

**Rapporteur's
Public Assessment Report
for paediatric studies submitted in accordance
with Article 46 of Regulation (EC) No1901/2006,
as amended**

**Prograf
Tacrolimus**

IE/W/003/pdWS/001

**Marketing Authorisation Holder:
Astellas Pharma Europe B.V.**

Rapporteur:	Ireland (Clinical assessor Dr. David Lyons)
Start of the procedure (day 0):	15 th September 2009
Date of this report:	23 rd November 2009
Deadline for Rapporteur's preliminary paediatric assessment report (PPdPAR)(day 70):	24 th November 2009
Deadline for CMS's comments:	9 th December 2009
Date re-start of procedure (day 90)	14 th December 2009
Deadline CMS's comments (day 115)	8 th January 2010
Finalisation procedure (day 120):	13 th January 2010

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Prograf(t)
INN (or common name) of the active substance(s):	Tacrolimus
MAH:	Astellas Pharma Europe B.V.
Currently approved Indication(s)	Prophylaxis of transplant rejection in liver, kidney or heart allograft recipients. Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products.
Pharmaco-therapeutic group (ATC Code):	Lo4AD02
Pharmaceutical form(s) and strength(s):	0.5 mg, 1 mg, 5.0 mg hard capsules.
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1. EXECUTIVE SUMMARY

The Marketing Authorisation Holder (MAH) for Prograf(t) (immediate release tacrolimus) provides a clinical trial comparing early withdrawal of oral corticoids (at day 4) supplemented with the anti-IL2 monoclonal antibody, daclizumab, and continued use of oral corticosteroids for 26 weeks in paediatric patients undergoing renal transplantation.

The study demonstrates a statistically significant benefit on growth for the early withdrawal arm and also a benefit in terms of fewer patients developing glucose intolerance or diabetes. Patients experiencing acute rejection episodes were numerically fewer in the steroid continuation arm 15, compared to 18 in the steroid withdrawal arm.

Because the marketing authorisation for daclizumab lapsed in January 2009 the steroid withdrawal regimen studied by the MAH is no longer feasible.

The MAH does not propose any changes to the product information for Prograf(t).

2. RECOMMENDATION

The MAH proposal for no regulatory action is supported. Force of circumstance has rendered the steroid withdrawal study irrelevant other than as a scientific pointer.

Further to the preliminary work-sharing assessment report on the use of tacrolimus in children comments were received from Germany and France agreeing with the report. However, Sweden made the following comment.

“The MPA agrees with the overall conclusion of the Rapporteur. However, the MPA considers the data from study PRG-EC-0243 to be of clinical importance and wants to emphasize to the sponsor the importance of publishing the study results”.

This is an important and helpful comment. Although from a regulatory point of view the study is superseded by the commercial non-availability of Zenapax[®] it does provide important, and probably novel, information on the time frame of systemic corticosteroid withdrawal in the context of paediatric renal transplantation. From a science perspective this information should be in the public domain and the Rapporteur endorses the MPA’s comment.

The Rapporteur therefore strongly recommends that the MAH publish the study.

The Marketing Authorisation Holder has indicated that the data from study PRG-EC-0243 have been submitted and accepted for publication.

3. INTRODUCTION

The MAH submitted a completed paediatric study for Prograf(t) in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Prograf(t) and that there is no consequential regulatory action.

4. SCIENTIFIC DISCUSSION

Information on the pharmaceutical formulation used in the study

Prograf(t) is presented as 0.5 mg, 1 mg, 5.0 mg hard capsules.

4.1. Clinical aspects

Please see below.

4.2. Clinical Study

➤ Description

Study PRG-EC-0243 (Tacrolimus and withdrawal of steroids - TWIST) was an open, 26 week, randomised, multi-centre, evaluation of the safety and efficacy of steroid withdrawal with tacrolimus, mycophenolate mofetil and daclizumab against tacrolimus, mycophenolate mofetil and steroids in children undergoing kidney transplantation. It was conducted in thirty-two centres from September 2005 to February 2008.

➤ Methods

Objectives

The primary objective of the study was to investigate the impact of early corticosteroid withdrawal in paediatric renal transplant patients on growth, expressed as change in height standard deviation score (SDS) from baseline to study-end.

The secondary objective was to compare the efficacy and safety profiles of the two regimens in paediatric renal transplant patients.

Study Design and Treatments

Patients were randomised to one of two treatment arms:

- **Arm 1:** Tacrolimus + MMF + Daclizumab + Corticosteroids (Rapid withdrawal Day 0-4)
- **Arm 2:** Tacrolimus + MMF + Corticosteroids (Taper over 26 weeks)

The doses studied were as follows, with tacrolimus and MMF being the same for treatment arms.

Tacrolimus

The initial daily dose was 0.3 mg/kg p.o. given in two doses post-operatively. The initial dose was administered within 12 hours of reperfusion. Subsequent doses were adjusted based on clinical evidence of efficacy and occurrence of adverse events, and observing the following recommended trough level ranges Day 0 to 21: 10 - 20 ng/mL Day 22 183: 5 -15 ng/mL

Mycophenolate Mofetil

The initial dose of 600 mg/m² was given pre-operatively. The first postoperative dose was administered within 12 hours of reperfusion. The daily dose was 1200 mg/m² given in two doses for the first two weeks, thereafter 600 mg/m² given in two doses. The total daily dose could be adjusted if clinically indicated.

Daclizumab

The first dose of daclizumab 1.0 mg/kg was administered intravenously within 24 hours before reperfusion. The second 1.0 mg/kg was given intravenously on postoperative Day 14.

Corticosteroids

The corticosteroid regimens by treatment arm are tabulated below.

Steroid withdrawal		Steroids	
Prednisolone of equivalent p.o.		Prednisolone of equivalent p.o.	
Study day	Dose	Study day	Dose
D 1	60 mg/m ²	D 1	60 mg/m ²
D 2	40 mg/m ²	D 2 – 7	40 mg/m ²
D 3	30 mg/m ²	D 8 – 14	30 mg/m ²
D 4	20 mg/m ²	D 15 – 28	20 mg/m ²
D 5 – 183	none	D 29 – 42	10 mg/m ²
		D 43 – 183	< 10 mg/m ²
Both treatment arms received a single peri-operative dose of 300 to 600 mg/m ² methylprednisolone or equivalent i.v			

Study Population

Eligible patients were male or female with end stage kidney disease who were suitable candidates for primary renal transplantation or re-transplantation, younger than 18 years old but not younger than 2 years old, regardless of race, with a skeletal age of boys ≤ 17 years old, and girls ≤ 15 years old. The principal exclusion criteria were the presence of other significant co-morbidity and the likeliness of intolerance to any of the proposed treatments.

Sample Size and Statistical Methods

The primary endpoint was growth from baseline to end of study, expressed as change in the height standard deviation (SD) score¹. The secondary endpoints of the study were: acute rejection; biopsy proven acute rejection; patient and graft survival; incidence of adverse events; absolute change in serum lipids; incidence and duration of delayed graft function; incidence of renal dysfunction; incidence of PTDM; and incidence of hypertension.

The sample size was based on the primary endpoint; assuming a standard deviation of 0.65, 75 patients per treatment group (150 patients in total) are needed to detect a 0.3 shift in change in height SDS from baseline with a power of at least 80%, significance level $\alpha = 5\%$ (2-sided). Under the additional assumption of 25% not evaluable patients, the sample size was determined to be 100 patients per group (200 patients in total).

The primary endpoint was analysed by ANCOVA with the factors; treatment group, pubertal status, and the covariate baseline height SDS on the primary analysis population. Height SDS at baseline, and at Month 6 were summarised by descriptive statistics.

For analysis of rejection episodes the overall frequency of AR and BPAR episodes for the period of 6 months was tabulated. The number of patients was compared between treatment arms with the 2-sided Mantel-Haenszel test, or for incomplete data Fisher's exact test (not stratified).

➤ **Results**

Recruitment and patient disposition

Two hundred and one patients were enrolled into the study in 13 countries. One patient was not randomised. Of the 200 patients randomised 196 underwent transplantation and received at least one dose of study medication, this constituted the full analysis [safety] population and was 98/treatment arm. The primary analysis population was those patients who were randomised, transplanted, received study treatment and had valid measurements of stature at baseline and month six; there were 93 patients in this population in treatment arm 1 (rapid steroid withdrawal) and 91 in arm 2.

Table 1 Patient disposition

	Steroid withdrawal	Steroids
Safety population	98	98
No. of deaths	1	0
Withdrawn	13	14

Baseline Demographic Data

Table 2 Patients' demographic data

	Steroid withdrawal n= 98	Steroids n = 98
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¹ SDS = height measured minus height of standard population/height of standard population. Data for the standard population are based on Reinken, van Oost, 1992

Male	66 (67.3)	59 (60.2)
Age distribution (years)		
2 – 5	16 (16.3)	11 (11.2)
6 – 11	27 (27.6)	35 (35.7)
≥ 12	55 (56.1)	52 (53.1)
Mean age (years)	10.8 (4.2)	11.3 (4.1)
Weight (kg)	34.6 (15.8)	34.2 (14.6)
Height (cms)	134.4 (24.9)	136.8 (23.9)
There were significantly more Caucasians (compared to all other races) in the steroid arm 91.8% compared to the steroid withdrawal arm 80.6% p = 0.023 Chi-squared. There were no other significant imbalances.		

➤ **Efficacy**

Figure 1 shows whole blood tacrolimus trough levels over the course of the study.

Figure 1 Group mean whole blood trough tacrolimus levels by time and treatment arm.

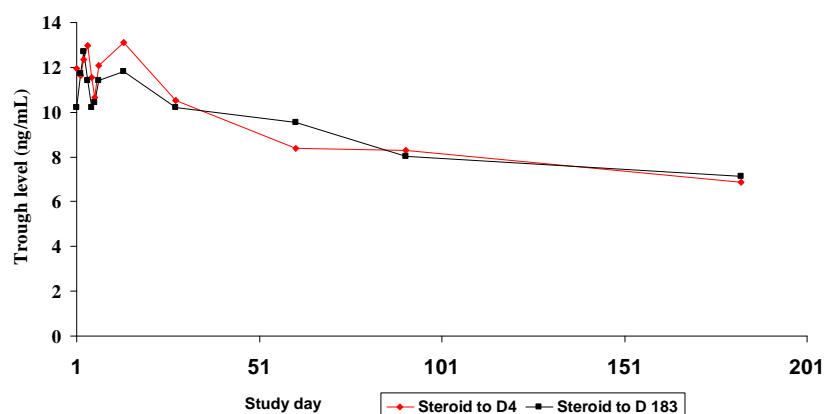


Table 3 Change in height SDS (primary efficacy variable)

	Steroid withdrawal	Steroids
Primary analysis population		
	n = 93	n = 91
Change in height SDS	0.17 (0.40)	0.04 (0.30)
Treatment difference = 0.14 (95% CI 0.04, 0.23) p = 0.005		
Full analysis population pre-pubertal		
	n = 48	n = 52
Change in height SDS	0.34 (0.44)	0.13 (0.32)
Treatment difference = 0.21 (95% CI 0.05, 0.36) p = 0.009		
Full analysis population post-pubertal		
	n = 50	n = 46
Change in Height SDS	- 0.01 (- 0.24)	- 0.06 (-0.23)
Treatment difference = 0.05 (95% CI -0.05, 0.14) p = 0.326		

Table 4 Change in height mean (s.d)

	Steroid withdrawal	Steroids
Full analysis population		
	n = 98	n = 98
Absolute change in height (CMS)	3.42 (2.22)	2.35 (1.60)
Full analysis population pre-pubertal		
	n = 48	n = 52
Absolute change in height (CMS)	4.52 (1.95)	3.07 (1.50)
Full analysis population post-pubertal		
	n = 50	n = 46
Absolute change in height (CMS)	2.36 (1.96)	1.53 (1.30)

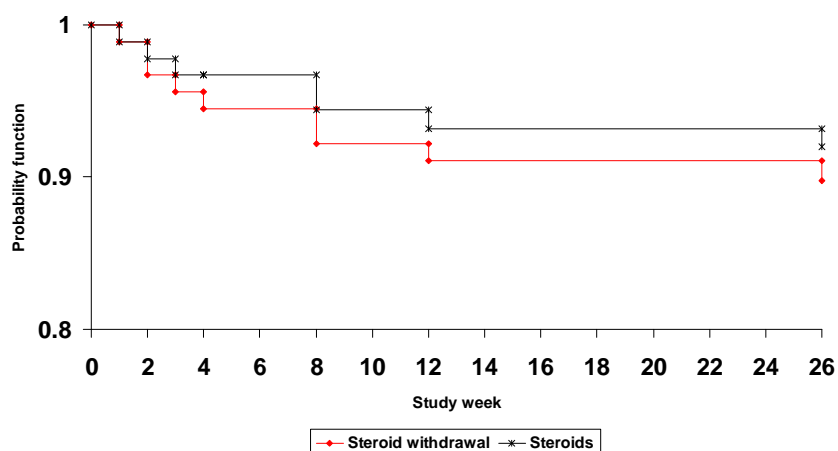
Table 5 Number of patients experiencing rejection episodes

	Steroid withdrawal n = 93		Steroids n = 91	
	Patients	Episodes	Patients	Episodes
Acute rejection	18 (19.4)	20	15 (16.5)	20
Resolved spontaneously		1	0	
Corticosteroid sensitive		18	13	
Corticosteroid resistant		1	3	
Resolved with further treatment		1	3	
Chronic rejections		0	1	
P = 0.62 by Mantel-Haenszel test for the number of patients experiencing an acute rejection				

Table 6 Data on graft function

Graft loss during study	2/98	1/98
Delayed graft function	4 /98	5/98

Figure 2 Probability of remaining free of a biopsy confirmed acute rejection episode by treatment and time.



➤ **Safety**

Table 7 Frequency of adverse events

	Steroid withdrawal	Steroids
Full analysis population		
	n = 98	n = 98
Adverse events	95 (96.9)	93 (94.9)
Serious adverse events	63 (64.3)	60 (61.2)
Causally related adverse events	76 (77.6)	79 (80.6)
Causally related serious adverse events	22 (45.8)	22 (42.3)

Table 8 Adverse events by organ system

	Steroid withdrawal	Steroids
Full analysis population		
	n = 98	n = 98
Infection & infestation	62 (63.3)	57 (58.2)
Gastrointestinal	39 (39.8)	41 (41.8)
Renal and urinary disorders	36 (36.7)	30 (30.6)
Investigations	36 (36.7)	27 (27.6)
Metabolism & nutrition disorders	23 (23.5)	38 (38.8)
Vascular disorders	23 (23.5)	33 (33.7)
Blood & lymphatic disorders	30 (30.6)	18 (18.4)
Injury poisoning & procedural disorders	24 (24.5)	24 (24.5)
Nervous system disorders	14 (14.3)	16 (16.3)
Respiratory disorders	15 (15.3)	10 (10.2)
Skin and subcutaneous disorders	14 (14.3)	11 (11.2)
Musculoskeletal & connective tissue disorders	11 (11.2)	12 (12.2)

➤ **Deaths**

A Caucasian male patient aged 14 was enrolled in the study and randomised to the steroid withdrawal arm. The primary indication for renal transplantation was uropathy. In December 2006 and January 2007, he experienced two episodes of rejection of the transplanted kidney. After a third episode, which was treated with a corticosteroid, plasmapheresis and intravenous immunoglobulin, he was withdrawn from the study on 17 January 2007. A left paranasal inflammatory swelling developed, which bled easily. A cerebral CT scan showed left pansinusitis. Rhinocerebral mycosis was suspected, which was treated with amphotericin B, without success. Septic shock of fungal origin developed and the patient died on 5 March 2007 (47 days after stopping tacrolimus).

RMS Comment

Somewhat unfortunately, and through no fault of the MAH, the study supporting early steroid withdrawal has become redundant from a regulatory point of view due to the fact that daclizumab is no longer marketed; therefore the experimental early steroid withdrawal regimen cannot be followed. The MAH considers that the anti-IL2 monoclonal antibody basiliximab should not be substituted due to its different properties to daclizumab – the RMS agrees.

Scientifically, the study points to an advantage in childrens' growth from the early withdrawal of steroids, and to a safety advantage in terms of less glucose intolerance and diabetes.

From point of view of graft rejection the steroid continuation arm did marginally better in terms of number of episodes and time to event; this does not seem sufficient to constitute an overall clinical disadvantage for early steroid withdrawal.

5. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

5.1. OVERALL CONCLUSION

The Marketing authorisation holder submits an open six month comparison of two immunosuppressant regimens in children receiving a renal transplant. The 'experimental' regimen involved the use of daclizumab and rapid withdrawal of oral corticosteroids. However, as daclizumab is no longer marketed the proposed treatment regimen is no longer valid.

5.2. RECOMMENDATION

see page 3 of this report.