



Australian Government

Department of Health and Ageing  
Therapeutic Goods Administration

## AusPAR Attachment 2

# Extract from the Clinical Evaluation Report for Everolimus

Proprietary Product Name: Certican

Sponsor: Novartis Pharmaceuticals Australia  
Pty Ltd

**Date of CER:**

**1 June 2012**

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## About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <<http://www.tga.gov.au/hp/information-medicines-pi.htm>>.

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## List of abbreviations

Abbreviation	Meaning
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AR	Acute rejection
ARF	Acute renal failure
AST	Aspartate aminotransferase
AUC	Area under the curve
AUCinf	Area under the drug concentration-time curve extrapolated to infinite time
AUCtau,ss	AUC over the dose interval (tau) at steady state
bid	Twice a day
BPAR	Biopsy proven acute rejection
BSA	Body Surface Area
CAN	Chronic allograft nephropathy
Certican	RAD001 / everolimus
CI	Confidence interval
CL/F	Apparent drug clearance
Cmax	Maximum drug concentration
Cmax,ss	Maximum drug concentration at steady state
CMH	Cochran-Mantel-Haenszel test
CMV	Cytomegalovirus S
CNI	Calcineurin inhibitor
CPK	Creatinine phosphokinase
CsA	Cyclosporine
CO	Whole blood concentration before morning dose

Abbreviation	Meaning
C0,ss	Whole blood concentration before morning dose at steady state
DGF	Delayed graft function
DMC	Data Monitoring Committee
DVT	Deep vein thrombosis
EBV	Epstein Barr virus
eCRF	Electronic case report/record Form
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
ESLD	End-stage liver disease
EU	Europe
EVR	Everolimus
FDA	US Food and Drug Administration
FMI	Final market image
GFR	Glomerular filtration rate
GGT	Gamma glutamate transferase
GL	Graft loss
HAT	Hepatic artery thrombosis
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
ILT	Interstitial lung disease
INR	International normalisation ratio
ISHLT	International Society for Heart and Lung Transplantation

Abbreviation	Meaning
ITBL	Ischemic type biliary lesion
ITT	Intent-to-treat
IV	Intravenous(ly)
IVRS	Interactive Voice Response System
IVUS	Intravascular ultrasound
LDL	Low density lipoprotein
LH	Luteinising hormone
LTF	Lost To Follow Up
MACE	Major adverse cardiac event
MDRD	Modification of Diet in Renal Disease
MDRD-4	Abbreviated MDRD formula (4 variables)
MedDRA	Medical dictionary for regulatory activities
MELD	Model for End-Stage Liver Disease
MI	Myocardial infarction
MMF	Mycophenolate mofetil
MPS	Mycophenolate sodium
mTOR	Mammalian target of rapamycin
Myfortic	Mycophenolic acid
NG	Nasogastric
NI	Non-Inferiority
NODM	New onset diabetes mellitus
od	Once daily
PK	Pharmacokinetics
PP	Per protocol
RBC	Red blood cell

Abbreviation	Meaning
ROW	Rest of World
SD	Standard deviation of the arithmetic mean
SAE	Serious Adverse Event
Simulect	Basiliximab
SMQ	Standardised MedDRA query
T <sub>½</sub>	Half life of elimination
TAC	Tacrolimus
tBPAR	Treated biopsy-proven acute rejection
TDM	Therapeutic drug monitoring
T <sub>max,ss</sub>	Time postdose when C <sub>max,ss</sub> occurs
ULN	Upper limit normal
V <sub>z,b/F</sub>	Apparent drug distribution volume
WBC	White blood cell
WHO	World health organization
wk	Week
WOCBP	Women of child-bearing potential
yr	year



# 1. Introduction

Everolimus (CERTICAN, AFFINITOR) is a mammalian target of rapamycin (mTOR) inhibitor related to the currently registered product temsirolimus (TORISEL). Everolimus is an analogue of rapamycin and mTOR is an intracellular protein with a key role in the cellular protein synthesis and energy balance that influences many aspects of cell growth and proliferation. Everolimus exerts its immunosuppressive effect by inhibiting cell cycle progression, as well as by inhibiting the activation of T and B-cells and interleukin clonal expansion.

Everolimus was first registered in Australia in 2005 with the trade name CERTICAN. The approved indication is:

*For the prophylaxis of organ rejection in adult patients at mild to moderate immunological risk receiving an allogeneic renal or cardiac transplant.*

In 2009, the indication was extended, under a new trade name of AFFINITOR, to include:

*Treatment of patients with advanced renal cell carcinoma after failure of treatment with sorafenib or sunitinib.*

The proposed indication for CERTICAN in this application is:

*Certican is indicated for the prophylaxis of organ rejection in adult patients at mild to moderate immunological risk receiving an allogeneic renal or cardiac or hepatic transplant.*

## 1.1. Dosage and administration

The proposed PI includes changes to the dosage and administration section as outlined below. These changes include new dosing for the hepatic transplant indication.

*An initial dose regimen of 0.75 mg twice a day is recommended for the general kidney and heart transplant population, administered as soon as possible after transplantation. **The dose of 1.0 mg twice a day is recommended for the hepatic transplant population with the initial dose approximately 4 weeks after transplantation.** The daily dose of Certican should always be given orally in two divided doses, consistently either with or without food **and at the same time as cyclosporin for microemulsion or tacrolimus.***

There are changes proposed for patients with impaired hepatic function. This includes a greater reduction in everolimus dose (from one half to two-thirds of the dose) in patients with mild hepatic impairment.

The section on cyclosporine dose recommendation in renal transplantation has been altered based on data from study A2309. There is also a new recommendation that everolimus “*should not be used long-term together with full doses of cyclosporine*”.

The section on cyclosporine dose recommendation in cardiac transplantation has also been altered based on data from study A2411 and A2310.

A new section has been included on tacrolimus dose recommendation in hepatic transplantation.

## 1.2. Other proposed changes to the PI

The proposed PI has a large number of other changes including:

- Data on pharmacokinetics in hepatic impairment.

- Updates in the clinical trials section on renal transplantation for study A2309, on cardiac transplantation from study A2411 and A2310 and on hepatic transplantation from study H2304.
- Rewording of the precaution in hepatic impairment.
- Additional information relating to cyclosporine dose in renal dysfunction.
- Rewording of precaution relating to wound healing complications.
- Additional data on drug interactions with midazolam.
- Updating of the adverse effects section with the additional clinical data.

## 2. Clinical rationale

Everolimus, or RAD001, exerts its immunosuppressant effect by inhibiting the proliferation of antigen-activated T-cells and clonal expansion driven by interleukins released from activated T-cells - the main mechanism underlying acute transplant rejection. It is currently approved in Australia for use in the prophylaxis of organ rejection following cardiac or renal transplantation. The application is to extend its use to the prevention of acute allograft rejection in adult patients who have received a liver transplant.

Renal function has been cited as an important prognostic factor post liver transplant. One of major contributors to this is the use of calcineurin inhibitors (CNIs) such as cyclosporine and tacrolimus. Consequently, it is believed that reducing exposure to CNIs post-transplant may improve renal function. Tacrolimus is generally the first line therapy in liver transplant due to improved results over cyclosporine on acute rejection, and graft loss and survival. The sponsor proposes that treatment with everolimus may allow a reduction or elimination of tacrolimus early post-transplant and may also improve progression of fibrosis in liver allografts in HCV positive patients.

### 2.1. Guidance

As there was no information provided, it appears that no pre-submission advice was provided.

During the course of the pivotal hepatic transplant study (H2304), the EMA published guidelines on the clinical investigation of immunosuppressants for solid organ transplant (CHMP 2009). The protocol of this study was subsequently amended to align with the guidelines (see section on *Clinical efficacy* below).

## 3. Contents of the clinical dossier

### 3.1. Scope of the clinical dossier

The submission's clinical information, apart from Module 1, was divided in three sections by therapeutic area outlined below.

- Module 1
  - Application letter, application form, draft Australian PI and CMI, FDA product information and European Summary of Product Characteristics with proposed changes in relation to hepatic transplantation, information on clinical experts and risk management system documents.

**Cardiac**

- Module 2
  - Clinical Overview and a “Briefing book” for study A2310.
- Module 5
  - One efficacy/safety study (A2310) and literature references.

**Hepatic**

- Module 2
  - Introduction, Clinical Overview, Summary of Biopharmaceutic Studies, Summary of Clinical Efficacy, Summary of Clinical Pharmacology, Summary of Clinical Safety, synopses of individual studies and literature references.
- Module 5
  - Two PK studies (X2102 and X2103).
  - One pivotal efficacy/safety studies in hepatic transplant (H2304) and a report on exploratory modelling of exposure-infection.
  - One dose-finding study (B158) with its extensions (B158E1 and B158E2) and associated PK report.
  - Two other efficacy/safety studies (HDE10, H2401 with 6 and 12 month reports)
  - A preliminary safety report for study H2301.
  - Appendixes for the Summary of Clinical Efficacy and Summary of Clinical Safety and literature references.
  - Post-marketing data including a PSUR bridging report and a PSUR addendum report.

**Renal**

- Module 2
  - Clinical Overview and a document on the rationale for the changes to the SPC.
- Module 5
  - One efficacy/safety study (A2309).
  - A comparative safety update for studies B251, B201 and A2309 in renal transplantation, data listings for appendix 3 of the Summary of Clinical Safety and literature references

**3.2. Paediatric data**

The submission did not include paediatric data.

**3.3. Good clinical practice**

The sponsor provided a statement in the Clinical Overview that all studies had been conducted in compliance with Good Clinical Practice.

## 4. Pharmacokinetics

### 4.1. Studies providing pharmacokinetic data

Table 1 shows the studies relating to each pharmacokinetic topic and the location of each study summary. None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

**Table 1. Submitted pharmacokinetic studies.**

PK topic	Subtopic	Study ID
PK in healthy adults	-	-
PK in special populations	TARGET POPULATION§ Hepatic transplantation	B158 H2304
PK in special populations	Hepatic Impairment	X2102
Gender/Genetic-related PK	-	-
PK interactions	Midazolam	X2103
	Cyclosporine	B158
	Tacrolimus	H2304
Population PK	-	-

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

### 4.2. Summary of pharmacokinetics

The dossier only proposes alterations to the pharmacokinetic sections of the PI in relation to PK in hepatic impairment and the drug interaction with midazolam.

The PI states that everolimus is rapidly absorbed after oral administration, with peak blood levels (T<sub>max</sub>) 1–2 hours post-dose. Everolimus blood concentrations are dose proportional over the dose range 0.25 to 15 mg in transplant patients. The relative bioavailability of the dispersible tablet compared with the tablet is 0.90. The elimination half-life in transplant patients is 28 hours (±7 h). Inter-patient variability is moderate with the coefficient of variation (CV) of approximately 50%. A high-fat meal results in a 60% reduction in C<sub>max</sub>, and a 16% reduction in AUC. In whole blood, approximately 80% of everolimus is contained in red blood cells and plasma protein binding is 47% in healthy subjects and those with moderate hepatic impairment. Everolimus is mainly metabolised by CYP3A4 in the liver and to some extent in the intestinal wall. Everolimus is also a substrate of P-glycoprotein (P-gp). Everolimus is eliminated by metabolism, mainly by hydroxylation, and then excreted in the faeces (80%).

#### 4.2.1. Pharmacokinetics in the target population - hepatic transplant

There were no new bioavailability, bioequivalence or food effect data. A previously submitted single dose PK study (B202) assessed factors which might alter the absorption of everolimus in liver transplantation. These included external bile diversion, administration via a nasogastric or

nasoduodenal tube and time post-transplant. The sponsor reported that these factors did not significantly alter the pharmacokinetics of everolimus. There are no labelling claims from this study.

In study B158 the PK of everolimus (0.5mg bid, 1 mg bid and 2mg bid) was assessed in 62 patients with *de novo* hepatic transplant receiving concomitant cyclosporine and prednisolone. The average C<sub>0,ss</sub> over 6 months of treatment was 3.0±1.7 ng/mL at 1 mg, 5.8±5.0 ng/mL at 2mg, and 8.9±5.0 ng/mL at 4 mg. At month 3, T<sub>max,ss</sub> was 1.6 h, 1.9 h and 1.2 h in the three groups, respectively. Trough everolimus concentrations were correlated with AUC<sub>tau,ss</sub> at steady state ( $r^2=0.91$ ). The regression slope for dose versus AUC<sub>tau,ss</sub> was 0.75 (90%CI: 0.57, 0.92) at week 1, 0.80 (90% CI: 0.58, 1.02) at month 2, and 0.82 (90% CI: 0.65, 0.98) at month 3. This relationship found that doubling the dose resulted in a 1.8 fold increase in AUC which indicated some under proportionality. There was a notable level of intra-subject (31.5% for AUC<sub>tau,ss</sub>) and inter-subject variability (26.7% for AUC<sub>tau,ss</sub>).

Study H2304 was the pivotal phase III trial in hepatic transplantation. In this study everolimus was given together with tacrolimus (TAC) and whole blood trough levels monitored for dose adjustment. In the everolimus and reduced TAC group, everolimus dose commenced at 1 mg bid with target levels of 3-8 ng/mL. When everolimus target was met, tacrolimus dose was tapered from full exposure ( $\geq 8$  ng/mL) to trough levels of 3-5 ng/mL. After one week, the mean C<sub>0,ss</sub> was 3.4 ng/mL with 48.4% of patients in the target window and over the first month there was a 62% increase in dose (1.73 mg bid) to reach a mean C<sub>0,ss</sub> of 4.8 ng/mL and 79% of trough levels within the target range. Between 6 and 12 months, the mean C<sub>0,ss</sub> was 5.6 ng/mL with 80% within the target range.

#### **4.2.2. Pharmacokinetics in other special populations**

##### **4.2.2.1. Pharmacokinetics in subjects with impaired hepatic function**

The PK in hepatic impairment was initially examined in A2303. This study was not included in the dossier as the sponsor stated that it had previously been submitted. The Sponsor reported that in this open-label, case-controlled study of a single 2 mg dose of everolimus, the mean exposure (AUC<sub>0-inf</sub>) to everolimus was increased 2-fold in patients with moderate hepatic impairment (Child-Pugh B) compared to healthy subjects.

In Study X2102, a single 10 mg dose of everolimus was administered to 13 healthy and 7, 8 and 6 subjects with mild, moderate and severe hepatic impairment, respectively. This found a rapid absorption after administration with T<sub>max</sub> at 1 hour in normal subjects compared to a median time to reach T<sub>max</sub> of 1.5 hours (range: 1–4 hours), 1.0 hour (range: 0.5–3.0 hours) and 2.25 hours (range: 0.5–4.0 hours) in mild, moderate, and severely hepatic impaired subjects, respectively. Peak concentrations (C<sub>max</sub>) were similar at 33.84±12.75 ng/mL, 31.34±5.57 ng/mL, 48.89±12.06 ng/mL, and 34.6±16.72 ng/mL in normal, mild, moderate and severely hepatic impaired subjects. Hepatic impaired subjects had higher mean total exposure.

The AUC<sub>(0-inf)</sub> in normal subjects was 317.44±55.44 ng.hr/mL compared to 990.48±485.45 ng.hr/mL for severely hepatic impaired subjects. The increased exposure in hepatic impairment was a factor of decreasing terminal elimination rate constant with increasing severity of impairment. The overall exposure (AUC<sub>0-inf</sub>) in subjects with mild hepatic impairment was nearly twice that of normal subjects (1.84 fold, 90% CI: 1.36-2.5), while it was approximately three times higher in moderate and severe impairment (3.15 fold, 90% CI: 2.36-4.21 and 3.64 fold, 90% CI: 2.64-5.0, respectively). In these groups, the apparent drug clearance (CL/F) was one third of normal subjects.

An analysis was also done based on the Child-Pugh classification of the study subjects at the end of the study (day 8) rather than at baseline. This was due to the shift of 3 subjects: two from mild to moderate impairment and one from moderate to mild. Taking this into account, the mean AUC reduced slightly in the mild impairment group and geometric mean ratio compared

to subjects with normal hepatic function for AUC(0-inf) was 1.60, 3.26 and 3.64 in the mild, moderate and severe impairment groups, respectively.

Given the results on the geometric mean ratio (90% CI) of AUC(0-inf), the sponsor calculated the dose required to adjust the exposure to that of subjects with normal liver function (given a 10 mg dose) would be 6.25 mg (4.7–8.3 mg), 3.07 mg (2.4–4.0 mg), and 2.75 mg (2.1–3.7 mg) in subjects of mild, moderate, and severe hepatic impairment, respectively based on the Child-Pugh classification on day 8 of the study.

The relationship between laboratory parameters and AUC(0-inf) were examined and found a moderate positive correlation between bilirubin ( $r^2=0.54$ ) and INR ( $r^2=0.65$ ) and a negative correlation with albumin ( $r^2=0.56$ ).

#### 4.2.3. Pharmacokinetic interactions

##### 4.2.3.1. Pharmacokinetic interactions demonstrated in human studies

Midazolam. In Study X2103 (the drug-drug interaction with midazolam was investigated in healthy male volunteers after 5 days of everolimus 10 mg daily to ensure therapeutic everolimus concentrations. Co-administration increased the midazolam C<sub>max</sub> by 25% (90% CI: 1.14-1.37) and the overall exposure (AUC<sub>0-inf</sub>) by 30% (90% CI: 1.22-1.39). There was a decrease in midazolam clearance by 23% with co-administration (63.45±25.91 L/h compared to 82.24±32.37 L/h when given alone) while the terminal half life was similar (5.33±1.79 h alone compared to 5.40±1.63 h with everolimus). The major metabolite of midazolam, 1-hydroxymidazolam, also increased with co-administration with a 20% increase in C<sub>max</sub> and 25% increase in AUC<sub>0-∞</sub>.

The PK parameters of everolimus when administered with midazolam included a median T<sub>max</sub> of 2.0 h (range 1.0-4.0 h), C<sub>max</sub> of 53.80±11.56 ng/mL, C<sub>min</sub> of 9.06±2.28 ng/mL and mean exposure, AUC(0-TLAST) was 418.01+86.64 ng.h/mL.

**Comment:** The sponsor stated this was comparable to monotherapy. The data were not available for evaluation.

Cyclosporine. Study B158 examined 454 evaluable trough cyclosporine levels in 94 patients with de novo hepatic transplant. There was some down titration of cyclosporine dose over time. The average dose at week 1 was 347±161 mg bid, in month 3 was 172±72 mg bid, and in month 6 was 152±67 mg bid and corresponding trough levels at week 1 of 258±121 ng/mL, at month 3 of 211±95 ng/mL, and at month 6 of 188±87 ng/mL (all everolimus doses combined). The cyclosporine trough levels in the placebo group were 277±121 ng/mL at week 1, 213±88 ng/mL at month 3 and 207±84 ng/mL at month 6. These CsA levels in the placebo group were similar to those found in the everolimus group.

The effect of concomitant CsA on everolimus levels in B158 was discussed above under *Pharmacokinetics in the target population – hepatic transplant*.

**Tacrolimus.** A specific drug interaction study with tacrolimus has not been performed. In H2304 there was also a tacrolimus control arm with target concentrations of 8-12 ng/mL as well as the everolimus + reduced tacrolimus group with a target level of 3-5 ng/mL. Down titration of tacrolimus took about 3 months to reach stable mean level of 5.7 ng/mL. There were 45 of subjects with targets above the upper level of the range.

#### 4.3. Evaluator's overall conclusions on pharmacokinetics

The dossier included PK studies in hepatic impairment and a drug interaction study with midazolam. There were also some PK data from two studies in the target population of hepatic transplantation. The sponsor only proposes alterations to the pharmacokinetic sections of the PI in relation to PK in hepatic impairment and the drug interaction with midazolam.

In the dose-finding study B158, the PK of everolimus was assessed when administered with cyclosporine and prednisolone in *de novo* hepatic transplant patients. This found that trough everolimus concentrations were correlated with  $AUC_{tau}$  at steady state and so supports use of trough levels for therapeutic drug monitoring. A doubling of the dose resulted in a 1.8 fold increase in AUC indicating some under proportionality. There was also a notable level of intra and inter subject variability for AUC (approximately 30% for both).

In the pivotal phase III hepatic transplantation study H2304, a commencing everolimus dose of 1 mg bid (2 mg/d) was given with tacrolimus and resulted in a mean trough level of 3.4 ng/mL after one week with 45% of samples in the target range (3-8 ng/mL). Consequently the dose needed to be up titrated by 62% (average 1.73 mg bid) in the first month to reach target levels.

A starting dose of 1 mg bid with concomitant tacrolimus compares to the 0.75 mg bid commencing dose with concomitant cyclosporine due to the ability of cyclosporine to increase everolimus exposure 2 to 3 fold.

The administration of everolimus in subjects with hepatic impairment (X2102) resulted in a significant increase in exposure. In subjects with mild hepatic impairment the mean  $AUC_{(0-inf)}$  of everolimus was increased by 1.6-fold and in subjects with moderate and severe hepatic impairment the mean  $AUC_{(0-inf)}$  increased by 3.2 fold and 3.6 fold, respectively. There was a positive correlation between everolimus exposure and bilirubin and INR and a negative correlation with albumin, although the relationships were not strong.

When midazolam (a CYP3A4 substrate) was co-administered with everolimus, there was a 25% increase in  $C_{max}$  and 30% increase in AUC with similar results for the major metabolite of 1-hydroxymidazolam. There was little effect on the terminal half life of midazolam. This demonstrates that everolimus is a weak inhibitor of CYP3A4. There was no reported effect of midazolam on the pharmacokinetics of everolimus.

Starting dose is dictated by which concomitant calcineurin inhibitor is used in hepatic transplantation and, as in other transplant patients, doses must continue to be tailored to patients by close therapeutic drug monitoring.

## 5. Pharmacodynamics

### 5.1. Studies providing pharmacodynamic data

There were no specific pharmacodynamic studies in the dossier. PD data were available from two studies in hepatic transplantation (B158 and H2304) in which the relationship between exposure and safety and efficacy were explored.

### 5.2. Summary of pharmacodynamics

Information from the PI states that everolimus is a proliferation signal inhibitor which exerts its immunosuppressive effect by inhibiting the proliferation, and thus clonal expansion, of antigen-activated T cells. The effect of everolimus is not restricted to T cells. It inhibits in general, growth factor-stimulated proliferation of haematopoietic as well as non-haematopoietic cells, like that of vascular smooth muscle cells.

#### 5.2.1. Relationship between drug concentration and pharmacodynamic effects

Study B158 in *de novo* hepatic transplant patients treated with everolimus and cyclosporine, assessed the exposure-safety relationship up to month 6 for cholesterol, triglycerides, platelets and leukocytes. This found significant relationships between increased cholesterol ( $>6.5$  mmol/L) ( $p=0.017$ ) and decreased platelets ( $p=0.037$ ) with increasing trough everolimus

levels (C<sub>0,ss</sub>). There was no significant relationship between triglycerides or leucocytes and everolimus trough levels.

In this study the exposure-efficacy relation was also assessed. Efficacy was assessed on treated biopsy-proven acute rejection (tBPAR) between day 1 and 225 post-transplantation. Exposure was assessed on the geometric mean everolimus trough levels at steady state divided into groups of <3, 3-6 and >6 ng/mL. Freedom from tBPAR was 63%, 50%, 86% and 88% in the 0 ng/mL (placebo), <3 ng/mL, 3-6 ng/mL and >6 mg/mL exposure groups, respectively. Logistic regression suggested increased efficacy with increased exposure (p=0.0137).

**Comment:** The numbers in each group were small and so data need to be interpreted with caution.

Exposure-efficacy analyses were also conducted in the pivotal hepatic transplantation study H2304. This was a 24 month multicentre, open label, randomised, controlled study in 719 *de novo* hepatic transplant patient who were randomised to one of 3 groups – everolimus (EVR) + reduced tacrolimus (TAC), everolimus + tacrolimus elimination and tacrolimus control. Trough EVR and TAC levels were collected for making dose adjustment decisions. For the primary efficacy composite outcome of tBPAR/graft loss (GL)/death, the rates in the everolimus + reduced TAC group were 17.6%, 5.3%, 15.4% in those with an average trough (C<sub>0</sub>) everolimus level of <3, 3-8 and >8 ng/mL, respectively. In patients with high everolimus levels (>8 ng/mL) there was one tBPAR, one GL and no deaths.

Using data from study H2304, exposure-safety analyses were performed including post-hoc exploratory modelling of exposure and infection. In subjects with available post-randomisation PK data, selected safety events were assessed up to the 12 month analysis cut-off, categorised by the average trough everolimus level up to the time of the event or censoring. Contrary to expectations, there was a higher rate of the selected AEs (e.g. creatinine  $\geq 200$   $\mu\text{mol/L}$ , peripheral oedema, stomatitis, new onset diabetes, neutropenia and infection) in subjects in the everolimus +reduced TAC group with lower everolimus trough levels (<3 ng/mL) than those with levels in the desired range (3-8 ng/mL).

The rate of infections was 78.8%, 43.8% and 45.5% in patients with an average trough everolimus level of <3, 3-8 and >8 ng/mL, respectively. The data for overall infection rate over time by treatment group demonstrates a higher infection rate soon after transplantation. Modelling found no evident relationships between everolimus or tacrolimus concentrations and infection incidence in either the EVR+reduced TAC or the TAC control groups as infection events were spread across the range of drug levels.

**Comment:** The sponsor contends that the unexpected finding of higher infection rate with lower exposure may be due to confounding by changes in the infection rate, immunosuppression and drug concentrations over time.

In study A2309 in renal transplantation, an assessment of the exposure-safety relationship found an increase in hypercholesterolaemia, hypertriglyceridaemia, new onset diabetes and wound healing problems with increasing everolimus trough levels of 8-<12 ng/mL. There was no evident relationship between increased everolimus trough level and events associated with low renal function apart from high urinary protein/creatinine ratio.

### 5.3. Evaluator's overall conclusions on pharmacodynamics

In hepatic transplantation patients, exposure-safety analyses (B158) found a positive relationship between increasing trough everolimus levels and increased cholesterol and reduced platelets. However no relationship was evident in H2304 when everolimus was used in combination with tacrolimus. In fact, contrary to expectations, there was a higher rate of the selected AEs including infection with lower trough levels. The reason for this is unclear.



In hepatic transplantation patients, exposure-efficacy analyses suggested increased efficacy with increased exposure in B158, although the numbers in this analysis were small. In H2304, the highest rate of efficacy failure was noted with levels <3 ng/mL, although a trend was not evident.

## 6. Dosage selection for the pivotal studies

Study B158 was randomised double-blind parallel group, dose-finding study in 119 de novo liver transplant recipients who received placebo, everolimus 0.5 mg bid, 1 mg bid or 2 mg bid together with cyclosporine and corticosteroids. Data from this study found a greater risk of acute rejection in patients with trough levels <3 ng/mL compared to those with levels ≥3 ng/mL.

The target trough level of everolimus for the pivotal study H2304 was based on data from other transplant indications and study B158. The target level was 3-8 ng/mL which aligns with the current product information for renal and cardiac transplantation.

The starting dose of 1.0 mg bid was higher than the 0.75 mg bid recommended for renal and cardiac transplantation. This was due to the concomitant use of cyclosporine in renal and cardiac transplantation which is known to increase everolimus concentrations, while in the hepatic transplantation study H2304 the concomitant CNI was tacrolimus which was expected to have less of an effect on everolimus levels.

## 7. Clinical efficacy

### 7.1. Hepatic transplant

#### 7.1.1. Pivotal efficacy study H2304

##### 7.1.1.1. Study design, objectives, locations and dates

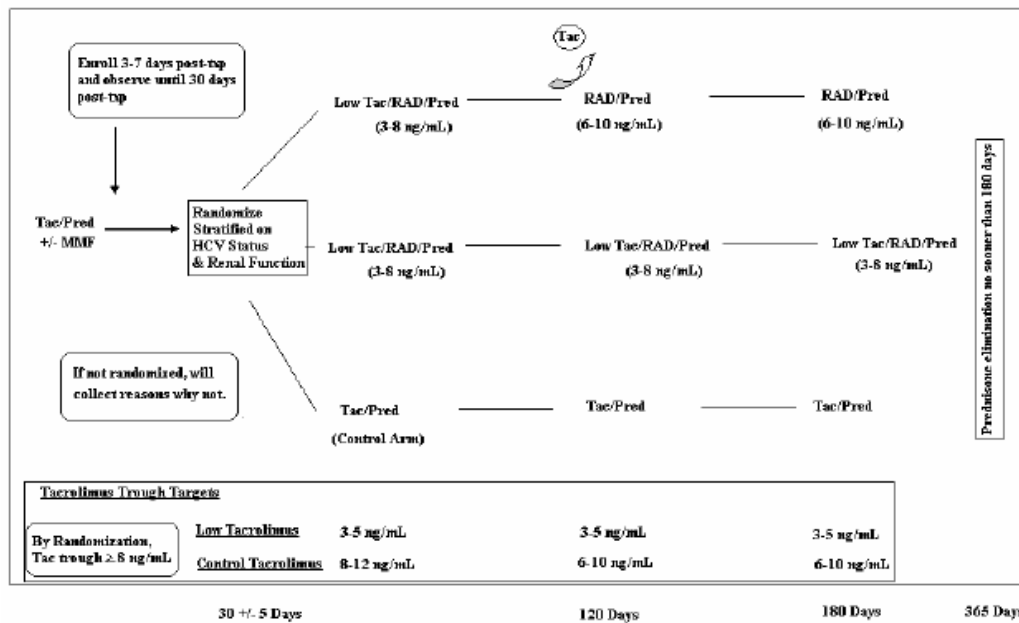
H2304 was a 24 month, phase III, multicentre, open label, randomised, controlled trial in 719 *de novo* liver transplant recipients which evaluated the efficacy and safety of concentration controlled everolimus with eliminated or reduced dose tacrolimus compared to a standard dose tacrolimus regimen. It was conducted between January 2008 and April 2011 (12 month data) at 89 centres in 19 countries (Australia, South America, North America, Western and Eastern Europe and Israel). There was a central laboratory, a central pathologist for liver biopsy review and an independent data monitoring committee (DMC). The clinical study report in the dossier was for the first 12 months of treatment.

**Design:** Subjects had a screening period prior to transplantation, a baseline period of 3 to 7 days post-transplantation and a run-in period to 30 days (±5 days) post-transplantation. In the baseline period, patients received a tacrolimus-based regimen with corticosteroids and with or without mycophenolate mofetil (MMF) according to the local practice. MMF was discontinued at randomisation. Patients were stratified on HCV status and renal function which was assessed by the abbreviated modification of diet in renal disease (MDRD)<sup>1</sup> formula. There were 3 treatment groups: 1. tacrolimus (TAC) elimination; 2. everolimus (EVR) + reduced TAC; and 3. TAC control (see Figure 1).

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<sup>1</sup> The abbreviated MDRD or MDRD-4 estimates GFR using four variables: serum creatinine, age, race, and gender. The original MDRD used six variables with the additional variables being the blood urea nitrogen and albumin levels. The equations have been validated in patients with chronic kidney disease.

Figure 1. H2304 Study design



Patient visits occurred at screening, baseline (days 3-7), week 2 (run-in period), weeks 4 (randomisation), 5, 6, 8, 12, 16 and 18, and then months 5, 6, 9, 12, 18 and 24. Patients who prematurely discontinued were followed up to month 24 (where possible). After completion of 24 months on study, patients could continue in a 12 month extension study (H2304E1).

At the DMC meeting of April 2010 it was recommended to cease enrolment in the TAC elimination group (1) due to an increased rate of acute rejection and discontinuation in this group. At this point, 690 patients had been randomised. There was no further randomisation into this group and enrolled patients, who had not reached day 180 post-randomisation, were discontinued and switched to local standard treatment. Those who were >180 days post-randomisation could continue on treatment or swap to local standard treatment. The remaining eligible patients (n=51) were randomised equally to groups 2 and 3.

The protocol was amended once to accommodate the cessation enrolment in group 1. In addition, changes were made to align with recent CHMP guidelines (2009). To assess the early impact of TAC minimisation, the primary endpoint was changed from graft loss/death/loss to follow up to tBPAR/graft loss/death. This resulted in a change in the non-inferiority margin from 10% to 12% (see section on *Statistical methods*, below).

**Objectives:** The primary objective was to compare at 12 months the composite efficacy failure rate of treated biopsy proven acute rejection (tBPAR), graft loss (GL) or death (D) with early tacrolimus minimisation (facilitated by everolimus introduction 4 weeks after liver transplantation), to standard exposure tacrolimus.

The main secondary objective was to evaluate the evolution of renal function, measured by estimated glomerular filtration rate (eGFR), between early tacrolimus minimisation, facilitated by everolimus introduction 4 weeks after liver transplantation, and standard exposure tacrolimus, from randomisation to Month 12. There were also a large number of other renal function-related secondary objectives.

Other secondary objectives included the composite tBPAR/GL/D/loss to follow up and each component; tBPAR by incidence, time to event, severity and diagnosis; acute rejection by incidence, time to event and severity; and the incidence of suspected, treated, biopsy-proven, treated biopsy-proven and subclinical acute rejection. Secondary objectives related to safety included incidence of AEs, SAEs, premature discontinuation, dose adjustment or interruption

and need to CNIs in the tacrolimus group. HCV related objectives included evaluation of HCV viral load, progression of HCV-related allograft fibrosis, incidence of HCV antiviral treatment, recurrence of hepatocellular carcinoma or *de novo* HCC malignancy.

Exploratory objectives included describing the change in patterns of specific biomarkers for renal injury in the urine throughout the study and assessing the immunosuppressive potency of everolimus (exposure-efficacy) in combination with reduced exposure tacrolimus relative to standard exposure tacrolimus.

#### **7.1.1.2. Inclusion and exclusion criteria**

Inclusion criteria were:

- 18-70 years and recipient of a deceased donor primary liver transplant.
- Allograft functioning at an acceptable level by randomisation, defined as AST, ALT, total bilirubin (BR) levels  $\leq 3 \times$  ULN, and ALP and GGT levels  $\leq 5 \times$  ULN. Elevated GGT alone did not exclude patients from randomisation.
- Recipients initiated an immunosuppressive regimen which included corticosteroids and tacrolimus, 3-7 days post-transplantation.
- Confirmed recipient HCV status at screening (either by serology or by PCR).
- Abbreviated MDRD eGFR  $\geq 30$  mL/min/1.73m<sup>2</sup>.
- Verification of at least one tacrolimus trough level of  $\geq 8$  ng/mL in the week prior to randomisation.
- Able to take oral medication.

Exclusion criteria were:

- Recipients of multiple solid organ or islet cell tissue transplants, or had previously received an organ or tissue transplant.
- Recipients of a liver from a living donor, or of a split liver.
- History of malignancy within 5 years other than non-metastatic basal or squamous cell carcinoma of the skin or HCC.
- HCC that did not fulfil Milan criteria (1 nodule  $\leq 5$  cm, 2-3 nodules all  $< 3$  cm), at the time of transplantation as per explants histology of the recipient liver.
- Any use of antibody induction therapy.
- Hypersensitivity to the study drugs or their class, or to any of the excipients.
- Recipients of ABO incompatible transplant grafts.
- Recipients of organs from donors positive for Hepatitis B surface antigen or HIV.
- Condition which might significantly alter the absorption, distribution, metabolism and excretion of study drug.
- Women of child bearing potential unless postmenopausal or using acceptable contraception
- History of coagulopathy or condition precluding liver biopsy post transplantation.

Exclusion at baseline:

- Spot urine protein/creatinine ratio indicating  $\geq 1.0$  g/24 hrs of proteinuria that cannot be explained by immediate post operative effects.
- Use of immunosuppressive agents or treatments after baseline not specified in the protocol.

Exclusion at randomisation:

- Severe hypercholesterolaemia (>350 mg/dL; >9 mmol/L) or hypertriglyceridaemia (>500 mg/dL; >8.5 mmol/L). Controlled hyperlipidaemia was accepted.

Platelet count < 50,000/mm<sup>3</sup>, absolute neutrophil count of <1,000/mm<sup>3</sup> or WBC count of <2,000/mm<sup>3</sup>.

- HIV positive.
- Significant systemic infection requiring active use of IV antibiotics.
- Requiring life support measures such as mechanical ventilation, dialysis, or vasopressor agents.
- Requiring renal replacement therapy for clearance within 7 days prior to randomisation.
- Presence of thrombosis via Doppler ultrasound of the major hepatic arteries, major hepatic veins, portal vein and inferior vena cava.
- Episode of acute rejection requiring antibody therapy or more than one steroid sensitive episode of acute rejection during the run-in period.

#### **7.1.1.3. Study treatments**

Everolimus was provided in 1.0 mg, 0.75 mg and 0.5 mg tablets. Tacrolimus was provided in 0.5 mg, 1.0 mg and 5.0 mg capsules and mycophenolate (MMF) in 500 mg film-coated tablets. Everolimus was taken each 12 hours together with tacrolimus. Drug level monitoring was mandated in the study. Central everolimus levels were used to adjust everolimus dosing and local TAC levels were used to adjust TAC dosing.

In group 1, TAC elimination, patients received low dose tacrolimus (until Month 4, then tacrolimus was eliminated) + everolimus + corticosteroids. Everolimus commenced within 24 hours of randomisation at 1.0 mg bid (2 mg daily) and everolimus whole blood trough levels (taken 5 d±2 d post dose change) were targeted to be maintained between 3-8 ng/mL. When everolimus trough levels were confirmed to be in the target range (3-8 ng/mL), tacrolimus tapering started, with a tacrolimus whole blood trough level target of 3-5 ng/mL by three weeks after randomisation. At day 120 (month 4) everolimus whole blood trough levels were targeted to 6-10 ng/mL and when in this range, TAC elimination started and was completed by the end of month 4 post-transplantation. TAC elimination did not commence until there was evidence of a functioning allograft (AST, ALT and total BR ≤3x ULN and ALP and GGT ≤5xULN)

In group 2, TAC minimisation (EVR+reduced TAC), patients received low dose tacrolimus + everolimus + corticosteroids. Everolimus was commenced (as per group 1) at 1.0 mg bid and the target trough level of 3-8 ng/mL was to be maintained for the duration of the study. The dose could be altered to maintain this level. As in group 1, TAC tapering began when everolimus was at this level to target a level of 3-5 ng/mL. It was maintained at this level for the study duration.

In group 3, TAC control, patients received tacrolimus + corticosteroids. TAC trough levels were targeted at 8-12 ng/mL to month 4 then decreased to 6-10 ng/mL for the rest of the study.

Corticosteroids were commenced at, or prior to, transplantation according to local practice. Treatment was required to continue until 180 days post transplantation.

Dose reduction of everolimus was permitted if there were decreases in WBC or platelets, increases in cholesterol or triglycerides, or AEs. Reduction was by 0.25 mg intervals. Everolimus was discontinued if trough levels ≥3 ng/mL could not be maintained due to toxicity. Everolimus was interrupted during antibody treatment of rejection episodes and switched to tacrolimus during surgical treatment.

Rescue medication was based on local practice. All patients received pneumocystis prophylaxis. CMV and hepatitis B prophylaxis was as per local practice. Oral candida treatment was topical and HCV treatment was only given for histological evidence of recurrent disease.

#### **7.1.1.4. Efficacy variables and outcomes**

The primary efficacy variable was the composite efficacy failure rate of tBPAR, graft loss or death (tBPAR/GL/D). BPAR was based on liver biopsy pathology which was read by a local pathologist (blinded to treatment) for patient management. Results were scored using the Banff score<sup>2</sup> (Demetris 1997). Biopsy slides were also sent to an independent central pathologist for blinded review. The biopsy was to be collected within 24 hours of the suspected rejection episode. Analysis of BPAR was based on the local pathology review. A BPAR was defined as an acute rejection confirmed by biopsy with a rejection activity index (RAI) score  $\geq 3$ . Treated BPAR was BPAR which was treated with anti-rejection therapy.

All suspected acute rejections episodes were documented and treated acute rejection was a clinically suspected acute rejection, whether biopsy proven or not, which had been treated and confirmed by the investigator. Liver biopsies were obtained at transplantation, month 12 and 24 in all HCV seropositive patients, read by the local pathologist and also the central pathologist. The allograft was presumed to be lost on the day the patient was newly listed for a liver allograft or the day they received an allograft re-transplant or died.

Renal function was assessed on the eGFR using the abbreviated MDRD formula. Creatinine and cystatin C, as well as GFR estimated by other formulae, were also assessed.

#### **7.1.1.5. Randomisation and blinding methods**

Patients were randomised by an IVRS to one of the 3 treatment arms in a 1:1:1 ratio, stratified by HCV status and quartile ranges of eGFR. After discontinuation of group 1, the remaining patients were randomised in a 1:1 ratio to the other 2 groups. The study was open label due to the requirement to actively monitor drug levels for safety and efficacy. The sponsor stated that the core study team, local pathologist and central pathologist were blinded to treatment.

#### **7.1.1.6. Analysis populations**

Efficacy and renal function (eGFR) analyses were based on the intention to treat (ITT) population which was all randomised patients. The per-protocol (PP) population (all randomised patients without major protocol deviations), was used for a second level efficacy analysis.

#### **7.1.1.7. Sample size**

A sample size of 242 patient per group gave the study 85% power to show non-inferiority (margin of 12%) of everolimus + reduced TAC compared to the TAC control group assuming a background rate of tBPAR/GL/D of 20% ( $\alpha=0.0125$ ). With a background composite failure rate of 24%, the power was 80%. For eGFR analysis, 217 patients per group gave the study 90% power to show non-inferiority margin of  $-6.0 \text{ mL/min/1.73 m}^2$  with a standard deviation of  $20 \text{ mL/min/1.73 m}^2$  and  $\alpha=0.025$ .

#### **7.1.1.8. Statistical methods**

Efficacy and renal function data were analysed for the first 12 months post-randomisation. The study aimed to show non-inferiority of the everolimus + reduced TAC treatment compared to the control arm at a one-sided significant level of 0.0125. The non-inferiority (NI) margin for tBPAR/GL/D was 12%. The sponsor states that this was based on a NI margin for graft loss or

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<sup>2</sup> The Banff score is a set of histopathologic criteria for grading acute rejection. Three specific features (portal inflammation, bile duct inflammation, and venular inflammation) are evaluated and scored on a scale of 0 to 3. The three scores are added to arrive at a final rejection activity index (RAI).

death of 10% and the inclusion of the additional component (tBPAR) would lead to a higher incidence of the composite endpoint in the control group.

Efficacy failure proportions were estimated using Kaplan Meier formula and Greenwood's formula to estimate the variance and derive Z-test based confidence intervals. If the upper bound of the 97.5% CI was below 0.12 in the everolimus + reduced TAC regimen, the result was deemed non-inferior to the control arm on the composite failure outcome.

With the reduction to two groups, after the cessation of group 1, comparisons were based on a two-sided significance level of 0.025 for the primary and key secondary objectives. Patients with missing efficacy evaluation for the 12 month analysis were censored at the latest day known to be free of the event. Supportive analyses of the primary endpoint were conducted using a CMH test stratified by HCV status. Subgroup analyses were for age, gender, race, region, HCV status, MELD score and diagnosis. For other efficacy endpoints treatment comparisons were made using Pearson Chi-square test or Exact test.

Analysis-of-covariance (ANCOVA) model was used for analysis of change in eGFR (MDRD-4) from randomisation to 12 months with treatment, pre-transplant HCV status and eGFR at randomisation as covariates. The EVR+reduced TAC treatment arm was compared against the control arm for non-inferiority with a margin of -6 mL/min/1.73m<sup>2</sup>. The EVR+reduced TAC regimen was to be claimed to have had non-inferior renal function at 12 months if the lower limit of the 97.5% CI of the adjusted mean difference was higher than -6. If the NI objective was met, superiority was then tested ( $\alpha=0.025$ ).

#### **7.1.1.9. Participant flow**

There were 1378 patients screened, 1147 received a liver transplant and entered the run-in period and 719 were randomised to study treatment. The screen failure and randomisation failure rates were 16.8% and 37.3%, respectively. The main reasons for randomisation failure were inadequate allograft function (5.9%), tacrolimus levels < 8ng/mL (5.7%), medical/surgical condition (5.5%), requiring critical care (3.6%), inadequate renal function (3.5%), antibody induction therapy (3.0%) and other (15.1%). The largest number of patients were randomised in USA (316), Germany (168) and Italy (118). There were 231, 245 and 243 patients in the EVR+TAC elimination, EVR+reduced TAC and TAC control groups, respectively, and the study medication completion rates were 44.2%, 73.1% and 77.8%, respectively.

Discontinuation of study medication occurred in 26.9% and 22.2% of the EVR+reduced TAC and TAC control groups, respectively, while in the terminated group 1 of EVR+TAC elimination the rate was 55.8%. The main reason for discontinuation of medication was AEs (19.5%, 19.2% and 11.1% of the EVR+TAC elimination, EVR+reduced TAC and TAC control groups, respectively). The rate of study discontinuation was 12.1%, 10.2% and 10.3% in the 3 groups, respectively.

The ITT population included all 719 subjects. The PP population consisted of 99 (42.9%), 157 (64.1%) and 161 (66.3%) patients in the EVR+TAC elimination, EVR+reduced TAC and TAC control groups, respectively.

#### **7.1.1.10. Major protocol violations/deviations**

The rate of major protocol deviations leading to exclusion from the PP population was similar between groups (19.0%, 16.7% and 19.3% in the EVR+TAC elimination, EVR+reduced TAC and TAC control groups, respectively). The main reasons were study drug dosing for <180 days (6 months), LFTs  $\geq 3 \times$  ULN at randomisation, and ANC <1000/mm<sup>3</sup>. The rate of protocol deviations over the 12 months was also similar in the three respective groups (74.0%, 76.3% and 74.5%). The main deviations were: medication related (38.1%), corticosteroid dose < 5mg/d (34.8%), inclusion criteria (32.5%), TAC trough level <8 ng/mL prior to randomisation (22.4%), exclusion criteria (28.0%). Treatment compliance was not analysed.



#### 7.1.1.11. *Baseline data*

Baseline demographics and other characteristics were balanced between groups. The mean age was 53-54 years, 71-74% were male, 80-85% Caucasian, 31-32% HCV positive, 36-42% diabetic with a mean baseline eGFR (by MDRD-4) of 79-83 mL/min/1.73m<sup>2</sup>. The proportion of patients who were Black, HCV positive, and pre-transplant diabetic were higher in North America compared to Europe or the rest of the world (ROW). There was some imbalance of eGFR between treatment groups at a regional level for North America and Europe with more North Americans having low or very low eGRF in the EVR+reduced TAC than the TAC control group. As noted above, randomisation was stratified by HCV status and eGFR and this was done at a global level.

The most common reason for end stage liver disease (ESLD) was hepatitis C, alcoholic cirrhosis and hepatocellular carcinoma and these primary diseases were roughly similar between groups. Median cold ischaemia time (7.1-7.7 hours), median model of end stage liver disease (MELD) score<sup>3</sup> (18.5-20.0) and identical ABO matching rates (73.6-78.2) were similar between groups. The rates of recipient/donor gender match and age match were also similar between groups.

Corticosteroids were the most commonly taken concomitant immunosuppressant, in particular prednisone (60.8%, 62.2% 60.6% in the EVR+reduced TAC, TAC elimination and TAC control group, respectively), prednisolone (22.0%, 19.6%, 17.8%) and methylprednisolone (18.0%, 23.9%, 26.1%). Concomitant lipid lowering agents (mainly statins) were taken by 23.3%, 23.5% and 17.8% of the three groups, respectively. Antiviral medications were taken by 67.3%, 65.2% and 68.5, the most common of which were valgancyclovir and acyclovir. PCP prophylaxis was taken by 71.4%, 77.0% and 75.1%, the most common of which was co-trimoxazole.

#### 7.1.1.12. *Drug concentrations*

In the EVR+reduced TAC group to month 2, 48.4% of patients were within the target everolimus trough level of 3-8 ng/mL. From month 2 to 12 the proportion within target was between 78% and 82%. The mean everolimus trough level ranged from 3.4 to 6.3 ng/mL between week 5 and month 12 in this group.

In the EVR+reduced TAC group prior to month 2, only 9-19% of patients had tacrolimus levels after tapering within the trough target level of 3-5 ng/mL. Between months 2 and 12, the proportion within the target range was between 32% at month 2 and 48% at month 12. At month 12, 16% were below, 48% within and 36% above TAC target. In the TAC control group, 54% were within the target range at month 12 with 19% above target and 27% below target. The difference in the mean tacrolimus trough levels between the EVR+reduced TAC and TAC control groups was 3.3 ng/mL at month 3 and 2.0 ng/mL at month 12. In general, the TAC level was just above the upper end of the range in the EVR+reduced TAC group and within range for the TAC control group.

**Comment:** This finding may indicate some reticence on the investigators to reduce tacrolimus to protocol defined levels in this open label study.

#### 7.1.1.13. *Results for the primary efficacy outcome*

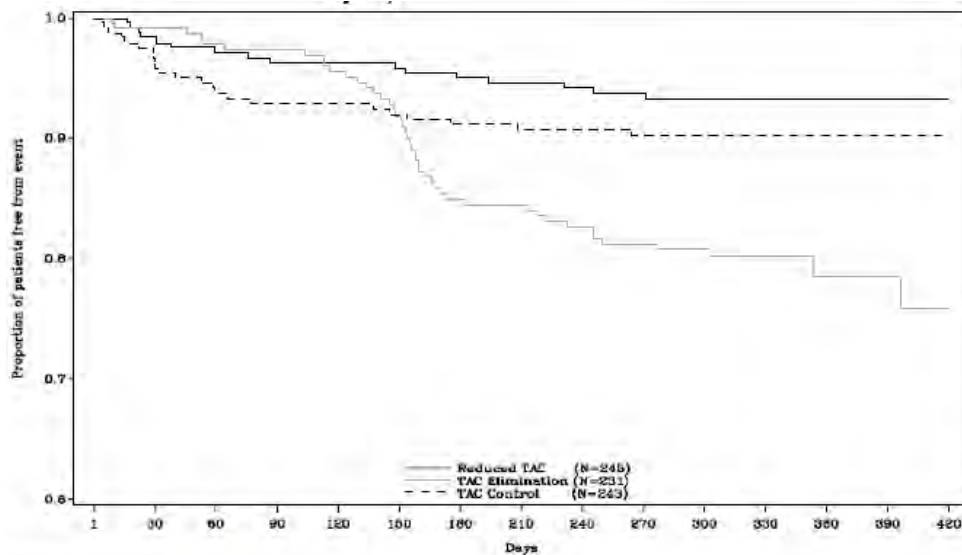
The rate of the composite primary endpoint (tBPAR/GL/D) at month 12 was slightly lower in the EVR+reduced TAC group compared to the TAC control group (6.7% vs 9.7%) with a difference of -3.0% (97.5% CI: -8.7%, 2.6%). As the upper bound of the CI was less than then NI margin of 12%, the EVR+reduced TAC treatment was found to be non-inferior to TAC control (p<0.001). In the PP population analysis, the rate of tBPAR/GL/D was 1.9% and 5.0% in the EVR+reduced TAC and TAC control groups, respectively, with a difference of -3.1% (97.5% CI: -7.6%, 1.5%). Again this result was non-inferior and statistically significant (p<0.001). The

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<sup>3</sup> MELD score uses the patient's values for serum bilirubin, serum creatinine, and the international normalised ratio for prothrombin time (INR) to predict survival.

Kaplan Meier plot for the primary endpoint is shown in Figure 2 and also demonstrates the adverse effect of TAC elimination. The rate of tBPAR/GL/D at month 12 in the EVR+TAC elimination arm was 24.2% and 19.2% in the ITT and PP populations, respectively.

**Figure 2. Study H2304. Kaplan-Meier plot for the proportion of patients free from primary composite efficacy failure tBPAR, graft loss or death (ITT population – 12 month analysis)**



When tBPAR was based on central laboratory pathology reading, the rate of tBPAR/GL/D was lower in both the EVR+reduced TAC and TAC control groups (5.9% vs 6.8%) and non-inferiority was still demonstrated (difference -0.9% with upper bound of the 97.5% CI at 4.1%,  $p < 0.001$ ).

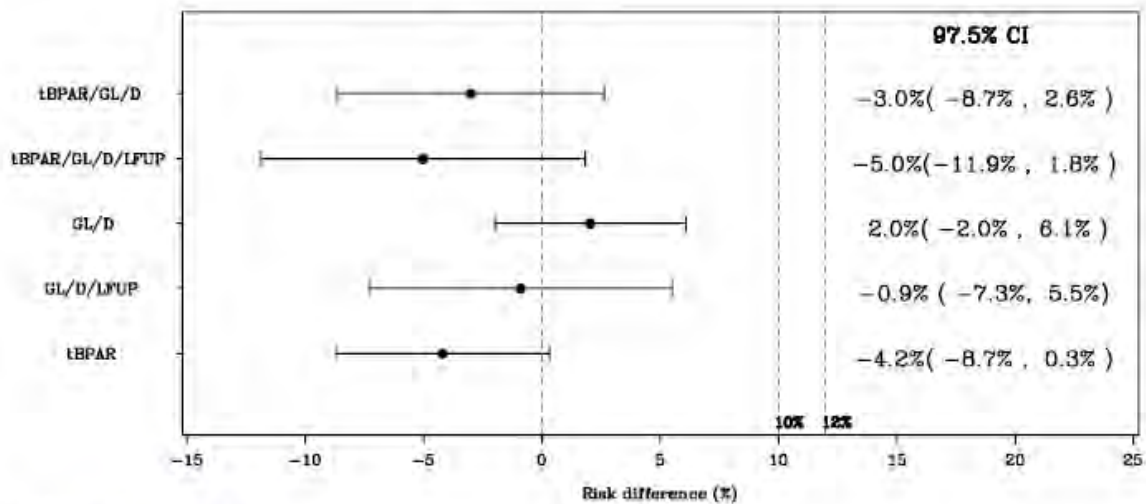
Subgroup analysis of age ( $\pm 60$  years), gender, race, region, eGFR ( $<30/30- <55/55- <70$ ), HCV status, MELD score ( $\leq 14/15-19/20-24/25-29/\geq 30$ ) and cause of ESLD found similar rates of tBPAR/GL/D between the EVR+reduced TAC and TAC control groups which were also consistent with the overall population.

When loss to follow up was added to the composite endpoint, the rate in the EVR+reduced TAC and TAC control groups were 10.6% and 15.6% respectively, with a -5.0% difference (97.5% CI: -11.9%, 1.8%) which remained non-inferior ( $p < 0.001$ ).

The original protocol's primary endpoint was graft loss/death/lost to follow-up and the rate of this composite endpoint was 9.0% in the EVR+reduced TAC and 9.9% in the TAC group. The difference (-0.9%) was statistically non-inferior (97.5% CI: -7.3% 5.5) using the original NI margin of 10%. The rate in the TAC elimination group was 12.1%. When examining GL/D at month 12, the rate was slightly higher in the EVR+reduced TAC group than the TAC control group (5.0% vs 3.0%) although the difference (2.0%, 97.5% CI: -2.0, 6.1%) was still statistically non-inferior (10% margin,  $p < 0.001$ ). A summary of efficacy endpoints is in Figure 3.



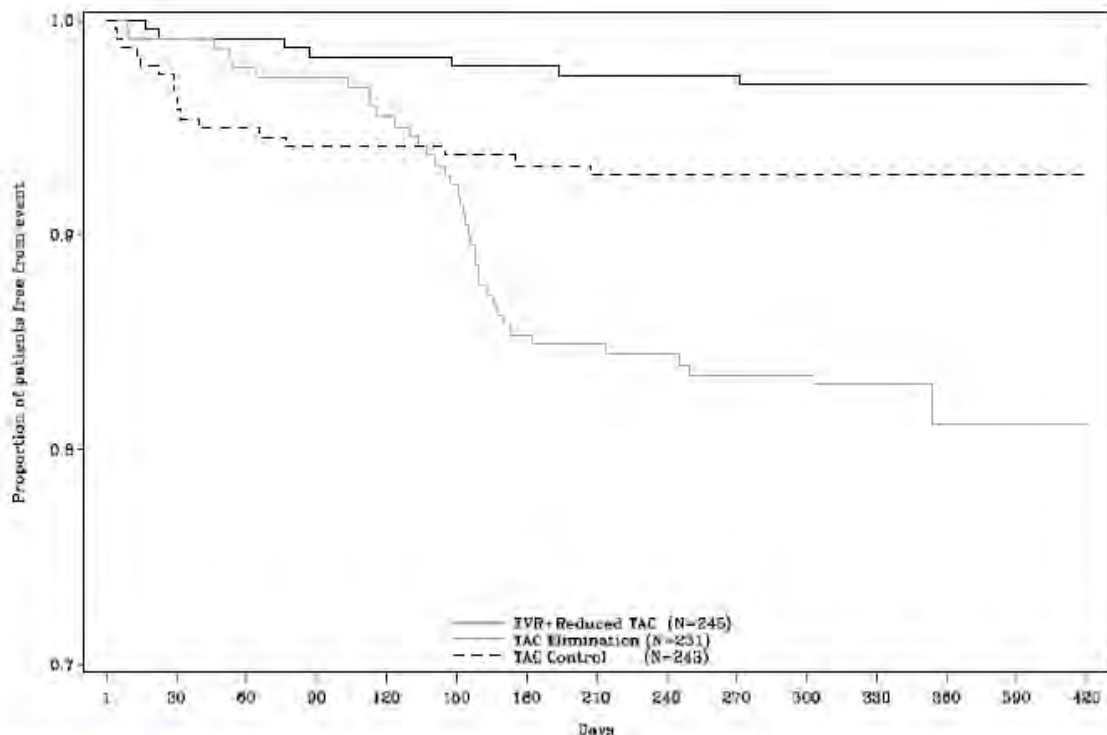
**Figure 3. Study H2304. Summary of efficacy endpoints. Rate differences between EVR+Reduced TAC vs. TAC control (ITT population – 12 month analysis)**



#### 7.1.1.14. Results for other efficacy outcomes

At 12 months, the rate of graft loss (2.4% vs 1.2%) and death (3.7% vs 2.5%) was higher in the EVR+reduced TAC compared to the TAC control group, however the risk difference was not statistically significant ( $p=0.504$  and  $p=0.602$ , respectively). The rate of acute rejection was lower in the EVR+reduced TAC group compared to the TAC control group (3.7% vs 10.7%) with a significant risk difference of -7.0% (95% CI: -11.6%, -2.5%,  $p=0.003$ ). This finding was consistent across the other definitions of acute rejection (treated, biopsy proven and treated biopsy proven). The Kaplan Meier plot of patients free from tBPAR at the 12 month analysis by treatment shows the poorer outcome in the EVR+TAC elimination group (Figure 4).

**Figure 4. Study H2304. Kaplan-Meier plot for the proportion of patients free from tBPAR (ITT population – 12 month analysis)**



In the EVR+reduced TAC group, the severity of BPAR (according to RAI score) was indeterminate/borderline in 2.0% and mild in 2.0%, with no moderate or severe cases. In the TAC control group, BPAR cases were more severe with 3.3% being indeterminate/borderline, 3.7% mild, 2.9% moderate and 0.8% severe. In patients with autoimmune causes<sup>4</sup> of ESLD, the rate of tBPAR was 0% (0/20) in the EVR+reduced TAC group compared to 23.7% (9/38) in the TAC elimination and 23.1% (6/26) in the TAC control groups.

There was a slightly higher rate of acute rejection in North America (6.2%, 20.6%, 11.5%) compared to Europe (2.0%, 13.8%, 5.3%) and Rest of the World (0.0%, 20.0%, 3.0% in the EVR+reduced TAC, TAC elimination and TAC control groups, respectively.)

### **Renal function**

The adjusted least squares (LS) mean change in eGFR (MDRD-4) from randomisation to month 12 in the ITT population was -2.23 mL/min/1.73m<sup>2</sup> in the EVR+reduced TAC group compared to -1.51 in the TAC elimination and -10.73 in the TAC control groups. The difference between the EVR+reduced TAC and TAC control group was 8.50 mL/min/1.73m<sup>2</sup> (97.5% CI: 3.74,13.27) which was non-inferior (-6 NI margin) and also statistically superior (p<0.001). Results from the PP population were similar with a LS mean difference of 10.40 mL/min/1.73m<sup>2</sup> (97.5% CI: 4.76, 16.05, p<0.0001). This effect on eGFR was statistically superior from month 2 through to month 12 in the ITT population. Similar results were also found when renal function was assessed by serum creatinine or when eGFR was estimated by other methods including Cockcroft-Gault, cystatin C, Nankivell, CKD-EPI formula and MDRD-6.

The improved renal function (eGFR by MDRD-4) in the EVR+reduced TAC group compared to the TAC control group at month 12 was consistent across the subgroups of age, gender, hepatitis C status, MELD category, cause of ESLD and eGRF strata at baseline. Despite imbalance in eGFR at baseline between regions, there was still a significant difference between the EVR+reduced TAC and TAC control groups in eGFR at month 12 in all regions (North America, Europe and Rest of world). For those with eGFR of 30-<45 at baseline, there was a greater rate of improvement to eGFR ≥60 in the EVR+reduced TAC group compared to the TAC control group (36.8% vs 18.8%). Preservation of eGFR ≥60 at baseline to ≥60 at 12 months was also greater in the EVR+reduced TAC group (88.6% vs 73.5%).

At month 12 the mean urine protein to creatinine ratio was higher in the EVR+reduced TAC group compared to the TAC control group (245.7 vs 151.2 mg/g). In the EVR+reduced TAC group there were no patients with a pre-existing proteinuria of ≥0.5 g/24 hours at one month post transplantation who had worsening proteinuria at month 12, while for those with proteinuria <0.5g/24 hours at baseline 7.6% shifted to 0.5-<1.0, 3.2% to 1.0-<3.0 and 0.5% (one case) to ≥3g/24 hours.

Renal replacement therapy was required in 6 (2.4%), 3 (1.3%) and 4 (1.6%) patients in the EVR+reduced TAC, TAC elimination and TAC controls groups, respectively. No patients remained on this therapy at 12 months.

Exploratory analyses were conducted on kidney biomarkers which may be indicative of renal injury. These included urinary cystatin C, microalbumin, β2 microglobulin, Kim-1 (kidney injury molecule 1), NGAL (neutrophil gelatinase-associated lipocalin). The latter 2 markers, which reportedly indicated kidney injury, showed reduced levels at month 12 in all treatment groups.

#### **7.1.1.15. Summary**

H2304 was the pivotal efficacy study in 719 *de novo* hepatic transplant patients. The study met its primary objective as treatment commencing one month post transplantation with everolimus and reduced dose tacrolimus regimen was found to be statistically non-inferior (NI

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<sup>4</sup> Primary biliary cirrhosis, sclerosing cholangitis and autoimmune liver hepatitis.

margin 12%) to treatment with a standard tacrolimus regimen when measured by the composite endpoint of tBPAR/GL/D at 12 months (6.7% vs 9.7%) with difference of -3.0% (97.5% CI: -8.7%, 2.6%). Non-inferiority was also achieved on other efficacy endpoints of GL/D/loss to follow up, GL/D and supported by the PP analysis. There was statistically superior renal function as measured by mean change in eGFR with a difference of 8.50 mL/min/1.73 m<sup>2</sup> (97.5% CI: 3.74, 13.27, p<0.001) in favour of everolimus+reduced TAC compared to TAC control groups at 12 months. Results of both primary and key secondary efficacy outcomes were consistent across subgroups of age, gender, race, region, eGFR, HCV status, MELD score and cause of ESLD. Elimination of tacrolimus when patients were treated with everolimus was associated with a significant risk of efficacy failure and treatment with the regimen was required to be prematurely terminated.

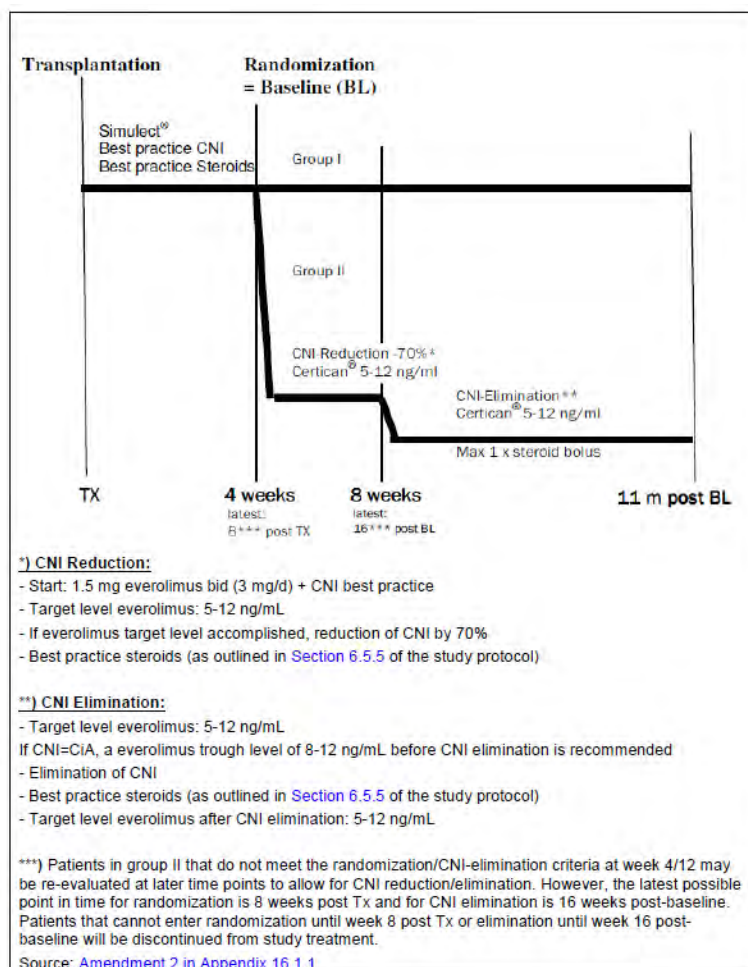
## 7.1.2. Other efficacy studies

### 7.1.2.1. Study HDE10

Study HDE10 was a 12 month, phase III, multicentre, randomised, open label, parallel group study of the safety, tolerability and efficacy of an everolimus-based regimen compared to a calcineurin inhibitor (CNI)-based regimen in 203 adult patients with *de novo* liver transplantation.

**Methods:** The study design and treatment are shown in Figure 5 and discussed in more detail in the section on *Safety*, below.

**Figure 5. Study HDE10. Study flowchart (up to Visit 17 = Month 11 post-baseline)**



The primary objective was to demonstrate, at 11 months post randomisation, superiority of renal function for the everolimus-based regimen with discontinuation of CNI therapy compared

to a CNI-based regimen. Efficacy was a secondary objective and assessed: the composite of BPAR, graft loss, death and loss to follow up; the rate of need to change immunosuppressive regimen; tBPAR; patient and graft survival; and HCV replication in HCV positive patients.

Patients received basiliximab induction treatment and then at week 4, if eligible, were randomised to either continued CNI therapy or EVR (1.5 mg bid) treatment with tapering CNI dose (reduced by 70% of dose then discontinued). EVR target level was 5-12 ng/mL.

**Results:** The study did not reach its primary endpoint of superiority of renal function with an everolimus-based immunosuppressive regimen. For the secondary objectives relating to efficacy, the rate of clinical events and their combinations in the ITT population are shown in Table 2. There were no significant differences between the treatment groups in single events or in the composite of efficacy failure (BPAR, graft loss, death, loss to follow up) (17.7% vs 14.3% p=0.56). There was also no significant differences in these endpoints on Kaplan Meier estimates.

**Table 2. Study HDE10. Incidence (crude rates) of clinical events and their combinations (ITT)**

Type of event	Everolimus N=96 n (%)	CNI N=98 n (%)	Fisher's exact test p-value
<b>Single events</b>			
Death*	4 ( 4.2)	4 ( 4.1)	1.000
Graft loss	2 ( 2.1)	2 ( 2.0)	1.000
BPAR	17 (17.7)	15 (15.3)	0.702
Treated BPAR	13 (13.5)	10 (10.2)	0.512
Lost to follow-up	0 ( 0.0)	1 ( 1.0)	1.000
Need for treatment change <sup>‡</sup>	77 (80.2)	72 (73.5)	0.309
<b>Combined events</b>			
Death or graft loss	5 ( 5.2)	5 ( 5.1)	1.000
Death or graft loss or BPAR	20 (20.8)	19 (19.4)	0.859
Death or graft loss or treated BPAR	17 (17.7)	14 (14.3)	0.561
Efficacy failure <sup>†</sup>	20 (20.8)	20 (20.4)	1.000

Source: PT-Table 14.2-3.1

‡: in other immunosuppressive medication.

†: This combined endpoint included BPAR, graft loss, death, or lost to follow-up from any reason.

\* Patient [Redacted information] is not included in this analyses since the patient was excluded from the ITT population.

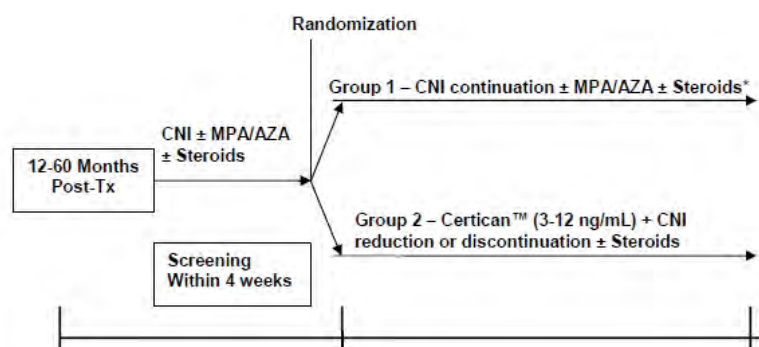
### 7.1.2.2. Study H2401

**Methods:** H2401 was a phase III, six month, multicentre, randomised, open-label study of the safety and efficacy of everolimus-based regimen compared to a CNI-based regimen in 145 maintenance liver transplant recipients with CNI-related renal impairment. The primary objective was to determine whether everolimus together with reduction or discontinuation of calcineurin inhibitor (CNI) in maintenance liver transplant patients with CNI-related renal impairment would improve renal function as measured by the change in calculated glomerular filtration rate (cGFR) from baseline to month 6. Measures of efficacy (BPAR, graft loss and death) and safety were secondary objectives. Patients were followed up again at 12 months. The study is discussed in the section on *Safety*, below. In this study, the median time from transplantation to study entry was 2.4 years and 3.1 years in the EVR and CNI control groups, respectively.

Patients were treated with either reduced CNI dose + everolimus 1.5 mg b.i.d ± steroids or standard CNI dose ± mycophenolate acid (MPA)/azathioprine (AZA) ± steroids (Figure 6). Open

label everolimus treatment commenced at 1.5 mg bid and the dose was adjusted to maintain a target trough level of 3-8 ng/mL with concomitant tacrolimus or cyclosporine and 6-12 ng/mL when these medications were ceased.

**Figure 6. H2401 Study design.**



\* Per protocol a reduction in CNI dose of up to 25% was allowed in Group 1.

**Results:** At 6 months, the composite efficacy failure (BPAR/GL/D) rate was 2.8% (n=2) in the everolimus group and 1.4% (n=1) in the CNI control group. The difference of 1.5% (95% CI: -3.2, 6.0%) was not significant (p=0.552). In the follow up from 7 to 12 months, there were a further 2 deaths and 2 cases of acute rejection in the EVR group and 2 deaths in the CNI control group. It was noted that after month 6 other immunosuppressant therapies were allowed.

### 7.1.2.3. Study H2301

**Methods:** An interim clinical study report for H2301 dated August 2011 was included in the dossier. H2301 was described as an exploratory study which aimed to assess the efficacy of everolimus in inhibiting fibrosis progression in 43 liver transplant recipients with recurrent hepatitis C. It is also known as REVERT. It was a 24 months, randomised, multicentre, open label, parallel group trial conducted at 6 centres in Argentina between November 2006 and January 2010. The study was terminated prematurely after the 12 month biopsy due to a high drop-out rate.

The primary objective was to demonstrate a slower progression of liver fibrosis as assessed by the Ishak-Knodell (IK) staging score<sup>5</sup> at 24 months post randomisation in Hepatitis C positive patients after orthotopic liver transplantation receiving everolimus versus standard treatment. Secondary objectives were the comparison between treatment groups at 12 and 24 months of BPAR, death, graft loss, renal function (GFR calculated using MDRD formula), Ishak-Knodell scores, Metavir scores<sup>6</sup>, HCV RNA viral load, and fibrosis area on histomorphometry. Biopsies were reviewed by a central pathologist.

Patients were screened at least 6 months after transplantation. Inclusion criteria were: ≥6 months post liver transplantation; laboratory confirmed HCV recurrence; histologically proved liver fibrosis (staging I-IV score in the Ishak-Knodell scale); CNI immunosuppression; and no anti-hepatitis C treatment at enrolment.

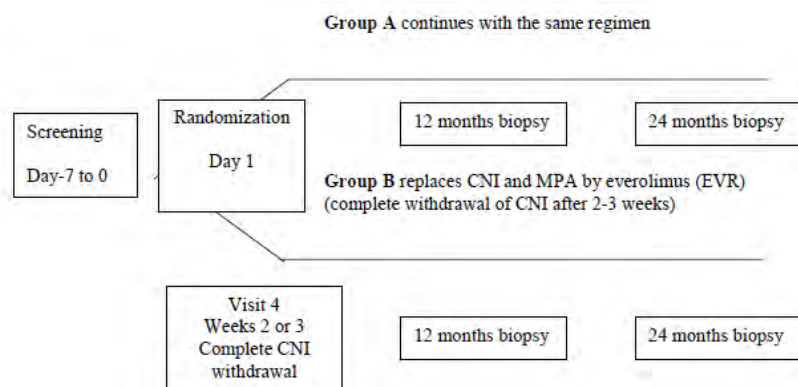
<sup>5</sup> The Knodell score is composed of the summation of four individual scores representing periportal and/or bridging necrosis, intralobular degeneration and focal necrosis, portal inflammation, and fibrosis; the score ranges from 0 to 2. The Ishak Knodell score is a modification with six stages of fibrosis, permitting more detailed evaluation of changes in fibrosis compared with the standard Knodell fibrosis score, which has only three stages.

<sup>6</sup> The Metavir score is a semiquantitative classification system consisting of an activity and a fibrosis score: The fibrosis score is assessed on a five point scale (0 = no fibrosis, 1 = portal fibrosis without septa, 2 = few septa, 3 = numerous septa without cirrhosis, 4 = cirrhosis). The activity score was graded according to the intensity of necroinflammatory lesions (A0 = no activity, A1 = mild activity, A2 = moderate activity, A3 = severe activity).



Patients were randomised in a 1:1 ratio to either continuing CNI ±MPA immunosuppression or everolimus with discontinuation of CNI/MPA after 2 to 3 weeks. Steroids were allowed in both groups (Figure 7). For patients on cyclosporine, the EVR dose commenced at 1.0 mg bid and for those on TAC was 1.5 mg bid. CNI was discontinued when EVR trough level was between 6-12 ng/mL.

**Figure 7. Study H2301: Schematic diagram of study design**



**Results:** There were 43 patients randomised, 22 in the EVR group and 21 in the CNI group. In July 2010, 15 and 7 patients, respectively had discontinued the study prior to month 24 and this high rate lead to the premature cessation of the study. Thirty-nine patients completed to month 12 (19 vs 20). Discontinuation of study medication was greater in the EVR group (36.4% vs 4.8%) and this was primarily due to AEs (22.7% vs 0.0%). Only 4 (18.2%) and 12 (57.1%) of the EVR and CNI groups, respectively completed the 24 months.

The groups were not well balanced. At baseline the EVR group was slightly younger (56 vs 60 years) with more men (68% vs 52%) and higher BMI (29.8 vs 27.5 kg/m<sup>2</sup>). The cGFR was similar (64.1 vs 63.7 mL/min/1.73m<sup>2</sup>). Most patients had HCV genotype 1b (68.2% vs 52.4%). The mean time from transplantation was 4.4 and 3.7 years, respectively. The mean IK fibrosis staging score at baseline was greater in the EVR group (2.6 vs 1.9).

The mean everolimus trough level between day 7 and month 24 ranged between 7.4 ng/mL and 9.0 ng/mL. Mean cyclosporine trough levels ranged from 95.1 to 134.8 ng/mL and tacrolimus trough levels between 4.7 and 6.6 ng/mL.

Due to premature termination the efficacy analysis was based on the last available biopsy from month 12 or later. At month 12 there were data on 32 biopsies and the mean IK score was lower with EVR (1.9 vs 2.2) with a greater change from baseline (-0.7 vs 0.2). The difference between groups in the change from baseline just reached statistical significance (p=0.046). Results up to month 24 were not significantly different. There were no significant difference on the Metavir fibrosis score at 12 or 24 months nor on other histological assessments.

There was one event of graft loss in the EVR group. There were no other events of BPAR or death in either group. There was no difference between groups in HCV viral load at month 12 or 24. The EVR group had a slightly higher LS mean eGFR at month 12 (65.6 vs 62.2) by the mean difference between groups of 3.4 was not significant (p=0.411).

**Summary:** This exploratory study in 43 liver transplant patients with recurrent HCV was terminated early due to a high drop-out rate, particularly due to AEs, and only an interim clinical study report was provided. Data were primarily based on 32 biopsies at 12 months, rather than at 24 months. In addition, the groups were not well balanced at baseline. The data showed a lower mean fibrosis (IK) score at month 12 with EVR compared to CNI treatment. However, due to the factors listed, the results of this study cannot be viewed as conclusive.

### 7.1.3. Analyses performed across trials (pooled analyses and meta-analyses)

None.

### 7.1.4. Evaluator's conclusions on clinical efficacy for hepatic transplantation.

The hepatic transplantation dossier included 4 phase III studies. Study H2304 was the pivotal study and provided the most appropriate data for assessing efficacy. There were two studies HDE10 and H2401 which were primarily safety studies assessing change in renal function with efficacy being a secondary objective. These studies provided minimal supportive evidence. Efficacy endpoints in the 3 studies are summarised in Table 3.

**Table 3. Efficacy endpoints across studies.**

	Study H2304			Study HDE10		Study H2401	
	EVR+Reduced TAC N=245 n (%)	TAC Elimination N=231 n (%)	TAC Control N=243 n (%)	EVR N=96 n (%)	CNI N=98 n (%)	EVR N=72 n (%)	CNI N=73 n (%)
Graft loss <sup>#</sup>	6 (2.4)	5 (2.2)	3 (1.2)	2 (2.1)	2 (2.0)	0	0
Death <sup>#</sup>	9 (3.7)	8 (3.5)	6 (2.5)	4 (4.2)	4 (4.1)	1 (1.4)**	0
BPAR	10 (4.1)*	46 (19.9)	26 (10.7)	17 (17.7)	15 (15.3)	1 (1.4)	1 (1.4)
tBPAR	7 (2.9)*	38 (16.5)	17 (7.0)	13 (13.5)	10 (10.2)	1 (1.4)	1 (1.4)
tBPAR/graft loss/death	16 (6.7) <sup>A</sup>	45 (24.2) <sup>A</sup>	23 (9.7) <sup>A</sup>	17 (17.7)	14 (14.3)	-	-
tBPAR/graft loss/death/Loss to Follow-up	26 (10.6)	63 (27.3)	38 (15.6)	-	-	-	-
BPAR/graft loss/death/Loss to Follow-up	-	-	-	20 (20.8)	20 (20.4)	-	-

\* Comparison of EVR+Reduced TAC vs. TAC Control statistically significant (p<0.05) in favor of EVR+Reduced TAC.

\*\*for 6 month study H2401: The endpoint is graft loss/death

<sup>A</sup> In H2304, Kaplan-Meier estimate of the event rates were calculated for tBPAR/graft loss/death

In Study H2304: # = exact confidence interval and two-sided Fisher exact test used for that variable. For others, asymptotic confidence interval and Pearson Chi-square test are used.

In Study HDE10: treatment comparisons used Fisher exact test.

Source: [Study H2304-Table 11-7], [Study H2304-Table 11-8], [Study H2304-Table 11-12], [Study HDE10-Table 11-17], [Study H2401-Table 11-9]

Study **H2304** is an ongoing 24 month, phase III, multicentre, open label, randomised, controlled trial in 719 *de novo* liver transplant recipients. It was a non-inferiority study comparing the efficacy and safety of concentration-controlled everolimus with reduced, or eliminated, tacrolimus to tacrolimus alone. Treatment with everolimus commenced one month post transplantation and whole blood monitoring targeted a trough level of 3-8 ng/mL. This level was lower than the target in HDE10 and H2401 where the upper limit was 12 ng/mL. For subjects in the EVR+reduced TAC group, the tacrolimus target level was 3-5 ng/mL after 3 weeks, while the control group's target was 6-10 ng/mL from month 4. Corticosteroids were allowed in all groups.

The study's group of everolimus in combinations with TAC elimination was discontinued prematurely due to a higher rate of acute rejection and adverse events. Discontinuation of study medication by month 12 was 26.9% in the EVR+reduced TAC group, compared to 22.2% in the TAC control group and 55.8% in the TAC elimination group.

The study met its primary objective as treatment commencing one month post transplantation with a regimen of everolimus + reduced tacrolimus was found to be statistically non-inferior (NI margin 12%) to treatment with tacrolimus alone at 12 months when measured by the composite endpoint of tBPAR/GL/D (6.7% vs 9.7%) with difference of -3.0% (97.5% CI: -8.7%, 2.6%, p<0.001). Non-inferiority was also achieved on other efficacy endpoints of GL/D/loss to follow up and GL/D and supported by the PP analysis. There was statistically superior renal function as measured by mean change in eGFR with a difference of 8.50 mL/min/1.73 m<sup>2</sup> (97.5% CI: 3.74, 13.27, p<0.001) in favour of everolimus + reduced TAC compared to TAC control groups. Results of both primary and key secondary efficacy outcomes were consistent across subgroups of age, gender, race, region, eGFR, HCV status, MELD score and cause of ESLD.

Overall, the effect appeared more related to a reduced rate of acute rejection episodes (3.7% vs 10.7%), rather than reduced graft loss or death. The study found that a reduction of tacrolimus was possible with the addition of everolimus post hepatitis transplantation without an increase in efficacy failure at 12 months post transplantation. It was also found that efficacy was unacceptable when everolimus was used without continuing tacrolimus concomitantly.

**HDE10** was a study in 203 de novo liver transplant patients. It did not reach its primary endpoint of superiority of renal function with an everolimus-based immunosuppressive regimen compared to a CNI-based regimen. Regarding efficacy, there were no significant differences between the treatment groups in single events or in the composite of efficacy failure (BPAR, graft loss, death, loss to follow up) (17.7% vs 14.3% p=0.56).

**H2401** examined the renal function in 145 patients with CNI-related renal impairment (GFR 20-60 mL/min) who were on average 3 years post hepatic transplantation. Efficacy was a secondary objective and the study did not find any significant difference in efficacy failure between groups after 6 months of treatment. The number of events was very limited.

The dossier also included an interim report for an exploratory study in 43 liver transplant patients with recurrent HCV (**H2301**). This study was terminated early due to a high drop-out rate and biopsy data were available at 12 months rather than the 24 month endpoint, and there were baseline imbalances between groups. There was an indication of a lower mean fibrosis (IK) score at month 12 with EVR compared to CNI treatment. However, due to the factors listed, the results of this study cannot be viewed as conclusive.

The pivotal trial was amended to comply with current EMA Guidelines (EMA 2008). The product information adequately summarises the clinical efficacy data in hepatic transplantation with the exception of a failure to state the risks of tacrolimus elimination. Further details are included in the sections on PI discussions<sup>7</sup>.

## **7.2. Cardiac transplantation**

### **7.2.1. Other efficacy studies A2310**

#### **7.2.1.1. Design, objectives, locations and dates**

Study A2310 was a 24 month, phase III, multicentre, randomised, open-label, parallel group non-inferiority efficacy and safety study comparing two exposures of concentration-controlled everolimus with reduced cyclosporine versus mycophenolate mofetil (MMF) with standard dose cyclosporine in de novo heart transplant patients. The dossier included the interim 12 month analysis report. The study commenced in January 2006 and the data cut-off date was July 2010. It was conducted at 63 centres in Europe, North America, Taiwan, Argentina, Australia and New Zealand. There was a central laboratory, central pathology for biopsies, central review of IVUS data and a DSMB.

The primary objective was to compare rates of the composite efficacy failure (biopsy-proven acute rejection of ISHLT grade  $\geq 3A^8$ , acute rejection episodes associated with haemodynamic compromise, graft loss/re-transplant, death, or loss to follow-up) between treatment with everolimus + reduced cyclosporine and MMF + standard dose cyclosporine at 12 months.

The main secondary objectives were: to assess incidence rate of graft loss/re-transplant, death or loss to follow-up at 12 months; and to demonstrate non-inferiority of renal function (assessed by calculated GFR by MDRD formula) between the groups at 12 months. Other secondary objectives were to assess the safety and efficacy of the two regimens at 6, 12 and 24 months post-transplantation.

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<sup>7</sup> These sections are not included in this Extract. See Attachment 1 of this AusPAR for the PI approved for this application.

<sup>8</sup> International Society for Heart and Lung Transplantation (ISHLT) grading system for acute cellular rejection (1990). Grade 0 no rejection, Grade 1 A/B mild (interstitial and/or perivascular infiltrate without myocyte damage), Grade 2 moderate (one focus of infiltrate with associated myocyte damage), Grade 3 A/B moderate (infiltrate with myocyte damage), Grade 4 severe (diffuse infiltrate with extensive myocyte damage, with or without oedema, haemorrhage, or vasculitis). A refers to focal and B refers to diffuse.



An intravascular ultrasound (IVUS) sub-study was performed at selected centres to assess the change in the average maximum intimal thickness at 12 months and the incidence of chronic allograft vasculopathy (CAV) defined as a 0.5 mm increase in maximum intimal thickness in at least one matched slice of an automated pullback sequence between baseline and Month 12.

In March 2008 following DSMB recommendations, randomisation into the everolimus 3 mg/day (1.5 mg bid) group was ceased due to higher mortality in the first 90 days post randomisation compared to the other groups. The deaths were related to infection and cardiovascular disorders. There were 168 patients in this group and those who had been on study for  $\leq 90$  days were changed to local practice immunosuppressive regimens. Subjects discontinuing study medication prior to month 24 were to continue with protocol specified visits.

There were 7 protocol amendments (3 global and 4 local). The main one related to the cessation of group 3.

#### **7.2.1.2. Inclusion and exclusion criteria**

Inclusion criteria were: males or females; 18-70 years of age; undergoing primary heart transplantation; functional graft at randomisation. Females were postmenopausal or using acceptable contraception.

The main exclusion criteria were: calculated CrCl  $< 40$  mL/min (using MDRD formula); platelets  $< 50,000/m^3$ ; ANC  $\leq 1500/m^3$  or WBC  $\leq 4000/m^3$ ; recipients of multiple solid organ or tissue transplants or had previously received organ transplants; severe hypercholesterolemia ( $\geq 350$  mg/dL;  $\geq 9$  mmol/L) or hypertriglyceridemia ( $\geq 750$  mg/dL;  $\geq 8.5$  mmol/L); donor  $> 65$  years and/or with known donor coronary or heart disease at the time of transplant; donor heart cold ischemic time  $> 6$  hours; induction therapy other than Simulect or Thymoglobulin; HIV or HCV or HBsAg positive; and malignancy within 5 years.

#### **7.2.1.3. Study treatments**

The three study treatment groups were:

- Group 1: everolimus 1.5 mg (0.75 mg bid) + cyclosporine reduced dose bid + steroids.
- Group 2: everolimus 3.0 mg (1.5 mg bid) + cyclosporine reduced dose bid + steroids.
- Group 3: Mycophenolate mofetil (MMF) 1500 mg bid + cyclosporine standard dose bid + steroids.

Treatment was planned for 24 months. Induction therapy was as per centre practice and was to be consistent at that centre (Simulect/basiliximab, Thymoglobulin/anti-thymocyte globulin rabbit or none).

Therapeutic drug monitoring (TDM) of trough (C0) levels of everolimus (EVR) and cyclosporine (CsA) was undertaken. The target levels for everolimus were 3-8 ng/mL in the everolimus 1.5 mg and 6-12 ng/mL in the 3.0 mg treatment groups.

In both everolimus groups, the CsA dose was adjusted to achieve trough levels approximately one half of that employed in the MMF arm (standard local practice), but falling within target ranges of: month 1, 200-350 ng/mL; month 2, 150-250 ng/mL; months 3 and 4, 100-200 ng/mL; months 5 and 6, 75-150 ng/mL; and months 7 to 24, 50-100 ng/mL.

Central laboratory C0 and C2 (2 hours post morning dose) levels were also measured in addition to local C0 levels. Dose reduction or interruption was allowed for AEs, decreased platelets, WBC or ANC or increased cholesterol or triglycerides.

CMV prophylaxis was mandatory in positive donors and negative recipients. Pneumocystis pneumonia prophylaxis was given to all patients for the first 6 months and then according to local practice. Systemic anti-fungals were not allowed. HMG CoA reductase inhibitors were given to all patients.

#### **7.2.1.4. Efficacy variable and outcomes**

Biopsy-proven acute rejection of ISHLT grade  $\geq 3A$  was diagnosed from endomyocardial biopsies performed at protocol-specified visits or for suspected rejection episodes. The biopsy was to be performed within 48 hours of the episode and was assessed by local and central pathologists.

Haemodynamic compromise was assessed on the CRF with recording of positive inotropic or vasoactive treatment. IVUS assessments, at specified centres, included the change in average maximum intimal thickness and the incidence of chronic allograft vasculopathy (CAV). The primary safety variable was renal function measured by calculated GFR (MDRD formula), calculated creatinine clearance (Cockcroft-Gault formula) and serum creatinine.

#### **7.2.1.5. Randomisation and blinding methods**

Patients were randomised to one of 3 groups in a 1:1:1 ratio within 72 hours after transplantation by an IVRS. Randomisation was stratified by centre (induction use status). Treatment was open label. The IVUS core laboratory reviewers were reported as blinded to treatment assignment.

#### **7.2.1.6. Analysis populations**

Analysis was based on the ITT population (all randomised patients) with supportive analyses on the PP population (all patients who completed at least 6 months of study medication and had at least one post baseline efficacy assessment on treatment and completed the study without major protocol deviations). The IVUS population was a subset of the ITT population who had a minimum of 11 matched slices between IVUS images from baseline and month 12.

#### **7.2.1.7. Sample size**

The original planned sample size was 630 patients or 210 per group. This gave the study a 90% power to detect a 4% difference in the composite efficacy failure rate. It was based on an estimated primary efficacy failure rate at 12 months of 45% in the MMF group and 41% in the EVR group (-4% difference), a non-inferiority margin of 13% and a two sided type I error rate of 2.5%. The 3 mg/day group was terminated when 168 patients were enrolled.

The IVUS sub-study required 91 evaluable patients per group to detect a 0.06 mm difference in the change in average maximum intimal thickness between baseline and month 12 (standard deviation of 0.13 mm) with 80% power and  $\alpha=0.025$ .

#### **7.2.1.8. Statistical methods**

With cessation of the everolimus 3mg/day group there was one between group comparison (EVR 1.5 mg vs MMF) The aim was to demonstrate non-inferiority of EVR 1.5 mg compared to MMF on the composite efficacy failure rate at 12 months using a Z-test statistic at a two sided significance level of 0.025. This significance level was to control for multiplicity. The non-inferiority margin was 13%. This was based on data from renal transplant studies. Secondary testing of no difference between treatment groups was also conducted at a two-sided significant level of 0.025. Event rates were also compared using Cochran-Mantel Haenszel and Breslow Day tests stratified by centre and induction therapy. Kaplan-Meier survival analysis was used for time to event assessment. Sensitivity analyses were performed using central pathology biopsy readings.

The difference in the rates of graft loss/retransplant/death/loss to follow up or acute rejection endpoints used a non-inferiority margin of 10% (one-sided  $\alpha=0.0125$ ). The primary IVUS efficacy variable (change in average maximum intimal thickness from baseline to month 12) was compared between using a two-sample t-test at a two-sided 0.025 significance level. Renal function (cGFR by MDRD formula) was assessed on the ITT population with a non-inferiority margin of -10 mL/min/1.73 m<sup>2</sup> (lower limit of 97.5% CI higher than -10 mL/min).

### **7.2.1.9. Participant flow**

There were 721 patients randomised with 282, 168 and 271 in the EVR 1.5 mg, EVR 3.0 mg and MMF groups, respectively and consisting the ITT population. Study completion rates were 88.7%, 88.7% and 91.5% in the three groups, respectively. There was a moderately high rate of medication discontinuation 31.2%, 48.8% and 24.0% in the three groups, highest in the ceased EVR 3.0 mg group and higher with the EVR 1.5 mg than MMF regimen. Discontinuation due to AEs was higher with everolimus (24.1%, 21.4% vs 12.5%) and in the EVR 1.5 mg group was higher in patients  $\geq 50$  years than  $< 50$  years (30.5% vs 14.8%). The IVUS population consisted of 226 patients (88, 37 and 101 from the 3 groups, respectively).

### **7.2.1.10. Major protocol violations/deviations**

The rate of protocol deviations was 34.4%, 38.7% and 42.1% in the three groups, respectively. The major deviation leading to exclusion from the PP population was less than 6 months of study medication (25.2%, 41.7% and 18.5%). The PP population (n=498) included 70.9%, 53.6% and 76.8% of the three groups.

### **7.2.1.11. Baseline data**

Demographics and baseline characteristics were balanced between groups. The mean age was 50.3 years, 82% were Caucasian and 80% male. The main reason leading to transplantation was idiopathic cardiomyopathy (40.9%) followed by coronary artery disease (21.1%). The mean cold ischaemia time was 3.2 hours (range 0.8 to 7.5 hours) and 73% of patients had  $\geq 3$  HLA mismatches. Donor characteristics were also similar between groups.

### **7.2.1.12. Drug concentrations**

From months 3 and 12, between 79% and 85% of the EVR 1.5 mg group had everolimus trough levels within the target range. From month 1, the mean everolimus trough level in the 1.5 mg group ranged from 5.1 to 5.7 ng/mL and in the 3.0 mg group from 7.0 to 8.6 ng/mL. Cyclosporine trough levels within target range occurred in about 50% of patients but were variable and in the everolimus groups it was frequent to have CsA levels above target. In the EVR 1.5 mg group, mean CsA trough levels were below target in the first week and above target from month 3 onwards. In the MMF group, CsA levels were low in the first week but then within target.

### **7.2.1.13. Results for the primary efficacy outcome**

In the ITT population, the rate of the composite efficacy failure endpoint (BPAR ISHLT grade  $\geq 3A$ , AR with haemodynamic compromise, death, graft loss/retransplant or loss to follow up) at month 12 was 35.1%, 35.1% and 33.6% in the EVR 1.5 mg, EVR 3.0 mg and MMF groups, respectively. The difference in rates between the EVR 1.5 mg and MMF groups of 1.5% (97.5% CI: -7.5%, 10.6%) met the non-inferiority criteria as the upper bound of the 97.5% CI did not cross 13% ( $p=0.002$ ).

The PP analysis found efficacy failure rates were 23.0%, 24.4% and 26.9% and the difference between EVR 1.5 mg and MMF groups was -3.9% (97.5% CI: -13.5, 5.7%) and non-inferior ( $p<0.001$ ). When central pathology reading of biopsies was used in the composite endpoint the rates were 35.1%, 31.0% and 33.9% in the three groups, respectively, with non-inferiority of EVR 1.5 mg again demonstrated ( $p=0.001$ ). Analysis based on Kaplan Meier estimates also found non-inferiority of EVR 1.5 mg to MMF on the primary efficacy endpoint. At month 6, the rate of the composite efficacy failure endpoint was 29.4%, 29.8% and 26.6% in the three groups, respectively.

There was an evident higher death rate with everolimus treatment, particularly in the 3.0 mg dose group (7.8%, 10.1% vs 4.8% in the EVR 1.5 mg, EVR 3.0 mg and MMF groups, respectively). The mortality rate was also notable in patients receiving induction with

Thymoglobulin in the EVR 1.5 mg group (14.0% compared to 9.8% in EVR 3.0 mg and 7.2% in MMF).

#### **7.2.1.14. Results for other efficacy outcomes**

At month 12 in the ITT population, the rate of graft loss/retransplant/death/loss to follow up was 11.7%, 11.9% and 8.9% in the EVR 1.5 mg, EVR 3.0 mg and MMF groups, respectively with a difference of 2.8% between EVR 1.5 mg and MMR which was non-inferior (10% margin) (97.5% CI: -2.9%, 8.9%,  $p=0.002$ ). This was supported by the PP analysis (non-inferiority test  $p<0.001$ ), although the rates were low (1.0%, 2.2%, 1.4%).

The rate of BPAR of ISHLT grade  $\geq 3A$  (local pathology) in the ITT population was 22.3%, 25.6% and 24.7% in the EVR 1.5 mg, EVR 3.0 mg and MMF groups, respectively, with non-inferiority demonstrated between the EVR 1.5 mg and MMF groups ( $p<0.001$ ). Non-inferiority was also found on the PP population as well as the ITT population with central pathology assessment of biopsies.

When the composite efficacy failure endpoint was examined by subgroup of time-normalised everolimus trough levels it was found that the highest rates for the EVR 1.5 mg were in patients with levels  $<3$  ng/mL (38.1%) and  $>8$  ng/mL (39.3%) and in the EVR 3.0 mg group in patients with trough levels  $>12$  ng/mL (61.5%).

**Comment:** It is noted that the numbers in some of these analyses were small.

Subgroup analysis of the composite efficacy failure rate found similar results for age and gender although the death rate in the EVR 1.5 mg group was higher in patients  $\geq 50$  years (10.8% vs 3.5%  $<50$  years) and males (8.9% vs 3.5% females). Findings for other subgroups (diabetes at baseline, hypertension and hyperlipidaemia history, HLA mismatch, gender mismatch, baseline CMV serology, ventricular assist device) were also consistent with the overall population.

In the IVUS subset, the mean change in average maximum intimal thickness from baseline to month 12 was 0.03, 0.04 and 0.07mm in the EVR 1.5 mg, EVR 3.0 mg and MMF groups, respectively. The difference between the EVR 1.5 mg and MMF groups was significant ( $p<0.001$ ). Per protocol analysis was also significant. Cardiac allograft vasculopathy (CAV) rates were 12.5%, 21.6% and 26.7% in the three groups, respectively, with higher rates in those with allografts from donors with donor disease. Results were consistent across subgroups of age, gender, diabetes, use of statins, and cholesterol and triglyceride levels. After adjustment for donor age and baseline LDL level, the risk of CAV was lower with everolimus 1.5 mg than MMF (odds ratio 0.26,  $p=0.003$ ).

#### **7.2.1.15. Results for renal function**

The mean baseline eGFR (MDRD) was 66.45 and 67.10 mL/min/1.73 m<sup>2</sup> in the EVR 1.5 mg and MMF groups, respectively which was not statistically different. In the ITT population with LOCF, the mean eGFR at month 12 was 58.83 and 64.37 mL/min/1.73 m<sup>2</sup> in the EVR 1.5 mg and MMF groups, respectively. The difference in means of -5.55 mL/min/1.73 m<sup>2</sup> (97.5% CI: -10.9, -0.2) did not meet the non-inferiority criteria as the lower bound of the CI was less than -10 mL/min. In addition, the eGFR in the everolimus group was significantly lower than the control MMF group ( $p=0.019$ ). Non-inferiority was found on the PP analysis (difference -3.98 mL/min/1.73 m<sup>2</sup>, 97.5% CI: -9.1, 1.2), while sensitivity analyses supported the ITT population findings. A further analysis using an ANCOVA model with LOCF (adjusting for baseline GFR, diabetes and post-operative acute renal failure) found the LS mean difference of -3.35 (95% CI -6.65, -0.06). The difference in cGFR between the groups was evident from day 4 though the study to month 12. The mean change from baseline to month 12 endpoint was greater though not significant with EVR 1.5 mg (-7.12 vs -2.89 mL/min/1.73 m<sup>2</sup>,  $p=0.211$ ), while the change from month 1 to month 12 was worse in the MMF group (-6.37 vs -13.66,  $p=0.002$ ).

The mean change in serum creatinine is consistent with eGFR results. The mean CrCl at month 12 was lower with EVR 1.5 mg (74.0 vs 81.1 mL/min,  $p=0.02$ ). There was also a higher mean

urinary protein/creatinine ratio from month 3 to 12, and statistically significantly higher from month 6 to 12, in the everolimus group.

As the results on GFR were unexpected, the sponsor conducted post-hoc analyses to assess the influence of CsA exposure, baseline characteristics and centre effects on the results. When eGFR was assessed by time-normalised CsA exposure (below, within, above target) there was some improvement in GFR in those with a below target CsA exposure in the MMF group, however this was not evident in the EVR 1.5 mg group. For those within target CsA level, the mean difference in eGFR was -3.2 (97.5% CI: -8.7, 2.2). Subgroups within the CsA target level groups were assessed and it was found in the below target group the EVR 1.5 mg group was slightly older (54 vs 49) and had more hypertension (44% vs 37%) than the MMF group. Despite this, the baseline eGFR was similar. It was found that 10 of the 63 centres did not achieve a clear separation in CsA exposure between the EVR and MMF groups. In the 10 centres with no reported difference between groups in CsA exposure ("non-compliant"), there was a mean difference in eGFR of -17.2 (97.5% CI: -37.2, 2.8), while at the other 53 centres, the mean difference was -3.6 (97.5% CI: -8.9, 1.8).

#### **7.2.1.16. Summary**

A2310 was a non-inferiority study which compared everolimus 1.5 mg/d + reduced CsA and everolimus 3.0 mg/d+reduced CsA with MMF + standard dose CsA in 721 *de novo* cardiac transplant recipients. The EVR 3.0 mg group was terminated prematurely due to a higher mortality rate. The primary endpoint of BPAR of ISHLT grade  $\geq 3A/AR$  associated with haemodynamic compromise/graft loss or re-transplant/death/loss to follow-up was 35.1% and 33.6% in the EVR 1.5 mg and MMF groups, respectively, with a difference of 1.5% (97.5% CI: -7.5%, 10.6%) which met the non-inferiority criteria of 13%. Results were supported by PP and sensitivity analyses.

There was an evident higher death rate with everolimus treatment, particularly 3.0 mg (7.8%, 10.1% vs 4.8% in the EVR 1.5 mg, EVR 3.0 mg and MMF groups, respectively). Patients who received induction with Thymoglobulin and everolimus 1.5 mg had a notably high mortality rate at 14%. An IVUS substudy found the change in average maximum intimal thickness was less in the everolimus than MMF groups, as was the rate of cardiac allograft vasculopathy.

At month 12, the study found that non-inferiority on estimated GFR was not demonstrated (NI margin of -10 mL/min/1.73m<sup>2</sup>) between the everolimus+reduced CsA and MMF+standard CsA groups. The decline in renal function was more marked in the first month. The poorer renal function results with everolimus were also seen for creatinine, CrCl and urinary protein/creatinine ratio. A post-hoc analyses suggested that non-compliance to the specified low CsA dose at certain study centres may have had an influence on the results.

Safety and the imbalance in mortality is discussed in the section on *Safety*, below.

### **7.3. Renal transplantation**

#### **7.3.1. Other efficacy studies A2309**

##### **7.3.1.1. Design, objectives, locations and dates**

Study A2309 was very similar in design to A2310. It was a 24 month, phase III, multicentre, randomised, open-label, parallel group, non-inferiority efficacy and safety study comparing two exposures of concentration-controlled everolimus with reduced cyclosporine versus Myfortic with standard dose cyclosporine in 833 *de novo* renal transplant patients. Like A2310, the dossier included the interim 12 month analysis report. The study commenced in October 2005 and the data cut-off date was September 2008. It was conducted at 63 centres in Europe, North



America, Asia, Australia and South Africa.<sup>9</sup> There was a central laboratory, central pathology for biopsies and a DSMB.

The primary objective was to demonstrate that at least one everolimus + reduced cyclosporine regimen was not inferior to enteric-coated mycophenolate sodium (Myfortic) + standard dose cyclosporine with respect to efficacy failure (tBPAR/graft loss/death/loss to follow-up) within 12 months of treatment. All patients received induction with basiliximab.

The main secondary objective was to assess incidence rate of graft loss/death/loss to follow-up at 12 months. The main safety objective was to assess non-inferiority of renal function (eGFR by MDRD formula) between the groups at 12 months.

There were 3 protocol amendments. Amendment 3 revised the inclusion/exclusion criteria regarding pregnancy testing and prevention due to published risks with mycophenolate-based immunosuppression and foetal malformations.

### **7.3.1.2. Inclusion and exclusion criteria**

Inclusion criteria were: males or females; 18-70 years of age; undergoing primary kidney transplantation; and with a functional graft at randomisation. Women needed a negative pregnancy test prior to randomisation and, if of child bearing potential, to be using effective contraception.

The main exclusion criteria were: no graft function at 24 hours post transplantation; kidney from HLA identical living related donor or from non-heart beating donor; donor >65 years; donor organ cold ischemic time >40 minutes; platelets <100,000/m<sup>3</sup>; ANC ≤1500/m<sup>3</sup> or WBC ≤4000/m<sup>3</sup>; recipients of dual kidney transplants or had previously received organ transplants; severe hypercholesterolemia (≥350 mg/dL; ≥9 mmol/L) or hypertriglyceridemia (≥500 mg/dL; ≥8.5 mmol/L); abnormal LFTs >3x ULN; anti-HLA class I panel reactive antibodies >20% by CDC assay or >50% by ELISA assay; ABO incompatible transplants; HIV or HCV or HBsAg positive; malignancy within 5 years; cardiac failure or severe cardiac disease; uncontrolled diabetes; and significant infection.

### **7.3.1.3. Study treatments**

The three study treatment groups were:

- Group 1: everolimus 1.5 mg (0.75 mg bid) + basiliximab + cyclosporine reduced dose bid ± steroids.
- Group 2: everolimus 3.0 mg (1.5 mg bid) + basiliximab + cyclosporine reduced dose bid ± steroids.
- Group 3: Myfortic (enteric coated mycophenolate sodium, MPS) 1.44 g (2x 360 mg bid) + basiliximab + cyclosporine standard dose bid ± steroids.

Treatment was planned for 24 months. Basiliximab (2 x 20 mg IV) was given 2 hours prior to transplantation and again on day 4 post transplant or according to local practice. TDM of trough levels of everolimus (EVR) and cyclosporine (CsA) was undertaken. The target levels for everolimus were the same as A2310, 3-8 ng/mL in the everolimus 1.5 mg bid and 6-12 ng/mL in the 3.0 mg bid treatment groups. Myfortic was given at the current standard dose.

Cyclosporine trough levels in the Myfortic group were 200-300 ng/mL from day 5 and 100-250 ng/mL from month 2 onwards. In the EVR groups, the CsA levels were 100-200 ng/mL from day 5, 75-100 ng/mL from month 2, 50-100 ng/mL from month 4 and 25-50 ng/mL from month 6 onwards.

**Comment:** These are lower CsA levels than in A2310.

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<sup>9</sup> Erratum: This Study was conducted at 79 centres in Europe, North and Latin America, Asia, and South Africa

Prophylaxis medication was as in A2310 except that HMG CoA reductase inhibitors were given as per local practice.

#### **7.3.1.4. Efficacy variable and outcomes**

Biopsy-proven acute rejection was diagnosed from renal biopsies performed at baseline and then month 12 (at selected sites), for all suspected rejection episodes, for proteinuria >0.5 g/day, or for renal function <50 mL/min/1.73 m<sup>2</sup> by MDRD. The biopsy was to be performed within 48 hours of the rejection episode and was assessed by local and central pathologists. Treated BPAR was defined as a biopsy graded IA, IB, IIA, IIB or III (Banff criteria) from local pathology which was treated with anti-rejection therapy. Graft loss was when dialysis started and was not subsequently ceased or retransplant occurred. Renal function was assessed by eGFR using MDRD and Nankivell formulas.

#### **7.3.1.5. Randomisation and blinding methods**

Patients were randomised to one of 3 groups in a 1:1:1 ratio within 24 hours after transplantation by an IVRS. The study was open label, the pathologists were reported to be blinded to treatment.

#### **7.3.1.6. Analysis populations**

Analysis was based on the ITT population (all randomised patients) with supportive analyses on the PP population (all patients who received basiliximab, completed at least 6 months of study medication, had at least one post baseline safety assessment and without major protocol deviations). Major deviations were multiple or previous transplants, cold ischaemia time >40 hours, donor age >65 years. Secondary efficacy analyses were on the ITT population.

#### **7.3.1.7. Sample size**

Sample size calculations were based on an estimated primary efficacy failure rate at 12 months of 20% in the MPS group and 19% in the EVR group (-1% difference), a non-inferiority margin of 10% and a two sided type I error rate of 2.5%. 275 patients per group gave the study an 84% power.

#### **7.3.1.8. Statistical methods**

Statistical methods were similar to A2310 except that there were 2 comparison group (EVR 1.5 mg vs MPS and EVR 3.0 mg vs MPS). Controlling for multiple comparison used the Bonferoni method. The non-inferiority margin for the primary composite efficacy endpoint was 10% (compared to 13% in A2310). For the justification of the choice of the 10% NI margin, the sponsor conducted a meta-analysis of historical trials to estimate the efficacy failure rate of Myfortic with basiliximab and standard dose CsA ( $\pm$  steroids) which was the putative placebo. The effect estimate was 26.4% with a 95% CI of 18.9% to 30.2%. The NI margin of 10% was chosen to represent a 50% preservation of the estimated control effect. The non-inferiority margin for renal function (eGFR by MDRD formula) was -8 mL/min/1.73 m<sup>2</sup>.

**Comment:** The NI margin for renal function in the previously evaluated renal<sup>10</sup> transplant study A2411 was -6 mL while in A2310 was -10 mL/min/1.73 m<sup>2</sup>.

#### **7.3.1.9. Participant flow**

There were 833 patients randomised with 277, 279 and 277 in the EVR 1.5 mg, EVR 3.0 mg and MPS groups, respectively. All were included in the ITT population. Study completion rates (to month 12) were 86.3%, 88.2% and 89.9% in the three groups, respectively. There was a higher rate of medication discontinuation with everolimus (30.0%, 34.1% vs 21.7%) with the highest in the EVR 3.0 mg group. Discontinuation due to AEs was higher with everolimus (18.1%, 20.4% vs 9.4%).

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<sup>10</sup> Erratum: studies A2411 and A2310 were both heart transplant studies.

### **7.3.1.10. Major protocol violations/deviations**

The rate major deviations leading to exclusion from the PP population was 22.4%, 26.5% and 17.0% of the three groups, respectively. The most common reason for exclusion from the PP population was having study treatment for <6 months (22.0%, 25.1% and 15.5%). The PP population included 650 (78%) patients.

### **7.3.1.11. Baseline data**

Demographics and baseline characteristics were balanced between groups. The mean age was 46.1 years, 66-70% were Caucasian and 63.5-68.5% male. The main reasons leading to transplantation were hypertension/nephrosclerosis, glomerulonephritis/glomerular disease and diabetes mellitus. There were slightly more patients in the EVR 1.5 mg group with  $\geq 3$  HLA mismatches (75.8%, 69.5% and 72.9%). Donor characteristics were also similar between groups, with the rate of living donor organs 53.0%, 54.1% and 53.5% in the EVR 1.5 mg, EVR 3.0 mg and MPS groups, respectively. Medical histories were similar between groups.

### **7.3.1.12. Drug concentrations**

From month 1 to 12, between 76-85% of the EVR 1.5 mg group had everolimus trough levels within the target range. Levels within target for lower for the EVR 3.0 mg group over the same period (60-69%) with more patients in the below target group (18-31%). Mean cyclosporine levels were lower in the EVR groups than the control group (as expected by the protocol) although they tended to be at the upper limit of the range for the everolimus groups and within range for the control groups.

### **7.3.1.13. Results for the primary efficacy outcome**

In the ITT population, the rate of the composite efficacy failure endpoint (tBPAR/GL/D/Loss to follow up) at 12 months was 25.3%, 21.5% and 24.2% in the EVR 1.5 mg, EVR 3.0 mg and MPS groups, respectively. The difference in rates between the EVR 1.5 mg and MPS groups was 1.1% (97.5% CI: -7.1%, 9.3%) and between the EVR 3.0 mg and MPS groups was -2.7% (97.5% CI: -10.7%, 5.3%). These both met the non-inferiority criteria as the upper bound of the 97.5% CI was below 10% ( $p \leq 0.007$ ). The Kaplan Meier plot shows similar trajectories of the curves.

In the PP population, the efficacy failure rates were 15.8%, 12.2% and 15.7% in the three groups respectively and both comparisons were non-inferior. The difference between EVR 1.5 mg and MPS was -0.2% (97.5% CI: -7.6%, 7.9%,  $p=0.002$ ) and between EVR 3.0 mg and MPS was -3.5% (97.5% CI: -10.9%, 4.0%,  $p < 0.001$ ). Sensitivity analysis using central pathology readings of biopsies confirmed non-inferiority for both groups.

### **7.3.1.14. Results for other efficacy outcomes**

At month 12 in the ITT population, the rate of graft loss/death/loss to follow up was 10.8%, 10.0% and 8.7% in the EVR 1.5 mg, EVR 3.0 mg and MPS groups, respectively. These results were also statistically non-inferior for both between group comparisons. The death rate in the 3 groups was 2.5%, 3.2% and 2.2%, respectively. Results at 6 months for the composite efficacy endpoint were also non-inferior for both EVR groups. Non-inferiority was also demonstrated with the PP population.

Non-inferiority was also found on the rates of tBPAR in the ITT population by local pathologist assessment (16.2%, 13.3% vs 17.0%) and by central pathologist assessment (7.2%, 5.0% vs 7.2%). Only 55.3% of biopsies were read centrally and concordance between local and central readings was not high (0.48, 0.47 and 0.48 kappa coefficients) although the coefficients were similar between groups.

Subgroup analysis found that females had lower efficacy failure than males. Within the group of female patients, efficacy failure was higher with everolimus than MPS (19.0%, 22.7% vs 12.5%) and the comparison between EVR 3.0 mg and MPS was significant ( $p=0.01$ ). Efficacy failure rates were somewhat higher in patients <50 years than  $\geq 50$ , in Blacks compared to non-Blacks



(although the number of Black patients was small) and in those with delayed graft function. Results for HLA mismatches (<3 or ≥3) were variable between groups. Donor subgroup analysis of efficacy failure was not remarkable. There were very few Black donors where a higher failure rate was noted.

Efficacy in terms of tBPAR, GL and death was assessed by everolimus trough levels (both dose groups combined). With increasing trough levels, there was a trend for reduced tBPAR, but not for graft loss. By contrast, the death rate appeared to increase with increasing levels (Table 4).

**Table 4. Study A2309. Efficacy events by average everolimus C<sub>min</sub> in combined everolimus dose groups – PK/efficacy population**

Everolimus C <sub>min</sub> *	Treated BPAR	Graft Loss	Death
<b>RAD001</b>	<b>79/547 (14.4%)</b>	<b>22/546 (4.0%)</b>	<b>15/549 (2.7%)</b>
<3 ng/mL	6/33 (18.2%)	4/35 (11.4%)	1/37 (2.7%)
3 – <4 ng/mL	13/76 (17.1%)	7/74 (9.5%)	4/73 (5.5%)
4 – <5 ng/mL	16/109 (14.7%)	5/111 (4.5%)	2/110 (1.8%)
5 – <6 ng/mL	16/92 (17.4%)	1/87 (1.1%)	1/89 (1.1%)
6 – <7 ng/mL	10/73 (13.7%)	1/74 (1.4%)	1/75 (1.3%)
7 – <8 ng/mL	9/65 (13.8%)	1/64 (1.6%)	1/64 (1.6%)
8 – <9 ng/mL	2/45 (4.4%)	0/46 (0.0%)	2/47 (4.3%)
9 – <10 ng/mL	5/22 (22.7%)	1/23 (4.3%)	1/22 (4.5%)
10 – <11 ng/mL	1/13 (7.7%)	2/14 (14.3%)	0/13 (0.0%)
11 – <12 ng/mL	1/6 (16.7%)	0/6 (0.0%)	0/6 (0.0%)
12 – <13 ng/mL	0/3 (0.0%)	0/3 (0.0%)	0/3 (0.0%)
≥13 ng/mL	0/10 (0.0%)	0/9 (0.0%)	2/10 (20.0%)
3 – <6 ng/mL	45/277 (16.2%)	13/272 (4.8%)	7/272 (2.6%)
6 – <8 ng/mL	19/138 (13.8%)	2/138 (1.4%)	2/139 (1.4%)
8 – <12 ng/mL	9/86 (10.5%)	3/89 (3.4%)	3/88 (3.4%)
≥12 ng/mL	0/13 (0.0%)	0/12 (0.0%)	2/13 (15.4%)
<b>Myfortic</b>	<b>47/277 (17.0%)</b>	<b>9/277 (3.2%)</b>	<b>6/277 (2.2%)</b>

\* Average trough levels calculated up to event or censored at cut-off day

### 7.3.1.15. Results for renal function

In the ITT population, the mean eGFR (MDRD formula) at month 12 was 54.6, 51.3 and 52.2 mL/min/1.73 m<sup>2</sup> in the EVR 1.5 mg, EVR 3.0 mg and MPS groups, respectively. The difference in means of 2.37 mL/min/1.73 m<sup>2</sup> (97.5% CI: -2.3, 7.0) for EVR 1.5 mg and -0.89 mL/min/1.73 m<sup>2</sup> (97.5% CI: -5.6, 3.8) for EVR 3.0 mg were both statistically non-inferior to the control MPS group (p<0.001 for both) as the lower limit of the 97.5% CI was higher than -8. The gain in renal function was evident by month one and maintained to month 12. The renal function was generally higher in the EVR 1.5 mg group compared to the EVR 3.0 mg and MPS groups by 3-4 mL/min/1.73 m<sup>2</sup> which was significant at months 1, 6, 7, 9 and 12. At month 12, the proportion of patients with eGFR 30-<60 mL/min/1.73 m<sup>2</sup> was 56.7%, 64.3% and 65.6%, and with eGFR ≥60 mL/min/1.73 m<sup>2</sup> was 41.6%, 33.6% and 31.5% in the EVR 1.5 mg, EVR 3.0 mg and MPS groups, respectively. These results were supported by results of GFR calculated using the Nankivell formula, serum creatinine and creatinine clearance (using Cockcroft-Gault formula). An analysis of renal function impairment (using multiple methods) by pooled treatment group everolimus trough levels did not find an increase in impairment with increased trough level exposure. Regression analysis found that having a grafts from a cadaveric donors was a significant risk factor for GFR <30 mL/min/1.73 m<sup>2</sup> at month 12 (p=0.036).

### 7.3.1.16. Summary

A2309 was a non-inferiority study which compared everolimus 1.5 mg/d + reduced CsA and everolimus 3.0 mg/d+reduced CsA with mycophenolate sodium + standard dose CsA in 833 de novo renal transplant recipients. The primary endpoint of tBPAR/graft loss/death/loss to follow-up at 12 months was 25.3%, 21.5% and 24.2% in the EVR 1.5 mg, EVR3.0 mg and MPS groups. The difference in rates between the EVR 1.5 mg and MPS groups was 1.1% (97.5% CI:

-7.1%, 9.3%) and between the EVR 3.0 mg and MPS groups was -2.7% (97.5% CI: -10.7%, 5.3%) with both meeting the non-inferiority criteria of 10% ( $p \leq 0.007$ ). Results were supported by PP analyses. Non-inferiority was also found on the efficacy endpoint of graft loss/death/loss to follow up and also at on analyses at 6 months. Subgroup analysis suggested a greater efficacy failure in females treated with everolimus 3.0 mg than MPS.

In contrast to A2310, renal function (assessed using eGFR by MDRD formula) at month 12 was non-inferior in both everolimus dose groups compared to the mycophenolate control group.

## 8. Clinical safety

### 8.1. Studies providing evaluable safety data

For the hepatic transplantation indication the safety data comes primarily from the pivotal study H2304. There was no pooling of safety data for this indication. A comparison of data from this study and the renal transplant study A2309 was also provided. H2304 extension study H2304E1 provided data on SAEs and deaths to the cut-off of 31 May 2011.

#### *Pivotal efficacy studies – Hepatic transplantation*

In the pivotal efficacy Study H2304, the following safety data were collected:

- General adverse events (AEs) were assessed by history, physical examination and vital signs. Events not considered SAEs were hospitalisation for routine monitoring or treatment not associated with deterioration and hospitalisation for acute rejection. However, unusually severe rejection episodes (e.g. requiring antibody therapy) and graft losses were an SAE.
- AEs of particular interest including infections, malignancies, wound healing complications, cardiac events, gastrointestinal ulcers, stomatitis/mouth ulceration, proteinuria, peripheral oedema, angioedema, fluid collection, new onset diabetes mellitus, haematological events, hyperlipidaemia, thrombotic and thromboembolic events and interstitial lung disease.
- Laboratory tests were performed at a central facility and included: haematology, biochemistry, viral serology for CMV, HIV, EBV, HBV and HCV; HCV viral load for HCV positive patients; and testosterone, FSH, LH for all males. Samples were collected after overnight fasting. Spot urinalysis was also conducted.
- Renal function was assessed by serum creatinine, Cystatin C and by estimated GFR using various formulae (MDRD-4/6, Nankivell, Cockcroft-Gault and Hoek formulae). Proteinuria was determined by a spot urine protein/creatinine ratio.
- New onset diabetes mellitus (NODM) was defined by any one of:
  - Two consecutive fasting plasma glucose  $\geq 126$  mg/dL (7.0 mmol/L) after day 30 post-transplantation.
  - HbA1c  $\geq 6.5$  % from Day 75 onward.
  - Diabetes reported as an AE that was prevalent after day 30.
  - Any concomitant medication with ATC level 2 code “A10” drugs used in diabetes, if prevalent after day 30 and used for more than 30 days.

#### *Studies that assessed safety as a primary outcome*

Studies HDE10 and H2401 were studies that assessed safety, in terms of renal function, as a primary outcome. These studies are described below under *Studies that assessed safety as a primary outcome* and also provided supportive safety data in liver transplant recipients.

### ***Dose-response and non-pivotal efficacy studies***

The dose-response and non-pivotal efficacy studies provided safety data, as follows:

- Study B158 with extensions B158E1 and B158E2 (fixed dose everolimus with standard dose CsA) provided long term data.
- Study H2301 was in recurrent hepatitis C patients and was prematurely discontinued. Deaths and SAEs were reported.

### ***Other studies evaluable for safety only***

Clinical pharmacology studies X2102 and X2103 provided little safety data. Studies not included in the dossier were B202 (single dose PK in liver transplant), A2303 (single dose PK in moderate hepatic impairment) and B258 (single dose PK in paediatric liver transplant patients)

### ***Cardiac transplant study A2310 and renal transplant study A2309***

The primary safety variable was renal function measured by calculated GFR using MDRD formula in both studies (Nankivell was also used in A2309), calculated creatinine clearance (Cockcroft-Gault formula) in A2310 and serum creatinine in both. Mid-stream spot urine was analysed for protein/creatinine ratio to assess proteinuria. Collection of AEs and SAEs together with monitoring of haematology, blood chemistry, urine, vital signs and physical examination were all undertaken. ECGs were conducted in A2310. Infections, severe rejection episodes, major cardiac events, wound healing events and other events of special interest were also assessed in both studies.

## **8.2. Studies that assessed safety as a primary outcome**

### **8.2.1. Study HDE10**

#### ***8.2.1.1. Study design, objectives, locations and dates***

Study HDE10 was a 12 month, phase III, multicentre, randomised, open label, parallel group study of the safety, tolerability and efficacy of an everolimus-based regimen compared to a calcineurin inhibitor (CNI)-based regimen in 203 patients with de novo liver transplantation. It was also known by the name "PROTECT". It was conducted between August 2006 and March 2010 at 16 sites in Western Europe. A DSMB reviewed data during the study. The CSR in the dossier was for the first year of data and the study protocol was amended to continue treatment for 5 years. Patients prematurely discontinuing study treatment were still to be followed up.

The primary objective was to demonstrate, at 11 months post-randomisation, superiority of renal function with the everolimus-based regimen and discontinuation of CNI therapy compared to a CNI-based regimen.

#### ***8.2.1.2. Inclusion and exclusion criteria***

Inclusion criteria were: male and female adult liver transplant recipients (allograft, living or cadaveric donor); 18 to 70 years of age; rejection-free period for at least 2 weeks prior to randomisation; platelet count  $\geq 50$  g/L, WBC  $\geq 2.5$  g/L and haemoglobin  $\geq 8$  g/dL; no severe hypercholesterolemia ( $\geq 9$  mmol/L) or hypertriglyceridemia ( $\geq 8.5$  mmol/L) in spite of lipid-lowering therapy; and cGFR  $> 50$  mL/min.

Exclusion criteria were: previous transplant; antiviral treatment for HCV; HIV positive; current severe infection; pre-existing renal dysfunction; prior basiliximab therapy; immunosuppressives within 2 months; and breast feeding or not using effective contraception.

#### ***8.2.1.3. Study treatments***

The study design and treatment are shown above under the section on *Efficacy*. Subjects were randomised at 4 weeks post-transplantation to either CNI treatment or everolimus with tapered

CNI treatment. The CNI treatment was cyclosporine or tacrolimus. CNI treatment was given according to local practice prior to randomisation in both groups and then post-randomisation in the CNI group. Everolimus treatment commenced at 1.5 mg bid (0.5 mg and 0.75 mg tablets) and the target trough level was 5-12 ng/mL. CNI dose reduction by 70% commenced when EVR trough levels were >5 ng/mL and the CNI was to be completely discontinued by 8 weeks (and at the latest by 16 weeks) post-randomisation. All subjects received 2 doses of basiliximab 20 mg (at transplantation and at day 4) and optional steroids according to local practice. For patients with hepatic impairment, if two of the following were present - bilirubin >34 µmol/L, albumin <35 g/L or prothrombin time >1.3 INR - then the dose of everolimus was to be halved.

#### **8.2.1.4. Safety variables and outcomes**

The primary variable was GFR calculated using the Cockcroft-Gault formula at 11 months post randomisation. Secondary endpoints were: renal function at 5 months, renal function at 11 months using MDRD formula to calculate GFR; the composite of BPAR/graft loss/death/loss to follow up; rate of need to change immunosuppressive regimen; tBPAR; patient and graft survival; HCV replication in HCV positive patients; and safety.

#### **8.2.1.5. Randomisation and blinding methods**

The study was open label. Patients were randomised centrally in a 1:1 ratio.

#### **8.2.1.6. Analysis populations**

The primary safety endpoint was analysed in the ITT population with last observation carried forward (LOCF). The ITT population was defined as all randomised patients with at least one post-randomisation measurement of renal function (cGFR).

#### **8.2.1.7. Sample size**

For sample size calculations, a mean treatment difference between groups in cGFR of 8 mL/min was assumed. With a standard deviation of 17 mL/min, a sample of 100 patients per group gave the study a 91% power (two-sided  $\alpha=0.05$ ).

#### **8.2.1.8. Statistical methods**

The assessment of superiority of everolimus to CNI treatment in cGFR levels after 11 months was analysed using an ANOVA model with treatment and centre as factors and cGFR at baseline as a covariate. Adjusted least squares (LS) mean of the cGFR were presented. There was no adjustment for multiplicity. Efficacy failure rates were compared using Fisher's exact test.

#### **8.2.1.9. Participant flow**

Of the 383 patients screened, 203 were randomised, 101 to everolimus and 102 to CNI treatment groups. One site included 54 of the randomised patients. While 86.1% and 88.2% of the EVR and CNI groups, respectively, completed the study, the treatment discontinuation rate was high, and more so in the everolimus group (49.5% vs 38.2%). The main reason for discontinuation of study drug was adverse events (27.% vs 15.7%).

The ITT population consisted of 95% (n=96) of the everolimus group and 96% (n=98) of the CNI group, while there was only 48 (47.5%) and 58 (56.9%) patients respectively in the PP population.

#### **8.2.1.10. Major protocol violations/deviations**

The rate of major protocol deviations was high (45.5% vs 33.3%), with the main deviation relating to missing 11 month cGFR value.

#### **8.2.1.11. Baseline data**

Treatment groups were balanced on age, BMI and race. The mean age was 52.6 years and 95% were Caucasian. There were fewer males in the everolimus group (56% vs 69%). The main

reason for liver transplantation was alcoholic cirrhosis (32.0%) hepatitis B (8.2%), hepatitis C (7.7%), sclerosing cholangitis (6.7%) and cryptogenic cirrhosis (5.7%). MELD score and HLA mismatches were similar between groups. The mean time from transplantation to randomisation was 43.1 and 42.5 days in the EVR and CNI groups, respectively, with a range of 25 to 73 days. Characteristics of the transplant, viral serology, transplant type and procedure were similar between groups. Most transplants were whole livers (90.2%) from heart beating cadavers (94.8%). Baseline medical conditions were similar between groups. During the study the everolimus group had higher use of ciprofloxacin (30.7% vs 23.5%) and fluvastatin (21.8% vs 3.9%) and simvastatin (10.9% vs 2.0%). Renal function at baseline was similar between groups with a mean cGFR of 83.5 mL/min and 82.2 mL/min by Cockcroft-Gault in the EVR and CNI groups, respectively.

#### **8.2.1.12. Drug concentrations**

The mean daily everolimus dose was 4.4 mg (range 1.4 to 9.9 mg). The mean trough level of everolimus ranged from 6.0 ng/mL at week 2 to 9.3 ng/mL at month 7. In the control group, the mean trough levels of tacrolimus and cyclosporine at month 11 were 8.0 ng/mL and 140 ng/mL, respectively.

#### **8.2.1.13. Results for the primary safety outcome**

The study did not meet its primary endpoint. At month 11 post randomisation in the ITT population with LOCF, the LS mean cGFR was 89.89 mL/min in the EVR group and 86.97 mL/min in the CNI group. The LS mean difference of -2.92 mL/min (95% CI: -10.66, 4.81) was not statistically significant ( $p=0.46$ ). Over the course of the study there was a small divergence in mean cGFR between groups which commenced at week 4 when CNI reduction commenced. At month 5 post baseline, the LS mean difference in cGFR was -5.10 mL/min (95% CI: -11.62, 1.42) which was also not significant ( $p=0.124$ ). In the PP population the between group difference at month 11 in cGFR was slightly more in favour of everolimus (-8.36, 95% CI: -17.29, 0.57) though still not significant ( $p=0.066$ ).

#### **8.2.1.14. Results for other safety outcomes**

In the ITT population, secondary analyses of GFR calculated by five other methods was conducted. The differences in cGFR at month 11 were: -7.78 mL/min,  $p=0.021$  with MDRD; -5.48 mL/min,  $p=0.105$  with MDRD-4; -5.57 mL/min,  $p=0.057$  with CKD-EPI; -5.08 mL/min,  $p=0.078$  with Nankivell; and -6.85 mL/min,  $p=0.033$  with MCQ (Mayo clinic quadratic equation). It should be noted that there was no adjustment for multiplicity and that there was some baseline differences in GFR by other methods, such as by MDRD (78.0 vs 74.9 mL/min). Other safety results are discussed below.

#### **8.2.1.15. Summary**

HDE10 assessed the effect on renal function of an everolimus-based regimen compared to a calcineurin inhibitor (CNI)-based regimen in 203 patients with de novo liver transplantation. The study did not meet its primary endpoint. After 11 months of treatment, there was little change in the cGFR (Cockcroft-Gault) in the everolimus group or CNI group (LS mean change 4.4 mL/min vs 0.9 mL/min). The LS mean difference of -2.92 mL/min (95% CI: -10.66, 4.81) was not significant ( $p=0.46$ ). The study had assumed a treatment difference of 8 mL/min which was greater than that found. Secondary analyses of the PP population and using different methods for calculating the GFR also found negative results. There was no significant difference between treatment regimens on clinical outcomes (BPAR/GL/D/loss to follow up).

### **8.2.2. Study H2401**

#### **8.2.2.1. Study design, objectives, locations and dates**

H2401 was a phase III, six month, multicentre, randomised, open-label study of the safety and efficacy of everolimus-based regimen compared to a CNI-based regimen in maintenance liver



transplant recipients with CNI-related renal impairment. It was also known as RESCUE. It was conducted between November 2005 and April 2007 at 29 centres in Europe and Argentina. There was an independent DSMB which reviewed efficacy and safety data each 3 months. There was a central laboratory and liver biopsy assessment was undertaken by local pathology. Patients were screened between 12 and 60 months post-transplantation and stratified by baseline GFR (20-≤40 mL/min or 40-60 mL/min). The primary analysis was at 6 months and patients were followed up to 12 months. The 12 month data in the dossier consisted of a synopsis and tables.

The primary objective was to determine whether everolimus together with reduction or discontinuation of calcineurin inhibitor (CNI) in maintenance liver transplant patients with CNI-related renal impairment would improve renal function.

#### **8.2.2.2. Inclusion and exclusion criteria**

Inclusion criteria were: male or females; aged 18 to 70 years; primary liver transplantation from a cadaveric or living donor 12 to 60 months before the start of the study; and a cGFR between 20 and 60 mL/min. Patients were to have been receiving tacrolimus with a trough (C<sub>0</sub>) level ≥3 and ≤8ng/mL, or cyclosporine with a trough level ≥50 and ≤150 ng/mL or with 2 hour post dose level ≥250 ng/mL and ≤650 ng/mL, with or without any of MPA, AZA or steroids.

Exclusion criteria were: multiple solid organ transplants; on dialysis; other cause of renal dysfunction; proteinuria ≥1.0 g/dL; acute rejection within past 6 months; platelets ≤50,000/mm<sup>3</sup> or WBC count ≤2,000/mm<sup>3</sup> or haemoglobin ≤8 g/dL; severe graft dysfunction; antiviral treatment for HCV; HIV positive; breast feeding; current severe systemic infection; signs of recurrent hepatocellular carcinoma; and use of immunosuppressives other than those required by the protocol.

#### **8.2.2.3. Study treatments**

In the everolimus group treatment was everolimus 1.5 mg bid + reduced CNI dose ± steroids. In this group, CNI dose was reduced by 50% when everolimus commenced and then by another 50% of the current dose at subsequent visits if cGFR was <baseline cGFR+10 mL/min. MPA and AZA were discontinued on day 1 and steroids maintained unchanged.

In the control group treatment was standard CNI dose±mycophenolate acid (MPA)/azathioprine (AZA)±steroids. The CNI dose was continued as given prior randomisation and the dose was not to be reduced by more than 25% of the baseline dose. MPA/AZA and steroids were maintained at the same dose through the study

Open label everolimus treatment commenced at 1.5 mg bid and the dose was adjusted to maintain a target trough level of 3-8 ng/mL with concomitant tacrolimus or cyclosporine and then to 6-12 ng/mL when these medications were ceased. Dose reduction was allowed for AEs if trough level remained ≥3 ng/mL.

#### **8.2.2.4. Safety variables and outcomes**

The primary variable was renal function which was assessed on the creatinine clearance (CrCl) using the Cockcroft-Gault formula. The primary endpoint was the change in from baseline to month 6 in the CrCl. Proteinuria and serum creatinine were also assessed. Measures of efficacy (BPAR, graft loss and death) were secondary objectives. Therapeutic drug monitoring was done on everolimus, tacrolimus and cyclosporine. There were no PK analyses.

#### **8.2.2.5. Randomisation and blinding methods**

The study was open label. Patients were randomised by an IVRS in a 1:1 ratio.

#### **8.2.2.6. Analysis populations**

Efficacy analysis was based on the ITT population which was defined as all randomised patient who received at least one dose of study medication. The safety population was the ITT

population who had at least one post baseline safety assessment and this population with LOCF was used to analyse the primary safety endpoint of renal function. The PP population was used for a sensitivity analysis.

#### **8.2.2.7. Sample size**

For sample size calculations, a mean treatment difference between groups in cGFR of 8 mL/min was assumed. With a standard deviation of 16 mL/min, a sample of 72 patients per group (68 per group with a 5% drop out rate) gave the study an 80% power (two-sided  $\alpha=0.05$ ). There was a blinded independent review of the pooled standard deviations of the baseline cGFR after 25% of patients had completed 6 months of the study. This concluded that there was no need to alter the sample size.

#### **8.2.2.8. Statistical methods**

The mean change in cGFR from baseline to month 6 was compared between treatment groups using an ANCOVA analysis with baseline creatinine clearance as a covariate. Supportive analyses were also conducted using ANCOVA. Efficacy event rates were compared using a Z statistic and 95% confidence intervals. Kaplan Meier estimates were also calculated.

#### **8.2.2.9. Participant flow**

There were 145 patients randomised, 72 to everolimus and 73 to CNI treatment groups. Most patients completed the study (98.6% vs 97.5%) but the treatment discontinuation rate was higher in the EVR group (25.0% vs 1.4%), with most due to AEs (19.4%). All patients were followed to month 12.

#### **8.2.2.10. Major protocol violations/deviations**

The rate of major protocol deviations leading to exclusion from the PP population was 42% and 23% of the EVR and control groups, respectively. The most common were GFR outside the 20-60 mL/min range (19% vs 22%) and prematurely discontinuing study medication (25% vs 1%). The ITT population included 145 (100%) patients, while the PP population included 98 (67.6%) patients.

#### **8.2.2.11. Baseline data**

Demographic and baseline characteristics were roughly balanced between treatment groups. The mean age was 57-58 years and most patients were Caucasian (95.8% -97.3%). There were slightly more males in the EVR group (62.5% vs 54.8%). The mean time since transplantation was 3.27 and 2.85 years in the EVR and CNI groups, respectively. The main causes of ESLD were alcoholic cirrhosis and hepatitis C. The mean donor age was 44 years and 46 years in the 2 groups, respectively, most were from heart beating cadavers (89% and 93%) and were whole liver transplants (82% for both).

#### **8.2.2.12. Drug concentrations**

From a starting dose of 3 mg, the mean daily dose of everolimus increased to 3.82 mg at month 6. The overall mean daily dose was 3.41 mg (range 1.42 mg to 6.06 mg) with a higher doses in those receiving tacrolimus than cyclosporine (3.70 mg vs 3.04 mg). Over 75% of patients had mean everolimus trough levels between 3 and 12 ng/mL at each visit. In the everolimus group, for those on cyclosporine the mean trough level decreased from 120 ng/mL at baseline to 10.3 ng/mL at month 6 and for those on tacrolimus the mean trough level decreased from 5.18 ng/mL to 1.59 ng/mL at month 6. In the control group, the mean trough levels of cyclosporine and tacrolimus from baseline to month 6 were 129 ng/mL to 107 ng/mL and 5.69 ng/mL to 5.13 ng/mL, respectively.

#### **8.2.2.13. Results for the primary safety outcome**

The study did not meet its primary endpoint. The mean in creatinine clearance (Cockcroft Gault) from baseline to month 6 was 0.99 mL/min and 2.26 mL/min in the EVR and CNI groups,



respectively. The mean difference of -1.07 mL/min (95%CI: -3.93, 1.80) was not statistically significant (p=0.463).

In the PP population, the mean change from baseline to month 6 in CrCl (2.38 vs 2.64 mL/min). This was also not significantly different between groups (difference of 0.42 mL/min, 95% CI: -3.06, 3.91, p=0.811). Over the 6 month study period, there was little difference in renal function between groups. When GFR was estimated using the MDRD formula there was still no significant difference between treatment groups.

There was no significant difference in renal function in subgroups of HCV status, age ( $\pm 50$  years), gender, time since transplant ( $\pm 3$  years), screening CrCl ( $\pm 40$  mL/min), and steroid use ( $\pm 7.5$  mg/d). Within the CNI control group there was no significant difference in the change in renal function (CrCl) over the 6 months for those receiving tacrolimus compared to those receiving cyclosporine (difference 0.63, 95% CI: -2.85, 4.11, p=0.718).

#### 8.2.2.14. Results for other safety outcomes

At 12 months in the ITT population, the LS mean change from baseline (with LOCF) in CrCl (Cockcroft-Gault) was 1.80 and 2.48 mL/min in the EVR and CNI control groups, respectively. The difference of -0.45 mL/min was not significant (95% CI -3.64, 2.75, p=0.782). In the PP population, the mean change in renal function (2.99 vs 3.25 mL/min) was also not significantly different (difference of 0.47, 95% CI: -3.57, 4.51, p=0.816).

AE and other laboratory data were not collected between 6 and 12 months. Further safety data to 6 months is in the section on *Adverse events*, below.

#### 8.2.2.15. Summary

H2401 examined the renal function in patients with CNI-related renal impairment (cGFR 20-60 mL/min) who were on average 3 years post-hepatic transplantation. The study did not meet its primary endpoint as there was no significant difference in renal function (as estimated by Cockcroft-Gault formula) after 6 months treatment following withdrawal of CNI in the everolimus group compared to continuing on the CNI-based regimen. 12 month follow-up still found no difference in renal function change.

**Comment:** The sponsor proposed that the lack of effect was contributed by the long time since transplantation, a low CNI dose at baseline and a decrease in CNI dose in the control group.

### 8.3. Patient exposure

In the controlled hepatic transplantation studies in the dossier there were 759 patients exposed to everolimus (Table 5).

**Table 5. Exposure to everolimus and comparators in clinical studies.**

Study type/ Indication	Controlled studies				Uncontrolled studies	Total Everolimus
	Everolimus	CNI (TAC/CsA)	Mycoph- enolate	Placebo	Everolimus	
Clinical pharmacology					59	59
Hepatic transplant						

Study type/ Indication	Controlled studies				Uncontrolled studies	Total Everolimus
	Everolimus	CNI (TAC/CsA)	Mycoph- enolate	Placebo		
H2304	475	241 (TAC)				475
HDE10	101	102 (either)				101
H2401	72	73 (either)				72
H2301	22	21 (either)				22
B158	89			30		89
Subtotal Hepatic Tx	<b>759</b>					<b>818</b>
<b>Cardiac transplant</b>						
A2310	444	*CsA	271			444
<b>Renal transplant</b>						
A2309	552	*CsA	273			552
<b>TOTAL</b>	<b>1755</b>					<b>1814</b>

\*Treatment was everolimus + reduced dose cyclosporine or myophenolate +standard dose CsA.

In H2304, the mean exposure was 284, 223 and 290 days in the EVR+reduced TAC, TAC elimination and TAC control groups, respectively. In the EVR+reduced TAC group (n=245), 73% of patients were exposed for  $\geq 286$  days. There are reported to be 400 patients in the extension study where treatment can continue with EVR+reduced TAC for up to 48 months.

In HDE10, CNI dose was tapered and discontinued (by week 16). The mean exposure to everolimus in the 101 patients was 213 days at a mean dose of 4.4 mg (range 1.4 to 9.9 mg). The mean duration of CNI exposure was 241 days. In H2401, the mean exposure duration was 155 and 178 days in the EVR+ reduced CNI and CNI control groups, respectively.

The dose ranging study B158 had small extension studies with 10, 7 and 2 patients in the 1 mg, 2 mg and 4 mg/day groups, respectively, continuing treatment for  $\geq 36$  months. In the prematurely-terminated small study in HCV (H2301), the mean exposure duration as 467 days in the 22 patients in the EVR group, 615 days in the 11 CsA patients and 618 days in the 10 TAC patients.

In A2309 in renal transplantation patients, the mean exposure duration was 289, 276 and 310 days in the EVR 1.5 mg, EVR 3.0 mg and MPS groups, respectively. The average daily dose was 2.64 mg and 5.81 mg the two respective everolimus groups and for MPS was 1.34 g.

In A2310 in cardiac transplantation patients, the mean exposure duration was 300, 245 and 315 days in the EVR 1.5 mg, EVR 3.0 mg and MMF groups, respectively. The proportions receiving study medication for  $\geq 316$  days were 68.5%, 50.9% and 75.4%, respectively.

#### **8.4. Adverse events**

##### **8.4.1. All adverse events (irrespective of relationship to study treatment)**

###### **8.4.1.1. Pivotal study H2304**

In H2304, AEs were reported in 94.7%, 93.9% and 95.0% of the EVR+reduced TAC, TAC elimination and TAC control groups, respectively. The most commonly reported primary SOCs were gastrointestinal disorders, infections/infestations, metabolism/nutrition disorders and general/administrative site conditions. Infections/infestations (50.2% vs 43.6%) and blood/lymphatic disorders (26.9% vs 19.5%) were notably more frequent in the everolimus 1.5 mg than the control group.

In H2304 over 12 months, the commonly reported AEs (rates for the EVR 1.5 mg vs TAC control group) were diarrhoea (19.2% vs 20.7%), headache (19.2% vs 19.1%), pyrexia (13.1% vs 10.4%), hypertension (17.1% vs 15.8%), peripheral oedema (17.6% vs 10.8%), nausea (13.5% vs 11.6%) and abdominal pain (13.1% vs 9.1%).

The rate of mild, moderate and severe AEs was 14.3%, 49.0% and 31.4% in the everolimus 1.5 mg group. These proportions were similar in the everolimus 3.0 mg group, while in the TAC control group there were more mild and less severe AEs (27.8%, 46.5% and 20.3%).

Compared to A2309 in renal transplant (EVR+reduced CsA group), the most frequent AEs did not occur at a higher rate in H2304 (EVR+reduced TAC group).

**Infections:** In H2304, the rate of infections was highest in the TAC elimination group (49.4%, 53.0% and 45.6% in EVR+reduced TAC, TAC elimination and TAC control groups). The most frequent infections were *E coli*, HCV, and unknown organism. In H2304, randomisation was stratified by HCV status.

Rates of specific interest AEs in H2304 and A2309 are compared in Table 6. This shows for the hepatic transplantation patients a lower rate of anaemia, angioedema, cardiovascular events, hyperlipidaemia, peripheral oedema, proteinuria, renal failure, thrombotic/thromboembolic events and wound healing complications. Hepatic transplant patients had higher rates of incisional hernia (6.9% vs 1.8%), ascites (4.1% vs 0.4%), thrombocytopenia (5.7% vs 2.9%) and new onset diabetes (19.6% vs 9.1%).

**Comment:** It is noted that in H2304 there was a one month delay post transplantation prior to commencing everolimus. The sponsor states this has assisted in reducing wound healing complications.

**Table 6. Number (%) of patients with selected adverse events of interest by treatment in Study H2304 compared to Study A2309 (Study H2304, Safety population – 12 month analysis; Study A2309, Safety population – 12 month analysis)**

Event	Study	EVR+Reduced CNI n/N (%)
Anemia	A2309	71/274 (25.9)
	H2304	19/245 (7.8)
Angioedema	A2309	11/274 (4.0)
	H2304	3/245 (1.2)
Ascites	A2309	1/274 (0.4)
	H2304	10/245 (4.1)
CMV infection	A2309	9/274 (3.3)
	H2304	11/245 (4.5)
Cardiovascular event (SMQ search)	A2309	11/274 (4.0)
	H2304	5/245 (2.0)
Gastrointestinal ulcers	A2309	2/274 (0.7)
	H2304	3/245 (1.2)
Hyperlipidemia	A2309	143/274 (52.2)
	H2304	58/245 (23.7)
Incisional hernia (Preferred term)	A2309	5/274 (1.8)
	H2304	17/245 (6.9)
Interstitial lung disease	A2309	2/274 (0.7)
	H2304	1/245 (0.4)
Lymphoma	A2309	0
	H2304	1/245 (0.4)
Malignancy	A2309	4/274 (1.5)
	H2304	8/245 (3.3)
Neutropenia	A2309	15/274 (5.5)
	H2304	35/245 (14.3)
New Onset Diabetes mellitus	A2309	25/274 (9.1)
	H2304	48/245 (19.6)
PTLD	A2309	0
	H2304	1/245 (0.4)
Peripheral edema	A2309	152/274 (55.5)
	H2304	48/245 (19.6)
Pleural effusion	A2309	8/274 (2.9)
	H2304	11/245 (4.5)
Proteinuria	A2309	30/274 (11.0)
	H2304	7/245 (2.9)
Renal failure-excluding proteinuria	A2309	73/274 (26.6)
	H2304	35/245 (14.3)
Stomatitis, mouth ulceration	A2309	24/274 (8.8)
	H2304	23/245 (9.4)
Thrombocytopenia	A2309	8/274 (2.9)
	H2304	14/245 (5.7)
Thrombotic and thromboembolic events	A2309	25/274 (9.1)
	H2304	13/245 (5.3)
Thrombotic microangiopathy	A2309	4/274 (1.5)
	H2304	0
Wound healing complications	A2309	89/274 (32.5)
	H2304	27/245 (11.0)

#### 8.4.2. Other studies

In HDE10, the AE rate was 97% and 94% in the EVR and CNI groups, respectively. The most frequent SOCs were similar to H2304 with rates generally higher in the EVR than CNI groups. AEs with a  $\geq 10\%$  difference between groups were diarrhoea (27.7% vs 13.7%), hepatic enzyme increased (22.8% vs 11.8%), hypercholesterolaemia (22.8% vs 10.8%), leukopaenia (20.8% vs 9.8%) and headache (19.8% vs 9.8%). Other higher AEs were oral herpes, sinusitis, wound infection, stomatitis, hypertension and anaemia. Infections were more frequent with everolimus (72.3% vs 54.9%).

In the 6 months of H2401, the AE rate was again higher in the EVR than CNI group (96% vs 70%).

**Comment:** The sponsor states this difference is due to inclusion criteria as the CNI group enrolled patients already tolerating CNI therapy.

The most frequent AEs were leucopaenia, hypercholesterolaemia, aphthous stomatitis, diarrhoea and nausea. These were all more common with everolimus. Infections occurred at a similar rate between groups (12.5% vs 13.7%).

In A2309 in renal transplant patients, AEs were virtually universal. Overall, the 1.5 mg dose trended to a better safety profile than the 3.0 mg group. The most frequent AEs were constipation, nausea, vomiting, anaemia, peripheral oedema, urinary tract infections, increased creatinine, hyperkalaemia, hyperlipidaemia and hypertension. AEs with 5% or more higher rate with either dose of everolimus, compared to MPS are show in Table 7. Infection rates were similar between groups (63.9%, 62.9% and 68.1% in the EVR 1.5 mg, EVR 3.0 mg and MPS groups, respectively), however there were more viral infections in the MPS group (9.9%, 7.2% vs 20.9%). Malignancy rates were slightly lower in the everolimus groups (3.3%, 2.9% vs 5.9%).

**Table 7. Study A2309. Incidence rates of adverse events/infections with a 5% or greater difference in incidence between everolimus and Myfortic treatment groups, by preferred term (Safety population – 12 month analysis)**

Preferred term	Everolimus 1.5 mg	Everolimus 3.0 mg	Myfortic 1.44 g
	N=274 n (%)	N=278 n (%)	N=273 n (%)
Abdominal pain upper	9 (3.3)	14 (5.0)	30 (11.0)
Anaemia	70 (25.5)	86 (30.9)	68 (24.9)
Acne	26 (9.5)	41 (14.7)	23 (8.4)
Cytomegalovirus infection	2 (0.7)	0 (0.0)	16 (5.9)
Dyslipidemia	41 (15.0)	36 (12.9)	24 (8.8)
Hypercholesterolaemia	47 (17.2)	50 (18.0)	34 (12.5)
Hyperlipidaemia	57 (20.8)	60 (21.6)	43 (15.8)
Leucopenia	8 (2.9)	6 (2.2)	33 (12.1)
Lymphocele	21 (7.7)	34 (12.2)	16 (5.9)
Oedema peripheral	123 (44.9)	120 (43.2)	108 (39.6)
Proteinuria	25 (9.1)	36 (12.9)	20 (7.3)
Tremor	23 (8.4)	22 (7.9)	38 (13.9)

Severe AEs were reported in (32.1%, 39.9% and 35.9%) with the highest frequency SOC for severe AEs being infections (5.8%, 10.1%, 7.3%). Notable severe AEs in the EVR groups, compared to the MPS group, were peripheral oedema, hyperlipidaemia, headache and lymphocele. Severe leukopaenia was greater with MPA (1.1%, 1.4% vs 8.1%).

In A2310 in cardiac transplantation, AEs were universal. Of note, there was a higher rate (everolimus 1.5 mg vs MMF) of pericardial effusion (39.8% vs 27.6%), insomnia (26.9% vs 20.1%), renal failure (16.1% vs 9.0%), cough (20.4% vs 15.7%), pleural effusion (25.4% vs 21.6%), peripheral oedema (44.4% vs 38.4) and anaemia (34.8% vs 25.7%). In this study, the rate of infections was similar between groups (64.9%, 63.5% and 63.1% in the EVR 1.5 mg, EVR 3.0 mg and MMF groups, respectively). Bacterial infections were higher with everolimus and viral infections higher with MMF. Adverse events of interest are summarised in Table 8. There were higher rates with everolimus 1.5 mg than MMF for hyperlipidaemia, wound events, effusions (pericardial and pleural), peripheral oedema, stomatitis, thrombotic and thromboembolic events and malignancy. Renal failure (16.1% vs 9.0%) and renal impairment (7.5% vs 3.4%) were also higher with everolimus. Neutropaenia was higher with MMF (15.8% vs 35.1%).



**Table 8. Study A2310. Number (%) of patients with selected adverse events/infections of interest (Safety population – 12 month analysis)**

Event	Everolimus	Everolimus	MMF
	1.5mg N=279 n (%)	3.0mg N=167 n (%)	N=268 n (%)
Anemia	23 ( 8.2)	5 ( 3.0)	21 ( 7.8)
Neutropenia	44 (15.8)	44 (26.4)	94 (35.1)
Hyperlipidemia	83 (29.8)	58 (34.7)	60 (22.4)
New Onset Diabetes	27 ( 9.7)	10 ( 6.0)	16 ( 6.0)
Proteinuria	9 ( 3.2)	5 ( 3.0)	5 ( 1.9)
Sternal wound	68 (24.4)	32 (19.2)	52 (19.4)
Non-sternal wound	37 (13.3)	24 (14.4)	35 (13.1)
Major wound	53 (19.0)	39 (23.4)	36 (13.4)
Pericardial effusion	121 (43.4)	63 (37.7)	76 (28.4)
Pleural effusion	78 (28.0)	40 (24.0)	62 (23.1)
Peripheral edema	151 (54.1)	89 (53.3)	133 (49.6)
Stomatitis, mouth ulceration	23 ( 8.2)	16 ( 9.6)	13 ( 4.9)
Malignancy	13 ( 4.7)	9 ( 5.4)	10 ( 3.7)
Thrombocytopenia	33 (11.8)	30 (18.0)	29 (10.8)
Thrombotic and thromboembolic events	43 (15.4)	22 (13.2)	25 ( 9.3)
Thrombotic microangiopathy	3 ( 1.1)	2 ( 1.2)	0 ( 0.0)
Gastrointestinal ulceration	6 ( 2.2)	2 ( 1.2)	5 ( 1.9)

### 8.4.3. Adverse Events of Clinical Interest

#### 8.4.3.1. Hepatic transplant studies

**Malignancy** rate was not higher in the everolimus than in the TAC control group in H2304 (2.4%, 3.0% vs 4.6%). There was one recurrence of hepatocellular carcinoma (HCC) in the TAC elimination group and one in the TAC control group. In HDE10, neoplasm SOC AEs were lower in the EVR than CNI group (4.0% vs 8.8%).

**Hepatitis C.** The mean hepatitis activity index (HAI) score at month 12 in H2304 was 3.4, 4.6, and 4.5 in the EVR+reduced TAC, TAC elimination and TAC control groups, respectively. Viral load increased over 12 months, although the mean change was similar between groups. (0.54, 0.51 and 0.51). In H2301, the HCV viral load at month 12 and mean change from baseline were similar between groups.

**Infections** in the hepatic transplant studies (H2304, HDE10 and H2401) were more frequent with everolimus treatment than in the control groups (Table 9).



**Table 9. Summary of infection information for Studies H2304, HDE10 and H2401.**

<b>Study H2304 (Safety population – 12 month analysis)</b>			
	<b>EVR+Reduced TAC N=245 n (%)</b>	<b>TAC Elimination N=230 n (%)</b>	<b>TAC Control N=241 n (%)</b>
Infections and infestations AEs	123 (50.2)	114 (49.6)	105 (43.6)
Severe Infections and infestations AEs	16 (6.5)	16 (7.0)	12 (5.0)
Infections and infestations SAEs	34 (13.9)	49 (21.3)	19 (7.9)
Infections as a contributory factor for death	4 (1.6)	4 (1.7)	5 (2.1)
Infections leading to discontinuation of study drug	13 (5.3)	7 (3.0)	5 (2.1)
<b>Study HDE10 (Post-randomization Safety population– 12 month analysis)</b>			
	<b>EVR N=101 n (%)</b>	<b>CNI N=102 n (%)</b>	
Infections and infestations AEs	74 (73.3)	61 (59.8)	
Severe Infections and infestations AEs	18 (17.8)	9 (8.8)	
Infections and infestations SAEs	27 (26.7)	19 (18.6)	
Infections as a contributory factor for death	1 (1.0)	3 (2.9)	
Infections leading to discontinuation of study drug	9 (8.9)	1 (1.0)	
<b>Study H2401(Safety population – 6 month analysis)</b>			
	<b>EVR N=72 n (%)</b>	<b>CNI N=73 n (%)</b>	
Infections and infestations AEs	23 (31.9)	16 (21.9)	
Infections and infestations SAEs	4 (5.6)	1 (1.4)	
Infections as a contributory factor for death	0	0	
Infections leading to discontinuation of study drug	0	0	

**Hepatic artery thrombosis** was reported in one TAC elimination group patient. During post transplantation phase (prior to study medication) there were 14 cases recorded.

**Comment:** Study drug was commenced one month post transplantation to reduce the risk of this event.

**Thromboembolic events** were slightly higher with EVR+reduced TAC (5.3%) than TAC elimination (3.5%) or TAC control (3.7%), the most frequent being deep vein thrombosis (2.0% vs 0.9%, 0.4%).

**Cardiovascular events** (ischaemic heart disease or cardiac failure) were not higher with everolimus (2.0%, 1.3% vs 3.7%) in H2304.

**Peripheral oedema** was more frequent with everolimus in H2304 (19.6%, 19.1% vs 12.4%) and HDE10 (15.8% EVR vs 8.8% CNI), while pleural effusion was similar in H2304 (4.5%, 2.6% vs 4.6%) and HDE10 (9.9% vs 7.8%).

**Interstitial lung disease.** There was one case in H2304 in the TAC elimination group which resulted in death. There was also one case in H2401 in the everolimus group.

**Gastrointestinal disorders of haemorrhage or perforation** were no greater with everolimus than in the TAC control group in H2304. Stomatitis and mouth ulcers were more frequent.

**Hyperlipidaemia** rates were notable with everolimus in H2304 (23.7%, 23.5% vs 9.5%), as they were in HDE10 and H2401, compared to CNI treatment. Concomitant statin use in H2304 occurred in 23.2%, 23.5% and 17.8% of the three groups, respectively.

**New onset diabetes mellitus** rates were high in H2304 and were slightly higher in the everolimus groups than the TAC control group (32.0%, 35.4% vs 28.6%).

**Angioedema** was reported in two everolimus patients, one in H2304 and one in HDE10, there was also one case in the TAC control group in H2304.

**Wound healing complications** were slightly higher in everolimus groups in H2304 (11.0%, 9.6% vs 7.9%) though the rate of wound complications was also higher in the baseline run-in period (18.0%, 15.2% vs 14.4%). The rate of hernias (abdominal or incisional) was also slightly higher in the everolimus groups (11.0%, 9.1% vs 7.5%).

#### **8.4.3.2. Renal and Cardiac transplant studies**

**Infections.** In the renal transplant study A2309, infection rate was similar between the EVR and MPS groups, though there were more CMV infections in the MPS group. Likewise, infections rates were similar between groups in cardiac transplant study A2310 and there was also more CMV syndrome (1.4% vs 6.7%) and CMV disease (1.8% vs 3.7%) in the MMF group.

**Malignancy.** The neoplasm rate in A2309 was 3.3%, 2.9% and 5.9% in the EVR 1.5 mg, EVR 3.0 mg and MPS groups, respectively. The most common were basal and squamous cell carcinomas. In contrast, the neoplasm rate was higher with everolimus 1.5 mg and 3.0 mg than MMF in A2310 (7.5%, 6.0% vs 4.1%) though the malignancy rate was similar between EVR 1.5 mg and MMF (3.6%, 5.4% vs 3.3%). The higher rate was in the benign subgroup (3.9%, 1.2%, 1.1%).

**Wound healing complications** were higher with everolimus in A2309 (35.0%, 38.8% vs 25.6%), particularly lymphocele in the 3.0 mg group (6.6%, 11.2%, 5.1%). Onset was generally with the first 5 to 75 days and rates of wound dehiscence tended to be greater in those with BMI >50<sup>th</sup> percentile.

Wound healing events in A2310 occurred in 34.1%, 29.9% and 29.1% for the EVR 1.5 mg EVR 3.0 mg and MPS groups, respectively. The rate in the EVR 1.5 mg group in patients with BMI  $\geq$ 30 kg/m<sup>2</sup> compared to <30 kg/m<sup>2</sup> was 40.4% vs 33.3%.

**Pleural and pericardial effusion.** In A2310, pleural effusion rates were 28.0% 24.0% and 23.1%, respectively and led to withdrawal of 2.2% of the EVR 1.5 mg group compared to none of the MMF group. Pericardial effusion rates were notably higher with everolimus (43.5%, 37.7% vs 28.4%). Compared to the MMF group, the EVR 1.5 mg group required more pericardiocentesis (9.3% vs 2.2%), surgical drainage (7.2% vs 2.6%), had more haemodynamic compromise (7.2% vs 1.5%) and a higher study drug discontinuation (2.9% vs 0.4%). In A2309, the difference in rates of peripheral oedema (44.9%, 43.2%, 39.0%) and pleural effusion (2.6%, 1.8%, 1.8%) were not as notable.

**New onset diabetes mellitus.** The rate of diabetes mellitus AE was similar across groups in A2309 (5.1%, 7.9% and 7.0%). Using more detailed analysis which included the appearance of a diabetes as an AE with high glycaemia levels and the absence of diabetes pre-transplant, the rate of NODM was higher with everolimus (9.1%, 12.2% vs 6.6%) although not as high as reported in liver transplant patients treated with everolimus and TAC.

In A2310, the NODM rate was 9.7%, 6.0% and 6.0% and the rate of hyperglycaemia/new onset diabetes SMQ was 19.0%, 18.6% and 19.4% in the 3 groups, respectively.

**Major cardiovascular adverse events** in A2309 were highest in the EVR 3.0 mg group (2.6%, 5.8% vs 2.9%) with a higher rate of acute myocardial infarction (0.7% 3.2% 1.5%). Reports of MACE in A2310 were similar (6.8%, 9.6%, 7.5%).

**Interstitial lung disease** in A2309 was noted in 6 everolimus-treated patients by using a standardised MedDRA query (SMQ). One was pulmonary alveolar proteinosis in a patient in the 1.5 mg group, four cases were believed to be infection-related and one was a miscoding. Of the 16 identified cases in A2310 (7, 7 and 2 cases in the three respective groups), three cases in the everolimus groups were deemed to be actual interstitial lung disease.

**Low testosterone.** In A2309 the mean testosterone level at study end (LOCF) was lower with everolimus compared to MPS (12.3, 11.5, 13.9 nmol/L) with associated increases in FSH and LH. There was also more erectile dysfunction in everolimus-treated patients (5.1%, 6.3% vs 2.1%).

**Thrombotic/thromboembolic events.** The rate of these AEs (via an SMQ search) was greater with everolimus (6.9%, 9.4% vs 4.0%). Thrombosis of renal vessels post transplantation leading to graft loss was higher with everolimus (EVR 1.5 mg: 2 renal vein thrombosis, 4 renal artery thrombosis; EVR 3 mg: 1 renal artery thrombosis, 3 infarcted kidneys; MPS: 1 renal artery thrombosis, 2 infarcted kidneys). The rate was also higher in A2310 (15.4%, 13.2% vs 9.3%) with a notably higher SAE rate (4.7%, 6.0% vs 1.9%).

**Cyclosporine-associated AEs** of tremor, gingival hyperplasia, gingival hypertrophy and hirsutism were lower in the EVR groups compared to MPS in A2309, however the rate of renal and urinary disorders were higher with everolimus 3.0 mg (40.9%, 51.4%, 45.4%)

#### 8.4.4. Treatment-related adverse events (adverse drug reactions)

##### 8.4.4.1. Pivotal study H2304

The rate of treatment-related AEs was higher with everolimus (65.3%, 63.9% vs 54.8%) with the most frequent being leukopaenia, diarrhoea, hypercholesterolaemia, hypertriglyceridaemia, headache, tremor, renal failure and hypertension (Table 10).

**Table 10. Number (%) of patients with AEs including infections suspected to be study drug related (≥5% of patients in any treatment group) by preferred term (Study H2304, Safety population – 12 month analysis)**

Primary System Organ Class Preferred Term	EVR+Reduced	TAC Elimination	TAC Control
	TAC N=245 n (%)	N=230 n (%)	N=241 n (%)
Any suspected AE (including infections)	160 (65.3)	147 (63.9)	132 (54.8)
Blood & lymphatic system disorders	37 (15.1)	30 (13.0)	7 (2.9)
Leukopenia	20 (8.2)	16 (7.0)	3 (1.2)
Gastrointestinal disorders	38 (15.5)	27 (11.7)	17 (7.1)
Diarrhea	15 (6.1)	11 (4.8)	13 (5.4)
Metabolism & nutrition disorders	53 (21.6)	44 (19.1)	24 (10.0)
Hypercholesterolemia	13 (5.3)	10 (4.3)	0
Hyperlipidemia	16 (6.5)	14 (6.1)	4 (1.7)
Nervous system disorders	32 (13.1)	32 (13.9)	37 (15.4)
Headache	13 (5.3)	11 (4.8)	15 (6.2)
Tremor	17 (6.9)	12 (5.2)	22 (9.1)
Renal and urinary disorders	27 (11.0)	23 (10.0)	29 (12.0)
Renal failure	13 (5.3)	10 (4.3)	17 (7.1)
Vascular disorders	20 (8.2)	14 (6.1)	20 (8.3)
Hypertension	16 (6.5)	14 (6.1)	17 (7.1)

##### 8.4.4.2. Other studies

In HDE10, treatment-related AEs occurred in 86.1% of the everolimus group and 67.6% of the CNI group. In H2401, treatment-related AEs were more frequent in the everolimus than in the CNI group (79.2% vs 17.8%). Similarly there were higher rates in the everolimus groups in A2309 (68.2%, 74.8% vs 54.6%) and in A2310 (61.3%, 61.1% vs 53.0%).

#### 8.4.5. Deaths

##### 8.4.5.1. Pivotal study H2304

In H2304, there were 23/719 (3.2%) deaths between randomisation and month 12. There were also 37/1147 deaths during the run-in phase. The death rate was 3.7%, 3.5% and 2.5% in the everolimus+reduced TAC, TAC elimination and TAC control groups, respectively. In the nine (3.2%) EVR+reduced TAC group deaths, one patient did not receive study treatment and one was a suicide. Most deaths were related to liver complications or infection. A further analysis to

data cut-off of 31 May 2011 reported an additional 5 deaths in the EVR+reduced TAC group and 4 each in the TAC elimination and TAC control groups.

A blinded adjudication committee reviewed deaths and graft losses and reported that most deaths were not related to study treatment with only 1 of 9 in the EVR+reduced TAC and 1 of 8 in the TAC elimination groups having a possible relationship to study medication. The case in the EVR+reduced TAC group was a the 66 year-old 70 kg Caucasian male who received an allograft from a 79 year old female donor with a CIT of 9 hrs. Following biliary complications (bile duct anastomosis stenosis, ITBL, stent), the patient experienced a cerebral infarction on a pre-existing carotic artery stenosis, developed cholangiosepsis and died on day 184 post-transplant. The case in the TAC elimination group was a 59 year-old, 74 kg, male Caucasian (HCV positive) who received an allograft from a 50 year old male donor with a CIT of 8 hrs. The patient developed a pulmonary infection on day 204, was diagnosed with interstitial lung disease by lung biopsy on day 241, developed respiratory failure consequently followed by intubation/ventilation on day 247, and died with respiratory failure, shock and cardiac arrest on day 251 post-transplant.

#### **8.4.5.2. Other studies**

In HDE10, there were 4 deaths both in the EVR and CNI groups with most associated with infection and none deemed treatment-related. There was one death in H2401 in the everolimus group which was due to arrhythmia. This patient had ceased study medication over 146 days prior. In B158 and B158E1 (to 36 months) there were 5 (17.9%), 1 (3.3%), 4 (12.9%) and 2 (20.0%) deaths in the EVR 1 mg, 2 mg, 4 mg and placebo groups, respectively. There were 2 further deaths in B158E2 (EVR 2 mg/d) (pneumonia and haemorrhagic stroke). There was one death in H2301 in the EVR group of ischaemic stroke.

In A2309, there was a slightly higher death rate with everolimus 3.0 mg (3.2%) and similar death rates in the everolimus 1.5 mg and MPS groups (2.6% and 2.2%). There were 19 deaths that occurred on treatment or within 30 days of discontinuation. There were 2 infection-related deaths in the EVR 1.5 mg group and 4 in the EVR 3.0 mg group, while there were none in the MPS group. There were also more deaths from myocardial infarction with everolimus (1 and 3) compared to only one with MPS.

In A2310, as noted earlier, there was a higher death rate with everolimus 3.0 mg (10.2%) compared to everolimus 1.5 mg (7.5%) or MMF (4.9%). Overall, there were 51 deaths with the most common reason being infection (2.9%, 2.4%, 1.5% in the EVR 1.5 mg, EVR 3.0 mg and MMF groups, respectively). A post-hoc analysis was undertaken and found the higher death rate in the EVR 3.0 mg group occurred primarily during the first 3 months post transplantation irrespective of induction therapy used, with causality attributed to infections and cardiovascular disorders. In the EVR 1.5 mg group, the death rate was also higher in the first 3 months but noticeably higher in those who received thymoglobulin (14.0%) compared to those who received basiliximab (5.0%) or no induction (4.3%). These patients receiving thymoglobulin and everolimus had a higher rate of severe infections and post-transplant lymphocyte depletion. Multivariate analysis found that in the thymoglobulin induction subgroup the higher mortality with everolimus 1.5 mg compared to MMF was significantly associated with left ventricular assistance devices (LVAD) and poor renal function at baseline (GFR).

#### **8.4.6. Serious Adverse Events and Graft Loss**

##### **8.4.6.1. Pivotal Study H2304**

Graft loss was reported in 2.4%, 2.2% and 1.2% of the EVR+reduced TAC, TAC elimination and TAC control groups, respectively, representing 6, 5 and 3 cases. Independent adjudication found all cases unrelated to study medication apart from one chronic rejection case in the TAC elimination group. There was also one case in the group that was not evaluable.



The rate of SAEs was greatest in the TAC elimination group (56.5%) compared to the EVR+reduced TAC and TAC control groups (49.8% and 43.2%). In the EVR+reduced TAC group, compared to the TAC control group there was a higher rate of pyrexia, cholangitis, cholestasis, hepatitis C, incisional hernia and renal failure. Serious bacterial infections (7.8%, 10.4% vs 4.6%) and viral infections (3.7%, 3.5% vs 2.1%) were more frequent with everolimus-treated patients. Recurrent HCV was an SAE in 3.3%, 3.0% and 1.7% of patients in the three group, respectively.

A comparison of SAEs between H2304 and A2309 found a greater rate of pyrexia, cholangitis, cholestasis, incisional hernia, hepatitis C, sepsis and acute renal failure in the liver transplant study and a greater rate of urinary tract infection, dehydration, gastroenteritis, deep vein thrombosis and lymphocoele in the renal transplant study.

#### **8.4.6.2. Other studies**

There were no graft losses in H2401, one in HDE10 and one in H2301 in the EVR groups. In B158 to 36 months there was one graft loss in each everolimus dose group.

In HDE10 the SAE rate was higher in the everolimus than the CNI group (66.3% vs 56.9%) with greater rates of pneumonia (5.0% vs 2.9%), pyrexia, liver abscess, abnormal LFTs or increased liver enzymes, abdominal pain, cholestasis, anaemia, leukopaenia and pericardial effusion. The CNI group had higher rates of CMV infection, cholangitis, bile duct stenosis, pancreatitis, ascites and ileus.

The SAE rates were also higher in the everolimus group in H2401 (25% vs 19%). In the EVR group, 9 SAEs (13%) were felt to be treated related – liver transplant rejection, fever, hyperglycaemia/ interstitial lung disease, cytolytic hepatitis, headache/leukopaenia/lung disorder, pulmonary fibrosis, toxic skin eruption, phlebitis, and acute renal failure/thrombotic microangiopathy.

In B158 and extension to month 36 the SAE rate was 71.4%, 70.0% and 80.6% in the, 1 mg, 2 mg, and 4 mg everolimus groups, respectively, compared to 56.7% in the placebo group. In the HCV study H2301, the SAE rate in the EVR group was 50% while there were no SAEs in the CNI group

In A2309 renal transplant study, the SAE rates were 56.6%, 60.4% and 53.8% in the EVR 1.5 mg, EVR 3.0 mg and MPS groups, respectively. The higher rate with everolimus 3.0 mg included myocardial infarction, hyperglycaemia, peripheral oedema. Lymphocoele was more frequent with EVR 1.5 mg than MPS (5.1% vs 2.6) and infections were less frequent (19.7% vs 25.3%).

There were 12, 14 and 9 cases of graft loss in the 3 treatment groups respectively, with the main cause in the EVR 1.5 mg group being renal artery/vein thrombosis.

In A2310 cardiac transplant study, the SAE rate was higher with everolimus 1.5 mg and 3.0 mg than MMF (71.0%, 65.3% vs 57.5%). Comparing the everolimus 1.5 mg group with the MMF control group, there was a higher rate of cardiac disorders (26.2% vs 15.3%), including pericardial effusion (13.3% vs 4.1%), and of pneumonia (4.7% vs 1.9%).

### **8.5. Discontinuation due to adverse events**

#### **8.5.1. Pivotal studies**

In H2304, the rate of study medication discontinuation was 26.9%, 55.8% and 22.2% in the EVR 1.5 mg, EVR 3.0 mg and TAC control groups, respectively. The rate of AEs leading to discontinuation of study medication was more frequent with everolimus than in the TAC control group (25.7%, 2.61% vs 14.1). The main AEs were proteinuria, hepatitis C, graft loss and pancytopenia.

### **8.5.1.1. Other studies**

In HDE10, the rate of discontinuation due to AEs was notably higher in the everolimus than CNI group (29.7% vs 13.7%), the main reasons being infections (8.9% vs 1.0%) and blood/lymphatic disorders (6.9% vs 0%). In H2401, the rate of study medication discontinuation due to an AE (up to month 6) was also notably higher with everolimus at 19.4% compared to 0% in the CNI control group. In the dose ranging study, the AE discontinuation rate at 12 months was similar in the everolimus groups (32.1%, 33.3% and 32.3% in the 1 mg, 2 mg and 4 mg per day groups, respectively) but notably higher than placebo (13.3%).

In the renal transplant study A2309, the rate of AEs leading to study drug discontinuation was 23.4%, 28.4% and 15.8% in the EVR 1.5 mg, EVR 3.0 mg and MPS groups, respectively. Compared to MPS the everolimus 1.5 mg group had higher discontinuations due to peripheral oedema, therapeutic agent toxicity, proteinuria, lymphocele and increased creatinine. The rate of AEs leading to discontinuation or dose adjustment/interruption was lower with everolimus 1.5mg than everolimus 3.0 mg or MPS (36.5 % vs 47.1%, 43.6%).

In A2310 cardiac transplant patients, the rate of study medication discontinuation was 31.2%, 48.8% and 24.0% in the EVR 1.5 mg, EVR 3.0 mg and MMF groups, respectively. The rate of AEs leading to premature discontinuation was higher with everolimus (29.7%, 30.5% vs 19.0%). Compared to the control MMF group, the EVR 1.5 mg group had more discontinuations due to respiratory, thoracic and mediastinal disorders (4.7% vs 0.4% particularly pleural effusion), blood and lymphatic system disorders (3.2% vs 0.7%), infections (3.9% vs 2.2%), cardiac disorders (3.6% vs 2.2%, particularly pericardial effusion) and general disorders and administration site conditions (2.2% vs. 0.7%). Renal disorders leading to discontinuation were similar (3.6% vs 3.4%).

## **8.6. Laboratory tests**

### **8.6.1. Liver function**

#### **8.6.1.1. Pivotal study H2304**

Creatine kinase and amylase increased in all groups during the study. Notable increased ALP and GGT were similar between the EVR+reduced TAC and TAC control groups, but higher in the TAC elimination group. The rate of increased ( $\geq 3 \times \text{ULN}$ ) AST (25%, 22% vs 11%) and ALT (27%, 30% vs 21%) was higher with everolimus. Notable increased bilirubin was similar between groups. There were 9 Hy's law cases (AST/ALT  $> 3 \times \text{ULN}$  with total BR  $> 2 \times \text{ULN}$  and ALT  $< 2 \times \text{ULN}$ ), 2 in each everolimus group (0.9%) and 5 (2.2%) in the TAC control group. These cases were associated with HCV recurrence (n=5), rejection (n=2), hepatic steatosis (n=1) and liver abscess (n=1).

#### **8.6.1.2. Other studies**

In A2310, high ALT and AST ( $> 3 \times \text{ULN}$ ) were greater in the everolimus groups (18.4%, 17.7% vs 11.2%) though not at extreme levels  $> 10 \times \text{ULN}$  (1.6%, 2.0%, 2.1%). In A2309, high LFTs were not more marked with everolimus.

### **8.6.2. Kidney function**

#### **8.6.2.1. Pivotal study H2304**

Renal function assessment was a main secondary objective of H2304. This found that the difference between the EVR+reduced TAC and TAC control group in eGFR at month 12 was 8.50 mL/min/1.73m<sup>2</sup> (97.5% CI: 3.74,13.27) which was non-inferior (-6 NI margin) and also statistically superior (p<0.001). The improvement was seen from month 2 onwards. In H2304, the rate of renal dysfunction AEs was slightly higher in the TAC control group than the everolimus groups (Table 11).



**Table 11. Number (%) of patients with renal dysfunction AEs by preferred term and treatment (Study H2304, Safety population – 12 month analysis)**

Preferred Term	EVR+Reduced TAC N=245 n (%)	TAC Elimination N=230 n (%)	TAC Control N=241 n (%)
Renal failure	15 (6.1)	13 (5.7)	21 (8.7)
Renal failure acute	12 (4.9)	6 (2.6)	8 (3.3)
Renal failure chronic	0	0	1 (0.4)
Renal impairment	4 (1.6)	9 (3.9)	9 (3.7)

### 8.6.2.2. Other studies

In HDE10, the LS mean CrCl (by Cockcroft-Gault) at 11 months was 89.9 and 87.0 mL/min in the EVR and CNI groups, respectively which was not significantly different. In this study, the rate of renal dysfunction AEs was lower in the EVR than the CNI group. In H2401, the mean change from baseline in CrCl (Cockcroft-Gault) after 6 months was 0.99 and 2.26 mL/min in the everolimus and CNI groups, respectively, which not was statistically different.

In A2309 at month 12, the renal function of patients treated with the everolimus regimen was non-inferior to those treated with MPS and a greater proportion of patients in the EVR 1.5 mg group had cGFR  $\geq 60$  mL/min/1.73 m<sup>2</sup> at month 1, 6 and 12. Renal biopsies at 12 months in patients with proteinuria  $>0.5$ g/d found the rate of chronic sclerosing nephropathy was higher with everolimus 3 mg (13.9%) compared to similar rates with everolimus 1.5 mg (8.5%) and MPS (9.0%).

There was an increased risk of proteinuria in all group and at month 12 71.3%, 68.5% and 77.1% had a UP/UC ratio of  $30 \leq 300$  mg/g compared to 3.8%, 3.9% and 2.4% at baseline. At month 12, the rate of nephrotic levels of proteinuria ( $\geq 3000$  mg/g) were highest with everolimus 3.0 mg (5.8%) compared to everolimus 1.5 mg (3.0%) and MPS (4.1%). The rate of proteinuria AEs was highest with everolimus 3.0 mg (9.1%, 12.9%, 7.3%) which was confirmed on modelling with an adjusted hazard ratio of 1.95 ( $p < 0.0001$ ) for everolimus 3.0 mg vs MPA.

In A2310: Renal function at month 12 in the cardiac transplant patients was lower in those treated with everolimus than MMF and non-inferiority was not demonstrated (see section on *Efficacy*, above).

### 8.6.3. Lipids

#### 8.6.3.1. Pivotal study H2304

The mean change in total cholesterol from baseline to month 12 was +39.7, +49.6 and -2.7 mg/dL in the EVR+reduced TAC, TAC elimination and TAC control groups, respectively. LDL-C and triglycerides showed similar trends. Notable levels of high total cholesterol, LDL-C, triglycerides and TC/HDL ratio were consistently greater with everolimus treatment than in the TAC control group.

#### 8.6.3.2. Other studies

In A2310, notably high total cholesterol, LDL and triglycerides was greater in the everolimus groups. In A2309, there were small increase in total cholesterol and LDL with everolimus compared to MPS. AE rates of hyperlipidaemia were higher in the everolimus groups.

### 8.6.4. Haematology

#### 8.6.4.1. Pivotal study H2304

In H2304, WBC and neutrophils stayed low, from a low baseline at randomisation, throughout the 12 month study. Notable low WBC ( $\leq 2.0 \times 10^9$ /L) was more frequent in the everolimus

groups (13.5%, 10.3% vs 6.6%). Low platelets ( $<50 \times 10^9/L$ ) were also more frequent (4.8%, 3.3% vs 21.3%). Mean haemoglobin levels tended to recover in all groups during the study.

In H2304, anaemia rates were 7.8%, 10.9% and 8.3% in the EVR+reduced TAC, TAC elimination and TAC control groups, respectively and the rates of haemoglobin  $<8.0 \text{ g/dL}$  were 2.2%, 3.2% and 1.3%. Thrombocytopenia AEs were higher in the everolimus groups (5.3%, 6.5% vs 1.7%) and the rate of platelets  $<30 \times 10^9/L$  were 0.9%, 0.9% and 0.4%, respectively. In H2304, the rate of neutropenia AEs (2.4%, 1.3% and 0.8%) and pancytopenia AEs (3.7% vs 0.9% and 0.8%) were higher in the EVR+reduced TAC group, although this was not seen in HDE10 or H2401.

#### **8.6.4.2. Other studies**

In HDE10, there was a higher rate of notable low WBC ( $\leq 2.8 \times 10^9/L$ ) (worst observation post-randomisation) in the EVR than the CNI group (24.8% vs 12.7%). Anaemia was also more frequent in the everolimus than CNI group in HDE10 (18.8% vs 10.8%) and H2401 (9.7% vs 4.1%).

In A2309, the rate of notable low haemoglobin ( $<60 \text{ g/L}$ ) was 1.5% with EVR 1.5 mg compared to 0.4% with EVR 3.0 mg and 0% with MPS. The rate of notable neutropenia was greater with MPS (1.8%, 3.6% vs 6.3%) and other haematological findings were comparable. Notable low WBC was higher with MMF in A2310 (10.8%, 13.8% vs 20.2%).

#### **8.6.5. Electrocardiograph**

##### **8.6.5.1. Other studies**

In A2310, the rate of clinically significant ECG abnormalities was similar between the EVR 1.5 mg and MMF groups (5.7% vs 6.7%).

#### **8.6.6. Vital signs**

##### **8.6.6.1. Pivotal study H2304**

Vital signs were not remarkable and notable levels of SBP or DBP were similar between groups.

##### **8.6.6.2. Other studies**

In HDE10, notable change in SBP was higher with EVR than CNI treatment (6.9% vs 2.0%) but similar for DBP (11.9% vs 10.8%). Vital signs were unremarkable in H2401.

In A2309, notably high SBP (2.9%, 3.2% vs 4.4%) and high DBP (6.6%, 6.1% vs 8.4%) were greater in the MPS group.

#### **8.6.7. Liver fibrosis**

##### **8.6.7.1. Pivotal study H2304**

In H2304, HCV positive patients had a liver biopsy at month 12. Progression of  $\geq 1$  grade on the fibrosis score (IK staging) between baseline and month 12 was less frequent in the EVR+reduced TAC than the TAC control group while the odds ratio was not significant. It was noted that 8% and 15% had missing baseline scores.

##### **8.6.7.2. Other studies**

At month 12 in the small study H2301, there was a possible trend for lower IK score in the EVR than the CNI group. The study was terminated early and 24 month data were not available.

### **8.7. Post-marketing experience**

The dossier included PSUR addendum report 03 covering 1 August 2009 to 31 July 2011. This included data from A2309, A2310 and H2304. It is estimated approximately 11,000 patients have been treated with everolimus. The sponsor stated the cumulative market exposure is approximately 105,204 patient years (based on a defined patient daily dose of 1.5mg and total

sales since launch of 57,599,632 kg of active substance). There were 1079 reported cases of which 38 were fatal (6 spontaneous and 22 from clinical trials). Issues identified for monitoring included interstitial lung disease, cardiac tamponade, polyomavirus infection, proteinuria and convulsion.

## **8.8. Safety issues with the potential for major regulatory impact**

The major safety issues with everolimus are outlined in the Product Information. These include serious and opportunistic infections, malignancy, renal dysfunction, interstitial lung disease, male infertility, diabetes and graft thrombosis.

## **8.9. Other safety issues**

### **8.9.1. Safety in special populations**

In H2304, a comparison of AEs in patients age <60 years to those aged ≥60 years did not show any notable increased event risk in older patients. Females compared to males treated with EVR+reduced TAC in H2304 had a similar overall AE rate (93.8% vs 95.0%) and higher rates of nausea (20.0% vs 11.1%) peripheral oedema (29.2% vs 13.3%), abnormal LFT (10.8% vs 5%) and headache (24.6% vs 17.2%). There were too few non-Caucasians in H2304 to examine AEs by racial group.

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

In the clinical trials everolimus was given with concurrent tacrolimus and corticosteroids in liver transplantation, cyclosporine, basiliximab and corticosteroids in renal transplantation and cyclosporine and corticosteroids in cardiac transplantation. Other immunosuppressive combinations with everolimus have not been the subject of major clinical trials. The increased bioavailability of everolimus with cyclosporine is currently outlined in the PI. The risk of rhabdomyolysis with concomitant statins use is also outlined in the PI and should be monitored.

## **8.10. Evaluator's overall conclusions on clinical safety**

### **8.10.1. Hepatic transplantation**

For the hepatic transplantation indication, the safety data comes primarily from the pivotal study (H2304) in 719 patients of whom 475 received everolimus. In addition, there were two hepatic transplant studies which examined renal safety as the primary outcome (HDE10 and H2304). In total, the hepatic transplant studies in the dossier included 759 patients exposed to everolimus. There was no pooling of safety data for this indication. The safety data from two other major studies, one in renal (A2309) and the other in cardiac transplant patients (A2310) was also reviewed. While the 3 main studies (H2304, A2309, A2310) were 24 month studies, all data presented was from the 12 month analyses. The mean exposure in H2304 was 284, 223 and 290 days in the EVR+reduced TAC, TAC elimination and TAC control groups, respectively. A comparison of notable events in H2304, HDE10 and A2309 is in Table 12.

**Table 12. Frequency of notable events across studies**

	Study H2304 (LTx 12 month)			Study HDE10 (LTx 12 month)		Study A2309 (RTx 12 month)		
	EVR+ Reduced TAC N=245 n (%)	TAC Elimin N=230 n (%)	TAC Control N=241 n (%)	EVR N=101 n (%)	CNI N=102 n (%)	EVR 1.5 mg N=274 n (%)	EVR 3.0 mg N=278 n (%)	Myfortic N=273 n (%)
Deaths	9 (3.7)	8 (3.5)	6 (2.5)	4 (4.0)	4 (3.9)	7 (2.6)	9 (3.2)	6 (2.2)
Graft loss#	6 (2.4)	5 (2.2)	3 (1.2)	2 (2.1)	2 (2.0)	-	-	-
SAEs	122 (49.8)	130 (56.5)	104 (43.2)	67 (66.3)	58 (56.9)	153 (55.8)	167 (60.1)	146 (53.5)
DAE	63 (25.7)	60 (26.1)	34 (14.1)	30 (29.7)	14 (13.7)	64 (23.4)	79 (28.4)	43 (15.8)
Dropouts due to:								
Adverse Events	47 (19.2)	46 (20.0)	27 (11.2)	28 (27.7)	16 (15.7)	50 (18.2)	56 (20.1)	26 (9.5)
Abnormal lab values	4 (1.6)	1 (0.4)	2 (0.8)	7 (6.9)	3 (2.9)	1 (0.4)	4 (1.4)	1 (0.4)
Abnormal test procedure results	0	1 (0.4)	0	1 (1.0)	0	0	1 (0.4)	0

# As Study A2309 is a renal transplant study comparisons to H2304 and HDE10 would not be applicable. Dropout due to notable events (recorded on Treatment and Study Completion CRF, with reason for premature discontinuation of study medication = Adverse events, Abnormal laboratory values or Abnormal test procedure results).

Adverse events were virtually universal in the transplant studies. In H2304 over 12 months, the most commonly reported AEs were diarrhoea, headache, pyrexia, hypertension, peripheral oedema, nausea, abdominal pain, hepatitis C, leukopaemia, anaemia, fatigue and tremor.

In H2304, AEs tended to be moderate (49%) or severe (31%) and the rate of severe events was greater than in the TAC control group (20.3%). The higher rate of severe AEs was also found in the supportive study HDE10 (52% vs 35%).

Compared to renal transplant study, there was a lower rate of anaemia angioedema, cardiovascular events, hyperlipidaemia, peripheral oedema, proteinuria, renal failure, thrombotic/ thromboembolic events and wound healing complications. Hepatic transplant patients had more incisional hernia, ascites, thrombocytopenia and new onset diabetes

In H2304 the mortality rate was slightly higher in the everolimus groups (3.7%, 3.5% vs 2.5%) although adjudication felt only 2 deaths in everolimus treated patients were treatment-related (biliary complications/cholangiosepsis/cerebral infarction and interstitial lung disease). Most deaths were related to liver complications or infection.

SAE rates were higher in the everolimus groups in the liver transplant studies, particularly the TAC elimination group in H2304 (49.8% 56.5% vs 43.2%). There were higher rates of pyrexia, cholangitis, cholestasis, hepatitis C, incisional hernia, renal failure and serious bacterial infection. Graft loss rates were low but higher with everolimus (2.4% 2.2% vs 1.2%).

Premature discontinuation due to AEs occurred in one quarter of patients treated with everolimus and reduced TAC and this was higher than the control regimen (25.7% vs 14.1%). Higher AE discontinuation rates with everolimus were also seen in HDE10 (29.7% vs 13.7%). These rates were similar to the discontinuation rates seen in the renal and cardiac transplant studies. The main reasons for discontinuation that occurred at a higher rate than the control group were proteinuria, hepatitis C, graft loss and pancytopenia.

In H2304 renal function was a main secondary objective and the everolimus+reduced TAC regimen resulted in a statistically superior renal function (cGFR) at month 12 of 8.5 mL/min/1.73m<sup>2</sup> (97.5% CI: 3.74, 13.27) compared to the standard tacrolimus regimen. An

improvement in renal function was seen from month 2 onwards. The result was robust across other renal function assessment methods and patient subgroups.

HDE10 assessed the effect on renal function of an everolimus-based regimen compared to a calcineurin inhibitor (CNI)-based regimen in 203 patients with de novo liver transplantation. The study did not meet its primary endpoint as, after 11 months of treatment, the cGFR by Cockcroft-Gault was not significantly different between the everolimus and CNI group (LS mean difference of -2.92 mL/min, 95% CI: -10.66, 4.81). Secondary analyses of the PP population and using different methods for calculating the GFR also found no significant differences.

H2401 examined the renal function in 145 patients with CNI-related renal impairment (cGFR 20-60 mL/min) who were on average 3 years post hepatic transplantation. The study did not meet its primary endpoint as there was no significant difference in renal function (as estimated by Cockcroft-Gault formula) after 6 months treatment in the everolimus group (with CNI withdrawal) compared to continuing on the CNI-based regimen. 12 month follow up still found no difference in renal function.

In hepatic transplantation patients, renal failure/impairment AEs occurred at a slightly lower rate in the everolimus-based regimens than in the control groups. Proteinuria levels and AE rates were higher with everolimus treatment.

For other events of clinical significance (comparing EVR+reduced TAC vs TAC control group in H2304) it was found that there was no higher rate of malignancy (2.4% vs 4.6%), major cardiovascular events (2.0% vs 3.7%) or gastrointestinal haemorrhage or perforation. Patients received pneumocystitis and CMV (if required) prophylaxis in H2304. The everolimus treated patients did have higher rates of infections in all three hepatic transplant studies (50.2% vs 43.6%) and discontinuation due to infections was also higher (5.3% vs 2.1%)

Recurrent hepatitis C was higher in the everolimus group (11.4% vs 7.9%) while the hepatitis C activity index was not higher and the mean change from baseline to month 12 in HCV viral load was similar. Data on the impact of everolimus on liver fibrosis was non-conclusive.

There was a higher rate of thromboembolic events (5.3% vs 3.7%) although the risk of hepatic artery thrombosis appears to be reduced by delayed treatment commencement, with only one case post randomisation in the TAC elimination group.

The rate of peripheral oedema was higher (19.6% vs 12.4%), although ascites and pleural effusion rates were similar. Wound healing complications were also more frequent (11.0% vs 7.9%) as were hernias (11.0% vs 7.5%), however the rates were lower than the renal transplant study where treatment was initiated earlier.

The increased risk of new onset diabetes was generally high (about one third of patients) with a slightly higher rate in the everolimus group (32.0% vs 28.6%).

Stomatitis and mouth ulcers were more frequent as is known to occur with mTOR inhibitors.

The known risks of angioedema and interstitial lung disease were rare in the liver transplant studies.

Anaemia rates and notably low haemoglobin rates were similar in H2304. Thrombocytopenia rates were higher although notably low platelets were infrequent. Neutropenia and pancytopenia rates were higher (2.4% vs 0.8% and 3.7% vs 0.8%, respectively) as was notably low WBCs (13.5% vs 6.6%). There were higher rates of increased AST and ALT though Hy's Law cases were no greater in the everolimus groups. Hyperlipidaemia (cholesterol and triglycerides) was notable with everolimus treatment.

While females had higher rates of some AEs, the overall rate was similar, as it was between those aged < 60 and ≥60 years. There were too few non-Caucasians to draw safety conclusions in other racial groups.

### 8.10.2. Renal transplantation

Study A2309 of 833 patients, 552 of whom were exposed to everolimus, found that after 12 months the cGFR was non-inferior with the everolimus+reduced CsA regimen compared to MPS+standard dose CsA. Overall, GFR remained steady with everolimus, with a mean increase of 2.37 mL/min/1.73 m<sup>2</sup>. Results were supported by other analyses. At 12 months there was a higher rate of patients with cGFR  $\geq$ 60 mL/min/1.73 m<sup>2</sup> in the EVR 1.5 mg group (41.6%, 33.6% and 31.5%).

This study demonstrated that in renal transplant patients the 3.0 mg-based regimen had a poorer safety profile than the 1.5 mg regimen. This included a higher rate of SAEs (60.4% vs 56.6%, 3.0 mg vs 1.5 mg) and discontinuation due to AEs (28.4% vs 23.4%). There were also higher rates of chronic nephropathy and nephrotic levels of proteinuria as well as major cardiovascular events with the 3.0 mg dose.

The most frequent AEs were constipation, nausea, vomiting, anaemia, peripheral oedema, urinary tract infections, increased creatinine, hyperkalaemia, hyperlipidaemia and hypertension. Notable severe AEs in the EVR groups compared to the MPSA group were peripheral oedema, hyperlipidaemia, headache and lymphocoele.

As the 3.0 mg everolimus regimen is not being pursued for treatment, comparison between the everolimus 1.5 mg and the MPS regimens are discussed. Severe leukopaenia was greater with MPS and, while the infection rates were similar, there were more viral infections with MPS. The everolimus-based regimen resulted in less cyclosporine related events of tremor, gingival hyperplasia/hypertrophy and hirsutism. There were also fewer neoplasms AEs with everolimus (3.3% vs 5.9%).

The everolimus-based regimen had higher rates of discontinuations due to adverse events (23.4% vs 15.8%) although the SAE rate was similar (56.6% vs 53.8%). There were numerically more graft losses with a higher rate of early graft loss through vascular thrombosis (2.2%, 1.8% vs 0.7%). Thrombotic/ thromboembolic events were more frequent with everolimus (6.9% vs 4.0%).

AEs of proteinuria were higher (9.1% vs 7.3%) as was new onset diabetes mellitus (9.1% vs 6.6%). Wound healing complications more frequent in the everolimus-treated patients, and rates tended to be greater in those with a higher body mass index on sub-group analysis. Major cardiovascular events were higher with the 3 mg dose but not the 1.5 mg (2.6%, 5.8% 2.9%). There were slightly higher rates of peripheral oedema (44.9% vs 39.0%) and pleural effusion (2.6% vs 1.8%).

The everolimus group had higher rates of low testosterone as well as erectile dysfunction (5.1% vs 2.1%). As known with mTOR inhibitors, everolimus results in more abnormally high lipid levels and a greater rate of stomatitis/mouth ulceration (8.4% v. 2.6%).

### 8.10.3. Cardiac transplantation

The main safety issue in the cardiac transplantation study A2310 was a higher death rate in patients receiving 3.0 mg dose regimen (10.2% vs 7.5% EVR 1.5 mg, 4.9% MMF). This led to the early termination of this dose group by the DMC. In the 3 mg group the deaths tended to occur in the first 3 months and were mainly infections and cardiovascular disorders. There was also a higher death rate in the 1.5 mg dose group. These also tended to occur within 3 months of transplantation but were due to infections and multi-organ failure and were associated with thymoglobulin induction (the rate in this group was 14%) with contributing factors of left ventricular assistance devices and poor baseline renal function.

The other main safety issue in A2310 was that renal function was lower in everolimus groups and non-inferiority on estimated GFR was not demonstrated (NI margin of -10 mL/min/1.73m<sup>2</sup>) at month 12 between the everolimus+reduced CsA and MMF+standard CsA groups. The decline in renal function was more marked in the first month. The poorer renal function results with



everolimus were also seen for creatinine, CrCl and urinary protein/creatinine ratio. A post-hoc analyses suggested that non-compliance to the specified lower CsA levels at certain study centres may have had an influence on the results.

Comparing the 1.5 mg dose regimen with the MMF control group, there were still safety issues. The AE discontinuation rate was higher (24.1% vs 12.5%) as was the SAE rate (71.0% vs 57.5%) with higher rates of cardiac disorders (26.2% vs 15.3%) including pericardial effusion (13.3% vs 4.1%) and pneumonia (4.7% vs 1.9%). The AE rate of pericardial effusions was 43.5% vs 28.4% and there were higher intervention rates and as well as haemodynamic compromise (7.2% vs 1.5%). While the rate of major cardiovascular events was similar (6.8% vs 7.5%) there were more thrombotic events (15.4% vs 9.3%).

There were also higher rates for the AEs of pericardial effusion, insomnia, renal failure, cough, pleural effusion, peripheral oedema and anaemia. The rate of wound-related events (34.1% vs 29.1%) and new onset diabetes mellitus (9.7% vs 6%) were slightly higher with everolimus. Neoplasms were higher (7.5% vs 4.1%) though this was driven by benign neoplasms as the malignant neoplasm rate was similar (3.6% vs 3.0%). The overall infection rate was similar (65% vs 63%), bacterial infections were more frequent (30.1% vs 22.0%), while CMV infections/syndrome/ disease was less frequent than with MMF (1.4% vs 6.7%).

## 9. Benefit-risk assessment

### 9.1. Assessment of benefits

The benefits of everolimus in the proposed usage are:

#### 9.1.1. Hepatic transplantation

- Treatment with everolimus allowed a reduction in tacrolimus exposure without affecting efficacy in terms of prevention of the composite endpoint of treated biopsy proven acute rejection, graft loss and death at 12 months post-transplantation.
- The everolimus and reduced dose tacrolimus regimen resulted in significantly fewer episodes of acute rejection than the standard dose tacrolimus regimen (3.7% vs 10.7%).
- Efficacy results were consistent across subgroups of age, gender, region, eGFR, HCV status, MELD score and cause of ESLD.
- Over the 12 months post-transplantation, the decline in renal function (eGFR by MDRD-4) with everolimus and reduced dose tacrolimus treatment was significantly less than with standard dose tacrolimus (-2.2 vs -10.7 mL/min/1.73 m<sup>2</sup>). The finding was consistent across other methods of renal function assessment and patient subgroups. The rate of renal failure/impairment AEs was slightly lower with everolimus.
- There were lower rates of malignancy in the everolimus and reduced dose tacrolimus group compared to the standard dose tacrolimus regimen (2.4% vs 4.6%).

#### 9.1.2. Renal transplantation

- Treatment with a regimen of everolimus 1.5 mg and reduced dose cyclosporine was found to be non-inferior to mycophenolate sodium with standard dose cyclosporine on the composite efficacy endpoint of tBPAR, graft loss, death and loss to follow up at 12 months post-transplantation.
- Renal function at 12 months was similar (and statistically non-inferior) between the treatment regimens.

- There were less cyclosporine-related adverse events of tremor, gingival hypertrophy and hirsutism with everolimus and reduced dose cyclosporine.
- There was less severe leukopaenia and, while infection rates were similar, there were fewer viral infections than with the mycophenolate control regimen.

### 9.1.3. Cardiac transplantation

- Treatment with a regimen of everolimus allowed a reduced cyclosporine dose while maintaining efficacy as the regimen was found to be non-inferior to mycophenolate mofetil with standard dose cyclosporine on the composite efficacy endpoint of BPAR, acute rejection with haemodynamic compromise, graft loss, death and loss to follow up at 12 months post-transplantation.
- The everolimus regimen resulted in a significantly lower risk of cardiac allograft vasculopathy with a lower mean increase in the average maximal intimal thickness on IVUS.
- There was a lower rate of CMV-related events with everolimus compared to mycophenolate regimens.

## 9.2. Assessment of risks

The risks of everolimus in the proposed usage are:

### 9.2.1. Hepatic transplantation

- Treatment with everolimus does not allow elimination of concomitant tacrolimus. Elimination of tacrolimus resulted in an unacceptable increased risk of acute rejection and treatment discontinuation.
- There was an increased risk of efficacy failure with everolimus trough levels <3 ng/mL and higher doses than recommended have an unacceptable safety profile. Everolimus treatment needs to be concentration-controlled though active therapeutic drug monitoring.
- Adverse events are virtually universal in this patient population and over the 12 months, the most commonly reported AEs were diarrhoea, headache, pyrexia, hypertension, peripheral oedema, nausea, abdominal pain, hepatitis C, leukopaenia, anaemia, fatigue and tremor.
- Compared to the renal transplantation study, there were higher rates of incisional hernia, ascites, thrombocytopenia and new onset diabetes. There were, however, lower risks of hyperlipidaemia, peripheral oedema, proteinuria, angioedema, cardiovascular events, renal failure excluding proteinuria, anaemia and thromboembolic events.
- There was a higher rate of severe AEs (31% vs 20%) and SAEs (50% vs 43%) with everolimus and reduced tacrolimus compared to the tacrolimus control regimen. There was also a higher rate of premature discontinuation due to AEs (26% vs 14%).
- There was an increase risk of thromboembolic events (5.3% vs 3.7%), however major cardiovascular events were not more prevalent (2.0% vs 3.7%) and the delayed treatment commencement at one month post transplantation appears to have reduced the potential risk of hepatic artery thrombosis.
- About one third of patients developed new onset diabetes mellitus with a slightly higher rate than the tacrolimus control group.
- Other known risks with everolimus were present including stomatitis and mouth ulcers, wound healing events, interstitial lung disease, angioedema, pleural effusion and infections.
- There are no long term efficacy data.
- There are only limited data on non-Caucasians.

### 9.2.2. Renal transplantation

- The safety profile of the everolimus 3.0 mg dose in renal transplant patients was unacceptable. This dose was associated with increase rates of mortality, SAEs, discontinuation due to AEs, and other AEs such as severe infections, major cardiovascular events, chronic nephropathy and nephrotic levels of proteinuria.
- There was an evident risk of renal graft vascular thrombosis early after transplantation.
- The safety risks found were in general consistent with the current labelling. Risks that were added to the core data sheet from this study included stomatitis/mouth ulceration, proteinuria, new onset diabetes, erectile dysfunction and associated low testosterone, early graft loss through vascular thrombosis and impaired wound healing and complications with a possible increased risk in patients with high body mass index.

### 9.2.3. Cardiac transplantation

- As in renal transplantation, the safety risks with the 3.0 mg everolimus dose were unacceptable. There was an increased mortality risk (10.2% vs 7.5% with 1.5 mg) which led to premature termination of this dose group.
- The everolimus 1.5 mg dose was also associated with an increased mortality risk (7.5% vs 4.9% MMF control), particularly in patients who had received thymoglobulin induction (14%). The mortality rate in patients receiving basiliximab with everolimus was comparable to those who did not receive induction therapy.
- Renal function at 12 months was lower (-5.5 mL/min/1.73 m<sup>2</sup>, 95% CI:-10.9,-0.2), and did not meet the non-inferiority criteria, in patients treated with everolimus and reduced dose cyclosporine compared to those treated with MMF and standard dose cyclosporine.
- Post-hoc analysis suggested the non-compliance with the reduced cyclosporine dose may have contributed to poorer renal function and as such treatment non-compliance by physicians is a risk of the everolimus treatment regimen.
- There is the evident risk of drug interactions with inhibitors and inducers of CYP3A4, particularly cyclosporine which can increase everolimus levels.
- The drug is potentially embryotoxic so must be avoided in pregnancy.

## 9.3. Assessment of benefit-risk balance

In Australia and New Zealand in 2010, there were 192 liver transplants in adults, with chronic viral hepatitis (HCV and HBV) being the most common primary indication. The one year survival in the 2005-2009 patient cohort was 92% for adults with an overall survival at 5 years was 75% (ANZLT 2010). The treatment of liver transplantation is a balancing act between the risk of rejection and the risk of toxicity from treatment. This occurs in a patient population that may tolerate a high risk of adverse effects due to the very serious nature of their condition. Nevertheless, with improvement in management of acute rejection, there is now a need to reduced the long term complications of immunosuppression including renal disease, hyperlipidaemia, diabetes and malignancy.

The clinical development program of everolimus in liver transplantation consisted of one main pivotal study H2304 and two supportive studies. There was a small study in hepatitis C patients which was terminated prematurely and did not provide conclusive results. The pivotal study, H2304, was in 719 patients with de novo liver transplantation of whom 475 were exposed to everolimus. The design, including primary efficacy endpoint, was in line with current EMA guidelines as it was amended following the implementation of the guidelines on immunosuppressants for solid organ transplantation (EMA 2008).

With decisions being based on only one pivotal efficacy study, guidelines state it should be large, multicentre, well-controlled, internally consistent and have robust results which are consistent across study subsets as well as being statistically persuasive. The results also need to be clinically relevant and able to be extrapolated to the target population. (EMA 2001, FDA 1998). Study H2304 was found to meet these methodological considerations and so the evaluator believes its results are valid for using in assessment of the proposed usage.

Given the non-inferiority design of the pivotal study, it was important to see that the results from the ITT population were supported by the PP population as this allows a more robust interpretation of the data (EMA 2000). The open label design was necessary for therapeutic drug monitor, however it could have introduced bias particularly in safety event ascertainment. As the primary safety endpoint was renal function based on spot urine analysis this should not have been greatly affected by such bias.

Study H2304 found that everolimus treatment allowed a reduction in the dose of tacrolimus without an increase in rejection and with a beneficial effect on renal function. The efficacy impact was most notable on a reduced rate of acute rejection rather than a reduction in mortality or graft loss. It was shown that everolimus cannot replace tacrolimus due to an unacceptably high efficacy failure rate (24.2%) in the treatment arm where concomitant tacrolimus was eliminated. This risk needs to be brought to the attention of prescribers. In addition, as the efficacy data was derived from a set treatment regimen with tacrolimus, the evaluator believes this should be reflected in the indication.

In the hepatic transplantation population, the safety risks of adding everolimus to reduced dose tacrolimus treatment were notable, with increased rates of severe AEs, SAEs and premature discontinuation due to AEs compared to those treated with the tacrolimus control regimen. There were also the significant adverse events which were, however, not unexpected as the safety profile of everolimus has been delineated in the renal and cardiac transplantation patient populations. In comparisons of data from H2304 and A2309, the safety profile was no worse than in renal transplantation with the exception of increased risks of incisional hernia, ascites, thrombocytopaenia and new onset diabetes. The delay in treatment commencement to one month post-transplantation appears to have assisted in reducing events of hepatic artery thrombosis and wound healing complications where the rate was lower than in the renal transplant study. There are other risks of peripheral oedema, mouth ulcers and erectile dysfunction which, while appearing less severe, may have a major impact on a patient's quality of life.

The drug interaction study with midazolam found that everolimus is a weak inhibitor of CYP3A4 and as such the possibility of an interaction between everolimus and contraceptive hormones is unlikely.

In hepatic impairment, the use of Child-Pugh scores was believed to offer a more conservative scale for reduction of dose compared to the use of bilirubin or INR level. Given the results from study X2102, the sponsor proposed dosage based on the Child-Pugh classification of hepatic impairment as follows: two thirds for mild impairment and half for moderate or severe impairment. The rationale for the dose to be only reduced by half in severe hepatic impairment was that if the exposure is too low there may be a risk of acute organ rejection. This appears too high a dose, however the evaluator acknowledges the potential counter risk of acute rejection and believes that the risk may in part be mitigated by the therapeutic drug monitoring. In general, for subjects with Child-Pugh C (severe) hepatic impaired status, the administration of everolimus should be with extreme caution and only when it is in the best interest of the subject. Vigilant therapeutic drug monitoring will be critical in these patients and these factors need to be adequately outlined in the Product Information.

The cardiac and renal transplantation studies demonstrated significant and unacceptable risks when the everolimus 3.0 mg per day dose was used with target trough levels of 6-12 ng/mL.

This risk must be thoroughly specified in the product information and communication plans. In addition, in cardiac transplant patients receiving induction with thymoglobulin there was an increased risk of death with the lower and recommended 1.5 mg dose. This risk needs to be included in the product information under a specific precaution.

Pericardial effusions were notable in cardiac transplant patients and there was an increased risk of haemodynamic compromise and requirement for surgical intervention as well as of resultant study drug discontinuation. Such risks need to be added to the precautions in the product information.

In the cardiac transplant study, efficacy was comparable to the mycophenolate control regimen and there were positive effects on cardiac graft vasculopathy. There was however, a deterioration in renal function with everolimus which was not evident in the hepatic or renal studies. It is felt by the sponsor that this risk was due to non-compliance by investigators to sufficiently lower the cyclosporine dose to the recommended levels. This reticence on the part of treating physicians may perhaps be due to a fear of graft rejection. Unless this poorer effect on renal function is appropriately addressed the evaluator contends that there appears no overwhelming reason why the everolimus regimen should be adopted. In order to ensure a potentially positive benefit-risk balance for everolimus in cardiac transplant, adherence to the reduced dose target levels of cyclosporine will need to be achieved and renal function monitored.

The cyclosporine trough levels used in A2309 and A2310 have been included in the proposed product information for both cardiac and renal transplant patients. The risk of everolimus and calcineurin inhibitor-induced renal dysfunction is also addressed. This, however may not be sufficient and the evaluator recommends further communication and education on these risks and dosing recommendations.

Therapeutic drug monitoring will be crucial, not just for everolimus but also for cyclosporine. The factors contributing to this are: the risk of CNI-induced renal dysfunction; the drug interaction with cyclosporine which results in increased everolimus levels so the dose changes in cyclosporine must lead to a careful monitoring of everolimus; the relatively long half life of everolimus which means that physicians must wait 5 days to measure trough levels after dose changes; and the increased risk of acute rejection if trough levels fall below 3 ng/mL. Again prescribers need to be made aware of these factors.

Cardiovascular events are a major cause of mortality in renal transplant patients and treatment with everolimus resulted in significant increased rates of the risk factors of diabetes, hyperlipidaemia and thrombogenicity. It is therefore feasible that this treatment may not have such an evident benefit in the longer term. Such potential effects need to be assessed and so it will be very important to evaluate the 24 month data from the three studies as well as any further long term extensions. Collection of prospective long term data should be considered.

In renal transplantation, the everolimus regimen resulted in comparable efficacy and renal function, with reduced rates of cyclosporine-related events and CMV infections. On the other hand there were greater risks of discontinuation due to AEs as well as of events such as graft thrombosis, proteinuria, new onset diabetes, interstitial lung disease, thrombocytopenia and hyperlipidaemia. In the context of significant toxicities with immunosuppressant drugs, the evaluator finds that the data from A2309 continue to support the current indication in renal transplantation. Treatment with everolimus 1.5 mg using therapeutic drug monitoring targeting trough levels of 3-8 ng/mL in combination with reduced doses of cyclosporine represents an alternative to a combination of mycophenolate and standard dose cyclosporine.

In cardiac transplantation the results from study A2310 are not as compelling. While the everolimus regimen allowed reduction in cyclosporine, maintained efficacy, reduced cardiac allograft vasculopathy and reduced CMV associated disease, it was at a cost of significant safety

concerns as outlined above. These risks will need to be managed by more stringent labelling, communication and education and ongoing close pharmacovigilance monitoring.

In conclusion, the evaluator finds the benefit-risk balance of everolimus, given the proposed usage in hepatic transplantation, is favourable subject to adoption of changes to the proposed product information [not included in this Extract] and a risk management plan that takes into account the issues discussed.

There is a manifest need to communicate the serious risks with everolimus to all those involved in organ transplantation. This needs to be fully captured within the risk management plan.

There is also an evident lack of long term data. The 24 months data from the three main transplants studies, together with any extensions, will be important to better delineate longer term risks of immunosuppression, such as chronic rejection, malignancy, renal function and cardiovascular disease.

## 10. Recommendation regarding authorisation

The evaluator recommends extension of the indication for everolimus (CERTICAN) to include hepatic transplant patients. This is subject to the proposed changes to the draft PI being satisfactorily addressed. In addition, a condition of this indication extension should be the submission of the further data from study H2304 as it becomes available. This includes the data to month 24 and then the extension study data. These need to be evaluated to ensure no alterations to the risk-benefit balance.

The proposed changes to the product information in relation to data from studies A2309 and A2310 are acceptable, apart from specified alterations [not included in this Extract]. Likewise, the 24 month data from these two studies must be submitted for evaluation as soon as available.

Regarding the proposed revisions to the Indication: The proposed wording is:

*Certican is indicated for the prophylaxis of organ rejection in adult patients at mild to moderate immunological risk receiving an allogeneic renal; cardiac or hepatic transplant.*

The semicolon after “renal” needs to be replaced by a comma.

The efficacy data in the 3 main transplant studies (A2310, A2309 and H2304) was obtained with a specific concomitant medication regimen in each study. The evaluator believes that this should be included in the indication as data with other regimens is either not available or not supportive of the indication. It is therefore recommended that the indication include wording to the effect of:

*In hepatic transplantation Certican should be used in combination with tacrolimus and corticosteroids.*

*In renal and cardiac transplantation Certican should be used in combination with cyclosporine microemulsion and corticosteroids.*

## 11. Comments on the product documentation

Details of these are not included in this Extract.

## 12. Clinical questions

None.



## 13. References

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