SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL MT18328)

COMPANY: NAME OF FINISHED PRODUCT: NAME OF ACTIVE SUBSTANCE(S):	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No / DATE OF REPORT	Abbreviated Clinical Study Report – MT18328: A prospective, open label, randomized, multicenter, multinational study evaluating the overall efficacy and safety including the effect on renal function of sirolimus (Rapamune®) replacing CNI in a standard care regimen of CNI, mycophenolate mofetil (MMF) and steroids in heart transplant patients. Research Report No. [redacted] / 18 August 2006		
INVESTIGATORS / CENTERS AND COUNTRIES (PLANNED AND ACTUAL)	**Planned:** Approximately 650 patients were to be enrolled, at approximately 60 centers, with each center enrollling between 6 and 60 patients. **Actual:** Multicenter study – 15 sites: Australia (2), the Czech Republic (2), France (1), Germany (3), Spain (1), and the United States of America (USA) (6).		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL	27 October 2005 to 06 April 2006	CLINICAL PHASE	IIIB/IV
OBJECTIVES	The primary objective was to evaluate efficacy and safety, including the effect on renal function, of sirolimus (Rapamune®) replacing calcineurin inhibitor (CNI) after 3 months in a standard care regimen of CNI, MMF, and steroids (Arm A) compared with a standard care regimen of CNI, MMF and steroids (Arm B) in heart transplant patients.		
STUDY DESIGN	A prospective, open label, randomized, multicenter, multinational, two parallel arm study.		
NUMBER OF SUBJECTS (PLANNED AND ANALYZED)	The study was prematurely terminated in response to a higher than expected early incidence of grade IIIA acute rejection in patients who were randomized to sirolimus (Arm A). Planned: 650 enrolled, 580 randomized Analyzed: 35 enrolled, 15 randomized		
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION / EXCLUSION	**Inclusion Criteria at Study Entry:** Patients aged ≥18 years who had received their first heart transplant (single organ transplant), and were on a standard care regimen of CNI, MMF, and steroids since transplantation. **Exclusion Criteria at Study Entry:** • Patients with a positive donor-specific cross-match at the time of transplantation • Patients with any panel reactive antibody (PRA) >25% • Patients with:		

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	○ Ejection Fraction (EF) of ≤40% ○ EF of 20% decrease from baseline, and the need for inotropic agents ○ Fractional shortening ≤20% or a 25% decrease from baseline, and the need for inotropic agents ○ Need for inotropic agents due to a cardiac index <2.0 L/min/m^2 or a 25% decrease from baseline • Patients with any antibody treated acute rejection **Additional Exclusion Criteria at Randomization:** • Patients no longer on a standard care regimen of CNI, MMF and steroids • Patients not on hydroxymethyl glutaryl coenzyme A (HMG CoA) reductase inhibitors ("statins") • Patients who required dialysis within 4 weeks prior to randomization • Patients with any biopsy proven acute rejection (BPAR) ≥International Society of Heart and Lung Transplantation (ISHLT) grade IIIA within 4 weeks prior to randomization • Patients with any BPAR ≥ISHLT grade IIIA more than 4 weeks prior to randomization without a subsequent biopsy of ISHLT grade 0 or IA • Patients with severe diarrhea or other gastrointestinal disorders that might have interfered with their ability to absorb oral medication • Sepsis or any severe active infection requiring intravenous antibiotics and/or hospitalization within the 2 weeks prior to randomization Patients who received sirolimus before randomization
INVESTIGATIONAL PRODUCT / (BATCH) No	Sirolimus (Rapamune®) 1 mg tablets; batch numbers [redacted] (USA sites) and [redacted] (International/non-USA sites).
DOSE / ROUTE / REGIMEN / DURATION (**Arm A**)	Sirolimus (Rapamune®) 6 mg single loading dose followed by 2-3 mg/day adjusted to maintain whole blood trough concentrations of 5-10 ng/mL [measured by high performance liquid chromatography (HPLC)], 6-12 ng/mL [measured by enzyme modified immunoabsorbent assays (EMIT) and microparticle enzyme immunoassay (MEIA – USA sites)], or 8-18 ng/mL (measured by MEIA – Australian sites).
STANDARD CARE REGIMENS	• CNI • MMF (CellCept®) • Corticosteroids } Patients were given commercial supply.
DOSE / ROUTE / REGIMEN / DURATION (**Arm B**)	• CNI - Administered following standard center practice • MMF - 1.5 g twice daily

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	• Corticosteroids - Administered following standard center practice with a minimum dose of 5 mg/day for the first year
CRITERIA FOR EVALUATION	
EFFICACY:	The intended primary endpoints were: Renal function (% change from randomization) assessed by calculated glomerular filtration rate (GFR) utilizing Modification of Diet in Renal Disease (MDRD)-6 at 24 months post-transplantation (PT) (21 months post-randomization) and a composite endpoint of incidence of BPAR or hemodynamic compromise (HDC), or graft loss (re-transplantation or death) or lost to follow-up in the interval between randomization and 12 months PT (9 months post-randomization). Due to the early termination of this study, only the following variables were assessed: • The number and percentage of patients with BPAR ≥ISHLT grade III, HDC, graft loss (re-transplantation or death) or loss to follow-up at study cessation, overall and by baseline CNI type. • The number and percentage of patients with: o BPAR from study entry to randomization and from randomization to study cessation o HDC treated with pulse immunosuppression from study entry to randomization and from randomization to study cessation • The number and percentage of deaths until study cessation. • Average daily dose of corticosteroids from transplant to study cessation. Steroids to treat rejection and maintenance steroids were summarized separately.
PHARMACODYNAMICS:	None
PHARMACOKINETICS:	None
SAFETY:	The following variables were assessed: • Duration of exposure to study drugs • Use of other immunosuppressant treatments • Incidence of adverse events, including serious adverse events • Incidence of opportunistic infections (OIs) • Laboratory variables
STATISTICAL METHODS	As the study was prematurely terminated, no statistical testing of hypotheses of treatment differences were performed. Data were summarized using descriptive statistics [N, mean,

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	standard deviation (SD), standard error of the mean (SEM), median, minimum, and maximum] for continuous variables and counts, percentages, and confidence intervals (CIs) for categorical variables. These summaries were derived for patients in the following groups: • Enrolled but not randomised • Randomized group sirolimus (Arm A) • Randomized group CNI (Arm B)

METHODOLOGY:

At Study Entry, 4-6 weeks after transplantation, patients were entered into the study, and baseline characteristics and data were collected. Patients continued on a standard care regimen of CNI, MMF, and steroids. During this period, treatment with HMG CoA reductase inhibitors ("statins") was initiated for patients who were not already receiving this. At 12 weeks after transplantation, patients were randomized into either Arm A (sirolimus) or Arm B (continuation of CNI), both in combination with MMF and steroids.

For patients randomized to Arm A, CNI was discontinued on the day of randomization and sirolimus introduced 12-24 hours after the last CNI dose, with a single loading dose of 6 mg. This was followed by 2-3 mg/day administered in a single daily dose adjusted to maintain whole blood trough concentrations of 5-10 ng/mL (HPLC), 6-12 ng/mL [EMIT and MEIA (USA sites)] or 8-18 ng/mL [MEIA (Australian sites)]. MMF was administered at 1.5 g twice daily and mycophenolic acid (MPA) levels were monitored after conversion from CNI to sirolimus until a minimum trough level of 2.0 µg/mL was obtained.

For patients randomized to Arm B, CNI was administered following center practice, and MMF was given at 1.5 g twice daily. In both arms, corticosteroids were given following center practice with a minimum dose of 5 mg/day for 1 year.

There were to be 12 study visits (Study Entry, Randomization, and post-transplant Weeks 13, 14, 16, 20, 24, 32, 40, 52, 78 and 104), with a safety follow-up visit at Week 108. On an ongoing basis, the following were recorded: assessment for patient and graft survival, recording of selected concomitant medications, adverse events, OIs and malignancies, and drug administration and accountability.

Patients who withdrew prematurely were to be followed up for selected parameters at Week 52 and Week 104. For safety reasons, any patient who had an ongoing adverse event at the end of the study or patients who discontinued sirolimus were asked to return for a follow-up visit.

EFFICACY RESULTS:

This report has focused on safety given the small number of patients who were randomized. However, the efficacy variables that were considered to be of clinical importance to these patients in the short time that they were in the study have been summarized.

Four patients (57.1%) in Arm A had BPAR, and one of these had HDC. There were no patients with graft loss and none was lost to follow-up after randomization [95% CI for the proportion of patients with an event (0.18, 0.90)]. Of the patients who experienced rejection, three were receiving cyclosporine and one was receiving tacrolimus. The rejections occurred from 2-5 weeks following the switch from CNI to

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sirolimus. No patient in Arm B had any of these events after randomization [95% CI for the proportion of patients with an event: (0.00, 0.37)].

The following patients experienced acute rejection during the study:

[redacted]

PHARMACODYNAMIC RESULTS: None

PHARMACOKINETIC RESULTS: None

SAFETY RESULTS:
The acute rejection episodes are detailed in the efficacy results section. The MMF doses received were similar between Arm A and Arm B. In general, most of the MPA pre-dose concentrations were above the minimum requirement of 2.00 µg/mL.

More than half the patients in Arm A and Arm B (57.1% and 62.5%, respectively) received at least one other IST for transplant, ie, for induction or renal insufficiency. In Arm A, one patient received other ISTs for renal insufficiency and three patients received other ISTs for induction. In Arm B, one patient received other ISTs for renal insufficiency and four patients received other ISTs for induction.

The overall incidence of post-randomization adverse events was higher in Arm B (62.5%) compared with Arm A (42.9%). However, no particular adverse event occurred at sufficient frequency for meaningful

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interpretation. In Arm A, one patient (Patient [redacted]) had a serious adverse event of sepsis, which began 19 days after last dose of sirolimus; the patient died during the follow-up period of the study. No other patients died before study cessation.

No post-randomization or serious OIs were reported during this study.

In general, there were no important differences in laboratory tests among the three groups. However, the mean serum creatinine levels were consistently higher across all time points from baseline to the last assessment in Arm B compared with Arm A, with Arm B levels tending to increase from baseline and Arm A levels tending to decrease: 124.1 (SD=28.71) to 145.0 (SD=45.92) and 99.9 (SD=27.02) to 88.6 (SD=9.57), respectively. Median levels also showed this trend.

The mean urea levels were also consistently higher across all time points from baseline to the last assessment in Arm B compared with Arm A, with Arm B levels tending to increase from baseline and Arm A levels tending to decrease: 10.13 (SD=3.232) to 10.63 (SD=5.724) and 8.38 (SD=4.283) to 6.80 (SD=1.645), respectively. Median levels also showed this trend.

There were no clinically significant changes in vital signs or clinically significant abnormal echocardiograms (ECGs) during the study.

CONCLUSIONS:

The study was stopped because the incidence of early acute rejection in patients in Arm A was higher than expected. There were no rejections in Arm B. However, there are not enough data to allow a firm conclusion to be drawn regarding the unexpected difference in rejection rate between the two treatment arms.

It is likely that the factors that led to rejection varied among the patients. It is possible that the sirolimus and MPA concentrations achieved were not adequate to maintain satisfactory immunosuppression.

No rejections ≥grade IIIA were observed in Arm B, in which the standard care regimen consisting of CNI, MMF and steroids was given. Thus, in this patient population, no specific safety concern was noticed regarding the use of MMF (CellCept®) in patients receiving the standard care regimen.