to reduce the risk of adverse effects in the kidney. Findings of haemorrhage and arteritis were reported in a combination toxicity study with everolimus and CsA in monkeys. Overall, administration of everolimus in combination with CsA to rats and monkeys resulted in an aggravation of pharmacological activity and toxicological profile of everolimus compared with monotherapy with each of the compounds.

To conclude, everolimus caused a variety of toxic effects in animals. Most of the toxic effects have been reported with other immunosuppressants or represented expected exaggerated pharmacological effects. The majority of reactions appeared common for everolimus and rapamycin and no statistically significant differences in the biological and toxicological response were identified in two studies in rat and monkey where sirolimus and everolimus were directly compared.

Reproductive toxicity

Male reproductive toxicity studies were conducted in rats given oral doses of up to 5mg/kg. Effects on spermatogenesis consisting of degeneration and depletion of testicular germ cells without affecting male or female fertility in rats were observed at 1.5mg/kg. At 5mg/kg these

changes were accompanied by decreased testosterone levels and marked effects on male fertility and none of the females mated with treated males became pregnant.

Female fertility and embryo/fetal development were studied in rats and rabbits. In rats, everolimus did not affect female fertility, but crossed the placenta and was toxic to the conceptus. Increased pre- and post-implantation losses and an increased incidence in skeletal retardations were evident down to the lowest dose of 0.1 mg/kg. Everolimus caused an increased incidence of non-specific malformations at 0.3 and 0.9 mg/kg. The majority of malformations in the treated animals affected thoracic vertebrae, ribs and sternebrae. Slightly increased incidence of fetuses with 14 ribs was observed at the maternally toxic dose of 0.9 mg/kg. The presence of sternal cleft, a major malformation, was also noted at 0.9 mg/kg in 2 out of 69 fetuses. In rabbits, effects on the embryo-fetal development were limited to a slight increase in the percentage of late resorptions, at the maternally toxic dose of 0.8 mg/kg. The NTEL for embryotoxicity was 0.2 mg/kg, although maternal toxicity was observed.

Systemic exposure levels in female reproduction toxicity studies causing reproduction toxicity were at the therapeutic exposure level or lower in humans, providing no exposure margin to the effects. Therefore the clinical dose of everolimus may be associated with a risk during pregnancy.

Effects of everolimus on the pre- and postnatal development of rats were limited to slightly affected body weight and survival in the F1-generation at ≥ 0.1 mg/kg, and did not indicate a specific toxic potential.

Genotoxic and carcinogenic potential

The genotoxicity of everolimus has been studied for gene mutations in bacteria and mammalian cells and chromosomal aberrations *in vitro* and *in vivo*. No genotoxic potential was evident at concentrations up to the limit of toxicity or clinical signs of toxicity.

Carcinogenicity studies were conducted in mice and rats. Non-neoplastic lesions in these studies were consistent with the mode of action of everolimus. There were no significantly increased incidences in neoplastic lesions in either study. In the mouse carcinogenicity study, systemic exposure to everolimus in blood was estimated to 0.6, 1.5 and 8.6-fold compared to clinical exposure at a dose of 3 mg/day. Corresponding values in the rat study were 0.01, 0.1 and 0.4-fold. Although carcinogenicity studies were negative, systemic exposures were low, especially in the rat, and in similarity to other immunosuppressants, everolimus has a potential to increase neoplasia.

The preclinical studies summarized above were performed between 1992 and 2003. Additonal toxicity studies have been performed and evaluated with everolimus since submission 2003. The new studies are a 4-week repeat dose assessment of buccal irritation in hamsters, single dose intra-arterial toxicity study in minipigs with a 2- or 4-week recovery period, examination of kidneys in recovery animals of the 6-month rat study and elctrophysiological safety measurements og hERG currents in stably transfected HEK293 cells. The results from these newly conducted studies are not considered to have changed the previously established and described nonclinical safety profile of everolimus, and thus these studies are not included in this assessment.

III.4 Ecotoxicity/environmental risk assessment

The Applicant has previously submitted an ERA in procedure SE/H/356/01-06/II/20 and SE/H/378/01-06/II/16, which has been assessed and the variation has been approved. The calculated PEC based on epidemiological data published by the World Health Organization (WHO, 2010) is 0.0005 µg/L, which is significantly below the trigger value for a Phase II assessment. The $logK_{ow}$ is below 4.5 and therefore screening for PBT is not warranted for Certican.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Basic pharmacokinetic characterisation was conducted in healthy volunteers (single dose) and in patients (renal, heart and liver transplants). Everolimus was detected in blood using LC/MS in the majority of studies. Everolimus is rapidly absorbed. Following a 2-mg dose in fasting volunteers, the maximal concentration of 17.9 ± 5.9 ng/ml was reached after about 0.5-1h. The absorption rate of the dispersible tablet was similar as for the tablet. Absolute bioavailability could not be determined but the bioavailability (in combination with CsA) is likely to be low. There was a significant food effect on the pharmacokinetics. In the fed state, t_{max} was delayed by 1.3h, C_{max} and AUC reduced by 60% and 16%, respectively, and thus Certican is recommended to be taken consistently with or without food.

Everolimus is distributed to blood cells, as it appears in a concentration dependent manner. The plasma/blood ratio increased from 17% to 73% in the range 5 to 5000ng/ml *in vitro*. The plasma protein binding was approximately 74 ± 2%. The distribution volume (V_z/F) in volunteers was 842 ± 315L. The everolimus concentration-time profile is characterised by a bi-phasic decline. The $t_{½.z}$ in volunteers and renal transplant patients following a single dose was approximately 30h. Oral CL is reduced in patients (8.3±3.1L/h) compared with volunteers, probably in part due the interaction with CsA in patients. The pharmacokinetics was dose- and time-independent.

Everolimus is mainly eliminated through metabolism. The major metabolism pathway seems to be hydroxylation in the first step. *In vitro* metabolism indicates that CYP3A4 is the major metabolising enzyme, everolimus being both a substrate and inhibitor of the CYP3A4. Everolimus is also a substrate for P-glycoprotein. Five metabolites were identified in blood, none of them likely to significantly contribute to the effect of everolimus. Everolimus and metabolites were mainly excreted in feces, indicating that everolimus is mainly excreted biliary. Sirolimus was present in blood as a minor peak representing about 1% of the total radioactivity. The maximal blood concentration of sirolimus was 1.0 ± 0.18 ng/ml.

Concentration-response modelling was conducted demonstrating E_{max}-type relationships between everolimus exposure and efficacy and safety endpoints. The relevance of concentration-efficacy/safety analyses using PK/PD-models for evaluating the optimal therapeutic window is acknowledged.

Steady-state was reached after approximately 4 days and the everolimus levels at steady-state was 2-3-fold higher compared with single-dose levels. The trough levels were relatively stable over time, average values being 4.1 and 7.1 ng/ml for the 0.75mg and 1.5mg, respectively. The variability was high, e.g. the inter- and intraindividual variability in C_{trough} were 59% and 44%, respectively. The inter-individual variability in CL/F and V/F were 27% and 36%, respectively. The minimal effective trough level of everolimus was defined as 3 ng/mL. No

evident upper cut-off was found although the incidence of adverse events was higher >8ng/ml compared with 3-8ng/ml and in the SPC the upper limit of the therapeutic range is recommended to be 8 ng/mL. Limited data are available with trough levels greater than 12 ng/mL. TDM (C0) is suggested to be used routinely in clinical practice and was prospectively studied in clinical trials.

In hepatic-impaired subjects, AUC was positively correlated with serum bilirubin concentration and with prolongation in prothrombin time and negatively correlated with serum albumin concentration. The everolimus dose should be reduced to one half of the normal dose if two of the following apply > 34μmol/L, prothrombin time was >1.3 INR (> 4 sec prolongation), and/or albumin concentration was < 35 g/L. Everolimus has not been evaluated in patients with severe hepatic impairment (Child-Pugh C). Renal dysfunction did not influence the everolimus pharmacokinetics. Blacks had an average 20% higher apparent clearance compared with non-Blacks and a doubled starting dose (1.5mg) is recommended. No marked pharmacokinetic differences were observed with respect to age or gender.

The *in vivo* interaction program includes CsA, atorvastatin, pravastatin, rifampicin, ketokonazole, erythromycin, verapamil, midazolam and octreotide. CsA gave an on average 3-fold increase in everolimus AUC, but the effect was highly variable. Concomitant administration of the "statins" gave no change in everolimus or "statin" pharmacokinetics, but the results from the present study cannot be extrapolated to HMG-CoA reductase inhibitors in general. Everolimus CL was increased by approximately 172% when co-administered with rifampicin. Ketoconazole increased everolimus AUC 15-fold while erythromycin and verapamil both increased everolimus AUC approximately 4-fold. Verapamil trough plasma concentrations doubled after single-dose coadministration of everolimus. Coadministration with everolimus increased midazolam AUC 1.30-fold while the half life of midazolam was unaltered. The study indicated that everolimus is a weak inhibitor of CYP3A4.
Everolimus was *in vitro* a competitive inhibitor of CYP3A and CYP2D6. It cannot be excluded that the inhibitory effect of everolimus on 2D6 and 3A4 is of clinical significance.

The clinical trial and final marketing formulations are considered bioequivalent. The relative bioavailability of the 0.25 mg dispersible tablet vs. the 0.75 mg tablet was 0.76 for $C_{max,b}$ and 0.90 for $AUC_{b.}$ The minor difference between formulations is not likely to be clinically significant.

IV.2 Clinical efficacy

IV.2.1 Renal Transplantation

The original dossier for the prophylaxis of organ rejection in patients receiving a renal transplant bwas mainly based on studies B201 and B251, which were double-blind, randomized controlled clinical trials in *de novo* renal transplantation that tested fixed doses of everolimus (1.5 mg and 3 mg daily divided in two doses) in combination with full-dose CsA, and corticosteroids.

Summary of active controlled studies in renal transplantation

Study	Objective, Population	No.	Time	Treatments	Efficacy Endpoint
Key Study A2309 (blood level control of everolimus, ***reduced dose*** CsA, steroids)					
A2309	efficacy / safety (renal, overall) of titrated everolimus with titrated reduced dose CsA versus Myfortic with titrated standard dose CsA (both with steroids and basiliximab induction) in *de novo* kidney recipients	833	12 mo + 12 mo	Everolimus 1.5 mg/d (C_0: 3-8ng/mL) Everolimus 3.0 mg/d (C_0: 6-12ng/mL) (with reduced CsA) versus Myfortic 1.44 g/d (with standard CsA)	tBPAR, GL, death, LtFU (6mo) tBPAR, GL, death, LtFU (12 mo) tBPAR, GL, death, LtFU (24 mo)
Earlier pivotal studies (fixed dose everolimus, ***standard dose*** CsA, steroids)					
B201	efficacy / safety of fixed dose everolimus with titrated standard dose CsA versus MMF with titrated standard dose CsA (both with steroids but no induction) in *de novo* kidney recipients	588	12 mo (dbl blind) + 12 mo (open label) + 12 mo (open label) + 24 mo (open label)	Everolimus 1.5 mg/d Everolimus 3.0 mg/d (with standard CsA) versus MMF 2 g/d (with standard CsA)	BPAR, GL, death, LtFU (6mo) GL, death, LtFU (12 mo) GL, death, LtFU (24 mo) GL, death, LtFU (36 mo) GL, death, LtFU (60 mo)
B251	efficacy / safety of fixed dose everolimus with titrated standard dose CsA versus MMF with titrated standard dose CsA (both with steroids but no induction) in *de novo* kidney recipients	583	12 mo (dbl blind) + 12 mo (open label) + 12 mo (open label) + 24 mo (open label)	Everolimus 1.5 mg/d Everolimus 3.0 mg/d (with standard CsA) versus MMF 2 g/d (with standard CsA)	BPAR, GL, death, LtFU (6mo) GL, death, LtFU (12 mo) GL, death, LtFU (24 mo) GL, death, LtFU (36 mo) GL, death, LtFU (60 mo)

MMF = mycophenolate mofetil, Myfortic® = enteric-coated mycophenolate sodium, CsA = cyclosporine A
BPAR = treated biopsy-proven acute rejection, dbl=double, LtFU = loss to follow up, g/d=grams per day, GL=graft loss, mo=month

In addition, and of importance, the proper dose of CsA was further investigated.

Summary of dose-comparative studies

Study	Objective, Population	No.	Time	Treatments	Efficacy Endpoint
Exploratory, uncontrolled studies (blood level control of everolimus, ***reduced dose*** CsA, steroids)					
A2306	efficacy / safety / tolerability of titrated everolimus with titrated reduced dose CsA (with steroids but no induction) in *de novo* kidney recipients	237	12 mo + 12 mo + 12 mo	Everolimus 1.5 mg/d Everolimus 3.0 mg/d (For both doses C_0: ≥3 ng/mL) *(with reduced CsA)*	Renal function (6mo, 12mo) BPAR, GL, death, LtFU (6mo) BPAR, GL, death, LtFU (12 mo) BPAR, GL, death, LtFU (24 mo) BPAR, GL, death, LtFU (36 mo)
A2307	efficacy / safety / tolerability of titrated everolimus with titrated reduced dose CsA (with steroids and basiliximab induction) in *de novo* kidney recipients	256	12 mo + 12 mo +12 mo	Everolimus 1.5 mg/d Everolimus 3.0 mg/d (For both doses C_0: ≥3 ng/mL) *(with reduced CsA)*	Renal function (6mo, 12mo) BPAR, GL, death, LtFU (6mo) BPAR, GL, death, LtFU (12 mo) BPAR, GL, death, LtFU (24 mo) BPAR, GL, death, LtFU (36 mo)

MMF = mycophenolate mofetil, Myfortic® = enteric-coated mycophenolate sodium, CsA = cyclosporine A
basiliximab = interleukin-2 receptor antagonist, BPAR = biopsy-proven acute rejection, LtFU = loss to follow up, mo=month, GL=graft loss

Licensure of Certican in 2003 was based on studies B201, B251 and studies A2306 and 2307 conducted with a reduced dose of CsA.

In the original AR it was concluded that everolimus 1.5 or 3 mg/d demonstrated incontrovertible anti-rejection efficacy as add-on to conventional doses of CsA and CS. Even though protocol-defined non-inferiority *vs.* the well-accepted comparator MMF was not fully achieved for both co-primary endpoints for both doses in both trials, it appears relevant to conclude that efficacy of RAD against acute rejection in this regimen is comparable with that of MMF. Data up to 36 months indicate that RAD plus conventional doses of CsA is

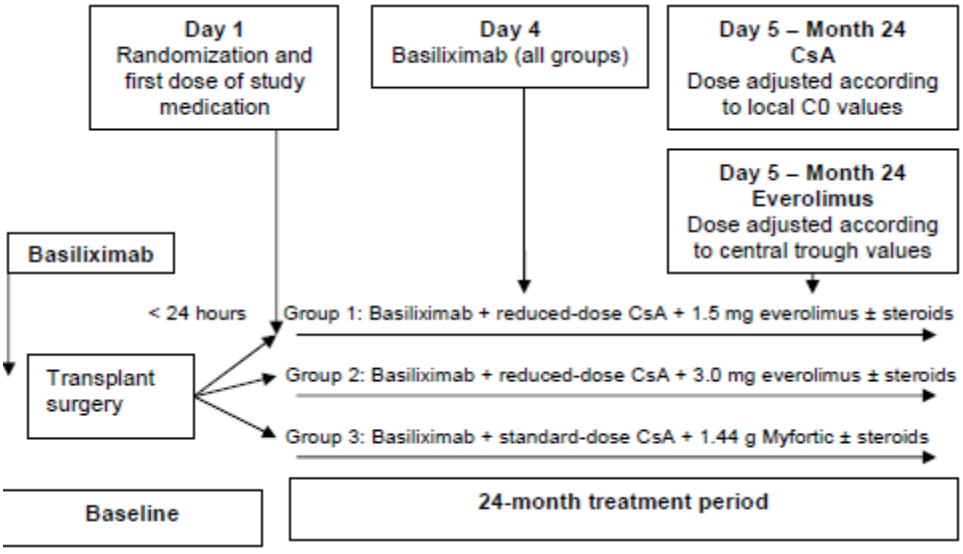
compatible with patient and graft survival, and cardiovascular morbidity rates comparable with those attained with MMF plus CsA. Retention on randomised therapy was, however, lower with everolimus compared with MMF, due to more discontinuations for AEs and inadequate efficacy, which reduces the reassurance which might be gained from this comparison.

Trials B201, B251 provided clear evidence of negative effects on graft function of the chronic use of everolimus plus full-dose CsA. This effect may be at least partially reversible upon tapering of CsA, but indications of higher incidences of CAN in everolimus groups create concern for long-term graft integrity. Consistent with what was concluded in the centralised procedure for sirolimus, everolimus plus full-dose CsA should not be considered an acceptable option for immunosuppression after renal transplantation.

Additional trials A2306, A2307 investigated TDM-based everolimus 1.5 mg and 3 mg initial doses as add-on to lower doses of CsA, monitored by C2h. These trials did not include non-everolimus control and interpretation of the findings rests on comparison with historical data from trials B201, B251 and other trials using MMF. With all the uncertainties involved in such comparisons, the overall impression is that this regimen provides anti-rejection efficacy and graft function generally comparable with what is achieved with MMF and conventionally dosed CsA.

Study A2309 was a 24-month, multicenter, randomised, open-label non-inferiority study of efficacy and safety comparing concentration-controlled Certican in two doses (1.5 and 3.0 mg/day starting doses) with reduced Sandimmun Neoral versus 1.44 g Myfortic with standard dose Neoral in *de novo* renal transplant recipients.

Study design



Non-inferiority analysis for treated BPAR, graft loss or death based on Kaplan-Meier cumulative event rates in Study A2309 (ITT and PP populations, 12 and 24 month analyses)

	ITT population			PP population		
Statistics	EVR 1.5mg N=277	EVR 3.0mg N=279	MPA N=277	EVR 1.5 mg N=215	EVR 3.0 mg N=205	MPA N=230
12 Months						
Number of patients with composite efficacy failure[+]	58	53	58	32	25	33
Rate of composite efficacy failure (%)	21.6%	19.4%	21.3%	15.0%	12.3%	14.5%
Difference in Rates (Everolimus - MPA)	0.2%	-1.9%		0.5%	-2.2%	
95% CI for (Everolimus - MPA)	(-6.7%, 7.2%)	(-8.7%, 4.9%)		(-6.1%, 7.2%)	(-8.6%, 4.2%)	
97.5% CI for (Everolimus - MPA)	(-7.7%, 8.2%)	(-9.6%, 5.8%)		(-7.0%, 8.1%)	(-9.6%, 5.1%)	
p-value of Z-test for (Everolimus - MPA = 0) (No Difference Test)	0.944	0.583		0.872	0.499	
p-value of Z-test for (Everolimus - MPA ≥ 0.1) (Non-inferiority Test)*	0.003	<0.001		0.003	<0.001	
24 Months						
Number of patients with composite efficacy failure[+]	70	61	64	42	31	39
Rate of composite efficacy failure (%)	26.2%	22.3%	23.5%	19.8%	15.2%	17.1%
Difference in Rates (Everolimus - MPA)	2.7%	-1.2%		2.7%	-1.9%	
95% CI for (Everolimus - MPA)	(-4.6%, 10.0%)	(-8.3%, 5.8%)		(-4.5%, 10.0%)	(-8.8%, 5.0%)	
97.5% CI for (Everolimus - MPA)	(-5.7%, 11.0%)	(-9.3%, 6.9%)		(-5.6%, 11.0%)	(-9.8%, 6.0%)	
p-value of Z-test for (Everolimus - MPA = 0) (No Difference Test)	0.471	0.736		0.463	0.593	
p-value of Z-test for (Everolimus - MPA ≥ 0.1) (Non-inferiority Test)*	0.025	<0.001		0.024	<0.001	

*p-value for non-inferiority test is for one-sided test and should be compared to 0.025 significance level for each comparison of everolimus

[+] censoring patients who were lost to follow-up

Non-inferiority analysis of renal function: calculated GFR (MDRD) by treatment group in Study A2309 (ITT and PP populations, 24-month analysis)

	ITT population			PP population		
Statistics	EVR 1.5 mg N=277	EVR 3.0 mg N=279	MPA N=277	EVR 1.5 mg N=215	EVR 3.0 mg N=205	MPA N=230
24-month mean GFR (mL/min/1.73 m^2)	52.20	49.44	50.51	55.24	54.39	53.51
Difference in mean (everolimus - MPA)	1.69	-1.07		1.73	0.88	
t-test based 95% CI for (everolimus - MPA)	(-2.1, 5.5)	(-4.8, 2.7)		(-2.2, 5.6)	(-3.1, 4.9)	
t-test based 97.5% CI for (everolimus - MPA)	(-2.7, 6.1)	(-5.4, 3.2)		(-2.7, 6.2)	(-3.7, 5.4)	
p-value of t-test for (everolimus - MPA = 0) (No Difference Test)	0.385	0.574		0.383	0.665	
p-value of t-test for (everolimus - MPA ≤ -8) (Non-inferiority Test)	<0.001	<0.001		<0.001	<0.001	

24 month GFR missing value imputation, Method-Best: graft-loss = assign GFR value of 0; death or lost to follow up at Month 24 for renal function = last-observation-carried-forward (End of Study (up to Month 24)). Everolimus is non-inferior to MPA if the lower limits of the CIs for the difference in mean GFR (MDRD) are greater than -8 mL/min/1.73 m^2.

P-value for Non-inferiority Test is for one-sided test and should be compared to 0.025 significance level for each comparison of Everolimus vs. MPA.

Overview of efficacy results in pivotal, active comparator studies

	B201 (standard dose CsA)			B251 (standard dose CsA)			A2309 (low vs. stand. dose CsA)		
	EVR 1.5 mg N=194 n (%)	EVR 3.0 mg N=198 n (%)	MPA N=196 n (%)	EVR 1.5 mg N=193 n (%)	EVR 3.0 mg N=194 n (%)	MPA N=196 n (%)	EVR 1.5 mg N=277 n (%)	EVR 3.0 mg N=279 n (%)	MPA N=277 n (%)
Composite endpoint[1]	58 (29.9)	60 (30.3)	61 (31.1)	48 (24.9)	51 (26.3)	54 (27.6)	70 (25.3)	60 (21.5)	67 (24.2)
BPAR /Treated BPAR	45 (23.2)	39 (19.7)	47 (24.0)	37 (19.2)	43 (22.2)	47 (24.0)	45 (16.2)	37 (13.3)	47 (17.0)
Graft loss	9 (4.6)	21 (10.6)	18 (9.2)	17 (8.8)	8 (4.1)	10 (5.1)	12 (4.3)	13 (4.7)	9 (3.2)
Death	10 (5.2)	8 (4.0)	5 (2.6)	6 (3.1)	7 (3.6)	4 (2.0)	7 (2.5)	9 (3.2)	6 (2.2)
Loss to follow-up	1 (0.5)	3 (1.5)	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)	12 (4.3)	7 (2.5)	9 (3.2)
Graft loss or death	18 (9.3)	29 (14.6)	21 (10.7)	21 (10.9)	14 (7.2)	12 (6.1)	18 (6.5)	21 (7.5)	15 (5.4)
Graft loss, death or loss to follow-up	21 (10.8)	33 (16.7)	23 (11.7)	22 (11.4)	15 (7.7)	13 (6.6)	30 (10.8)	28 (10.0)	24 (8.7)

[1]Composite endpoint: BPAR (treated BPAR for Study A2309), graft loss, death or loss to follow-up
Patients are counted in all rows that apply: individual components of efficacy failure are not mutually exclusive
For the 12-month efficacy analyses, all deaths up to the efficacy cut-off at Day 381 were included

Table 17. Non-inferiority analysis for the incidence of BPAR, graft loss, death, or loss to follow-up in Studies B201, B251 and A2309 (ITT population, 12 month analyses)

	B201 (standard dose CsA)			B251 (standard dose CsA)			A2309 (low vs. stand. dose CsA)		
Number of patients with composite efficacy failure	EVR 1.5 mg N = 194	EVR 3.0 mg N = 198	MPA N = 196	EVR 1.5 mg N = 193	EVR 3.0 mg N = 194	MPA N = 196	EVR 1.5 mg N=277	EVR 3.0 mg N=279	MPA N=277
Rate of composite efficacy failure within 12 months (BPAR, graft loss, death or loss to follow-up), n (%)	58 (29.9)	60 (30.3)	61 (31.1)	48 (24.9)	51 (26.3)	54 (27.6)	70 (25.3)	60 (21.5)	67 (24.2)
Diff in Rates (Everolimus - MPA)	-1.2%	-0.8%	–	-2.7%	-1.3%	–	1.1%	-2.7%	
95% CI for (Everolimus - MPA)	(-10.3,7.9)	(-9.9,8.3)	–	(-11.4,6.0)	(-10.1,7.5)	–	(-6.1,8.3)	(-9.7,4.3)	
97.5% CI for (Everolimus - MPA)	(-11.7,9.3)	(-11.2,9.6)	–	(-12.7,7.3)	(-11.4,8.8)	–	(-7.1,9.3)	(-10.7,5.3)	
p-value of Z-test for (Everolimus - MPA = 0) (No Difference Test)	0.797	0.863	–	0.545	0.772	–	0.767	0.451	

Study A2309 may be viewed as confirmatory to studies B201 and B251, but also confirming the results of studies A2306 and A2307 in relation to reduced dose CsA and reduced renal toxicity with maintained and acceptable rejection control..

The study was planned and started before the CHMP guideline came into effect in 2009. The study is however in most respects carried out in accordance with the guideline. The study design and the study objectives are reasonable and in accordance with those used in many other studies with immunosuppressant in organ transplantation. More patients in the EVR treatment groups than in the Myfortic group had protocol violations that led to exclusion from the PP population. More patients in the everolimus treatment arms than in the control arm discontinued study medication. Overall study discontinuation rates were, however, mainly as expected.
Recipient age in this study is lower than in many European renal transplant populations and so is donor age. Sensitised patients and retransplanted patients were excluded from study participation.

Noninferiority to the comparator arm was demonstrated for both everolimus treatment arms for the primary efficacy failure parameter (treated BPAR, graft loss, death, or loss to follow-up). The 3 mg everolimus arm had the lowest rate of biopsy-verified acute rejection but the highest incidence of death and graft loss or death.

Everolimus trough levels were within the target levels at all time points during the study. Ciclosporin trough levels were at the upper limit of or above the recommended target levels at the beginning of each time span during the first 12 months for both everolimus treatment groups while it was within the target levels for the Myfortic groups. The rate of chronic allograft damage did not differ between treatment groups for those patients who had both a baseline biopsy and a biopsy at 12 months. The percentage of patients treated BPAR, graft loss or death tended to decrease with increasing everolimus concentrations. The present recommendation is a target concentration of 3 – 8 ng/ml for everolimus.

In conclusion, 12- month efficacy data in study A2309 showed noninferiority for the primary efficacy composite endpoint (treated BPAR, graft loss, death, or loss to follow-up) as well as for secondary endpoints for the 1.5 mg and for 3 mg everolimus when used in combination with ciclosporin, steroids and basiliximab in this concentration-controlled everolimus study with low ciclosporin target levels.

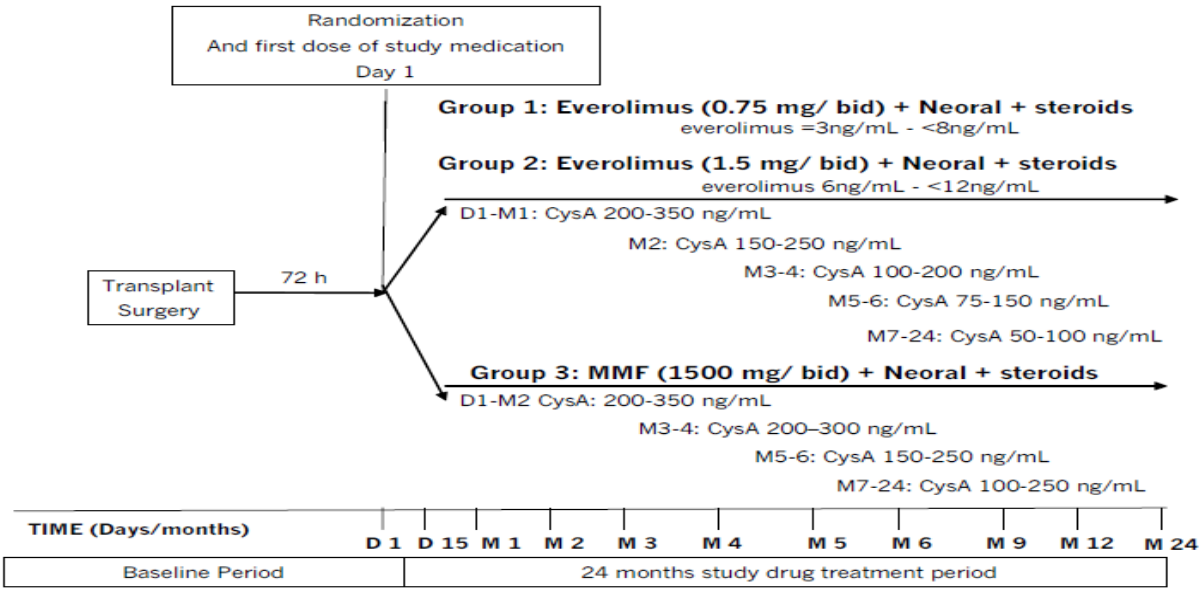
IV.2.2 **Heart transplantation**

Summary of active controlled trials

Study	Objective, population	No. of patients	Treatment duration	Medication dose/day	Efficacy endpoint
A2310	Efficacy & safety of concentration-controlled everolimus with reduced dose CsA vs. MMF with standard dose CsA (both with steroids; induction/no induction therapy per site practice) in *de novo* cardiac transplant recipients	721	24 months (core phase 12 months)	Everolimus: 1.5 mg/d (C0: 3-8ng/ml) 3.0 mg/d (C0: 6-12ng/ml)# MMF: 3.0 g/d (open-label)	Composite efficacy failure: BPAR ISHLT ≥ 3A, AR with HDC, Death, Graft Loss/re-transplant, Loss to follow-up
A2411	Efficacy & safety of concentration controlled everolimus with reduced dose CsA vs. MMF with standard dose CsA (both with steroids; induction/no induction therapy per local practice) in *de novo* cardiac transplant recipients	176	12 months	Everolimus: 1.5 mg/d (C0: 3-8 ng/mL) MMF: 3.0 g/d (open-label).	BPAR ISHLT ≥ 3A, Renal function
B253	Efficacy & safety of fixed dose everolimus with standard dose CsA vs. azathioprine with standard dose CsA (both with steroids; induction/no induction per site practice) in *de novo* cardiac transplant recipients	634	24 months (core phase 12 months)	Everolimus: 1.5 mg/d 3.0 mg/d AZA: 1-3 mg/kg/d (1-year double-blind, 1-year open label)	Composite efficacy failure: BPAR ISHLT ≥ 3A, AR with HDC, Death, Graft Loss, Loss to follow-up

# Further enrollment in 3.0 mg/d group stopped on 27-Mar-2008 at Data Monitoring Committee (DMC) request.
MMF = mycophenolate mofetil, CsA = cyclosporine A,
BPAR = biopsy-proven acute rejection, AR = acute rejection, HDC = hemodynamic compromise, ISHLT = International Society of Heart and Lung Transplantation

Study A2310 was a 24-month, multicenter, randomized, open-label, parallel group study of efficacy and safety in 721 adult *de novo* heart transplant recipients



The 3 mg everolimus arm was stopped by the DMC due to an apparent increase in death rate.

Composite endpoint analysis by treatment group (ITT and PP population) (Study A2310 - 12 and 24 month analyses)

	ITT population				PP population			
Efficacy variable	**EVR 1.5 mg n (%)**	**EVR 3.0 mg n (%)**	**MMF n (%)**	**Difference EVR 1.5 mg – MMF (97.5% CI)**	**EVR 1.5 mg n (%)**	**EVR 3.0 mg n (%)**	**MMF n (%)**	**Difference EVR 1.5 mg – MMF (97.5% CI)**
Month 12	**N=282**	**N=168**	**N=271**		**N=200**	**N=90**	**N=208**	
Composite efficacy failure (incl. loss to follow up)	99 (35.1)	59 (35.1)	91 (33.6)	1.5% (-7.5, 10.6)	46 (23.0)	22 (24.4)	56 (26.9)	-3.9% (-13.5, 5.7)
Acute rejection associated HDC	11 (3.9)	5 (3.0)	7 (2.6)	1.3% (-2.1, 4.7)	7 (3.5)	3 (3.3)	5 (2.4)	1.1% (-2.7, 4.9)
BPAR of ISHLT grade ≥ 3A	63 (22.3)	43 (25.6)	67 (24.7)	-2.4% (-10.5, 5.7)	39 (19.5)	21 (23.3)	51 (24.5)	-5.0% (-14.2, 4.2)
Death	22 (7.8)	17 (10.1)	13 (4.8)	3.0% (-1.6, 7.6)	1 (0.5)	2 (2.2)	2 (1.0)	-0.5% (-2.3, 1.4)
Graft loss/re-transplant	4 (1.4)	5 (3.0)	5 (1.8)	-0.4% (-2.8, 2.0)	1 (0.5)	0 (0.0)	1 (0.5)	0.0% (-1.5, 1.6)
Loss to follow-up*	9 (3.2)	3 (1.8)	10 (3.7)	n.a.	1 (0.5)	0 (0.0)	1 (0.5)	0.0% (-1.5, 1.6)
Graft loss/re-transplant, death, or loss to follow-up **	33 (11.7)	20 (11.9)	24 (8.9)	2.8% (-2.9, 8.6)	2 (1.0)	2 (2.2)	3 (1.4)	-0.4% (-2.9, 2.0)
Acute rejection treated with antibody	13 (4.6)	5 (3.0)	9 (3.3)	n.a.	6 (3.0)	2 (2.2)	5 (2.4)	0.6% (-3.0, 4.2)
Composite efficacy failure (without loss to follow up)	90 (34.2)	56 (34.6)	81 (33.2)	1.1% (-9.5, 11.6)	45 (24.5)	22 (25.2)	55 (29.4)	-4.9% (-16.4, 6.7)
Month 24	**N=282**	**N=168**	**N=271**		**N=200**	**N=93**	**N=211**	
Composite efficacy failure (incl. loss to follow up)	111 (39.4)	69 (41.1)	112 (41.3)	-2.0% (-11.3, 7.4)	53 (26.5)	28 (30.1)	75 (35.5)	-9.0% (-19.2, 1.1)
Acute rejection associated HDC	12 (4.3)	6 (3.6)	14 (5.2)	-0.9% (-5.0, 3.1)-	8 (4.0)	4 (4.3)	11 (5.2)	-1.2% (-5.8, 3.4)
BPAR of ISHLT grade ≥ 3A	68 (24.1)	48 (28.6)	74 (27.3)	-3.2% (-11.5, 5.1)	42 (21.0)	24 (25.8)	58 (27.5)	-6.5% (-15.9, 3.0)
Death	30 (10.6)	20 (11.9)	25 (9.2)	1.4% (-4.3, 7.1)	6 (3.0)	4 (4.3)	12 (5.7)	-2.7% (-7.2, 1.8)
Graft loss/re-transplant	7 (2.5)	5 (3.0)	10 (3.7)	-1.2% (-4.5, 2.1)	4 (2.0)	0 (0.0)	7 (3.3)	-1.3% (-4.9, 2.2)
Loss to follow-up*	10 (3.5)	5 (3.0)	14 (5.2)	n.a.	1 (0.5)	1 (1.1)	4 (1.9)	-1.4% (-3.8, 1.0)
Graft loss/re-transplant, death, or loss to follow-up **	43 (15.2)	27 (16.1)	41 (15.1)	0.1% (-6.7, 7.0)	7 (3.5)	6 (6.5)	17 (8.1)	-4.6% (-9.7, 0.6)
Acute rejection treated with antibody	14 (5.0)	6 (3.6)	11 (4.1)	n.a.	7 (3.5)	3 (3.2)	7 (3.3)	0.2% (-3.8, 4.2)
Composite efficacy failure (without loss to follow up)	101 (37.6)	64 (38.6)	98 (42.0)	-4.4% (-16.4, 7.6)	52 (27.5)	27 (29.1)	71 (39.7)	-12% (-26.2, 1.8)

Whilst the predefined NI margin (13%) might be viewed as too liberal, the outcome is reasonably reassuring in the ITT as well as PP population, especially at month 24. With respect to deaths, note that the apparent difference in number was reduced at month 24.

Incidence rates of efficacy endpoints by treatment group (ITT population) (active controlled Studies Study A2310, A2411 and B253 – 12 and 24 month analyses)

	A2310			A2411		B253		
Efficacy variable	**EVR 1.5 mg N=282 n (%)**	**EVR 3.0 mg N=168 n (%)**	**MMF N=271 n (%)**	**EVR 1.5mg N=92 n (%)**	**MMF N=84 n (%)**	**EVR 1.5 mg (N=209) n (%)**	**EVR 3 mg (N=211) n (%)**	**AZA (N=214) n (%)**
Month 12								
Composite efficacy failure (incl. loss to follow-up)	99 (35.1)	59 (35.1)	91 (33.6)	30 (32.6)	35 (41.7)	87 (41.6)	68 (32.2)	113 (52.8)
Acute rejection associated HDC	11 (3.9)	5 (3.0)	7 (2.6)	2 (2.2)	1 (1.2)	17 (8.1)	14 (6.6)	23 (10.7)
BPAR of ISHLT grade ≥ 3A	63 (22.3)	43 (25.6)	67 (24.7)	21 (22.8)	25 (29.8)	64 (30.6)	45 (21.3)	98 (45.8)
Death	22 (7.8)	17 (10.1)	13 (4.8)	10 (10.9)	10 (11.9)	18 (8.6)	24 (11.4)	17 (7.9)
Graft loss/re-transplant	4 (1.4)	5 (3.0)	5 (1.8)	1 (1.1)	2 (2.4)	7 (3.3)	11 (5.2)	10 (4.7)
Loss to follow-up*	9 (3.2)	3 (1.8)	10 (3.7)	n.a.	n.a.	0	0	2 (0.9)
Acute rejection treated with antibody	13 (4.6)	5 (3.0)	9 (3.3)	5 (5.4)	2 (2.4)	15 (7.2)	7 (3.3)	15 (7.0)
Composite efficacy failure (without loss to follow up)	90 (34.2)	56 (34.6)	81 (33.2)	n.a.	n.a.	n.a.	n.a.	n.a.
Month 24								
Composite efficacy failure (incl. loss to follow-up)	111 (39.4)	69 (41.1)	112 (41.3)	n.a.	n.a.	96 (45.9)	76 (36.0)	123 (57.5)
Acute rejection associated HDC	12 (4.3)	6 (3.6)	14 (5.2)	n.a.	n.a.	19 (9.1)	17 (8.1)	28 (13.1)
BPAR of ISHLT grade ≥ 3A	68 (24.1)	48 (28.6)	74 (27.3)	n.a.	n.a.	73 (34.9)	48 (22.7)	103 (48.1)
Death	30 (10.6)	20 (11.9)	25 (9.2)	n.a.	n.a.	21 (10.0)	29 (13.7)	24 (11.2)
Graft loss/re-transplant	7 (2.5)	5 (3.0)	10 (3.7)	n.a.	n.a.	10 (4.8)	14 (6.6)	13 (6.1)
Death or Graft loss/retransplant	na	na	na	n.a.	n.a.	na	na	na
Loss to follow-up *	10 (3.5)	5 (3.0)	14 (5.2)	n.a.	n.a.	0	0	2 (0.9)
Acute rejection treated with antibody	14 (5.0)	6 (3.6)	11 (4.1)	n.a.	n.a.	15 (7.2)	9 (4.3)	18 (8.4)
Composite efficacy failure (without loss to follow up)	101 (37.6)	64 (38.6)	98 (42.0)	n.a.	n.a.	n.a.	n.a.	n.a.

Legend from Study A2310: Composite efficacy failure is defined as BPAR of ISHLT grade ≥ 3A, acute rejection associated with HDC, Graft loss/re-transplant, death or loss to follow-up.
BPAR = Biopsy Proven Acute Rejection episode; HDC = Hemodynamic Compromise. n.a. = not available
The identification of rejection is based on local laboratory biopsy results.

No 24-month data for A2411.

* Loss to follow-up for composite efficacy failure.

The totality of data available and derived from pivotal study B253 supported by studies A2310 and A2411 documents an acceptable efficacy profile of everolimus at a dose of 0.75 mg twice daily followed by TDM.

In study A2310, MMF was the comparator whilst azathioprin was used in B253. Therefore A2310 is considered pivotal. The NI margin set in this trial for the at that time standard composite 13%, might be regarded as too liberal but available results rather meets a margin <10%. This is found acceptable.

IV.2.3 **Liver Transplantation**

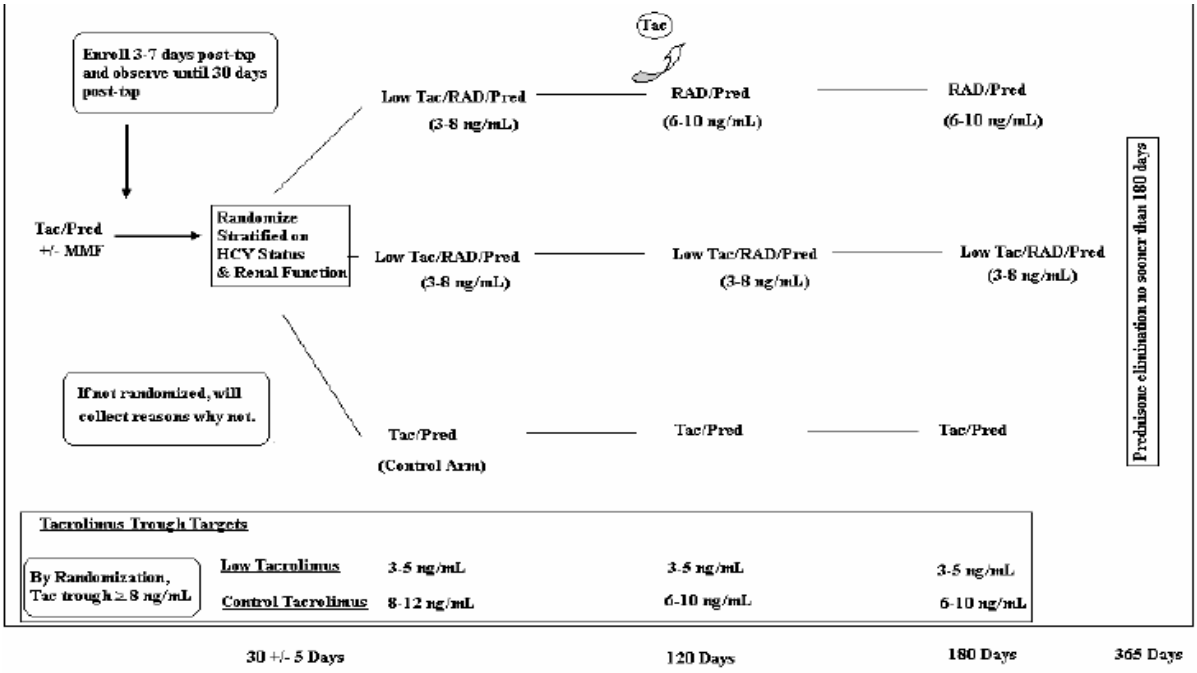
Overview of trials

Source of data	Study	Details
Dose-selection trial	**B158**	One-year, multicenter, randomized, placebo controlled double-blind, parallel group, EVR dose-finding study, phase II
Core controlled trial	**H2304**	Multi-center, open-label, randomized, controlled study to evaluate the efficacy and safety of concentration-controlled EVR to eliminate or to reduce TAC compared to TAC in de novo LTx recipients, phase III
Supportive controlled trials	**HDE10**	Multicenter, randomized, open-label study of safety, tolerability and efficacy of EVR -based regimen versus CNI based regimen in de novo LTx recipients, phase III
	H2401	Multi-center, open-label, randomized, controlled study with EVR versus CNI reduction/elimination in maintenance LTx patients, phase III

Study B158 was performed to determine the long-term tolerability and safety of everolimus at 3 dose levels (1 mg/ day, 2 mg/day and 4 mg/day) over 1 year. After completion of the 12-month double-blind period, patients were followed in an open-label treatment protocol for an additional 2 years. Patients also took oral CsA at doses necessary to maintain trough levels in the following target ranges: weeks 1 to 4, 150 to 450 ng/mL; months 2 to 6, 100 to 300 ng/mL; and months 7 to 12, 75 to 300 ng/mL. Intravenous methylprednisolone was administered before, during, or immediately after transplantation. Oral prednisone (or its methylprednisolone equivalent) was tapered to 5.0 mg/day by month 3, after which it was given at maintenance doses, was tapered further, or was discontinued.

There were no significant dose-related or between group differences in rates of the composite end point of efficacy failure or its individual components although the overall incidence of specific AEs, of infections, of non-fatal SAEs and of treatment discontinuation due to AEs were higher in the 2 and/or 4 mg/day everolimus group than in the everolimus 1 mg/day.

Study H2304: Study design



Group 1: T**acrolimus Elimination Arm**
After everolimus blood trough levels were confirmed to be in the target range (3-8 ng/mL), TAC tapering was started, achieving a target TAC whole blood trough level of 3-5 ng/mL by three weeks after randomization.
Beginning at Month 4 post-transplant (Day 120), TAC elimination was started. TAC was tapered after everolimus whole blood trough levels were within the target range of 6-10 ng/mL. TAC was completely eliminated by the end of Month 4 post-transplantation.

In April 2010, an independent Data Monitoring Committee (DMC) recommended discontinuation of enrollment into the TAC Elimination arm due to a higher rate of acute rejection and discontinuations in this group during the first 180 days postrandomization.

Health authority advice on a proposal to modify the study protocol following this action was sought from the EMA, the Medicinal Products Agency and from the US Food and Drug Administration.

The amended study protocol (Amendment 1) followed the EMA guideline on clinical investigation of immunosuppressants for solid organ transplantation. In consequence, the primary endpoint assessed the composite efficacy failure rate of treated biopsy proven acute rejection, graft loss or death between an early (4 weeks after liver transplantation) everolimus-facilitated tacrolimus minimization relative to standard exposure tacrolimus at 12 months.

Prior to Amendment 1, study H2304 had two co-primary endpoints: 1- the efficacy endpoint was defined as graft loss, death or loss to follow up (excluding acute rejection); 2- renal function. With Amendment 1 renal function became the key secondary objective evaluating the evolution of renal function mea

Group 2: Tacrolimus Minimization Arm
Low dose Tacrolimus (TAC reduced) + everolimus + corticosteroids

Everolimus was initiated within 24 hours of randomization. TDM was mandatory throughout the duration of study (C-0h 3-8 ng/mL).

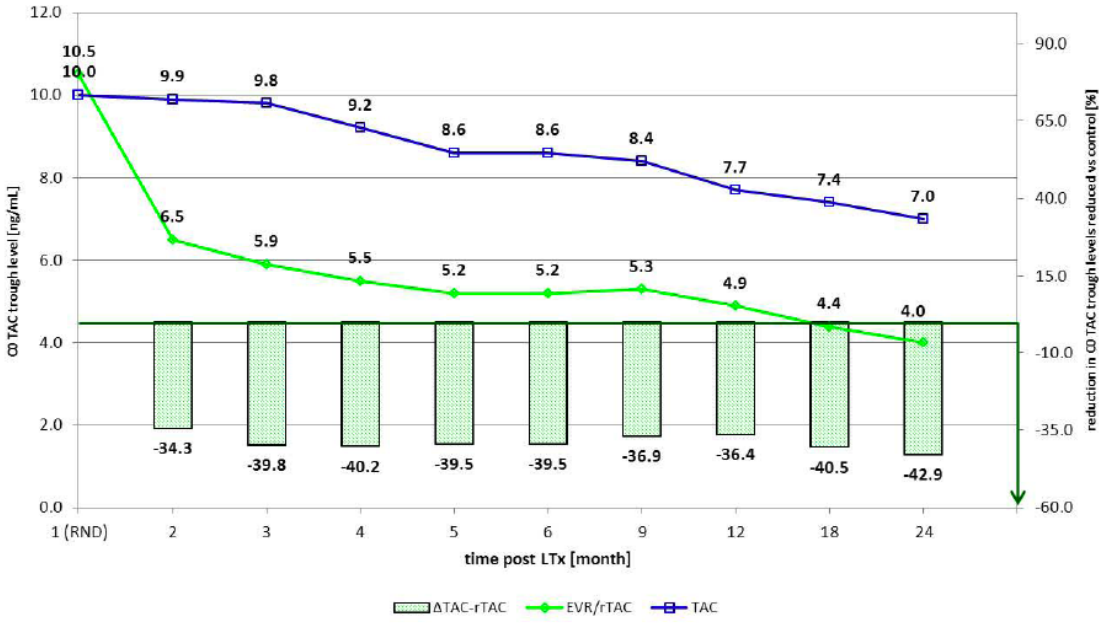
After everolimus whole blood trough levels were confirmed to be in the target range (3-8 ng/mL), TAC tapering began, achieving a target TAC whole blood trough (C-0h) levels of **3-5 ng/mL** by three weeks after randomization and continuing through the remainder of the study.

Group 3: TAC Control Arm
Control dose TAC + corticosteroids

TAC dosing: TAC trough levels were targeted to be maintained at 8-12 ng/mL until Month 4. At Month 4, TAC whole blood trough (C-0h) levels were decreased to a target trough level **of 6-10 ng/mL** for the remainder of the study.

Achievment of target tacrolimus C_0

Mean tacrolimus C_0 trough exposure (ng/mL) over time for EVR+Reduced TAC and TAC Control (Safety population).



Source: Table 14.3-1.8a

***Primary objective**:* This was the composite efficacy failure rate of treated biopsy-proven acute rejection, graft loss or death, according to the amended study protocol.

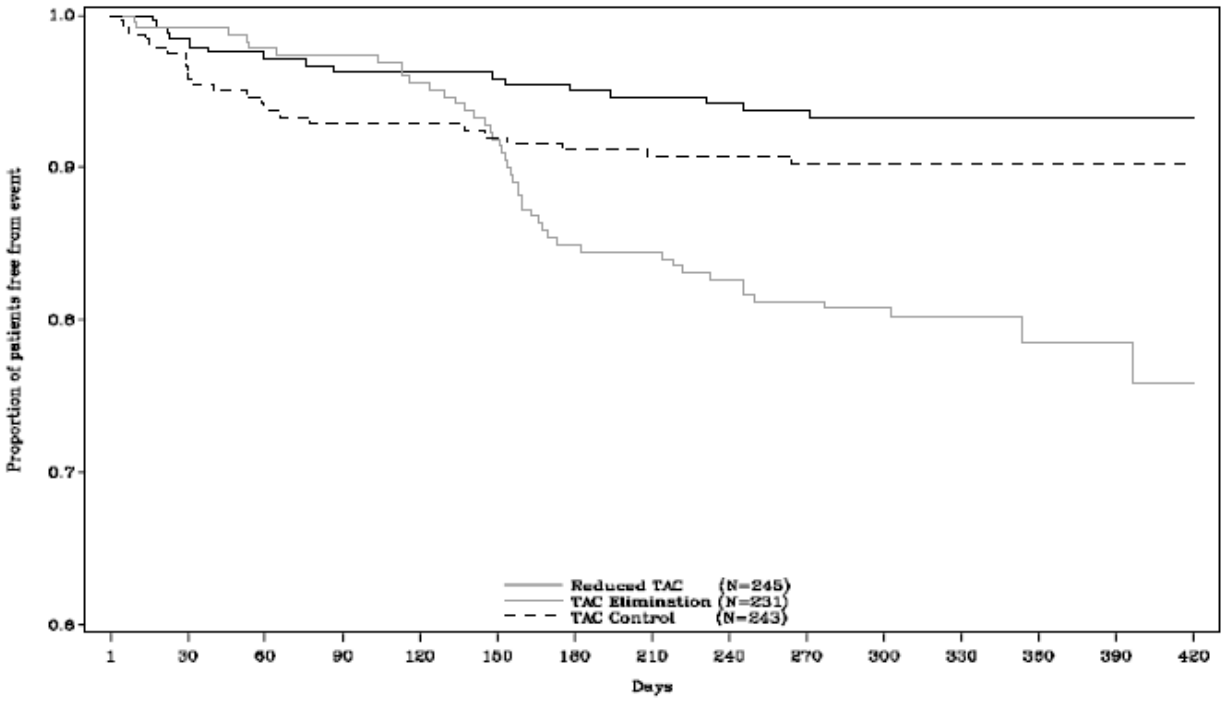
Comparison between treatment groups for Kaplan-Meier incidence rates of primary efficacy endpoint, ITT population,12 month analysis, study H2304

Statistic	EVR+Reduced TAC N=245	TAC Elimination N=231	TAC Control N=243
Number of composite efficacy failure (tBPAR, graft loss or death) from randomization till Month 12	16	45	23
KM estimate of incidence rate of composite efficacy failure (tBPAR, graft loss or death) at Month 12	6.7%	24.2%	9.7%
Difference in KM estimates (vs. Control)	-3.0%	14.5%	
97.5% CI for difference	(-8.7%, 2.6%)		
P-value of Z-test for (Reduced TAC - Control = 0) (No Difference Test)	0.230		
P-value* of Z-test for (Reduced TAC - Control ≥ 0.12) (Non-inferiority Test)	<0.001		

1. tBPAR = treated biopsy proven acute rejection. Local laboratory biopsy results are used to define tBPAR.
2. *Z-test p-value for non-inferiority test (non-inferiority margin = 12%) is for one-sided test and was compared to 0.0125 significance level.
3. In Kaplan-Meier estimate, the censoring day for patients without event is the last contact day.

Both treatment arms had lower rate of primary efficacy endpoint failure when based on central lab biopsy results, the EVR + Reduced TAC arm 5.9% and TAC Control arm, 6.8%, respectively.

Kaplan-Meier plot for the proportion of patients free from primary composite efficacy failure tBPAR, ITT population,12 month analysis, study H2304



Comparison between treatment groups for the incidence rate of graft loss, death or loss to follow-up, ITT population,12 month analysis, study H2304

Statistic	EVR/Reduced TAC N=245	TAC Elimination N=231	TAC Control N=243
Number of composite efficacy failure (graft loss, death or loss to follow-up) from randomization till Month 12	22	28	24
Incidence rate of composite efficacy failure (graft loss, death or loss to follow-up) from randomization till Month 12	9.0%	12.1%	9.9%
Difference in incidence rates (*vs.* Control)	-0.9%	2.2%	
97.5% CI for the difference	(-7.3%, 5.5%)		
P-value of Z-test for (EVR/Reduced TAC - Control = 0) (No Difference Test)	0.735		
P-value * of Z-test for (EVR+Reduced TAC - Control ≥ 0.10) (Non-inferiority Test)	<0.001		

1. Loss to follow-up for 'graft loss, death or loss to follow-up' is defined as a patient who does not die, does not have graft loss, and whose last day of contact is prior to the lower limit of the Month 12 visit window.
2. * The maximum likelihood estimate under the constraint of null hypothesis (NI margin= 10%) is used for the variance of proportion difference between treatment groups. Asymptotic CI and Non-inferiority test are calculated using this variance.

Efficacy update, primary endpoint, 24 month data

	12 month analysis			24 month analysis		
Statistic	EVR+Reduced TAC N=245	TAC Elimination N=231	TAC Control N=243	EVR/Reduced TAC N=245	TAC Elimination N=231	TAC Control N=243
Number of composite efficacy failure (tBPAR, graft loss or death) from randomization till Month 12 and 24	16	45	23	24	55	29
KM estimate of incidence rate of composite efficacy failure (tBPAR, graft loss or death) at Month 12 and 24	6.7%	24.2%	9.7%	10.3%	26.0%	12.5%
Difference in KM estimates (vs. Control)	-3.0%	14.5%		-2.2%	13.5%	
97.5% CI for difference	(-8.7%, 2.6%)			(-8.8%, 4.4%)		
P-value of Z-test for (EVR+Reduced TAC - Control = 0) (No Difference Test)	0.230			0.452		
P-value* of Z-test for (EVR+Reduced TAC - Control ≥ 0.12) (Non-inferiority Test)	<0.001			<0.001		

1. tBPAR = treated biopsy proven acute rejection. Local laboratory biopsy results are used to define tBPAR.
2. *Z-test p-value for non-inferiority test (non-inferiority margin = 12%) is for one-sided test and was compared to 0.0125 significance level.

The endpoints according to Amenment 1 in study H2304 are in accordance with the CHMP guideline on clinical investigation of immunosuppressants for solid organ transplantation (CHMP/EWP/263148), coming into effect 1 Febr 2009). The study design is reasonable. The delay in initiation of everolimus is intended to avoid initial early problems with wound healing, fluid collections, and hepatic artery thrombosis seen in earlier liver transplantation studies with mTOR inhibitors initiated at the time of transplantation. With a total of 1147 patients entering the run-in period whereof 719 were randomised, the randomisation failure rate was 37.3%. The reasons for failure have been accounted for. The most frequent reasons for randomisation failure were: inadequate allograft function, failure to achieve a tacrolimus level equal or greater than 8 ng/mL, surgical/medical condition, patient still requiring critical care, inadequate renal function, use of antibody induction therapy and, other.

There is a known difference in pharmacokinetics when everolimus is co-administered with tacrolimus, compared to when it is co-administered with ciclosporin. The blood concentration of everolimus is expected to be about the double when co-administered with ciclosporin, compared to tacrolimus. To achieve target blood concentrations, everolimus doses were frequently increased early after initiation of the drug.

Amendment 1 was done after most patients had already been included in the study. The change of primary endpoint, and other major study amendments, was done after discussion with regulatory authorities in the US and EU; this amendment adapted endpoints to current guidelines. It cannot be excluded that the termination of the TAC Elimination arm has influenced the care of patients in the two other treatment arms, considering that this was an open study.

There were no differences of importance between treatment groups in baseline characteristics. The absolute majority of patients were Caucasian, just over 70 % were male. Mean age was 54 years, Nearly one third of patients were HCV-positive. Thirty-six to 42 % of patients in the 3 treatment groups were diabetics at the time of randomisation in the study. The most common diagnoses leading to liver transplantation were hepatitis C, alcoholic cirrhosis, and hepatocellular carcinoma.

The main and sensitivity analyses, ITT and PP respectively, of the composite primary endpoint of treated biopsy-proven acute rejection, graft loss or death, support a conclusion of non-inferiority. The upper limit of the 97.5% CI is well below the non-inferiority margin of 12%, ranging from 1.5% to 2.6% with the difference between the two groups being in favour of the EVR + Reduced TAC arm (approximately -3.0%). In the PP population 35.9% and 33.7% of the patients in EVR + Reduced TAC and TAC Control group respectively were excluded.

In the analyses of the primary endpoint, local biopsy readings were used to determine the occurrence of tBPAR (one of the components). Also presented is the corresponding analysis based on central laboratory biopsy readings. Due to fewer events in the control arm the difference is no longer of the same magnitude as in the analysis based on local readings but non-inferiority is still shown (the difference being -0.9% with the upper limit of the 97.5% CI being 4.1%).

Non-inferiority was clearly demonstrated for the EVR + Reduced TAC treatment group, compared to the TAC Control group, independent of analyses of subgroups and different methods for calculating GFR.

Efficacy conclusion: In the pivotal liver study H2304, non-inferiority was demonstrated for the primary composite endpoint of treated biopsy-proven rejection, graft loss or death in the EVR + Reduced TAC study group, compared to the TAC Control group. For the key secondary endpoint of renal function, superiority of EVR + Reduced TAC arm versus TAC Control was demonstrated.

IV.3 Clinical safety

The safety profile of everolimus is considered well established and mature based on about 9200 individuals in clinical studies as of July 2012 and about 140 thousand patient-years post marketing (2003).

In the pivotal studies for the three approved indications the following AEs were reported in higher or lower incidences as compared with the reference product.

Kidney transplantation, study A2309: AEs for which there was a ≥ 5% higher incidence at Month 12 in the everolimus 1.5 mg group compared with MPA included dyslipidemia (15.0% vs. 8.8%), hyperlipidemia (20.8% vs. 15.8%) and peripheral edema (44.9% vs. 39.6%)

AEs for which there was a ≥ 5% lower incidence at Month 12 in the everolimus 1.5 mg group compared with MPA included vomiting (14.6% vs. 22.0%), tremor (8.4% vs. 13.9%), dyspepsia (4.4% vs. 11.4%), abdominal pain upper (3.3% vs. 11.0%), leukopenia (2.9% vs. 12.1%) and CMV infection (0.7% vs. 5.9%)

Heart transplantation, study A2310, the following AEs were more frequent (difference ≥ 5%) in the everolimus group than in the MPA group at Month 12: anemia (34.8% vs. 25.7%), pericardial effusion (39.8% vs. 27.6%), peripheral edema (44.4% vs. 38.4%), insomnia (26.9% vs. 20.1%) and renal failure (16.1% vs. 9.0%)

Less frequently (difference of ≥ 5%) reported in the everolimus group than in the MPA group at Month 12 were anaemia (12.2% vs. 23.1%), vomiting (10.4% vs. 15.7%), diarrhea (18.3% vs. 23.5%), nausea (20.8% vs. 26.5%) and CMV infections (5.4% vs. 10.4%)

Liver transplantation study H2304 (in which everolimus was combined with tacrolimus) at Month 12 the following AEs were more frequently reported (difference ≥°5%) in the everolimus + reduced TAC group and/or the TAC elimination group than in the TAC control group: leukopenia (11.8%, 9.1% and 5.0%, respectively), peripheral edema (17.6%,18.3% and 10.8%), pyrexia (13.1%, 19.6% and 10.4%), hypercholesterolemia (9.4%, 7.8%and 2.5%), hyperlipidemia (7.3%, 7.8% and 2.1%) and hypertriglyceridemia (6.5%, 3.5% and 1.2%)

The incidence of the following AEs at Month 12 were lower (difference ≥ 5%) in the everolimus + reduced TAC group and/or the TAC elimination group than in the TAC control group: hyperkalemia (4.1%, 3.5% and 9.5%), blood creatinine increased (1.2%, 2.6% and 6.2%); each in the EVR+reduced TAC group, TAC elimination group and TAC controlmgroup, respectively)

Post marketing surveillance

Relevant safety findings identified in PSUR review periods

Safety finding	Identified	Proposed action
Acute tubular necrosis	PSUR 1	Subject to standard pharmacovigilance procedures since PSUR 2 on the basis of cumulative evidence
Biliary disorders/ hepatotoxicity disorders	PSUR 1	Hepatotoxicity proposed for inclusion in Core Data Sheet as undesirable effect. Subject to standard pharmacovigilance procedures Biliary disorders remained under intensive monitoring subject to standard pharmacovigilance procedures since PSUR 3 on the basis of cumulative evidence
Bronchial dehis-cence/ vascular dehiscence	PSUR 1	Subject to standard pharmacovigilance procedures since PSUR 5 on the basis of cumulative evidence

Safety finding	Identified	Proposed action
Hemorrhagic events	PSUR 1	Further intensive monitoring
	PSUR 7	Post-procedural hemorrhages considered as listed events of delayed wound-healing. Cumulative analysis not suggestive for an association of everolimus with a general bleeding diathesis, although thrombocyte counts should be monitored as everolimus can be associated with thrombocytopenia. Standard pharmacovigilance monitoring procedures.
Interstitial lung disease	PSUR 1	PSUR 8 concludes that the reported frequency and characteristics is in line with the core data sheet (CDS). Further intensive monitoring
Lymphocele	PSUR 1	Subject to standard pharmacovigilance procedures since PSUR 2 on the basis of cumulative evidence
Malignancies	PSUR 1	Subject to standard pharmacovigilance procedures since PSUR 3 on the basis of cumulative evidence
Myotoxicity	PSUR 1	Subject to standard pharmacovigilance procedures since PSUR 2 on the basis of cumulative evidence
Pancreas AEs, pancreatitis	PSUR 1	Subject to standard pharmacovigilance procedures since PSUR 2 on the basis of cumulative evidence. Amended to the CDS as common ADR and routine pharmacovigilance as of PSUR 6.
	PSUR 6	
Pericardial effusion	PSUR 1	Subject to standard pharmacovigilance procedures since PSUR 2 on the basis of cumulative evidence
	PSUR 5	Further intensive monitoring
	PSUR 7	Amended to the CDS
Renal failure	PSUR 1	Subject to standard pharmacovigilance procedures since PSUR 3 on the basis of cumulative evidence
Thromboembolic events	PSUR 1	Subject to standard pharmacovigilance procedures since PSUR 2 on the basis of cumulative evidence
Thrombotic thrombocytopenic purpura	PSUR 1	Subject to standard pharmacovigilance procedures since PSUR 2 on the basis of cumulative evidence
Toxicoderma	PSUR 1	Subject to standard pharmacovigilance procedures since PSUR 2 on the basis of cumulative evidence
Urinary leak	PSUR 1	Subject to standard pharmacovigilance procedures since PSUR 2 on the basis of cumulative evidence
Right heart failure	PSUR 3	Subject to standard pharmacovigilance procedures since PSUR 4 on the basis of cumulative evidence
Pulmonary hypertension	PSUR 3	Subject to standard pharmacovigilance procedures since PSUR 4 on the basis of cumulative evidence
Stomatitis/ Tongue swelling	PSUR 3	Subject to standard pharmacovigilance procedures since PSUR 3 on the basis of cumulative evidence
Angioneurotic edema	PSUR 3	Identified as a relevant safety finding in PSUR 3 and has been monitored from PSUR 4 to PSUR 6.
	PSUR 6	Subject to standard pharmacovigilance procedures since PSUR 3 on the basis of cumulative evidence
Rhabdomyolysis/CK increase	PSUR 5	Further intensive monitoring
	PSUR 7	Accumulated data on rhabdodomyolysis / elevated CK does not suggest everolimus to be a causal agent. CDS sufficiently addresses that patients on HMG-CoA reductase inhibitor and/or fibrate should be monitored for the possible development of rhabdomyolysis.
Cardiac failure	PSUR 5	Analysis in PSUR 8 concluded that reports of cardiac failure are secondary to other disorders or associated with confounding factors. No evidence of a direct effect of everolimus on cardiac function. Standard pharmacovigilance procedures.
Vasculitis	PSUR 6	Leukocytoclastic vasculitis was amended to the CDS based on postmarketing experience.
	PSUR8	

Safety finding	Identified	Proposed action
Pancytopenia	PSUR 6	No evidence that pancytopenia is an ADR of everolimus, in addition to the single-cell line hematopoietic disorders of leukopenia, thrombocytopenia and anemia established in PSUR 8. Subject to standard pharmacovigilance procedures.
Stomatitis	PSUR 7	Included in CDS and will be subject to routine monitoring.
Polyomavirus infections	PSUR 7 PSUR 8	Polyomavirus infection in everolimus-treated patients included in the CDS. Continue to be closely monitored
Interaction with valganciclovir	PSUR 7	An evaluation will be carried out with a view to the event being considered for inclusion in the CDS of Certican
	PSUR 8	Interaction has not been confirmed. Routine monitoring.
Cardiac tamponade	PSUR 7 PSUR 8	Assessment report of PSUR 7 requested an analysis to assess the need for inclusion of cardiac tamponade in the CDS. Analysis in PSUR 8 considers pericardial effusion, including cardiac tamponade, as post-operative complication of heart transplantation. No evidence to include cardiac tamponade as an ADR. Further close monitoring.
Proteinuria	PSUR 8	Worsening proteinuria, often of nephrotic severity (3g/24h) discussed in previous PSURs on the basis of a small number of similar case reports received for everolimus-treated patients (PSUR 6). Re-discussed after receipt of literature reports. CDS amended accordingly. Further close monitoring.
Convulsions	Assessment Report PSUR 8	Novartis has agreed to review the topic of convulsions in the next PSUR as requested by the assessor in the PSUR 8 Assessment Report.

Source: PSUR 1, PSUR 2, PSUR 3, PSUR 4, PSUR 5, PSUR 6, PSUR 7, PSUR 8, Assessment Report PSUR 8,

Adverse events of special interest

Kidney function

Reduced target concentrations for CsA in patients undergoing kidney and liver transplantation were compatible with less adverse effect on eGFR than the reference regimens. In heart transplantation this was not achieved and month 12 eGFR was about 5.5 mL/min lower in the 1.5 mg everolimus group compared with the MMF group. This might relate to non-adherence to target CsA exposure in 10 out of 63 study centres.

Wound healing complications

Everolimus 3.0 mg is consistently associated with an increased incidence of wound healing complications whilst in general the 1.5 mg dose results in similar event rates as the comparator.

The incidence rate of pleural effusion events in study A2310 (heart transplantation) at Month 12 was higher in the everolimus 1.5 mg group compared to the MMF group (28.0% vs. 23.1%). Similarly the incidence of pericardial effusion events was higher in the everolimus 1.5 mg group (43.4% and 28.4%), reported as an SAE (13.3% vs. 4.1%) and discontinuation due to pericardial effusion 8 patients (2.9%) vs. 1 patient (0.4%). Pericardial effusion accompanied by symptoms of hemodynamic compromise was reported in 7.2% and 1.5% of patients in the everolimus 1.5 mg and the MMF group, respectively. Cardiac tamponade as assessed by echocardiography was reported in 5.7% vs. 3.0% of patients in the everolimus 1.5 mg and the MMF groups, respectively.

The majority of the effusion events occurred within the first month after heart transplantation. No patient died due to tamponade.

In the pivotal liver transplantation study, everolimus was started one month post transplantation. Over 24 months, wound healing complications were reported for 27 (11.0%)

EVR+Reduced TAC, 25 (10.9%) TAC Elimination and 20 (8.3%) TAC Control patients, with incision site pain again being the most frequently reported event (EVR+Reduced TAC 2.4% and TAC Elimination 0.9% vs. TAC Control 3.7%).

Renal graft thrombosis

Graft loss and causes in study A2309 (ITT population, 24-month analysis

Cause of graft loss	Everolimus1.5mg N=277	Everolimus 3mg N=279	MPA N=277
Total graft loss: n(%)	16 (5.8)	19* (6.8)	11# (4.0)
Renal artery thrombosis	4	4	3
Renal vein thrombosis	2	–	–
Rejection/chronic allograft nephropathy	5	7	3
Primary non-function	1	3	2
Infection	1	2	1
Thrombotic thrombocytopenic purpura	1	–	–
Proliferative glomerulonephritis	1	–	–
Urological complications	–	–	1
Complication after biopsy	1	–	–
IgA crescentric nephropathy	–	1	–
Non-compliance	–	2	1

* Includes two patients in the everolimus 3.0 mg group who were excluded from efficacy analyses in [SCE Kidney Table 3-14]: patient A2309-0511-00017 whose graft loss occurred on Day 0 and patient A2309-0520-00019 who had delayed graft function, allograft infarction reported as an AE on Day 6, withdrew consent and was lost to follow-up from Day 25.
# Includes patient A2309-0543-00007 in the MPA group who did not receive study medication [Study A2309-12m Listing 16.2.5-1.1a]; and [SCE Kidney Table 3-14] also includes this patient).

In addition to above events of special interest, malignancies, microangiopathies, interstitial lung disorders have been reported and are considered possibly related to everolimus as no differences to reference regimens were demonstrated and as these regimens with variable strength of evidence are considered related to these events.

Summary of adverse reactions as reflected in section 4.8 of the SPC

Table 2 contains adverse drug reactions possibly or probably related to Certican seen in phase III clinical trials. Unless noted otherwise, these disorders have been identified by an increased incidence in the phase III studies comparing Certican treated patients with patients on a non-Certican, standard-therapy regimens (see section 5.1). Except where noted otherwise, the adverse reaction profile is relatively consistent across all transplant indications. It is compiled according to MedDRA standard organ classes:

Adverse reactions are listed according to their frequencies which are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

Table 2: Adverse drug reactions possibly or probably related to Certican

Body system	Incidence	Adverse reaction
Infections and infestations	Very common	Infections (viral, bacterial, fungal), upper respiratory tract infection
	Common	Sepsis, urinary tract infections, lower respiratory tract infection, wound infection
Blood and lymphatic system disorders	Very common	Leucopaenia[1]
	Common	Thrombocytopaenia[1], pancytopenia[6,8], anaemia[1], coagulopathy, thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome
	Uncommon	Haemolysis
Endocrine disorders	Uncommon	Hypogonadism male (testosterone decreased, FSH and LH increased)
Metabolism and nutrition disorders	Very common	Hyperlipidaemia (cholesterol and triglycerides), new onset diabetes mellitus[9]
Cardiac disorder	Very common	Pericardial effusion[2]
Vascular disorders	Very Common	Hypertension
	Common	Lymphocoele[3], venous thromboembolism, graft thrombosis[3]
	Rare	Leukocytoclastic vasculitis[6]
Respiratory, thoracic and mediastinal disorders	Very common	Pleural effusion[2]
	Uncommon	Interstitial lung disease
	Rare	Pulmonary alveolar proteinosis
Gastrointestinal disorders	Very Common	Abdominal pain[9]
	Common	Diarrhoea, nausea, pancreatitis, vomiting, stomatitis/mouth ulceration, oropharyngeal pain
Hepato-biliary disorders	Uncommon	Hepatitis, hepatic disorders, jaundice

Skin and subcutaneous tissue disorders	Common	Angioneurotic oedema[5], acne, surgical wound complication
	Uncommon	Rash
Musculoskeletal and connective tissue disorder	Uncommon	Myalgia
Renal and urinary disorders	Common	Proteinuria
	Uncommon	Renal tubular necrosis[3], pyelonephritis
Reproductive system and breast disorders	Common	Erectile dysfunction
General disorders and administration site conditions	Very common	Peripheral oedema, incisional hernia[7]
	Common	Pain, impaired healing
Investigations	Common	Hepatic enzyme abnormal[4,8]

[1]A dose dependent effect was established or a significantly higher incidence was seen in patients receiving 3 mg/day

[2]In cardiac transplantation

[3]In renal transplantation mostly within the first 30 days after transplantation surgery

[4]γ-GT, AST, ALT elevated

[5]predominantly in patients receiving concomitant ACE inhibitors

[6]post marketing finding

[7] in liver transplantation

[8] in renal and heart transplantation uncommon

[9] in renal and heart transplantation common

Preclinical toxicology studies having shown that everolimus can reduce spermatogenesis, male infertility must be considered a potential risk of prolonged Certican therapy. There are literature reports of reversible azospermia and oligospermia in patients treated with mTOR inhibitors.

In controlled clinical trials in which a total of 3256 patients receiving Certican in combination with other immunosuppressants were monitored for at least 1 year, a total of 3.1% developed malignancies, with 1.0% developing skin malignancies and 0.60% developing lymphoma or lymphoproliferative disorder.

The occurrence of the adverse events may depend on the immunosuppressive regimen (i.e. degree and duration).In the studies combining Certican with ciclosporin elevated serum creatinine was observed more frequently in patients dosed with Certican in combination with full dose ciclosporin for microemulsion than in control patients. The overall incidence of adverse events was lower with reduced dose ciclosporin for microemulsion (see section 5.1).

The safety profile of Certican administered with reduced-dose ciclosporin was similar to that described in the 3 pivotal studies in which full dose of ciclosporin was administered, except that elevation of serum creatinine was less frequent, and mean and median serum creatinine values were lower, than in the phase III studies.

Cases of interstitial lung disease, implying lung intraparenchymal inflammation (pneumonitis) and/or fibrosis of non-infectious etiology, some fatal, have occurred in patients receiving rapamycin and derivatives, including Certican. Mostly, the condition resolves after

discontinuation of Certican and/or addition of glucocorticoids. However, fatal cases have also occurred."

Pharmacovigilance system

The Applicant/Proposed Future MAH has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System (variation IA SE/H/356/IA/023/G). Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

Risk Management Plan

Identified risks in the RMP for Certican/Zortress Periodic Safety Update Report (PSUR)

Risk	Frequency in clinical trials of Certican/Zortress	Comment
Everolimus and calcineurin inhibitor (CNI) induced renal dysfunction	General effect	CsA nephrotoxicity is potentiated by mTOR inhibitors. Consequently, CNI exposure should be reduced when combined with everolimus (Certican). Blood concentration monitoring of both drugs is standard practice in addition to that of CNI with recommended blood level windows. Regular monitoring of renal function is also standard. Assessment of renal dysfunction must take into account all potential causes (CNI nephrotoxicity and interaction of mTOR inhibitors, but also potential rejection, infection, and other drug reactions).
Proteinuria in transplant and in maintenance setting after introduction of everolimus	Common (> 1%, < 10%) (reported as AE)	Regular monitoring of proteinuria is required for transplant patients.
Wound-healing complications	Very common (> 10%) (all complications)	Anti-proliferative action of mTOR inhibition provides plausible mechanism to explain effect. Adverse reaction is relevant in indications which involve surgery such as organ transplantation. Physicians should consider interrupting everolimus administration 4-5 days (with compensatory increase of CNI dosing) before major elective surgery and reintroduction of everolimus around 1 month after surgical intervention.
Hyperlipidemia	Very common (> 10%)	CNI treatment is associated with increases in serum lipids. In the phase 3 program, serum lipids were further increased in the CsA/everolimus regimen in comparison to control. Both triglycerides and cholesterol were affected. The prescribing information states that the patients receiving Certican should be monitored for hyperlipidemia and, if necessary, treated with lipid-lowering medicinal products and appropriate dietary adjustments made. The risk/benefit should be considered in patients with established hyperlipidaemia before initiating an immunosuppressive regimen including Certican. Similarly the risk/benefit of continued Certican therapy should be re-evaluated in patients with severe refractory hyperlipidaemia.
Renal graft thrombosis	Common (> 1%, < 10%)	Strength of data for this risk is not strong.
New onset diabetes mellitus	Common (> 1%, < 10%)	Increased frequency of NODM is the result of the inclusion of WHO criterion for random plasma glucose value.
Thrombotic microangiopathies	Common (>1%, < 10%)	The concomitant administration of Certican with a CNI may increase the risk of CNI-induced hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, and thrombotic microangiopathy. Apart from pre-transplant screening of individuals who are particularly at risk, the essential prevention activity is to monitor patients carefully in the *de novo* transplant period, considering the possible diagnosis in the presence of signs and symptoms mentioned above, and discontinuing CNI or mTOR inhibitor therapy immediately along with initiating appropriate therapy, including plasma exchange, as soon as possible.

Risk	Frequency in clinical trials of Certican/Zortress	Comment
Interstitial lung disease	Uncommon (>0.1%, < 1%)	ILD has been observed in patients receiving both everolimus and comparator treatments. The prescribing information states that a diagnosis of ILD should be considered in patients presenting with symptoms consistent with infectious pneumonia but not responding to antibiotic therapy and in whom infectious, neoplastic and other non-drug causes have been discounted through appropriate investigations. Cases of ILD have been reported with Certican which resolve on drug interruption with or without glucocorticoid therapy. However, some cases with fatal outcome have been reported.
Infections	Common (>1%, < 10%)	Infections in patients treated with Certican/CNI regimens, as approved, do not appear to be more frequent or serious than in non-Certican control groups.
Malignancies	2.6% overall.	Malignancies in transplant recipients on Certican/CNI regimens do not appear to be more frequent or severe than in those on non-Certican control therapy. The antiproliferative effect of mTOR inhibition may even be protective against malignancies.
Angioedema	Common (> 1%, < 10%)	Angioedema has been observed in patients receiving both everolimus and comparator treatments; however the event appears to occur at a higher frequency in everolimus treated patients and predominantly in patients receiving concomitant treatment with ACE inhibitors.
Edema/edema peripheral	Common (> 1%, < 10%)	Peripheral edema can be observed in patients receiving both everolimus and comparator treatments.
Teratogenicity	Not applicable	There are no adequate data from the use of Certican in pregnant women. Studies in animals have shown reproductive toxicity effects including embryotoxicity and fetotoxicity. The potential risk to humans is unknown. Certican should not be given to pregnant women unless the potential benefit outweighs the potential risk to the fetus. Women of childbearing potential should be advised to use effective contraception methods while they are receiving Certican, and for up to 8 weeks after ending treatment.

V. OVERALL CONCLUSION

User consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The risk/benefit ratio is considered positive and Certican, 0.25 mg, 0.5 mg, 0.75 mg, 1.0 mg tablets and 0.1 mg, 0.25 mg, dispersible tablets, are recommended for approval.

VI. APPROVAL

The Mutual recognition procedure for Certican, 0.25 mg, 0.5 mg, 0.75 mg, 1.0 mg tablets and 0.1 mg, 0.25 mg, dispersible tablets was successfully finalised on 2014-10-08.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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