European Medicines Agency

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ASSESSMENT REPORT FOR PROTOPIC

International Nonproprietary Name:
tacrolimus

Procedure No. EMEA/H/000374/II/0034

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

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I. SCIENTIFIC DISCUSSION

1.1. INTRODUCTION

Protopic is a topical formulation of tacrolimus, an immunosuppressant, used for the treatment of moderate to severe atopic dermatitis in adults who are not adequately responsive to or are intolerant of conventional therapies such as topical corticosteroids. The 0,03% formulation is also indicated for the treatment of moderate to severe atopic dermatitis in children (2 years of age and above) who failed to respond adequately to conventional therapies such as topical corticosteroids.

Protopic was authorised by the centralised procedure (EU/1/02/201) on 28 February 2002.

In this Type II variation the Marketing Authorisation Holder (MAH) applied to extend the indication to include maintenance treatment. In support of this indication the MAH submitted the results from two clinical trials (study FG-506-06-40 and FG-506-06-41) and three non-clinical studies (1 pharmacokinetic and 2 carcinogenicity).

1.2 NON CLINICAL ASPECTS

The MAH provided an addendum to Module 2.4 'Nonclinical Overview' submitted with the renewal application in May 2006. This addendum reflected the results from three additional studies (1 pharmacokinetic and 2 carcinogenicity) that were performed after the renewal application and presented the data in the context of the new indication of maintenance therapy filed with this Type II variation application. In addition to the addendum the MAH submitted the full study reports for the three studies.

1.2.1 Pharmacokinetic

1.2.1.1 A Whole Blood and Tissue Pharmacokinetics Study of FK506 Following Twice-Daily Topical Application of 0.1% Tacrolimus Ointment to Male Yucatan Minipig Swine for 14 Days

Whole blood and lymphoid tissue concentrations of tacrolimus were determined following topical administration of 0.1% tacrolimus ointment to male Yucatan minipigs for up to 14 days followed by 2 weeks of recovery. Tacrolimus was applied topically (2 mg/cm2 where individual doses ranged from ~0.1 to 0.2mg/kg) twice daily approximately 12 hours apart, for up to 13 consecutive days to approximately 20% of the total body surface area for each animal in 8 groups (n=5). A control group of 5 minipigs were sham dosed and subject to blood sampling procedures only. Necropsies were carried out on Days 1, 7, 10, 14, 15, 17, 21 and 28 (Groups 2, 3, 4, 5, 6, 7, 8 and 9, respectively) and were performed approximately 12 hours after first daily dose on days 1, 7, 10 and 14. Blood samples were also taken prior to necropsy. Prescapular, subiliac, popliteal and mesenteric analyses were performed following necropsy.

Mean concentrations of tacrolimus were generally higher in spleen, thymus and lymph nodes than in whole blood. After repeat dosing, mean concentrations were generally higher indicating possible accumulation in tissue. Elimination of tacrolimus was gradual from all tissue with no detectable presence of the drug in blood by day 21. Tacrolimus was still present in the lymph nodes on day 28.

The tacrolimus blood levels in humans following topical application of 0.1% tacrolimus ointment are essentially the same as those found in mini and micropigs (see Table 1).

Table 1: FK506 Blood Levels in Minipigs, Micropigs, Mice and Humans Following Topical Application of 0.1% Tacrolimus Ointment

Species	Study	Lymphoid Tissue Findings	Blood Level * (ng/ml)
Mouse	2-yr	lymphomas	3.1 – 10
Micropig	13-wk	None	0.254
Micropig	52-wk	None	0.430
Minipig	2-wk	NA	0.312 - 0.416
Human		None	0.2 - 0.5

* Trough level (prior to dosing) NA – not applicable

The CHMP commented that the highest concentrations of tacrolimus were observed in the draining lymph nodes (precapsular) at the site of application, followed by remote skin-draining lymph nodes, remote visceral lymph nodes, thymus and finally spleen. Tacrolimus was still present in the lymph nodes on day 28. It was considered that minipig is a relevant model for human safety given the similarity of tacrolimus blood levels.

1.2.2 Toxicology

Two carcinogenicity studies were undertaken to assess the effect of 0.1% tacrolimus ointment on papilloma formation in a two step carcinogenesis mouse model and to assess the effects on Cutaneous T Cell Lymphoma.

1.2.2.1 Investigation on Co-promoting Potential of Protopic Ointment in a Two-stage Skin Carcinogenesis Model using Mice.

CD-1(ICR) female mice were treated once daily with 0.1% or 0.03% tacrolimus ointment, tacrolimus ointment vehicle, absorptive ointment or macrogol ointment. Tumour promotion was induced with twice a week treatment of TPA (5 nM) for 18 weeks starting from 2 weeks after 50 μg of DMBA initiation. The numbers of skin nodules were counted over time and were histopathologically examined at 20 weeks after initiation by DMBA. A sham group received the same procedures to mimic the ones carried out in the test group. The results from this study are presented in table 2 below.

Table 2: Tumor Findings in Initiation-Promotion Study in Mouse Skin

Group number	Treatment	No. of animals/ group	No. of tumours/mouse [mean ± SD]	Percentage of mice with tumours [%]	No. of tumours/mouse/ week between weeks 14 and 20 [mean ± SD]
1	DMBA+TPA (SHAM)	26	18.8 ± 14.0	25 (96)	7.3
2	DMBA+ TPA +absorptive ointment	26	25.0 ± 9.8*	26 (100)	7.8
3	DMBA+TPA +macrogol ointment	26	11.2 ± 14.5*	20 (77)*	5.3
4	DMBA+TPA+ tacrolimus ointment vehicle	26	16.3 ± 13.3	24 (92)	7.3
5	DMBA+TPA+ 0.03% tacrolimus ointment	26	10.9 ± 12.1*	20 (77)*	6.2
6	DMBA+TPA+ 01% tacrolimus ointment	26	6.3 ± 12.2**##	14 (54)**##	3.3

.*, **: Significantly difference from control group 1 at p <0.05, 0.01 respectively
#, ##: Significantly difference from control group 4 at p <0.05, 0.01 respectively

1.2.2.2 Tacrolimus Effects on Cutaneous T Cell lymphoma, Lymphocyte and Dendritic Cells

The effects of tacrolimus (0.01, 0.1, 1, 10, 50, 100 ng/ml) were examined on proliferation, cell recovery and viability of cultured cutaneous T cell lymphoma lymphocytes (CTCL) and dendritic cell (DC) from patients with cutaneous T cell lymphoma. The results are presented in table 3, 4 and 5.

Table 3: CTCL Proliferation

	Patient 1		Patient 3		Patient 4		Patient 5		Means	
Dose (ng/ml)	CPM	SD	CPM	SD	CPM	SD	CPM	SD	CPM	SD
0	4831	2235	430	105	718	93	563	140	1635.5	2133.5817
0.01	4637	944	508	35	946	128	1273	129	1841.0	1890.1635
0.1	6211	2569	347	84	972	118	1034	194	2141.0	2731.0161
1	ND	ND	814	360	873	207	1444	294	1043.7	347.9516
10	2350	1416	216	29	526	104	424	208	879.0	989.1148
50	455	43	349	118	269	56	294	84	341.8	82.5646
100	215	105	177	54	168	29	438	117	249.5	127.3067

CPm: cell proliferation mean (average of five experiments per patient)
SD: Standard Deviation

Table 4: CTCL Cell number (x 10^6/ml)

Dose(ng/ml)	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
0	1.54	4.11	0.12	1.68	0.76
0.01	1.24	2.67	0.18	0.98	0.48
0.1	0.84	3.12	0.44	2.72	0.80
1.0	ND	ND	0.26	0.85	0.44
10	1.48	5.07	0.20	1.12	0.44
50	1.04	3.30	0.16	1.20	0.76
100	0.56	0.54	0.06	0.18	0.44

Table 5: CTCL Cell Viability

	Viable cells (%) : Mean of two measurements				
Dose (ng/ml)	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
0	87	94	92	81	80
0.01	78	84	89	96	75
0.1	76	89	70	92	93
1.0	ND	ND	95	83	94
10	82	90	69	45	94
50	62	80	65	85	81
100	22	67	55	26	48

Tacrolimus was found to maintain CTLC cell proliferation and cell recovery at 0.1 to 10 ng/ml but was inhibitory at >10 ng/ml. Additionally tacrolimus severely reduced the CTCL viability at 50 and 100 ng/ml. The viability and recovery of CTCL cells and DCs exposed to tacrolimus were similarly affected. The MAH concluded that tacrolimus tended to maintain CTCL cell proliferation and cell recovery at 0.1 and 10 ng/ml but was inhibitory at >10ng/ml. Overall, the MAH concluded that tacrolimus may inhibit the development of cutaneous lymphoma at 10 ng/ml or higher, while having little influence on it at concentrations less then 10 ng/ml.

The CHMP was of the opinion that the overall MAH conclusion, that tacrolimus may inhibit the development of cutaneous lymphoma at 10 ng/ml, was not substantiated. While tacrolimus was found to inhibit CTLC cell proliferation and cell recovery at concentrations >10 ng/ml, cell viability was severely reduced in all cases, especially at the 100 ng/ml dose. Additionally, the large variability between the experiments influences the ability to draw clear conclusions on the effect of tacrolimus on the development of cutaneous lymphoma. Moreover, no statistical analysis was performed for this experiment so the significance of the results is unclear.

So, while tacrolimus was found to inhibit CTLC cell proliferation and cell recovery at concentrations >10 ng/ml, cell viability was severely reduced in all cases, especially at the 100 ng/ml dose. The MAH was therefore asked to comment on the significance of these results and to what extent the reduction in proliferation rates merely reflects overall cell death at higher concentrations.

The MAH responded that the co-culture of CTCL cells and DC in the presence of FK506 (the Berger technique) as described previously suggests that FK506 is inhibitory to CTCL cells at concentrations of FK506 >10 ng/mL. The MAH acknowledged that the cell culture data obtained from this technique is not confirmatory for the effects of FK506 in skin during the use of tacrolimus ointment in the topical treatment of AD. It does, however, suggest that topical FK506 in humans could have inhibitory effects on CTCL in skin, depending on the prevailing concentration of FK506 in skin. The culture data from the study indicates that this is most likely at a FK506 concentration of 100 ng/mL; however, it is not possible to indicate with certainty whether the cytotoxicity observed with the Berger technique at 100 ng/mL is an indication of general cell death or in any way specific to CTCL. Published information indicates that CTCL cells originate in skin and not in the systemic circulation (Berger et al 2002). The available data also suggests that the FK506 concentrations in human skin following topical application of 0.1% tacrolimus ointment cover the range from 200-800 ng/g. As with the data from the Berger technique, neither of these articles is confirmatory for these observations, but on the other hand, there is some reason to believe that CTCL proliferation in skin of humans being treated with tacrolimus ointment for AD may be inhibited. In the final analysis, there is no evidence for enhanced CTCL cell proliferation at high doses of tacrolimus in vitro.

The CHMP acknowledged the suggestion by the MAH that topical FK506 in humans could have inhibitory effects on CTCL in skin depending on the prevailing concentration of FK506 in skin and that the concentration seen in this study (100 ng/ml) would substantiate this theory. While tacrolimus was found to inhibit CTLC cell proliferation and cell recovery at concentrations >10 ng/ml, cell viability was severely reduced in all cases, especially at the 100 ng/ml dose which would in turn influences the ability to draw any conclusion as to the effect of tacrolimus on CTCL cell proliferation.

1.3 CLINICAL ASPECTS

Clinical Efficacy

The MAH conducted 2 studies (i.e. the CONTROL studies) with identical study designs.
Studies **FG506-06-40** (in adults, ≥ 16 years old) and **FG506-06-41** (in children, 2 to 15 years old) were Phase III, multicentre, 1:1 randomized, double-blind, vehicle-controlled studies. The objective of both studies was to compare the efficacy and safety of a tacrolimus ointment regimen to a vehicle-based regimen administered to control atopic dermatitis over a period of 12 months. The design of the studies was basically as follows:

- A screening period of up to 1 week
- An open label period (OLP) in which patients received treatment with twice daily tacrolimus ointment (0.1% for adults, 0.03% for children) for a maximum of 6 weeks. Patients were withdrawn from the study if they did not respond to treatment by the end of the OLP (response defined as Investigator's Global Assessment [IGA] ≤ 2, i.e. clear, almost clear or mild disease). The purpose of the OLP was to allow stabilisation of the disease, so that patients would enter the disease control period (DCP) in a relatively symptom-free condition at baseline.

- A subsequent randomised double-blind disease control period (DCP) of 12 months. During the DCP patients were randomized to receive twice weekly treatment with either vehicle or tacrolimus ointment. Both treatment groups received twice daily tacrolimus ointment at times of disease exacerbations during the DCP. For the purpose of this document, the efficacy results are presented for the DCP only.

  A duration of 12 months was selected for the DCP because this would, according to the MAH, allow an assessment of prevention of flares over a period of time during which relapse would be expected to occur on a regular basis. Thus, the frequency of relapses could be measured, in addition to the time to first relapse, to assess the utility of long-term maintenance therapy.

Table 6: Design of CONTROL Studies

Study Patients [Report No.]	**Design**	**Objective**	**Enrolled in OLP Randomized into DCP [Planned for DCP: 200]**
FG-506-06-40 Adult patients, ≥ 16 years old, with mild to severe AD [FG506-06-40-R-CR-1]	Phase III, multicentre, 1:1 randomised, double-blind vehicle-controlled study consisting of a screening period of up to 1 week, an open label period (OLP) for a maximum of 6 weeks for atopic dermatitis (AD) stabilisation, in which patients received treatment with twice-daily tacrolimus ointment (0.1% for adults, 0.03% for children) and a subsequent randomized double-blind disease control period (DCP) of 12 months. For the DCP, patients were randomised to receive twice-weekly treatment with either vehicle or tacrolimus ointment. Both treatment groups received twice-daily tacrolimus ointment at times of disease exacerbation during the DCP.	To compare the efficacy and safety of once-daily, twice per week tacrolimus ointment versus once-daily, twice per week vehicle ointment to control AD over a period of 12 months.	Total study population: 257 (APS) 224 (FAS) Moderate to severe subset: 183 (APS), 155 (FAS)
FG-506-06-41 Paediatric patients, 2-15 years old, with mild to severe AD [FG506-06-41-R-CR-1]			Total study population: 267 (APS) 250 (FAS) Moderate to severe subset: 166 (APS) 153 (FAS)

Tacrolimus ointment concentration chosen for the CONTROL studies
Based on Phase II dose-response studies in adults and children it has been established that the optimal concentrations of tacrolimus ointment for treatment of atopic dermatitis (AD) are 0.03% and 0.1%. Both concentrations are approved for the second-line treatment of AD in adults, whereas only the lower 0.03% strength is approved for second-line treatment in children. In line with the current SPC,

the approved strengths of tacrolimus ointment - 0.03% for children (2-15 years old) and 0.1% for adults (≥ 16 years old) were used in the CONTROL studies FG-506-06-40 and FG-506-06-41.
Overall, the design of both trials was considered acceptable by the CHMP. The CONTROL trials did not examine both tacrolimus ointment i.e. 0.03% and 0.1% doses in adults for maintenance treatment, i.e. the lower dose 0.03% was not examined in adults for maintenance treatment. While it was considered acceptable that the MAH is not seeking an indication in adults for the lower dose the MAH was asked to provide justification as to why the 0.03% strength was not studied in adults as a maintenance treatment.

The MAH replied that they had decided to investigate a regimen aiming to prevent or at least delay exacerbations of the disease following the acute treatment of an existing flare, in the context of the post- marketing development phase of Protopic ointment.

In the case of the ointment strength to be studied in adult patients, tacrolimus 0.1% ointment had shown in pivotal efficacy studies to be more effective than the 0.03% strength in patients with moderate to severe atopic dermatitis, while retaining an acceptable safety profile. The design of the maintenance study in adult patients included all disease severities (mild, moderate and severe atopic dermatitis) and therefore it was considered that two thirds of the total target population were more likely to have a greater benefit from treatment with the higher strength. With the most common drawback likely to be a higher incidence of episodes of skin irritation. In this context, the potential benefits of using tacrolimus 0.1% ointment for maintenance treatment were considered to exceed the risk for increased skin irritation. An additional consideration was that adults with atopic dermatitis may have their disease for many years, perhaps even decades, and are known to require more potent therapies to keep their chronic disease under control. Previous studies to treat acute flares had confirmed this, making the 0.1% strength more suitable for the conduct of a study aiming at long term disease control in adults.
Prescription data collected by the MAH supports *a posteriori* that the choice made for the study was consistent with the prescription pattern of physicians using Protopic in adult patients.

The CHMP agreed with the MAH response.

Frequency of application chosen for the CONTROL studies
The selection of once a day, twice-weekly application of tacrolimus ointment for the CONTROL studies FG-506-06-40 and FG-506-06-41 was based on pharmacokinetic considerations supported by evidence from clinical practice.

Pharmacokinetic considerations:
Following topical application of tacrolimus ointment, tacrolimus is selectively delivered to the target tissue – the skin compartment. For disease control, presence of tacrolimus in the skin is pre-requisite. The half-life of tacrolimus after topical application is approximately 3 days and is reflective of a slow elimination of tacrolimus from the skin compartment. Percutaneous absorption of tacrolimus into healthy skin is lower than into diseased skin. Thus, the application frequency which reflects the apparent absorption half-life, i.e. approximately every 3 days is expected to maintain sufficient concentration of tacrolimus in the skin for the control of the disease. Therefore, once a day, twice-weekly application was used in the studies.

Evidence from clinical practice:
A retrospective analysis indicated that long-term intermittent treatment with tacrolimus ointment in patients with moderate to severe AD may reduce the risk of AD relapse (Alomar et al. 2004). This has led some dermatologists to develop a flare control strategy for selected patients. On a case by case basis, it has been shown that some patients can suffice with once weekly treatment, whereas others may require up to three times weekly application to control their disease. During protocol development, the twice per week application scheme was a consensus choice made after extensive discussion with a panel of medical experts. The MAH did not discuss any other potential treatment regimens. However, choice of treatment frequency was justified based on the application frequency, which reflects the apparent absorption half-life. The CHMP agreed that application approximately

every 3 days is expected to provide a sufficient concentration of tacrolimus in the skin for the control of the disease. Therefore, once a day, twice-weekly application was considered acceptable.

Patient population
Selection criteria for the CONTROL studies **FG-506-06-40** (adult patients ≥ 16 years old) and **FG-506-06-41** (paediatric patients, 2-15 years old) were consistent with the pivotal trials for treatment of AD, except that the CONTROL studies enrolled patients with mild to severe AD and the pivotal trials enrolled patients with moderate to severe AD. In all trials the severity of AD was graded according to the criteria of Rajka and Langeland (Rajka and Langeland, 1989).

Mild AD was included in the selection criteria of the CONTROL studies, because it was anticipated at the time of study design to expand the indication of tacrolimus ointment to include these patients. It was later decided to continue with only moderate to severe AD for twice-daily treatment of AD flares and also for the once a day, twice-weekly maintenance regimen. Thus, additional analyses which included the subpopulation of patients with moderate and severe AD were conducted for all endpoints used in both CONTROL studies. The statistical analyses based on the subpopulation of moderate and severe patients were performed retrospectively. However, given the high level of statistical significance observed in the analyses of the key endpoints for both the total trial population and the moderate to severe subset, the post hoc nature of the subset analyses was not considered by the MAH to raise any concerns for their interpretation.

The CHMP understood why patients with mild AD were included as it was anticipated that the SPC would be expanded for the treatment of mild AD. However, the CHMP requested the MAH to explain how the removal of patients with mild AD from the results of the CONTROL studies FG-506-06-40 and FG-506-06-41 affected the power of the study in its ability to detect any differences between the treatment regimens. The MAH was also asked to comment on whether post hoc analysis affected the analysis of the results in any significant way.

The MAH responded and explained that for studies FG-506-06-40 and FG-506-06-41, sample size calculation determined that 200 patients (100 per arm) with at least 50 patients in each disease severity stratum would be required. It was assumed that 30% of patients in the vehicle arm would experience no exacerbation, and the MAH aimed to detect a 25% difference in the exacerbation-free rate between the tacrolimus arm and the vehicle arm. It was further supposed that, of the patients who would experience a flare, the proportions experiencing 1, 2, 3 and > 4 flares would be uniformly distributed (a conservative approach). Under these assumptions, to power the study at 90%, to detect a difference between the treatment arms with a two-sided significance level of 5%, approximately 100 patients per arm were required. In summary, under either the protocol assumptions or the observed results the post-hoc power was considered high. Given the high level of statistical significance ($p< 0.001$) observed in the analyses of the primary endpoint (and several key secondary endpoints) for both the total study population and the combined moderate to severe subpopulation in both studies, the MAH did not consider that the post hoc nature of the subpopulation analyses raises any concerns for their interpretation.

The CHMP agreed with the MAH response.

<u>Study FG506-06-40 (adult patients ≥ 16 years old)</u>

A considerably lower percentage of patients in the tacrolimus ointment group than in the vehicle group discontinued treatment during the DCP. Lack of efficacy and withdrawal of consent were the most common reasons for discontinuation during the DCP. Few patients (0 patients in the tacrolimus ointment group versus 5 patients in the vehicle group) discontinued due to an adverse event (AE). Patient disposition for the moderate to severe AD subset was consistent with the main findings (FAS, DCP). Treatment groups were well balanced with regard to demographic and baseline characteristics, for the total population as well as for the moderate to severe subset.

Patients in the tacrolimus ointment group stayed on average longer in the DCP compared with the vehicle group (292.1 days versus 226.5 days). The mean percentage of treatment days for disease exacerbations during the DCP was lower between the treatment groups and was seen across all strata. See table 7 below for a detailed listing.

Table 7: Study Drug Exposure during the Double-blind Disease Control Phase, Study FG506-06-40

	Days in disease control phase				Percentage of days of treatment for disease exacerbation during the disease control phase			
	0.1% Tac		Vehicle		0.1% Tac		Vehicle	
	N	Mean± SD	N	Mean±SD	N	Mean±SD	N	Mean±SD
All patients	116	292.1 ± 122.9	108	226.5 ± 149.8	112	12.4 ± 21.0	106	31.5 ± 27.6
Mild	36	315.5 ± 114.1	35	246.0 ± 152.0	35	4.1 ± 8.3	35	15.6 ±18.6
Moderate	45	283.2 ± 126.5	42	230.1 ± 147.9	43	15.6 ± 24.5	41	34.6 ± 27.3
Severe	35	279.4 ± 127.0	31	199.7 ± 150.7	34	17.0 ± 23.4	30	45.8 ± 28.3
Moderate to severe	80	281.5 ± 125.9	73	217.2 ± 148.9	77	16.2 ± 23.8	71	39.4 ± 28.1
Completers	81	366.3 ± 15.0	55	361.7 ± 8..6	81	9.1 ± 17.2	55	24.0 ± 25.5
Mild	29	366.9 ± 13.3	21	362.8 ± 8.9	29	4.1 ± 8.3	21	11.3 ± 13.2
Moderate	30	364.6 ± 10.3	21	361.6 ± 6.6	30	13.8 ± 23.2	21	23.1 ± 24.0
Severe	22	367.9 ± 21.6	13	359.8 ± 11.0	22	9.3 ± 14.9	13	46.2 ± 29.1
Moderate to severe	52	366.0 ± 16.0	34	360.9 ± 8.4	52	11.9 ± 20.1	34	31.9 ± 28.1

Patient base (full analysis set, FAS): all randomised patients in the disease control period who applied study medication at least once or had any post-baseline data reported (primary analysis set). Tac: tacrolimus ointment

As expected there were higher numbers of subjects leaving the vehicle arm of the study as time progressed in the clinical trial. The MAH was requested by the CHMP to confirm whether any cases of withdrawal of consent were patients who experienced adverse events. In response, the MAH provided details of withdrawals for consent for both studies (adults and children) during the open labelled period and disease control period (see table 8 below).

Table 8: Adverse Event Related Withdrawals of Consent in Studies FG-506-06-40 (Adult) and FG 506-06-41 (Pediatric)

		Tacrolimus	Vehicle
OLP	Adults (N=257)	3/7	NA
	Children (N=267)	0/6	NA
DCP	Adults (N=224)	3/9	8/14
	Children (N=250)	4/7	8/13

NA = not applicable

Overall, very few patients withdrew consent due to AEs in the OLP, all of them were adults. In the DCP the number of patients who withdrew consent due to AEs in the tacrolimus arm was lower than in the vehicle arm. However, this difference was driven by the increased numbers withdrawing consent due to lack of efficacy in the vehicle arm. The AEs reported are consistent with the known safety profile of tacrolimus ointment.

The CHMP acknowledged that the level of patients withdrawing consent was higher in the vehicle treatment group than in the maintenance group. The additional data did not highlight any additional safety concerns.

The percentage of overall days in treatment for a disease exacerbation were lower for the moderate and severe groups of AD receiving maintenance treatment then for all patients (ITT) and for the completers (PP). Of the completers, the severe AD group appeared to have considerably lower percentage of days in exacerbation than placebo and the relative magnitude was greater for severe AD than for moderate AD. The effect of maintenance treatment relative to vehicle appears to be greater for severe AD versus moderate AD patients (for both the ITT and PP population). Based on this the

CHMP requested the MAH to comment on the differences in efficacy seen between moderate and severe AD patients, both in the adult and the paediatric patients.

The MAH responded that the percentage of days in disease exacerbation was one of the key secondary endpoints directly related to the assessment of flares. The MAH acknowledged that in the adult study the severe patients appeared to have a higher beneficial effect than the moderate patients and yet in the paediatric study the opposite effect was observed. However, the studies were not designed to provide precise treatment effects within each stratum and, though there was some variation in the observed treatment benefits among the severity subgroups, the results were consistently in favour of the tacrolimus arm.

For adult patients, a significant clinical advantage of the tacrolimus arm over the vehicle arm for the studied population (mild to severe patients) has been demonstrated and is maintained for the target sub-population (moderate to severe patients) (Table 9).

Table 9: Treatment Effect (Percentage of Days) and P-Values for Within Strata Comparisons Study FG-506-06-40 (Adults)

	Mean difference	Median difference (95% CI) †	P-value
All patients (mild to severe) (N=116 tacrolimus ; N=108 vehicle)	-19.2	-15.21 (-22.73; -8.65)	< 0.001 ‡
Moderate (N=45 tacrolimus ; N=42 vehicle)	-19.0	-17.3 (-34.9;-5.8)	< 0.001 §
Severe (N=35 tacrolimus ; N=31 vehicle)	-28.8	-25.4 (-45.2;-14.5)	< 0.001 §
Moderate to severe (N=80 tacrolimus ; N=73 vehicle)	-23.2	-23.61 (-34.77; -13.77)	< 0.001 ‡

For adults the benefit was statistically significant in all cases ($p< 0.001$). Looking at the size of the observed treatment effects in the study, both the mean and median differences were greater for the severe stratum than the moderate stratum. However, the 95% confidence intervals around the median differences show considerable overlap in the plausible range for the treatment effect.

As for adult patients, the paediatric study showed clinical advantage of the tacrolimus arm over the vehicle arm for the population defined upfront (mild to severe patients) and the effect is consistent when looking at the subgroup of moderate to severe patients and also within the subgroups of patients with moderate and severe AD respectively. This advantage was statistically significant within the moderate stratum but did not reach statistical significance within the severe stratum (Table 10).

Table 10: Treatment Effect (Percentage of Days) and P-Values for Within Strata Comparisons Study FG-506-06-41 (Pediatric)

	Mean difference	Median difference † (95% CI)	P-value
All patients (mild to severe) (N=125 tacrolimus ; N=125 vehicle)	-11.3	-6.20 (-11.78; -2.14)	< 0.001 ‡
Moderate (N=41 tacrolimus ; N=39 vehicle)	-16.6	-13.3 (-24.4;-3.7)	< 0.001 §
Severe (N=37 tacrolimus ; N=36 vehicle)	-8.8	-6.0 (-15.6;0.7)	0.124 §
Moderate to severe (N=78 tacrolimus ; N=75 vehicle)	-13.0	-10.05 (-17.48; -3.19)	< 0.001 ‡

The MAH highlighted that the results obtained based on the breakdown of data by strata should be interpreted with caution. They cannot be fully substantiated as the study was not powered for these within-stratum analyses, and the patient numbers within individual strata are quite small. A factor that

may have contributed to the findings is the less chronic disease status (shorter history of disease) in children when compared to adult patients, influencing responses to treatment.

When looking at the population with the highest perceived medical need (moderate to severe atopic dermatitis), the study reached its objective to show a significant reduction in the number of flares requiring substantial therapeutic intervention. The MAH further clarified that this is an additional treatment option that may benefit patients and is not a replacement for any current therapeutic regimen. Starting a maintenance therapy regimen should be at the discretion of the treating physician and information about the maintenance therapy option should be made available to patients in all subpopulations.

Tacrolimus ointment use

Table 11 below summarizes average tacrolimus ointment use per day. For the tacrolimus ointment group this combined double-blind DCP treatment and open-label disease exacerbation treatment. For the vehicle group, this was only open-label treatment for disease exacerbations.

Table 11: Average per Day Tacrolimus Ointment Use [g] during the Disease Control Period, Study FG506-06-40

	0.1% Tac		Vehicle	
	N	**Mean ± SD**	**N**	**Mean ± SD**
Total study population	112	1.38 ± 1.59	102	1.60 ± 2.47
Mild	34	0.71 ± 0.79	32	0.30 ± 0.69
Moderate	44	1.62 ± 2.04	39	1.71 ± 2.80
Severe	34	1.75 ± 1.34	31	2.81 ± 2.61
Moderate to severe subset	78	1.68 ± 1.76	70	2.20 ± 2.75

Patient base (full analysis set, FAS): all randomized patients in the disease control period who applied study medication at least once or had any post-baseline data reported (primary analysis set). Tac: Tacrolimus ointment.
Source: Report FG506-06-40-R-CR-1, Table 13.2.3.19; Moderate to severe subset, Table 13.4.3.19

Because of the widely scattered and skewed data distribution the data on tacrolimus ointment use are difficult to interpret. However, for the moderate to severe subset the application of tacrolimus ointment once daily, twice per week as maintenance treatment did not lead to an increase in the total average per day tacrolimus ointment use compared with the vehicle group when both maintenance treatment and disease exacerbation treatment were combined. The MAH pooled the results for moderate and severe AD groups and concluded that an increased use of tacrolimus as maintenance compared with the vehicle group was not observed. However, the difference between the treatment groups and the vehicle group is modest for the moderate group and there is a real difference seen for less daily average use in the severe group.

Results

Primary Endpoint

The primary endpoint in study FG506-06-40 was the number of disease exacerbations that required a substantial therapeutic intervention adjusted for time in the disease control period. Findings from this analysis are summarized in the table 12 below.

Table 12: Primary Endpoint: Frequency of Disease Exacerbations that Required a Substantial Therapeutic Intervention Adjusted for Length of Time at Risk during Disease Control Period, No. Patients (%), Study FG506-06-40.

Frequency of disease exacerbations:	Total study population		Moderate to severe subset	
	0.1% Tac (N=116)	Vehicle (N=108)	0.1% Tac (N=80)	Vehicle (N=73)
0	66 (56.9)	32 (29.6)	39 (48.8)	13 (17.8)
1 (> 0 < 1.5)	11 (9.5)	11 (10.2)	9 (11.3)	7 (9.6)
2 (1.5 - < 2.5)	14 (12.1)	9 (8.3)	10 (12.5)	5 (6.8)
3 (2.5 - < 3.5)	7 (6.0)	4 (3.7)	5 (6.3)	3 (4.1)
4 (3.5 - < 4.5)	4 (3.4)	4 (3.7)	3 (3.8)	2 (2.7)
5 (4.5 - < 5.5)	4 (3.4)	8 (7.4)	4 (5.0)	7 (9.6)
6 (5.5 - < 6.5)	3 (2.6)	11 (10.2)	3 (3.8)	11 (15.1)
7 (6.5 - < 7.5)	2 (1.7)	6 (5.6)	2 (2.5)	4 (5.5)
8 (7.5 - < 8.5)	3 (2.6)	8 (7.4)	3 (3.8)	7 (9.6)
9 (8.5 - < 9.5)	1 (0.9)	5 (4.6)	1 (1.3)	5 (6.8)
10 (9.5 - < 10.5)	0 (0.0)	3 (2.8)	0	3 (1.4)
≥ 10.5	1 (0.9)	7 (6.5)	1 (1.3)	6 (8.2)

Substantial therapeutic intervention is defined as a disease exacerbation lasting greater than 7 days and an IGA of 3-5 at DE day1

Adjusted for the length of time in the DCP, the number of disease exacerbations that required a substantial therapeutic intervention was significantly lower in the tacrolimus group than in the vehicle group for both the main analysis of patients with mild to severe AD and the moderate to severe subset (both analyses: $p < 0.001$, 2-sided Wilcoxon rank sum test).

In the main analysis of all patients with mild to severe AD, the median number of disease exacerbations was lower in the tacrolimus ointment group (0.0, N=116) than in the vehicle group (3.0, N=108). Consistent findings were shown for the moderate to severe subset, for which the median number of disease exacerbations was also lower in the tacrolimus ointment group (1.0, N=80) than in the vehicle group (5.3, N=73).

In relation to the primary endpoint the CHMP agreed with the MAH that there are numerically more patients not experiencing any flare in the 0.1% Tacrolimus treatment group compared with vehicle (48.8% versus 17.8% in moderate to severe AD). With maintenance tacrolimus treatment, fewer patients experienced 5 or more disease exacerbations than vehicle. However there are more patients experiencing disease exacerbations (DE) with a frequency of 1 to 4 in the 0.1% tacrolimus arm when compared with placebo. Overall, there is a shift toward fewer or no exacerbations with maintenance treatment compared with vehicle.

Secondary Endpoints

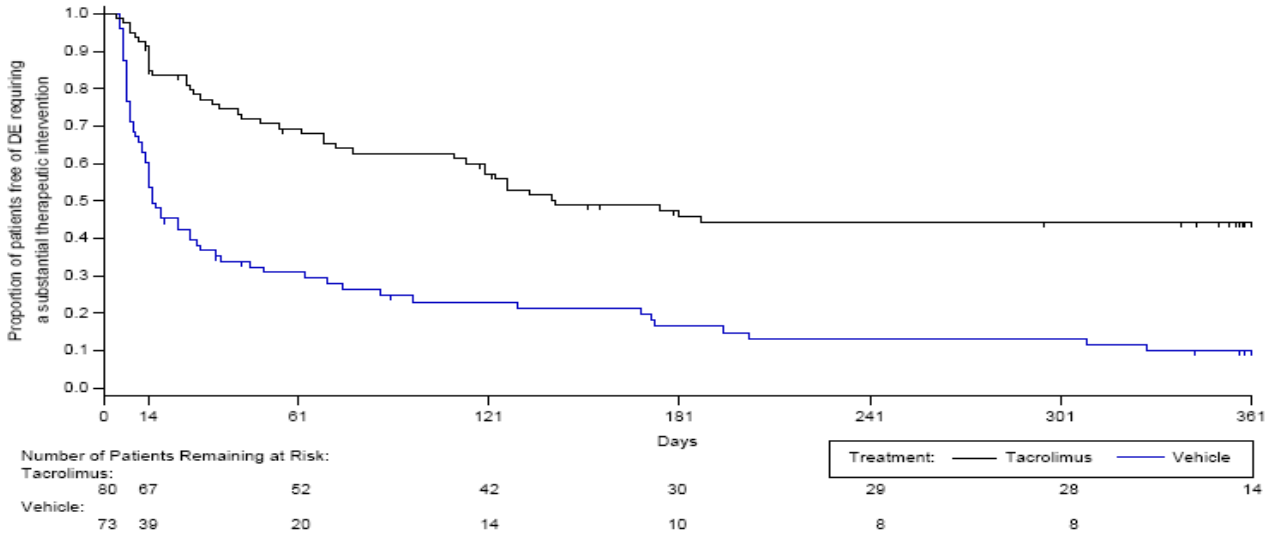
The Kaplan-Meier analysis of the time to first disease exacerbations requiring a substantial therapeutic intervention is summarized in the table 13 below.

Table 13: Kaplan-Meier Estimates of Proportion of Patients without Disease Exacerbation that Required a Substantial Therapeutic Intervention During Disease Control Period, Study FG506-06-40

	Tacrolimus ointment			Vehicle		
	Patients with event	**Patients at risk**	**Survival estimate**	**Patients with event**	**Patients at risk**	**Survival estimate**
Total study population						
N	116			108		
Week 2	13	102	0.888	42	66	0.611
Month 2	27	82	0.762	63	40	0.410
Month 4	37	70	0.668	72	28	0.314
Month 6	49	54	0.551	78	22	0.247
Month 8	51	51	0.531	81	19	0.213
Month 10	52	49	0.520	83	17	0.190
Month 12	52	28	0.520	85	3	0.168
Moderate to severe subset						
N	80			73		
Week 2	12	67	0.849	34	39	0.534
Month 2	24	52	0.693	50	20	0.308
Month 4	33	42	0.572	55	14	0.230
Month 6	41	30	0.458	59	10	0.164
Month 8	42	29	0.443	61	8	0.131
Month 10	42	28	0.443	61	8	0.131
Month 12	42	14	0.443	63	0	0.098

For the total study population the estimated rate of patients without any disease exacerbation requiring a substantial therapeutic intervention was higher in the tacrolimus group than in the vehicle group throughout the study ($p < 0.001$, Log rank test). At Month 12, the disease exacerbation-free rate was 52.0% (tacrolimus ointment group) compared with 16.8% for vehicle. Similarly a statistical significant difference in favour of tacrolimus is observed in the moderate to severe AD stratum ($p < 0.001$, Log rank test); the estimated rate of patients without any disease exacerbations at 12-month was 44.3% (tacrolimus ointment) compared with 9.8% for vehicle.

Kaplan Meier Curve: Time to first Disease Exacerbation Requiring a Substantial Therapeutic Intervention in Study FG506-06-40 (Moderate to severe Subset, FAS)



For the moderate to severe subset, the median number of disease exacerbations was 1.0 (tacrolimus ointment) versus 6.8 (vehicle), and the estimated DE-free rates at 12 months were 37.8% (tacrolimus ointment) versus 9.3% (vehicle).

The CHMP agreed with the MAH that the proportion of patients without disease exacerbation that required a substantial therapeutic intervention during disease control period was in favour of maintenance treatment versus vehicle. It was also noted that although patients receiving tacrolimus ointment as maintenance had fewer exacerbations the average number of patients at risk (of a disease exacerbation) was higher in the tacrolimus ointment group than in the vehicle arm.

The moderate to severe AD subset, post-baseline mEASI values, Eczema Area and Severity Index (EASI) and post-baseline values of affected BSA were consistently lower for the tacrolimus ointment group than for the vehicle group during the DCP (see tables 14 and 15 below for detailed listings).

Table 14: Modified Eczema Area and Severity Index during Disease Control Period, Study FG506-06-40

	Total study population				Moderate to severe subset			
	0.1% Tac		Vehicle		0.1% Tac		Vehicle	
	N	Mean±SD	N	Mean±SD	N	Mean±SD	N	Mean±SD
Day 1	108	3.0 ± 3.5	101	3.3 ± 3.3	75	3.8 ± 3.9	70	4.0 ± 3.5
Month 2	109	4.5 ± 6.6	106	6.9 ± 9.2	76	5.7 ± 7.0	72	8.2 ± 9.8
Month 4	98	4.2 ± 6.1	67	6.9 ± 9.1	68	5.4 ± 6.9	44	8.8 ± 10.4
Month 6	94	4.8 ± 7.9	62	7.8 ± 12.0	63	6.2 ± 9.1	40	10.6 ± 14.1
Month 6, LOCF	112	5.6 ± 8.4	106	9.0 ± 12.3	77	7.1 ± 9.2	72	11.3 ± 13.5
Month 8	85	4.2 ± 6.1	60	6.7 ± 11.3	55	4.9 ± 6.7	38	9.0 ± 13.4
Month 10	82	3.6 ± 6.1	60	6.3 ± 7.1	52	4.7 ± 7.2	38	8.5± 7.7
Month 12	76	2.3 ± 3.7	56	6.1 ± 9.9	48	2.7 ± 4.2	35	8.3 ± 11.8
EOS, LOCF	112	4.3 ± 7.2	106	8.3 ± 11.3	77	5.3 ± 7.8	72	10.4 ± 12.2

Table 15: Affected Body Surface Area during Disease Control Period, Study FG506-06-40

	Total study population				Moderate to severe subset			
	0.1% Tac		Vehicle		0.1% Tac		Vehicle	
	N	Mean±SD	N	Mean±SD	N	Mean±SD	N	Mean±SD
Day 1	116	6.7 ± 10.1	108	6.7 ± 8.1	80	8.7 ± 11.5	73	8.6 ± 8.9
Month 2	106	6.7 ± 12.3	98	10.2±13.7	74	8.9 ± 14.1	67	13.2 ± 15.4
Month 4	98	6.0 ± 9.4	67	11.1±14.2	68	7.8 ± 10.6	44	14.5 ± 16.1
Month 6	95	6.7 ± 10.4	62	9.6 ± 14.2	64	8.6 ± 11.9	40	12.7 ± 16.7
Month 6, LOCF	116	8.4 ± 13.0	108	11.7±16.2	80	10.6±14.6	73	14.8 ± 18.1
Month 8	85	6.3 ± 9.8	61	9.7 ± 14.2	55	7.7 ± 11.3	39	12.8 ± 16.5
Month 10	82	5.1 ± 9.4	60	8.9 ± 11.6	52	6.5 ± 11.3	38	11.7 ± 13.2
Month 12	76	3.4 ± 6.2	56	8.7 ± 13.7	48	3.8 ± 6.8	35	11.7 ± 16.3
EOS, LOCF	116	6.6 ± 12.2	108	11.3 ± 15.8	80	8.1 ± 13.9	73	14.4 ± 17.5

Both the investigators global assessment score and dermatology life quality index were superior for tacrolimus versus placebo. See tables 16 and 17 below for detailed results.

Table 16: Investigator's Global Assessment of Clear, Almost Clear or Mild (≤ 2) during Disease Control Period, Study FG506-06-40

	Total study population				Moderate to severe subset			
	0.1% Tac		Vehicle		0.1% Tac		Vehicle	
	N	No. (%)	N	No. (%)	N	No. (%)	N	No. (%)
Day 1	116	116 (100)	108	108 (100)	80	80 (100)	73	73 (100)
Month 2	106	91 (85.8)	99	66 (66.7)	74	70 (94.6)	68	62 (91.2)
Month 4	98	83 (84.7)	67	45 (67.2)	68	53 (77.9)	44	28 (63.6)
Month 6	95	81 (85.3)	62	45 (72.6)	64	50 (78.1)	40	25 (62.5)
Month 6, LOCF	116	92 (79.3)	108	66 (61.1)	80	57 (71.3)	73	39 (53.4)
Month 8	85	77 (90.6)	61	45 (73.8)	55	50 (90.9)	39	27 (69.2)
Month 10	82	72 (87.8)	60	47 (78.3)	52	44 (84.6)	38	26 (68.4)
Month 12	76	70 (92.1)	56	47 (83.9)	48	43 (89.6)	35	27 (77.1)
EOS, LOCF	116	92 (79.3)	108	70 (64.8)	80	58 (72.5)	73	42 (57.5)

Table 17: Dermatology Life Quality Index, Total Score

	Total study population				Moderate to severe subset			
	0.1% Tac		Vehicle		0.1% Tac		Vehicle	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Day 1	107	3.7 (3.7)	99	4.8 (4.5)	74	3.9 (3.5)	68	5.6 (4.8)
Month 2	107	3.7 (3.6)	98	6.3 (5.7)	75	4.1 (3.7)	67	7.1 (6.0)
Month 4	97	3.6 (3.4)	66	5.4 (4.9)	68	4.0 (3.6)	43	6.2 (5.2)
Month 6	92	3.2 (2.9)	60	5.5 (5.5)	62	3.6 (3.2)	39	6.9 (6.2)
Month 6, LOCF	110	3.5 (3.4)	99	6.8 (6.4)	76	3.8 (3.5)	68	8.1 (6.9)
Month 8	83	3.6 (3.8)	58	5.9 (5.5)	54	3.6 (3.8)	37	7.2 (6.2)
Month 10	79	3.0 (2.7)	59	5.7 (4.9)	51	3.4 (2.8)	37	7.0 (5.3)
Month 12	75	3.2 (3.0)	55	4.8 (4.9)	48	3.5 (2.9)	34	5.9 (5.6)
EOS, LOCF	110	3.6 (3.5)	99	6.8 (6.4)	76	3.8 (3.3)	68	7.9 (6.9)

Study FG506-06-41 (Paediatric patients 2-15 years old)

The objective of this study was to compare the efficacy and safety of a tacrolimus ointment 0.03% regimen to a vehicle-based regimen administered to control AD in paediatric patients over a period of 12 months.

Regarding patient disposition, a lower percentage of patients in the tacrolimus ointment group (24.0%, 30/125) than in the vehicle group (34.4%, 43/125) discontinued treatment during the DCP. The most common reasons for discontinuation were withdrawal of consent, IGA > 2 at end of OLP and lack of efficacy. The CHMP considered that the treatment groups were generally well balanced with regard to demographic and baseline characteristics.

In the table on study drug exposure (Table 18) for all patients, the moderate to severe AD groups of patients receiving tacrolimus maintenance treatment were noted to have a longer duration in the DCP compared with the vehicle group. The moderate to severe AD group receiving maintenance tacrolimus ointment, recorded fewer days of open-label treatment for disease exacerbations compared with the vehicle group as the percentage of days of treatment for disease exacerbations are lower in the maintenance group versus placebo.

Table 18: Study Drug Exposure during the Disease Control Phase, Study FG506-06-41

	Days in disease control phase				Percentage of days of treatment for disease exacerbation during the disease control phase			
	0.03% Tac		Vehicle		0.03% Tac		Vehicle	
	N	Mean± SD	N	Mean±SD	N	Mean±SD	N	Mean±SD
All patients	125	316 ± 98	125	295 ± 111	125	13.9 ± 20.7	125	25.2 ± 25.9
Mild	47	336 ± 84	50	318 ± 100	47	8.8 ± 17.0	50	18.1 ± 22.9
Moderate	41	324 ± 91	39	280 ± 118	41	10.9 ± 14.2	39	27.5 ± 23.1
Severe	37	282 ± 116	36	278 ± 116	37	23.7 ± 27.1	36	32.5 ± 30.4
Moderate to Severe	78	304 ± 105	75	279 ± 116	78	16.9 ± 22.1	75	29.9 ± 26.8
Completers	95	362 ± 7	82	365 ± 11	95	8.0 ± 11.3	82	15.6 ± 19.1
Mild	41	362 ± 7	39	364 ± 10	41	5.7 ± 7.7	39	17.3 ± 28.8
Moderate	31	363 ± 8	24	363 ± 10	31	8.4 ± 11.6	24	20.8 ± 19.8
Severe	23	361 ± 7	19	366 ± 16	23	11.5 ± 15.3	19	15.2 ± 15.5
Moderate to severe	54	362 ± 8	43	365 ± 12	54	9.7 ± 11.3	43	18.3 ± 18.0

On review of the percentage of days of treatment for disease exacerbation during the disease control period for all patients in a moderate AD category, the CHMP observed a significant difference between the maintenance tacrolimus phase and the vehicle arm. This effect was considerably less for the severe AD groups. This effect was also seen in the patients who completed the study. The number of patients were however low and the results are recorded with wide standard deviations so it was considered difficult to draw any firm conclusions.

The MAH concluded in their application that 'However, for the moderate to severe subset the application of tacrolimus ointment once daily, twice per week as maintenance treatment did not lead to an increase in the total average per day tacrolimus ointment use compared with the vehicle group, when both maintenance treatment and disease exacerbation treatment were combined.'

Although this is true, the moderate group have an increased use of tacrolimus ointment use. Only the severe group have less average daily use of tacrolimus. As the amount used is a sum of maintenance and disease exacerbation use the Committee concluded that the severe group had less numbers of disease exacerbation then the vehicle severe group, where as this benefit is not seen for the moderate AD group. Therefore, the lower incidence of disease exacerbations seen in moderate AD using tacrolimus maintenance treatment might be at the expense of increased tacrolimus use.

Results

Primary Endpoint

The primary endpoint in study FG506-06-41 was the number of disease exacerbations that required a substantial therapeutic intervention adjusted for time in the disease control phase. Findings from this analysis are summarized in the table 19 below.

Table 19: Primary Endpoint: Frequency of Disease Exacerbations that Required a Substantial Therapeutic Intervention Adjusted for Length of Time at Risk during Disease Control Period, No. Patients (%), Study FG506-06-41

Frequency of disease exacerbations	Total study population		Moderate to severe subset	
	0.03% Tac (N=125)	Vehicle (N=125)	0.03% Tac (N=78)	Vehicle (N=75)
0	63 (50.4)	37 (29.6)	36 (46.2)	16 (21.3)
1 (> 0 < 1.5)	19 (15.2)	18 (14.4)	8 (10.3)	10 (13.3)
2 (1.5 - < 2.5)	13 (10.4)	14 (11.2)	10 (12.8)	11 (14.7)
3 (2.5 - < 3.5)	13 (10.4)	12 (9.6)	10 (12.8)	8 (10.7)
4 (3.5 - < 4.5)	6 (4.8)	5 (4.0)	6 (7.7)	3 (4.0)
5 (4.5 - < 5.5)	2 (1.6)	12 (9.6)	1 (1.3)	9 (12.0)
6 (5.5 - < 6.5)	3 (2.4)	7 (5.6)	3 (3.8)	6 (8.0)
7 (6.5 - < 7.5)	6 (4.8)	11 (8.8)	4 (5.1)	5 (6.7)
8 (7.5 - < 8.5)	0	4 (3.2)	0	3 (4.0)
9 (8.5 - < 9.5)	0	2 (1.6)	0	1 (1.3)
10 (9.5 - < 10.5)	0	2 (1.6)	0	2 (2.7)
≥ 10.5	0	1 (0.8)	0	1 (1.3)

Substantial therapeutic intervention is defined as a disease exacerbation lasting greater than 7 days and an IGA of 3-5 at DE day1.

Adjusted for the length of time in the DCP, the number of disease exacerbations that required a substantial therapeutic intervention was significantly lower in the tacrolimus group than in the vehicle group for the main analysis of patients with moderate to severe subset.

Consistent findings were shown for the moderate to severe AD stratum, for which the median number of disease exacerbations was also lower in the tacrolimus ointment group (1.0, N=78) than in the vehicle group (2.9, N=75).

While the CHMP acknowledged that the tacrolimus 0.03% treatment arm had fewer numbers of disease exacerbations, the benefit was not seen in all frequencies. However, the overall results show a shift toward none or fewer disease exacerbations with tacrolimus treatment compared to placebo treatment.

Secondary Endpoints

The Kaplan-Meier estimate of time to first disease exacerbation requiring a substantial therapeutic intervention is summarized in the table 20 below.

Table 20: Kaplan-Meier Estimate of Proportion of Patients without a Disease Exacerbation that Required a Substantial Therapeutic Intervention during Disease Control Period, Study FG506-06-41

	0.03% Tacrolimus ointment			Vehicle		
	Patients with event	Patients at risk	Survival estimate	Patients with event	Patients at risk	Survival estimate
Total study population						
N	125			125		
Week 2	19	105	0.848	33	92	0.736
Month 2	29	95	0.767	65	60	0.480
Month 4	43	79	0.651	74	49	0.407
Month 6	51	68	0.583	81	40	0.347
Month 8	55	64	0.549	85	36	0.313
Month 10	62	56	0.489	88	32	0.286
Month 12	63	27	0.480	89	17	0.277
Moderate to severe subset						
N	78			75		
Week 2	15	63	0.808	25	50	0.667
Month 2	22	56	0.718	45	30	0.400
Month 4	32	44	0.585	51	22	0.317
Month 6	37	36	0.515	57	14	0.227
Month 8	39	34	0.486	59	12	0.194
Month 10	43	30	0.429	59	11	0.194
Month 12	43	14	0.429	60	6	0.177

For the moderate to severe subset, the results were similar to the analysis of the total study population: the estimated rate of patients without disease exacerbation requiring a substantial therapeutic intervention was significantly higher in the tacrolimus ointment group than in the vehicle group throughout the DCP ($p < 0.001$, Log rank test). The 12-month disease exacerbation-free rate was 42.9% (tacrolimus ointment) versus 17.7% (vehicle). The median time to first disease exacerbation requiring a substantial therapeutic intervention was 217 days in tacrolimus ointment group and 36 days in the vehicle group.

The analyses of frequency and time to first disease exacerbation including those not requiring a substantial therapeutic intervention were significantly in favour of tacrolimus ointment versus vehicle. For the moderate to severe subset, the median number of disease exacerbations was 1.5 (tacrolimus ointment) versus 3.5 (vehicle) and the estimated DE-free rates at 12 months were 37.6% (tacrolimus ointment) versus 11.8% (vehicle). The median time to first DE was 146 days (tacrolimus ointment) and 17 days (vehicle).

The CHMP acknowledged the MAH conclusion as by patients without a disease exacerbation that required a substantial therapeutic intervention during disease control period was found in favour of tacrolimus maintenance treatment. The median time to first DE was 146 days (tacrolimus ointment) and 17 days (vehicle). The median number of disease exacerbations was 1.5 versus 3.5 for tacrolimus ointment maintenance versus vehicle.

Secondary endpoints mEASI, EASI, affected BSA and IGA were found to be in favour of maintenance treatment versus vehicle in adults however the same efficacy was not seen in children as some of the endpoint at 12 months maintenance treatment was no different than vehicle. The MAH was therefore requested by the CHMP to comment.

The MAH responded that the parameters mEASI, EASI, IGA and affected BSA, were included in the studies purely to monitor the disease status over time. It was never planned to formally compare tacrolimus versus vehicle arm at any study time-point for these non-flare related secondary parameters. The MAH had no expectation to see main improvement in the tacrolimus arm compared to the vehicle arm for these non-flares related secondary endpoints, since the endpoints mEASI, EASI,

BAS and IGA are considered not to be appropriate endpoints for the study objective of assessing flare prevention. Data for these endpoints were collected at all scheduled visits and comparisons of tacrolimus versus vehicle over time do not take into account whether patients were being treated with disease control treatment or with disease exacerbation treatment.

The MAH believed that the small observed differences for mEASI, EASI, IGA and affected BSA during DCP do not translate into clinical relevance. The MAH further believed that for the assessment of flare prevention, only flare-specific endpoints can address this question. These secondary endpoints were collected at pre-defined time points and so may not be sensitive to disease exacerbations which could occur at any time point.

The CHMP agreed with the MAH explanation.

For both the total population and the moderate to severe AD subset, post-baseline affected BSA values were generally lower for the tacrolimus ointment group than for the vehicle group during the DCP (FAS).

For the total population as well as the moderate to severe AD subset, the proportion of patients with a post-baseline IGA score of ≤ 2 was higher for the tacrolimus ointment group than for the vehicle group throughout the DCP (FAS). The scores of the Infants Dermatology Life Quality Index (IDLQI) and Children's Dermatology Life Quality Index (CDLQI) assessments were similarly low in both treatment arms throughout the study.

Discussion of Clinical Efficacy results

As the primary and secondary endpoints were pooled for moderate and severe AD patients the CHMP requested the MAH to provide a separate breakdown of the primary and secondary endpoints for these categories separately.

The MAH responded that the clinical development supporting the indication of maintenance treatment with Protopic was designed to show patient benefit in terms of reduction in number of disease flares over a period of 12 months. This period was considered by the MAH as long enough to allow detection of improvement even in those subjects with less severe disease or fewer flares.

The pre-defined primary endpoint for both studies FG-506-06-40 and FG-506-06-41 was the number of disease exacerbations (DE) that required substantial therapeutic intervention during the Disease Control Period (DCP).

Key secondary endpoints related to disease exacerbations in both studies were:

- Time to the first disease exacerbation requiring "substantial therapeutic intervention"
- Total number of disease exacerbations during the Disease Control Period (including those that did not require "substantial therapeutic intervention")
- Time to the first disease exacerbation (including those that didn't require "substantial therapeutic intervention")
- Percentage of days of disease exacerbation treatment.

When assessing efficacy outcome by severity strata in the adult population, the data consistently showed a statistically significant difference in favour of the tacrolimus treatment arm (maintenance arm) versus the vehicle arm, regardless of disease severity as assessed at the start of the study. This was the case for the primary and all secondary endpoints related to disease exacerbations. An overview of the efficacy by severity strata is included in tables 21 and 22 below.

Table 21: Overview of Efficacy for Study FG-506-06-40 (Adults)

	Moderate		Severe	
	Tacrolimus 0.1% Twice weekly (N=45)	Vehicle Twice weekly (N=42)	Tacrolimus 0.01% Twice weekly (N=35)	Vehicle Twice weekly (N=31)
Primary endpoint				
Median number of DEs requiring substantial intervention adjusted for time at risk (% of patients without DE requiring substantial intervention)	0.0 (55.6)	4.5 (21.4)	1.0 (40.0)	6.0 (12.9)
Secondary endpoints				
Median time to first DE requiring substantial intervention	> 365 †days	29 days	120 days	13 days
Median number of DEs adjusted for time at risk (% of patients without any DE periods)	1.0 (46.7)	6.2 (14.3)	1.4 (37.1)	7.0 (9.7)
Median time to first DE	127 days	14 days	78 days	12 days
Mean (SD) percentage of days of DE exacerbation treatment	14.9 (24.1)	34.6 (27.0)	17.5 (23.2)	45.0 (28.2)
Median (25%, 75%) percentage of days of DE exacerbation treatment	0.3 (0.0; 21.8)	36.5 (6.5;54.5)	8.7 (0.0; 33.2)	52.4 (22.2;71.2)

Table 22: Overview of Efficacy for Study FG-506-06-41 (Pediatric)

	Moderate		Severe	
	Tacrolimus 0.03% Twice weekly (N=41)	Vehicle Twice weekly (N=39)	Tacrolimus 0.03% Twice weekly (N=37)	Vehicle Twice weekly (N=36)
Primary endpoint				
Median number of DEs requiring substantial intervention adjusted for time at risk (% of patients without DE requiring substantial intervention)	0.0 (51.2)	3.1 (20.5)	2.0 (40.5)	2.5 (22.2)
Secondary endpoints				
Median time to first DE requiring substantial intervention	295 days	45 days	122 days	32 days
Median number of DEs adjusted for time at risk (% of patients without any DE periods)	1.0 (46.3)	4.1 (15.4)	2.0 (35.1)	3.1 (13.9)
Median time to first DE	217 days	31 days	92 days	14 days
Mean (SD) percentage of days of DE exacerbation treatment	10.9 (14.2)	27.5 (23.1)	23.7 (27.1)	32.5 (30.4)
Median (25%, 75%) percentage of days of DE exacerbation treatment	2.2 (0.0 ; 18.0)	24.0 (3.7;49.2)	14.0 (0.0; 36.3)	20.5 (6.9; 64.8)

The analysis for intra stratum comparisons in the paediatric patients, which are presented in Table 23, revealed that significance for all endpoints could be achieved in the moderate severity group. In the severe stratum the time to first disease exacerbation requiring substantial therapeutic intervention, as well as the time to first disease exacerbation were statistically significant at the 5% level.
However, the improvements in the number of disease exacerbations requiring substantial therapeutic intervention, the number of disease exacerbations, and the percentage days of disease exacerbation treatment during DCP were not statistically significant.

For all key endpoints numerical trends in favour of tacrolimus were observed. Whether these findings reflect true differences between the strata or a by-chance finding is according to the MAH, difficult to assess, since it needs to be considered that the study was not powered to show significance for intra stratum comparisons.

Table 23: P-values for Intra Stratum Comparisons (Additional Analysis) Study FG-506-06-41 (Pediatric)

	Moderate N=80 (41 tacrolimus + 39 vehicle)		**Severe N=73 (37 tacrolimus + 36 vehicle)**	
	Treatment effect	P-value	Treatment effect	P-value
Primary endpoint				
Number of disease exacerbations requiring substantial therapeutic intervention adjusted for length of time at risk †	-2.03 (-3.00;-0.93)	< 0.001	-0.96 (-2.01;0.00)	0.243
Secondary endpoints				
Time to first disease exacerbation requiring substantial therapeutic intervention §	0.382 (0.216;0.673)	< 0.001	0.575 (0.329; 1.002)	0.045
Number of disease exacerbations adjusted for length of time at risk †	-2.18 (-4.08;-1.00)	< 0.001	-1.03 (-2.98;0.00)	0.147
Time to first disease exacerbation §	0.383 (0.221;0.663)	< 0.001	0.520 (0.305;0.887)	0.012
Percentage of days of disease exacerbation treatment during DCP †	-13.3 (-24.4;-3.7)	< 0.001	-6.0 (-15.6;0.7)	0.124

When looking at the values for the endpoints there are numerical differences in favour of the tacrolimus arm (maintenance arm). However, the differences were not statistically significant. The fact that a numerical trend exists would support the hypothesis that intra stratum analyses, because performed on smaller groups, are prone to higher variability in analyses outcomes, leading to results which are not in line with clinical experience i.e. that both moderate and severe paediatric patients do respond to treatment with tacrolimus.

The MAH believed that these data indicate that adults and children benefit substantially from maintenance therapy. Considering the fact that the studies were not designed to show differences at strata level, the strength of the observed effect clearly favours maintenance therapy. The MAH further argued that this is an additional treatment option that may benefit patients and is not a replacement for any current therapeutic regimen. Starting a maintenance therapy regimen should be at the discretion of the treating physician and information about this maintenance therapy option should be made available to patients in all subpopulations.

The CHMP was of the opinion that when assessing efficacy outcome by severity strata in the adult population, the data consistently show a statistically significant difference in favour of the tacrolimus treatment arm (maintenance arm) versus the vehicle arm, regardless of disease severity as assessed at the start of the study. This was the case for the primary and all secondary endpoints related to disease exacerbations. In paediatric patients efficacy outcome showed statistically significant difference in favour of maintenance treatment with tacrolimus in patients with moderate AD. Statistical significance was not shown for severe AD in children for maintenance tacrolimus treatment versus vehicle (acute treatment of flare up). While the study was not powered to show treatment difference per severity of disease there is a trend in favour of maintenance treatment.

Allowing for the possibility of disease differences in adults and children, the CHMP requested the MAH to comment on differences in effect seen in the two groups and comment on, and consider whether this effect could be due to suboptimal treatment in paediatric group or an inappropriate treatment regimen for children.

The MAH emphasised in their response that it is important to consider that the CONTROL studies FG-506-06-40 and FG-506-06-41 were designed to show differences in the primary endpoint for the mild to severe population. The effect shown for the primary endpoint and key secondary endpoints was strong enough to be detected and to be significant for the smaller moderate to severe subgroup, in spite of the fact that the studies were not designed to show differences at that level of analysis. Beyond that, a high variability appeared to influence the outcomes of assessments conducted at the level of individual severity strata, particularly in the paediatric population and results should be interpreted with caution.

No evidence is available to favour a particular hypothesis regarding factors influencing response to treatment, except the fact that these studies were not designed to run meaningful severity strata sub-analyses. Children being less chronically affected than adults may be an important factor.

Further, a patient with moderate disease may be expected to respond more easily to any treatment than a patient with severe disease. Compliance is also known to be different in paediatric versus adult therapy overall. The MAH suggested that it is probably a combination of all these factors is closer to reality than one single factor.

Data from study FG-506-06-41 show that 51.2% of paediatric patients with moderate AD at study entry had no flare over a period of 12 months maintenance treatment with tacrolimus ointment compared to 20.2% in the vehicle arm. In the group of paediatric patients with severe AD the pattern in favour of maintenance therapy was similar with 40.5% of patients in the tacrolimus arm presenting no flare versus 22.2% in the vehicle arm (Table 24). These differences are considered clinically meaningful to the affected patients.

Table 24: Percentage of Patients without a Disease Exacerbations Requiring Substantial Therapeutic Intervention Adjusted for Length of Time at Risk, Study FG-50606-41

FG-506-06-41	Moderate		Severe	
Number of disease exacerbations (frequency class)	Tacrolimus N=41	Vehicle N=39	Tacrolimus N=37	Vehicle N=36
0	21 (51.2)	8 (20.5)	15 (40.5)	8 (22.2)

The MAH concluded that differences have been observed between adults and children in the response to maintenance treatment especially at the severity strata level. However, the meaning of such differences has to be interpreted with caution considering that the clinical studies conducted were not designed to show statistically significant differences at that level. The MAH was of the opinion that the magnitude of the response to maintenance therapy (reduction in number of disease exacerbations) in paediatric patients indicates that the large number of patients having no flare over a period of 12 months in the maintenance therapy group represents a true clinical benefit to both moderate and severe paediatric patients and provides evidence that the investigated regimen was effective.

The MAH argued further that the results for patients with moderate-to-severe AD are consistent with those published recently from a post-marketing clinical study conducted with tacrolimus ointment in maintenance therapy (Study 20-04-002; Breneman et al, 2008). This was a multicentre study with 384 adults and children, designed to assess the impact of topical corticosteroids on the safety and efficacy of tacrolimus ointment in the short-term treatment of AD and to evaluate the long-term efficacy and safety of 3-times-weekly use of tacrolimus ointment. The results showed that patients treated with tacrolimus ointment had a significantly greater number of flare-free treatment days compared with vehicle (mean, 177 vs. 134 days). Similarly, median time to first relapse was significantly longer for patients treated with tacrolimus ointment compared with vehicle (169 days vs. 43 days). Overall, the

number of disease relapses per patient was significantly reduced in favour of tacrolimus and the mean number of disease relapse days was significantly less for tacrolimus (46 days) compared with vehicle (65 days). Disease relapse treatment with twice-daily tacrolimus ointment was successful in 83% of patients in each group. Finally, the MAH concluded that the results of this study, together with the CONTROL studies confirm that maintenance treatment of AD is an effective paradigm, and that two applications per week are sufficient for clinical efficacy.

The CHMP acknowledged the MAH response. In the CONTROL studies patients were categorised into mild, moderate, and severe categories according to Rajka Langeland criteria. To gain more insight, the CHMP requested that the MAH should indicate the number of disease exacerbations of the patients enrolled in each category. The MAH was also asked to propose suitable and specific wording for the SPC with respect to patients most suitable for maintenance treatment, specifically the criterion number of flares per year, in line with the scoring criteria of moderate and severe categories. The MAH response is discussed in section 3.4 of this report.

The CHMP agreed with he MAH that efficacy has been shown for maintenance treatment. Twice weekly maintenance treatment has shown to result in less flares of AD and prolong time to flare relapse. It should be noted that the additional summary study submitted by the MAH (Study 20-04-002; Breneman et al, 2008) was not submitted in full by the MAH. However, the CHMP was of the opinion that the additional study was in support of the pivotal CONTROL studies.

Clinical safety

Exposure to the Drug

At the time of the Protopic Renewal 2006, a total of 17,449 patients with AD had been treated (at least one application) with tacrolimus ointment in a clinical trial. To date a total of 24,166 patients have received tacrolimus ointment in clinical studies.

Study FG-506-06-40: CONTROL Study (Adults)

Open-Label Period

The most frequently reported application-site adverse events (AEs) during the OLP (N=257, ≥ 3%), irrespective of causality, were irritation (32.3%), pruritus (18.7%) warmth (7.0%) and folliculitis (4.3%). Frequently reported treatment-related AEs during the OLP (N=257, ≥ 3%), which occurred at application-site were: irritation (32.3%), pruritus (17.9%), warmth (7.0%) and folliculitis (4.3%).
There were no Serious Adverse Events (SAEs) or deaths during the OLP. Two patients had a treatment-related non-serious AE that led to discontinuation (application-site pruritus; application-site irritation) during the OLP.

Disease Control Period

See table 10 for the most frequently reported treatment related AEs that occurred during the DCP.

Table 25: Incidence of Most Frequently Reported Treatment-related Adverse Events during Disease Control Period, Study FG-506-06-40

	Mild to severe AD		Moderate to severe AD	
MedDRA preferred term	**0.1% Tac**	**Vehicle †**	**0.1% Tac**	**Vehicle**
	N=116	N=108	N=80	N=73
Application-site				
Application-site pruritus	13 (11.2)	12 (11.1)	9 (11.3)	9 (12.3)
Application-site folliculitis	6 (5.2)	8 (7.4)	6 (7.5)	7 (9.6)
Application-site irritation	6 (5.2)	7 (6.5)	4 (5.0)	6 (8.2)
Application-site infection	6 (5.2)	2 (1.9)	5 (6.3)	2 (2.7)
Herpes simplex	4 (3.4)	3 (2.8)	3 (3.8)	3 (4.1)
Impetigo	2 (1.7)	4 (3.7)	2 (2.5)	4 (5.5)
Non-application-site				
Pruritus	4 (3.4)	6 (5.6)	2 (2.5)	4 (5.5)

The CHMP concluded that the application site reactions application-site pruritus and application-site infection occurred more frequently in the tacrolimus ointment group versus vehicle (moderate to severe AD groups). For non application site reactions nasopharyngitis, headache and respiratory tract infection viral occurred more commonly in the tacrolimus ointment group versus vehicle (moderate to severe AD groups).

Serious Adverse Events
Overall, eight patients experienced a SAE. Five patients in the tacrolimus ointment arm and three in the vehicle arm. Six of the SAEs were considered by the investigator to be unrelated to study medication. These comprised one patient each with renal cell carcinoma, food allergy, cholelithiasis, dermatitis exfoliative, prostate cancer and breast hyperplasia. Two patients had a SAE during the DCP, which was considered by the investigator to be treatment-related: application-site infection with outcome "recovered" after study medication was discontinued, and Kaposi's varicelliform eruption. The study medication was reduced and the patient recovered.

Other Adverse Events
Study discontinuation:
Three patients had a non-serious AE that led to discontinuation, all in the vehicle group. Two of the AEs were considered by the investigator to be unrelated to study medication. Application-site paraesthesia (verbatim: extreme paraesthesia) was the only AE which was assessed as possibly related to study drug and resulted in discontinuation. No patient in the tacrolimus ointment arm discontinued the study due to an adverse event.

Neoplasm:
Neoplasms were diagnosed in seven patients during the DCP. They were warts or verrucae (4), Ledderhose's disease (1), renal cell carcinoma (1) and prostate carcinoma (1). All but the patient with prostate carcinoma recovered within the study period. Only one neoplasm was assessed as related to study medication: one case of viral warts in the vehicle arm was assessed as probably related to study medication.

Alcohol intolerance:
Six patients experienced alcohol intolerance during the DCP, and all cases were assessed as probable or highly probable related to study medication. Most episodes were short and resolved on the day of onset, but there were three reports of ongoing adverse events at end of the study. The reported alcohol intolerance in two patients had already an onset during the OLP and continued into the DCP.

Safety conclusion on study FG-506-06-40
The MAH concluded that the nature and incidence of AEs in study FG-506-06-40 were consistent with those listed in the approved SPC for tacrolimus ointment, with no apparent differences between patients with mild to severe AD and those with moderate to severe AD. Frequently reported treatment-related AEs were application-site pruritus, folliculitis, irritation, infection, herpes simplex and impetigo and at non-application-site pruritus. One treatment-related AE, application-site paraesthesia, led to discontinuation. In seven patients neoplasm was reported, one case (warts) was assessed as being causally related to study treatment.

The CHMP concluded that in general the adverse events recorded during study FG-506-06-40 did not highlighted any new safety findings. Of the application site reactions application-site pruritus and application-site infection occurred more frequently in the tacrolimus ointment group versus vehicle (moderate to severe AD groups). For non application site reactions nasopharyngitis, headache and respiratory tract infection viral occurred more commonly in the tacrolimus ointment group versus vehicle (moderate to severe AD groups.

Study FG-506-06-41 CONTROL Study (Paediatric patients)

Open-label period
The most frequently reported application-site AEs during the OLP (N=267, ≥ 3%), irrespective of causality, were application-site pruritus (14.2%) and application-site irritation (6.0%). The most

frequently reported non-application-site AE during the OLP, irrespective of causality, was nasopharyngitis (5.6%). There were no SAEs or deaths during the OLP. Two patients experienced a treatment-related adverse event that led to discontinuation during the OLP (eczema herpeticum, application-site pruritus). Both were of moderate intensity, in one patient the event was reported as ongoing and in the other as recovered.

The CHMP acknowledged that application site pruritus and irritation (application site reactions) and nasopharyngitis (non application site reactions) were the most common AE's reported. Application site burning and application site pruritus are listed adverse events in section 4.8 of the SPC

Disease Control Period
Table 26 below illustrates the most frequently reported treatment related AE's occurring during the DCP.

Table 26: Incidence of Most Frequently Reported Treatment-related Adverse Events during Disease Control Period, Study FG-506-06-41

	Mild to severe AD		Moderate to severe AD	
	0.03% Tac	**Vehicle**	**0.03% Tac**	**Vehicle**
MedDRA preferred term	N=125	N=125	N=78	N=75
Application-site				
Application-site pruritus	9 (7.2)	12 (9.6)	**8 (10.3)**	**8 (10.7)**
Impetigo	7 (5.6)	2 (1.6)	**6 (7.7)**	**2 (2.7)**
Application-site infection	5 (4.0)	3 (2.4)	**5 (6.4)**	**3 (4.0)**
Skin papilloma	2 (1.6)	4 (3.2)	**2 (2.6)**	**3 (4.0)**
Non-application-site				
Pruritus	10 (8.0)	2 (1.6)	**7 (9.0)**	**2 (2.7)**
Nasopharyngitis	7 (5.6)	6 (4.8)	**7 (9.0)**	**5 (6.7)**
Eczema infected	2 (1.6)	4 (3.2)	**2 (2.6)**	**4 (5.3)**

The CHMP acknowledged that application site infection and impetigo are assessed as treatment related AE's and that these occurred at a higher frequency with maintenance treatment compared to vehicle treatment. Nasopharyngitis and pruritus are assessed as treatment related, non application site, AE's occurring more frequently with maintenance treatment compared with vehicle. Findings in the moderate to severe subpopulation were similar to those of the total population with mild to severe AD.

No patient died during the study.
Serious Adverse Events
Overall, eight serious adverse events occurred. Seven in patients treated in the tacrolimus ointment arm (5.6%) and one in the vehicle arm (0.8%). The reported serious adverse events were asthma, bronchopneumonia, eczema herpeticum, eczema infected, gastroenteritis, sleep apnoea syndrome and staphylococcal infection. Two of the serious adverse events, eczema infected and eczema herpetic, were reported in the same patient and were assessed by the investigator as probably related to study drug. The patient was withdrawn from the study on the day of onset of these adverse events, but the reported reason for discontinuation was lack of efficacy of treatment.

Other Adverse Events
Study discontinuation:
Two patients in the tacrolimus ointment arm discontinued the study prematurely due to non-serious adverse events. One patient experienced leukocytoclastic vasculitis (verbatim: urticaria vasculitis), which was considered by the investigator to be unrelated to study medication. The other patient had a non-serious eczema weeping (verbatim: weeping and crusting) that led to discontinuation and was rated by the investigator as possibly treatment-related. No patient in the vehicle arm discontinued the study due to an adverse event.
Neoplasm:
No malignant neoplasm occurred. Benign neoplasms, mainly skin papillomas and one case of a benign tumour of the finger, were diagnosed in five patients during the OLP. In addition, skin papilloma was diagnosed in eight patients during the DCP. Six of the cases were assessed as not treatment related

(five cases of skin papilloma, one case of benign tumour of finger), the other seven benign neoplasms (all cases of skin papilloma) were rated by the investigator as being causally related to treatment
Five of the patients with skin papilloma recovered during the study. The warts were still present at the end of the study in the two patients whom developed the warts late in the study, and in one patient who was prematurely withdrawn from the study due to an IGA > 2 after 6 weeks of disease exacerbation treatment.

Safety conclusion on study FG-506-06-41
The CHMP concluded that in the open-label period (OLP), application site pruritus, irritation and nasopharyngitis were the most common AE's reported. In the disease control period (DCP) period eight serious adverse events occurred. Seven in patients treated in the tacrolimus ointment arm (5.6%) and one in the vehicle arm (0.8%). The reported serious adverse events were asthma, broncho-pneumonia, eczema herpeticum, eczema infected, gastroenteritis, sleep apnoea syndrome and staphylococcal infection. The tacrolimus ointment arm was associated with increase frequency of application site infection, application site impetigo, nasopharyngitis these were deemed to be treatment related. Eczema herpticum and ecezema infection occurred in one patients leading to discontinuation of treatment. Seven benign neoplasms (all cases of skin papilloma) were rated by the investigator as being causally related to treatment. There was also an increase in frequency of respiratory tract disorders such as asthma, influenza, bacterial bronchitis and upper respiratory tract infection and there was also an increased frequency of Molluscum contagiosum noted in the tacrolimus ointment arm. However, these were not judged to be causally related by the investigators.

Additional long term treatment safety studies supportive of the proposed maintenance treatment

The MAH presented a number of clinical safety results from previous pre- and post-marketing long-term safety studies conducted with the currently approved twice-daily treatment regimen. The MAH considered these studies to be also of relevance for the clinical safety of the new proposed twice-weekly maintenance regimen. The main criterion for selection of these studies was that all were large (> 200 patients) and had twice-daily treatment with tacrolimus ointment for 6 months or longer. The majority of the studies described had already been included in previous submissions. The long-term (≥ 6 months, more than 200 patients) safety and efficacy studies are listed in Table 27. They were conducted by the MAH in Europe and the USA and included more than 10,000 patients treated with tacrolimus ointment.

Table 27: Overview of Long-term Studies

Study	Design and objective	Tacrolimus ointment treatment regimen	Patient N	Age groups
96-0-025	Open-label, non-comparative, multi-centre, US Objective: long-term safety and efficacy	0.1% twice/day	**255** 115 140	 2-6y 7-15y
97-0-038	Open-label, non-comparative, multi-centre, US, follow-up of 94-0-008, 95-0-003, 95-0-009, 95-0-013, 96-0-025, 97-0-030, 97-0-035, 97-0-036, 97-0-037 Objective: long-term safety and efficacy Indication: mild to severe AD	0.1% twice/day	**799** 185 206 408	 2-6y 7-15y ≥ 16y
99-0-054	Open-label, non-comparative, multi-centre, US Objective: long-term safety and efficacy Indication: mild to severe AD	0.1% (7341 patients) twice/day or 0.03% (582) twice/day	**7923** 2259 1700 3964	 2-6y 7-15y ≥ 16y

FG-506-06-12	Open-label, non-comparative, multi-centre, EU Objective: long-term safety and efficacy	0.1% twice/day	**316**	Adults
FG-506-06-21	Open-label, non-comparative, multi-centre, follow-up of FG-506-06-12, FG-506-06-18, FG-506-06-19, FG-506-06-22, FG-506-06-23 and FG-506-06-30 Objective: long-term safety	0.1% twice/day treatment episodes (at least 7 days of consecutive treatment)	**782** 127 180 475	 2-6y 7-15y ≥ 16y
FG-506-06-25	Open-label, non-comparative, multi-centre, follow-up of FG-506-06-24 Objective: long-term safety	0.1% twice/day or 0.03% twice/day treatment episodes (at least 7 days of consecutive treatment)	**466** 233 233	 2-6y 7-15y
FG-506-06-26	Randomised, double-blind, comparative, multi-centre Objective: efficacy and safety comparison	0.1% twice/day or 0.1% hydrocortisone acetate/ 1% hydrocortisone butyrate-ointment (HC) twice/day	**972** 487 Tac* 485 HC†	 Adults Adults
FG-506-06-31	Open-label, non-comparative, multi-centre, follow-up of FG-506-06-26 Objective: long-term efficacy and safety	0.1% twice/day (for 3 weeks), followed by 0.1% once/day treatment episodes (at least 7 days of consecutive treatment)	**672**	Adults

Table 28: Long-term Study and Immunocompetence

FG-506-06-27	Randomized, double-blind, comparative, parallel-group, multi-centre Objective: demonstrate the equivalence of the immunological response to a vaccination with a protein-conjugate meningococcal serogroup C vaccine	0.03% or 1% hydrocortisone acetate (or 0.1% hydrocortisone butyrate)-ointment (HC)	**257** 133 Tac* 124 HC†	 2-11y 2-11y

These studies were included by the MAH as supportive evidence, since they have already been conducted to support the marketing authorization they are not discussed further in this report. None of the clinical trials involved the proposed maintenance treatment regimen of twice weekly application. However, some of the trials listed used tacrolimus for up to 6 months continuously.

As the proposed maintenance treatment regimen is supported by two 12 month control studies the CHMP requested the MAH to summarise all safety information available to specifically justify maintenance treatment in patients for more than 12 months.

The MAH responded that the clinical and post-marketing information collected to date with the intermittent use of tacrolimus ointment is extensive and represents one of the largest clinical developments conducted for a dermatology product approved in Europe. Based on this information the safety profile as specified in the currently approved Summary of Product Characteristics has been defined for total time of up to 4 years in clinical studies. To date the CONTROL studies FG-506-06-40 and FG-506-06-41 are the only evidence available to support the clinical safety of the recommended dosing regimen for maintenance therapy (twice weekly, once a day) and this for up to 12 months. The MAH argued that it is fair to assume that patients applying tacrolimus ointment on a cleared to mildly affected skin will be doing so on tissue which has recovered its integrity to a large extent. This in turn will substantially limit the penetration of the active substance into the skin and subsequently into systemic circulation. The total amount of tacrolimus ointment applied on the skin over 12 months of maintenance therapy in the CONTROL studies was similar or lower than the amount applied after 12 months in clinical safety studies conducted for up to 4 years in which tacrolimus ointment was used as intermittent therapy twice daily (see table 29).

Table 29: Ointment Utilization Across Selected Studies. Month 12 data

	Days in Study (d)		Grams Tac-O Use/Day (g/day)		Cumulative Tacrolimus Ointment Use (g)	
	Mean ± SD	Median (25^{th}-75^{th} P)	Mean ± SD	Median (25^{th}-75^{th} P)	Mean ± SD	Median (25^{th}-75^{th} P)
ADULTS						
Maintenance						
FG-506-06-40* (OLP+DCP)	305 ± 127 (N=80)	374 (190, 391) (N=80)	2.1 ± 2.1 (N=74)	1.4 (0.8, 2.8) (N=74)	590 ± 541 (N=73)	450 (233, 782) (N=73)
Long-Term Safety						
FG-506-06-12	317 ± 100 (N=116)	361 (N=116)	3.1 ± 3.2 (N=34)	2.3 (0.9, 4.0) (N=34)	856 ± 600 (N=35)	728 (316, 1409) (N=35)
FG-506-06-21	339 ± 89 (N=467)	366 (355, 373) (N=467)	Not done	Not done	866 ± 887 (N=475)	591 (302, 1061) (N=475)
PEDIATRICS						
Maintenance						
FG-506-06-41* (OLP+DCP)	331 ± 105 (N=78)	377 (330, 401) (N=78)	1.5 ± 1.4 (N=77)	1.1 (0.6, 2.0) (N=77)	500 ± 480 (N=77)	387 (171, 656) (N=77)
Long-Term Safety						
FUSA-96-0-025[$§]	315 ± 104 (N=255)	361 (337, 372) (N=255)	1.9 ± 3.1 (N=111)	0.9 (0.5, 2.1) (N=111)	567 ± 806 (N=111)	308 (118, 725) (N=111)
FG-506-06-21[$]						
2-6 years old	349 ± 83 (N=125)	368 (364, 379) (N=125)	Not done	Not done	383 ± 448 (N=127)	318 (127, 476) (N=127)
7-15 years old	355 ± 75 (N=179)	368 (360, 378) (N=179)	Not done	Not done	506 ± 454 (N=180)	374 (184, 678) (N=180)

The MAH was therefore of the opinion that the overall exposure to drug is similar, or lower, in the CONTROL studies at 12 months utilisation than at 12 months in previous clinical studies with an intermittent twice daily regimen conducted beyond a year.

The CHMP agreed that safety has been assessed for 12 months maintenance treatment. However, the safety beyond 12 months of maintenance treatment has not been established. The MAH points out that once the exacerbation has settled and skin integrity has been restored the amount of systemic absorption will be less than treating patients during acute disease exacerbations. Table 29 shows that for adult patients the amount of tacrolimus ointment used during maintenance treatment is less than the amount used in treatment of acute exacerbations over 12 months by comparing the control study with long term safety studies over 12 months.

It was not clear to the Committee whether the patients in the studies listed in table 29 are comparable in terms of disease severity. With respect to paediatric data table 29 shows that patients using maintenance treatment (2-6 years and 7-15 years) utilise more tacrolimus ointment during maintenance treatment than treating acute exacerbations. However, the benefit of using maintenance treatment results in a lower incidence of disease exacerbations and longer disease free intervals. No additional safety data has been seen between 12 months maintenance treatment and treatment of acute disease exacerbations. The Committee therefore recommended that the SPC shall specify that safety of maintenance treatment beyond 12 months has not been established.

Furthermore, the MAH argued that the adverse event profile at 12 months of maintenance therapy is essentially the same as the profile observed in all long-term clinical investigations conducted and submitted to date for periods of follow-up beyond 12 months. Therefore, the MAH thought it reasonable to assume that the safety profile with tacrolimus ointment during maintenance therapy when applied for longer than 12 months should be similar to that seen in long-term studies using the currently approved regimen. The MAH assessed the available information from the perspective of the total number of days treated in clinical studies using the standard long-term intermittent paradigm for which follow-up periods beyond 12 months are available (see table 30 for details).

The safety reported from long-term studies (>12 months) with intermittent long-term use and a high percentage of days in treatment are relevant to estimate the long-term safety of maintenance treatment after 12 months.

Table 30: Percentage of Days with Tacrolimus Ointment Treatment

	Days with tacrolimus ointment treatment (%)			Days with tacrolimus ointment treatment (%)	
	N	Mean ± SD		N	Mean ± SD
ADULTS			**PEDIATRICS**		
Maintenance			*Maintenance*		
FG-506-06-40 DCP	77*	16.2 ± 23.8[†]	FG-506-06-41 DCP	78*	16.9 ± 22.1[†]
Long-Term Safety			*Long-Term Safety*		
FG-506-06-12	116[§]	85.9 ± 16.5	FUSA-96-0-025[‡]	255[¶]	87.1 ± 20.8
FG-506-06-21	467[§] 462**	75.1 ± 24.2 66.3 ± 28.6	FG-506-06-21[‡] 2-6 years old: 7-15 years old:	 125[§] 122** 179[§] 177**	 68.7 ± 28.9 49.1 ± 33.0 76.5 ± 27.1 53.7 ± 35.8
FG-506-06-31[††]	640[§] 640**	74.6 ± 25.4 65.6 ± 28.5	FG-505-06-25[§§]	460[§] 460**	74.9 ± 25.3 63.7 ± 27.6

Maintenance = tacrolimus arm; DCP, disease-control period

*Moderate-to-severe group

[†]Only for disease exacerbations within DCP

[§]Missing diary information is assumed as treated

[‡]Patients received tacrolimus 0.1% ointment in this study

[¶]Ointment use not split by age strata

**Missing diary information is assumed not treated

[††]Contains a mix of once and twice daily treatment

[§§]Patients could use 0.03% and 0.1% tacrolimus ointment

Sources:

FG-506-06-40: Additional analysis moderate to severe subset, Table 13.4.3.6; FG-506-06-12: EOTT 13.3.1, (Month 12 data); FG-506-06-21: EOTT 13.3.1 (up to Month 12); FG-506-06-31: EOTT 13.3.1; FG-506-06-41: Additional analysis moderate to severe subset, Table 13.4.3.6; FUSA-96-0-025: EOTT 13.3.1; FG-506-06-21; FG-506-06-25 EOTT 13.3.1

There are two main studies that the MAH considers relevant (FG-506-06-21 and FHI-97-038), both of which are of 4 years' duration and represent the longest follow-up relevant to maintenance therapy. Although presented already in previous submissions, a brief overview of the safety results of these two studies is included in this report for selected events relevant to the question and for the sake of completeness.

FHI-97-038

The objective of this study was to evaluate the long-term safety and efficacy of 0.1% tacrolimus ointment when used twice-daily either continuously or intermittently for the treatment of AD in adult and paediatric patients. The four most common drug-related adverse events were skin burning (25.2%), pruritus (22.8%), skin erythema (9.5%) and skin infection (which included all cutaneous infections not otherwise specified, such as bacterial infections, molluscum and pyoderma) (5.5%). Hazard rates for individual events were calculated and showed there was no clinically meaningful increase in risk for any adverse event, including infections, over time. The assessment of the incidence of infections of clinical interest showed that, in general, the overall incidence of infections tended to be greater in paediatric patients compared with adults. Individual infections that tended to occur with substantially greater incidence among paediatric patients were those that would be expected in a paediatric population over a 4-year period: skin infection, pustular rash, skin neoplasm benign, flu-like symptoms, fever, pharyngitis, increased cough and otitis media. The incidence of skin infections in adults and children treated with topical tacrolimus in this study was consistent with, or lower than previous reports in AD in general (David et al, 1986). The incidence of cutaneous infections such as herpes simplex, eczema herpeticum, warts or molluscum contagiosum among patients treated with

tacrolimus ointment in this study was lower than or consistent with previously published reports (Bonifazi et al, 1985; David and Longson, 1985; Bork et al,1988).

During the study, five patients were diagnosed with seven skin cancers: three basal cell carcinomas (BCCs), three SCCs and one sebaceous carcinoma (SC). Two of these patients had a prior history of skin cancer and, in one patient, both BCC and SCC were detected before first exposure.

FG-506-06-21
The primary objective of this study was to obtain further information on the safety of 0.1% tacrolimus ointment when used continuously or intermittently for up to four years in patients previously enrolled into company-sponsored clinical studies with tacrolimus ointment for the treatment of AD. A total of 782 patients were treated with study medication in 39 centres in twelve European countries. The four most common causally related adverse events in all patients were skin burning (282 patients, 36.1%), pruritus (108 patients, 13.8%), folliculitis (78 patients, 10.0%) and skin infection (77 patients, 9.8%). The percentage of days treated for disease exacerbation with tacrolimus ointment (i.e. twice-daily treatment) is lower in the paediatric and adult CONTROL studies with the maintenance regimen compared with long-term studies. Adding the percentage of days treated with the maintenance regimen (i.e. once-daily, twice-weekly tacrolimus ointment) would yield a similar or lower percentage of days treated with tacrolimus ointment.

The two clinical studies presented above are those with the longest intermittent twice daily treatment available to date. The safety profile of tacrolimus ointment after up to 4 years intermittent therapy in these studies was very similar to that after 1 year of maintenance therapy in the CONTROL studies and is also similar to that in study 20-04-002. The MAH believed, therefore, that the long-term safety of tacrolimus ointment when used as maintenance therapy for longer than 12 months should not be different to the profile reported for studies such as FHI-97-038 and FG-506-06-21.

Epidemiological and Drug Utilization Studies

Epidemiological Data
It has been suggested that a sub-chronic state of inflammation in certain tissues makes it likely that atopy is responsible for positive associations with cancer risk (Wang and Diepgen 2006). Conversely, when atopy is regarded as a hyper reactive state of the immune system, it is usually assumed to reflect a shift in the T lymphocyte response away from Th1- towards Th2-dominated activity, although coexistence of Th1-mediated diseases and Th2-induced disorders have been described (Wang et al 2006). Theoretically, this hyper reactive state could be accompanied by enhanced immune surveillance, which in turn may decrease the chance of proliferation of aberrant cells and reduce cancer risk.

Epidemiological studies have therefore been conducted to try to resolve this apparent contradiction.

In 23 publications, AD was implicated in the risk of hematological (childhood leukemia, adult leukemia, non-Hodgkin's lymphoma [NHL] and different hematological cancers), pancreatic, skin and brain malignancies. The overall picture from these studies, however, shows that a history of AD may be associated with a decreased risk of pancreatic cancer, brain tumour and childhood leukemia, although in most instances the findings were not statistically significant. Nevertheless, the findings of the epidemiological studies tend to support a lower risk of cancer among persons with a history of AD. Although a more careful definition of AD is needed, these epidemiological studies could provide an estimate of the background cancer risk in patients with AD when the long-term effects of AD treatments are assessed.

The CHMP acknowledged that the findings of the epidemiological studies tend to support a lower risk of cancer among persons with a history of AD.

Drug Utilisation Studies (DUS)
On 28 June 2006 the MAH provided a proposal to CHMP to conduct Drug Utilization Studies (DUS) prior to the planned submission of a protocol for an epidemiological study. The DUS intended to allow a better characterization of the use of Protopic in Europe, and to provide an indication whether there is sufficient exposure since product launch in the EU, prior to making a proposal for a protocol for the requested epidemiological study. The DUS were conducted in two well recognized population databases (General Practice Research Database [GPRD], UK and PHARMO RLS, Netherlands).
The primary objective of these studies was to characterize the profile of topical calcineurin inhibitor (TCI) users in Europe as well as the overall exposure to this therapeutic class, i.e. the number of users of tacrolimus ointment and/or pimecrolimus cream in the UK and the Netherlands and, if possible, the duration of use of tacrolimus ointment and/or pimecrolimus cream. Additionally, exploratory analyses were conducted on the basis of the collected information, as to describe outcomes, specifically skin cancer, in patients using these drugs.

Overall, the results of these studies suggested that apart from some small exceptions, the way tacrolimus ointment and pimecrolimus cream are used in the Netherlands and in the UK are comparable. The outcome of the exploratory analyses showed no statistically significant association between the use of TCIs and the development of skin cancer. However, due to the recent introduction of TCIs in both countries, the duration of follow-up (on average approximately two years) was relatively short as well as the treatment durations of tacrolimus ointment and pimecrolimus cream. In addition, details were not available on the site and extent of exposure of TCI (i.e. the size of BSA treated), on the location of the skin cancer on the body, and hence whether the skin cancer occurred at the site of TCI application.

The GPRD concluded that 'if any adverse effect of TCI exposure would only occur after prolonged exposure and several years after exposure, this GPRD study is unlikely to have been able to detect such an effect. For this reason, it is recommended that further research is conducted once more long term data on TCI exposure is available on larger number of patients'.

The Pharmo Institute concluded that 'The main conclusion was the drug utilization of TCI's is in accordance with the Dutch treatment guidelines in the Netherlands and that no association between TCI use and incidence of skin cancer could be established. The low skin cancer incidence, the short follow up duration, the limited information on volume of ointment or cream applied, the lack of information on the size and localization of the skin surface treated and the lack of information about key risk factors such as ultraviolet light exposure necessitates research in the later future in order to obtain conclusive results'.

The CHMP acknowledged that while no direct association could be found both studies have stated limitations with the studies and the ability to detect incidence of skin cancer. It was also stated that further research would be necessary to conclude whether an association exists.

In an effort to better understand the risk of lymphoma in patients with atopic dermatitis compared with the general population, a systematic review of epidemiological data in the literature was sponsored by Astellas (Diepgen 2007). Two of three cohort studies showed evidence for a trend towards a slightly increased risk of lymphoma for patients with AD. However, this association could not be confirmed by any case-control study included in the systematic review. The absence of a consistent trend in the outcome of the reviewed literature supports the absence of a relationship between AD and the risk of lymphoma. A nested case-control study in the PharMetrics database evaluated the association between topical immunosuppressants and lymphoma in a cohort of patients with AD (Arellano et al., 2007). The analysis of 294 cases of lymphoma that was performed in 293,253 patients, 81 of which were in patients younger than 20 years, did not find an increased risk of lymphoma in patients treated with topical calcineurin inhibitors. An adjusted analysis showed severity of AD as the main factor associated with an increased risk of lymphoma.

Tacrolimus usage – Maintenance vs. Intermittent use

As described earlier in this report the data showed that the mean total amount of tacrolimus ointment use (g) in patients randomised in the tacrolimus arm is similar in adult patients to that in the vehicle arm (including intermittent treatment in case of a flare). The corresponding data in the paediatric population showed a higher tacrolimus ointment use in the tacrolimus arm. Because more patients withdrew in the vehicle arm compared with the tacrolimus arm, however, drug usage was also calculated on a per-patient basis taking into consideration the number of days in the DCP for the individual patient. This calculation showed that the mean daily usage of tacrolimus ointment was not higher in the tacrolimus arm compared with the vehicle arm in either the adult or paediatric populations.

It is difficult to compare the tacrolimus arm to the vehicle arm with respect to daily tacrolimus ointment use, however, as a result of the wide and treatment regimen-dependent distribution of the data. It is perhaps more important to consider systemic, as well as skin compartment, tacrolimus exposure over time. The MAH provided data showing that tacrolimus ointment use to treat disease exacerbations is markedly less for the tacrolimus arm than the vehicle arm. When tacrolimus ointment is applied for maintenance treatment to skin in remission, this will lead to minimal exposure to tacrolimus in the skin and in the systemic circulation. Furthermore, in a twice weekly regimen, based on the data from study FG-506-06-30, The MAH postulated that at the end of the period between two applications, the skin compartment will be almost devoid of tacrolimus.

Although patients on maintenance therapy may overall have lower total tacrolimus dose than patients on intermittent therapy, maintenance therapy would represent continuous exposure of the skin to tacrolimus. The CHMP therefore requested the MAH to discuss whether patients on maintenance treatment regimen are at an increased risk of developing skin cancer such as cutaneous t cell lymphoma.

The MAH responded that tacrolimus is a highly lipophilic molecule and thus an intact stratum corneum is likely to be the main barrier to percutaneous absorption. The combination of large molecular weight and high lipophilicity means that tacrolimus will be selectively delivered to the skin, with minimal exposure into systemic circulation. The MAH also discussed dermal pharmacokinetics in ex vivo models. Using a Franz diffusion cell the rate and extent of penetration through intact epidermis was low. The rate of tacrolimus penetration was approximately seven-fold higher in skin sections devoid of stratum corneum, as compared to intact skin. This difference strongly suggests that the intact stratum corneum is the main rate-limiting barrier to cutaneous permeability of tacrolimus (Undre et al, 2003). Following that the MAH continued to discuss pharmacokinetics in healthy adult subjects, clinical data on systemic exposure in patients with moderate to severe AD and finally drugs usage (maintenance versus intermittent use).

In conclusion the MAH argued that available data from systemic immunosuppressive agents in transplant patients suggests that prolonged and sustained immunosuppression is associated with an increased risk of developing lymphomas and skin malignancies. The more likely conclusion is therefore that the total cumulative exposure in the new proposed maintenance treatment regimen (once a day, twice weekly) will be lower than in the currently registered treatment regimen. The MAH thus concluded that the patients on maintenance treatment regimen are unlikely to be at an increased risk of developing skin cancer such as cutaneous T cell lymphoma.

The CHMP acknowledged the MAH explanation that the systemic absorption is very low and having an intact stratum corneum is the main rate-limiting barrier to cutaneous permeability of tacrolimus and that the MAH has shown that systemic absorption in patients with moderate to severe atopic dermatitis decreases as skin heals and becomes intact. When tacrolimus ointment is applied for maintenance treatment to skin in remission, this will lead to minimal exposure to tacrolimus in the skin and in the systemic circulation. Based on the data provided by the MAH from study FG-506-06-30, the committee was of the opinion that it can be postulated that at the end of the period between two applications (of maintenance treatment), the skin compartment will be almost devoid of tacrolimus. In the ‘intermittent treatment’ (treatment of acute exacerbations) paradigm approximately 7-fold higher

skin concentrations as well as systemic exposure can be postulated based on extrapolation from ex vivo dermal permeability experiment. Therefore, the CHMP agreed that the cumulative absorption to both the skin and systemic compartments will be lower in patients treated as maintenance therapy than patients being treated during acute exacerbations. Overall, the CHMP agreed with the MAH response. However, the Committee requested that the MAH should be specifying in the SPC that safety beyond 12 months maintenance treatment has not been established.

In addition, the CHMP still had concerns regarding the long term safety and risk of lymphoma, including cutaneous T cell. The MAH had provided a justification for 12 months continuous maintenance treatment but as patients may use tacrolimus beyond 12 months, a concern existed for long term safety in patients in this situation. Therefore, before an indication for maintenance treatment could be granted, the CHMP was seeking further assurance on the long term safety for the proposed indication for maintenance treatment. The MAH was subsequently requested to provide a detailed discussion of the benefit risk of continuous treatment of tacrolimus in adults and children. In the context of continuous treatment indication the MAH was requested to provide a detailed overview of the following points:

- The effects on the adult immunological system and on a developing immune system.
- Summary results of relevant follow-up measures (FUMs; including APPLES study), completed studies and ongoing studies.
- Post marketing safety data detailing long term use applicable to the proposed indication for continuous treatment.
- Risk of developing skin cancer, cutaneous T cell lymphoma and lymphomas with continuous maintenance treatment.
- Overall benefit risk of continuous tacrolimus treatment in children and adults with atopic dermatitis (AD).

In response to the CHMP request the MAH provided a detailed response to the points listed. The following paragraph includes summaries of the responses provided by the MAH.

Effects on the immune system

A vaccination study was performed in over 200 children treated with moderate to severe AD who were treated for the latter with either a standard corticosteroid regimen or 0.03% tacrolimus ointment. The immune response was equivalent in the two groups and ointment application did not affect the immediate response to vaccination, generation of immune memory or humoral and cell-mediated immunity. Overall, studies in patients with AD suggest that topical long-term treatment with tacrolimus ointment does not cause systemic immunosuppression. A comparative study in 21 adults with AD investigated the effects of twice daily tacrolimus 0.1% ointment or triamcinolone acetonide 0.1% on immunological markers including CD4 and CD8 cell counts. The results indicated that local immunocompetence was not adversely affected by topical tacrolimus application. Recall antigen testing shows that patients with active AD have impaired reactions compared with the general population. A study in 48 adults with moderate-to-severe AD showed that skin healing after tacrolimus ointment treatment led to significant improvement in skin immunity.

Summary results of relevant FUMs, APPLES, completed studies and ongoing studies.

Non-clinical studies did not raise any major concerns that prohibited approval of tacrolimus ointment. The MAH believed that, if these studies are considered with a maintenance regimen of tacrolimus ointment in mind, the risk/benefit remains the same as for the present indication. *Ex vivo* data indicate that percutaneous absorption through healed skin, as in the case of maintenance therapy, will be approximately 7-fold lower than absorption through inflamed (damaged) skin. The clinical development program of tacrolimus was one of the largest ever undertaken in the field of dermatology. None of the completed or ongoing studies have suggested a major long-term safety issue with tacrolimus. The CONTROL studies show that maintenance therapy with once-daily, twice-weekly tacrolimus ointment is effective in reducing the number of disease exacerbations and delaying the time to first exacerbation when compared with standard, intermittent therapy. Exposure to tacrolimus ointment (based on the percentage of days of treatment) was similar or lower in the CONTROL studies to that in long-term (≤4 years) studies using traditional intermittent treatment. There is,

therefore, no reason to believe that the safety of long-term intermittent treatment. Results from a clinical trial of three-times weekly tacrolimus ointment provide further evidence of the efficacy and safety of the maintenance treatment paradigm. Clinical data published by independent investigators and drug utilization studies conducted by the MAH have not indicated that topical calcineurin inhibitor use is associated with an increased risk of developing non-melanoma skin cancer (NMSC) or lymphoma.

Post-marketing safety data detailing long-term use applicable to the proposed indication of continuous treatment

Two recently completed studies may provide additional evidence for the safety of tacrolimus ointment because of the large number of patients treated or the duration of their follow-up. Study FJ-00A02 examined long-term (3 years) treatment with tacrolimus 0.1% ointment in adults with AD. Study FJ-00B02 was a 12 week study enrolling over 1000 paediatric patients, applying tacrolimus 0.03% ointment once or twice daily. Safety findings from these studies were commensurate with safety findings presented in previously submitted dossiers and demonstrated acceptable profiles. No cases of skin malignancies were recorded in either trial.

Risk of developing CTCL, lymphoma and skin malignancies with continuous maintenance treatment

As in previous responses the MAH reiterated that it is known that sustained systemic immunosuppression using substantial doses of one or more immunosuppressive drugs in transplant patients is associated with an increased risk of developing lymphomas and skin malignancies. Although there is greater absorption through diseased or damaged skin compared with healthy skin, all studies in patients to date have demonstrated that systemic absorption after topical application tacrolimus ointment is minimal (approximately 30-fold less than that seen with oral immunosuppressive doses in kidney and liver transplant patients). Extrapolation from ex vivo dermal permeability experiments suggests that the 'intermittent treatment' paradigm will be associated with approximately 7-fold higher skin concentrations and systemic exposure. Thus, from a cumulative exposure point of view, the total amount of tacrolimus in the skin as well as in the systemic compartment is likely to be higher with intermittent treatment compared with maintenance treatment. Patients receiving maintenance treatment are therefore unlikely to be at an increased risk of developing systemic lymphoma and skin cancer, including CTCL, based on systemic immunosuppression.

Overall benefit risk of maintenance in children and adults

The CONTROL studies clearly indicated that, compared to a standard tacrolimus ointment regimen, maintenance treatment over 12 months lead to improvements including:

- Fewer major flares
- A longer time to relapse (first flare)
- A lower number of days using twice-daily flare treatment
- The above efficacy results were achieved with no major differences in the safety profiles of the two regimens and no substantial increase in ointment use in the maintenance arm.

In summary, the MAH believed that there is a strong case to allow physicians the AD treatment option of maintenance therapy with tacrolimus ointment. The MAH concedes that there are theoretical risks with use of tacrolimus ointment for periods of much greater than 12 months. Measures have been proposed, however, to minimize these risks and ensure that these can be monitored and kept to within acceptable levels.

The CHMP acknowledged the MAH response and agreed that based on the current data the safety profile appears non-problematic. However, the safety profile is to some degree based on indirect evidence/arguments. The CHMP therefore had some concerns regarding the chronic use beyond 12 months in children. The Committee therefore requested the MAH to commit to undertake a long term follow-up pf paediatric patients under maintenance therapy. The MAH agreed to the CHMP request (see section IV for a listing of follow-up measures).

In addition to the CHMP concern regarding long term safety in children, the Committee asked the MAH to further elucidate on a few other safety concerns. The MAH was therefore asked to comment

on how patients are to avoid or minimise sunlight exposure with maintenance treatment. As the safety of tacrolimus treatment has not been established in pregnancy, the MAH was requested to explain preventative measures to minimise inadvertent use of tacrolimus during pregnancy. Finally, the MAH was requested to explain whether there is a risk of misuse of tacrolimus ointment and inappropriate self medication with tacrolimus ointment and whether risk minimisation measures are proposed.

The MAH responded that in the absence of conclusive data allowing the exclusion of a risk of photocarcinigenicity when topically treating with tacrolimus ointment, the MAH proposed the following wording for Section 4.4. "Special warnings and precautions for use" as stated in the currently approved SPC to address UV and sunlight exposure while under treatment with tacrolimus ointment:

"Exposure of the skin to sunlight should be minimised and the use of ultraviolet (UV) light from a solarium, therapy with UVB or UVA in combination with psoralens (PUVA) should be avoided during use of Protopic ointment (see section 5.3). Physicians should advise patients on appropriate sun protection methods, such as minimisation of the time in the sun, use of a sunscreen product and covering of the skin with appropriate clothing."

Since approval in February 2002 and the finalisation of the renewal procedure in March 2006, some additional data and publications both of animal and human data have been made available, indicating there is no increased risk when exposed to UV-light while receiving tacrolimus ointment treatment. In their response, the MAH summarised some of the relevant studies. In the view of the MAH, the data provided evidence supporting the absence of increased risk from UV exposure concomitant to treatment with tacrolimus ointment. The MAH believed that the current wording addresses the issue sufficiently and in an adequate manner, also for patients being under a maintenance regimen.

In relation to pregnancy it was the opinion of the MAH that the current wording accurately reflects the status of scientific information both for the approved indication and the proposed maintenance treatment regimen. The application of tacrolimus ointment on skin lesions in remission or only mildly affected during maintenance therapy is not expected to increase identified or potential risks as the amount present in the skin is expected to be very low and the fraction that could potentially reach systemic circulation even lower.

Regarding the risk of misuse and inappropriate self medication the MAH responded that considering the fact that tacrolimus ointment is applied at home by the patient or by the care giver in case of children, misuse and inappropriate self medication cannot be excluded, and it is beyond the MAH to entirely prevent this. The MAH proposed to address the issue with two risk minimization measures based on the education of both prescribing physicians and patients/care givers. The proposed measures are further discussed in section 3.5 of this report.

The CHMP acknowledged that the MAH has adequately addressed this issue and the warning should remain in section 4.4 and the wording to section 4.6 should not be amended.

1.4 SPC and PL

The CHMP requested the MAH to propose a suitable wording for section 4.1 and 4.2 for the categories of patients most suitable for maintenance treatment. The criteria of Rajka and Langeland were to be explained in the SPC. The MAH was also asked to include clear guidance to indicate which patients are considered suitable for maintenance treatment.

The MAH replied that the criteria of Rajka and Langeland are a simple system for baseline grading of the severity of atopic dermatitis in clinical practice. The grading, which may be carried out on the basis of one single consultation, permits distinction between mild, moderate and severe atopic dermatitis by means of a score summation using the following parameters:

1. Extent (by "rule of nine" division of the body surface: head and upper extremity 9% each, anterior and posterior body and lower extremity 18% each, genital area 1%)
2. Course (via history: more or less than 3 months remission during a year or continuous course)
3. Intensity (disturbance of night's sleep by itching).

The MAH was of the opinion that the criteria of Rajka and Langeland are not easy to translate into SPC language helping prescribers to identify which patients are to be considered suitable for maintenance treatment. Instead the MAH argued that a wording in line with the criteria used in the clinical trials supporting this application to define success of the Open Label Period i.e. Investigator Global Assessment (IGA) may be easier to understand by the majority of prescribers and also easier to translate into lay language in the Patient Information. Accordingly the MAH suggested an updated wording of sections 4.1 and 4.2.

The CHMP did not fully agree with the wording suggested by the MAH as the proposed information did not clarify that a benefit /risk assessment should be undertaken and safety data beyond 12 months maintenance treatment is not available. In addition the CHMP was of the opinion that recommendations for stopping treatment should be included. Subsequently the Committee recommended the following wording.

Section 4.1:
'Maintenance treatment of moderate to severe atopic dermatitis for the prevention of flares and the prolongation of flare-free intervals in patients experiencing a high frequency of disease exacerbations (i.e. occurring 4 or more times per year) who have had an initial response to a maximum of 6 weeks treatment of twice daily tacrolimus ointment (lesions cleared, almost cleared or mildly affected).'

Section 4.2:
'Maintenance
Patients who are responding to up to 6 weeks treatment using tacrolimus ointment twice daily (lesions cleared, almost cleared or mildly affected) are suitable for maintenance treatment.

Protopic ointment should be applied once a day twice weekly (e.g. Monday and Thursday) to areas commonly affected by atopic dermatitis to prevent progression to flares. Between applications there should be 2-3 days without Protopic treatment.

Adult patients (16 years of age and above) should use Protopic 0.1% ointment, children (2 years of age and above) should use the lower strength Protopic 0.03% ointment.

If signs of a flare reoccur, twice daily treatment should be re-initiated (see treatment section above).

After 12 months, a review of the patient's condition should be conducted by the physician and a decision taken whether to continue maintenance treatment in the absence of safety data for maintenance treatment beyond 12 months. In children, this review should include suspension of treatment to assess the need to continue this regimen and to evaluate the course of the disease.'

SPC Section 4.4:
As a further risk minimization measure the CHMP recommended the inclusion of the following sentence to section 4.4 of the SPC.

'The development of any new change different from previous eczema within a treated area should be reviewed by the physician.'

SPC Section 4.8
Based on the observed difference in frequency of maintenance treatment versus vehicle treatment the CHMP requested the MAH to list the two in tabular form in section 4.8.

The MAH responded that the term tacrolimus ointment group is used when referring to maintenance treatment and vehicle group is used when referring to tacrolimus ointment intermittent use as approved. The most frequently reported AEs (≥3%) reported, irrespective of relationship to the study drug in adult patients (FG-506-06-40) were the application-site adverse events pruritus, folliculitis, irritation, infection, herpes simplex and impetigo. The most frequent non-application site adverse events (≥3%) were nasopharyngitis, headache, pruritus, influenza, herpes simplex, pharyngolaryngeal pain, pyrexia and viral respiratory tract infection. The incidences of these AEs are summarised in Table 31.

Table 31: Incidence of Most Frequently Reported Adverse Events, Regardless of Relationship to Study Drug, During Disease Control Period, Study FG-506-06-40 (Adults).

MedDRA preferred term	Mild to severe AD		Moderate to severe AD	
	0.1% Tac	Vehicle †	0.1% Tac	Vehicle †
	N=116 (%)	N=108 (%)	N=80 (%)	N=73 (%)
Application-site				
Application-site pruritus	18 (15.5)	16 (14.8)	14 (17.5)	11 (15.1)
Application-site folliculitis	6 (5.2)	9 (8.3)	6 (7.5)	8 (11.0)
Application-site irritation	6 (5.2)	7 (6.5)	4 (5.0)	6 (8.2)
Application-site infection	7 (6.0)	4 (3.7)	6 (7.5)	3 (4.1)
Herpes simplex	4 (3.4)	4 (3.7)	3 (3.8)	4 (5.5)
Impetigo	3 (2.6)	4 (3.7)	3 (3.8)	4 (5.5)
Non-application-site				
Nasopharyngitis *	14 (12.1)	7 (6.5)	11 (13.8)	6 (8.2)
Headache	12 (10.3)	8 (7.4)	9 (11.3)	3 (4.1)
Pruritus	8 (6.9)	8 (7.4)	4 (5.0)	4 (5.5)
Influenza	8 (6.9)	4 (3.7)	3 (3.8)	4 (5.5)
Herpes simplex	2 (1.7)	4 (3.7)	1 (1.3)	2 (2.7)
Pharyngolaryngeal pain	1 (0.9)	4 (3.7)	0	4 (5.5)
Pyrexia	1 (0.9)	4 (3.7)	1 (1.3)	2 (2.7)
Respiratory tract infection viral	4 (3.4)	0	3 (3.8)	0

In the target population for the variation application (moderate to severe AD patients) application-site infection, nasopharyngitis, headache and respiratory tract infection viral were reported more frequently in the tacrolimus arm than in the vehicle arm. However, when looking at adverse events assessed by the investigator and defined as highly probable, probable, possible or missing relationship to study medication, then only application site infection is reported more frequently in the tacrolimus group than in the vehicle group (Table 32). None of the other adverse events, nasopharyngitis, headache and respiratory tract infection was considered by the investigator to be at least possibly related to study drug in the tacrolimus ointment group and were therefore not considered for addition to the proposed draft SPC.

Table 32: Incidence of Most Frequently Reported Treatment-Related Adverse Events During Disease Control Period, Study FG-506-06-40 (Adults).

MedDRA preferred term	Mild to severe AD		Moderate to severe AD	
	0.1% Tac	Vehicle †	0.1% Tac	Vehicle
	N=116 (%)	N=108 (%)	N=80 (%)	N=73 (%)
Application-site				
Application-site pruritus	13 (11.2)	12 (11.1)	9 (11.3)	9 (12.3)
Application-site folliculitis	6 (5.2)	8 (7.4)	6 (7.5)	7 (9.6)
Application-site irritation	6 (5.2)	7 (6.5)	4 (5.0)	6 (8.2)
Application-site infection	6 (5.2)	2 (1.9)	5 (6.3)	2 (2.7)
Herpes simplex	4 (3.4)	3 (2.8)	3 (3.8)	3 (4.1)
Impetigo	2 (1.7)	4 (3.7)	2 (2.5)	4 (5.5)
Non-application-site				
Pruritus	4 (3.4)	6 (5.6)	2 (2.5)	4 (5.5)

The incidence of application site (skin) infections reported in adult AD patients across the long-term studies has been variable in a range from 2.4% up to 7.3% and the rate reported in study FG-506-06-40 in the maintenance group (5.2% mild to severe, 6.3% moderate to severe) is within that range. Atopic dermatitis patients are known to be at increased risk for developing skin infections per se; the MAH believed that the difference observed in the CONTROL study are within the variability one may expect when conducting clinical studies. In the case of study FG-506-06-40, the difference between treatment arms in the moderate to severe group is 3.6% which corresponds to an absolute number of about 3 patients, and is not thought to deserve separate listing in the SPC.

Paediatric data
When looking at adverse events assessed to be at least possibly related to study medication by the investigator (Table 33), only application-site impetigo, application-site infection, pruritus and nasopharyngitis were reported more frequently in the tacrolimus group.

Table 33: Incidence of Most Frequently Reported Treatment-Related Adverse Events During Disease Control Period, Study FG-506-06-41 (Paediatrics).

	Mild to severe AD		Moderate to severe AD	
	0.03% Tac	Vehicle	0.03% Tac	Vehicle
MedDRA preferred term	N=125 (%)	N=125 (%)	N=78 (%)	N=75 (%)
Application-site				
Application-site pruritus	9 (7.2)	12 (9.6)	8 (10.3)	8 (10.7)
Impetigo	7 (5.6)	2 (1.6)	6 (7.7)	2 (2.7)
Application-site infection	5 (4.0)	3 (2.4)	5 (6.4)	3 (4.0)
Skin papilloma	2 (1.6)	4 (3.2)	2 (2.6)	3 (4.0)
Non-application-site				
Pruritus	10 (8.0)	2 (1.6)	7 (9.0)	2 (2.7)
Nasopharyngitis	7 (5.6)	6 (4.8)	7 (9.0)	5 (6.7)
Eczema infected	2 (1.6)	4 (3.2)	2 (2.6)	4 (5.3)

The MAH was therefore of the opinion that the incidences of skin infections at the application site in the CONTROL study were within the range of what has been reported in previous studies. The MAH had no explanation on why in the CONTROL study a higher incidence of non-application site pruritus has been reported for children in the tacrolimus arm.

Considering all the above, the MAH believed that there are no clinically relevant differences in the safety profile of tacrolimus ointment when used in a maintenance regimen as compared to the safety profile approved in the current SPC. Therefore, the MAH was of the opinion that Section 4.8 of the SPC covers both indications and does not require any update.

Following the MAH response the CHMP was of the opinion that the control studies are the pivotal studies which support the variation to the SPC. An increased rate of application site infections was noted to occur in patients on maintenance treatment (6.3% versus 2.7%) in adult patients with AD. Differences were also noted to occur in paediatric patients with AD treated with tacrolimus maintenance treatment versus vehicle. As the additional studies are not the basis of this application, the CHMP was of the opinion that the additional adverse events noted to occur were assigned as probable or possibly related to tacrolimus maintenance treatment should be added to section 4.8 of the SPC and also mentioned in the patient information leaflet. The recommended wording for inclusion in section 4.8 was therefore as follows:

'In a study of maintenance treatment (twice weekly treatment) in adults and children with moderate and severe atopic dermatitis the following adverse events were noted to occur more frequently than in the control group: application site impetigo (7.7% in children) and application site infections (6.4% in children and 6.3% in adults).'

SPC Section 5.1
With this variation the MAH also updated Section 5.1 with a description of the two studies submitted and the results (see attachment 1 for the full text).

1.5 Pharmacovigilance and Risk Management Plan

Risk Management Plan
Together with this application the MAH submitted a first version of the Risk Management Plan (RMP). The RMP initially submitted was not considered by the CHMP to be consistent with Volume 9A and the RMP template (EMEA/192632/2006). The MAH was therefore requested to refer to the relevant guidance and amend the RMP accordingly.

The MAH submitted a revised RMP to comply with the RMP template (EMEA/192632/2006). Furthermore, the summary of the RMP was revised to summarise routine and additional pharmacovigilance activities and risk minimization measures. However, the lack of clarity with regard to what constitutes pharmacovigilance activities as opposed to risk minimisation measures remained.

In the second response from the MAH, the lack of clarity with regard to what constitutes pharmacovigilance activities as opposed to risk minimization measures was addressed. SPC and PIL wording was described as a routine risk minimisation measure rather than a proposed pharmacovigilance activity. Educational material was appropriately described as an additional risk minimisation measure.

As requested by the CHMP, the MAH agreed to provide a DHPC providing recommendations for the use of Protopic ointment as maintenance therapy, including reminders covered by the current MA as well as all identified and potential risks with the use of Protopic ointment. The CHMP clarified that the final wording of the DHPC will only be agreed once the variation to permit maintenance treatment is approved. Therefore, the precise wording of the DHPC is not further discussed in this report.

Following a request from the CHMP the MAH also agreed to add application site burning as an important identified risk in all relevant sections of the RMP.

Regarding the detailed action plan for specific safety concerns, the MAH was requested to present the details of the additional measures which may be adopted on the basis of the results of the following actions and the decision criteria for initiating such measures in the following cases:

- Margolis *et al* (2007) case control study (non melanoma skin cancer).
- Mechanistic *in vitro* study. "Tacrolimus effect on cutaneous T cell lymphoma lymphocyte and dendritic cells".
- Long-term EU epidemiological study (long-term effect on the skin with respect to malignancies).
- APPLES study – prospective paediatric longitudinal observational study.
- Long-term observational studies in Japan.

The MAH provided a detailed response for each of the five cases as follows:

Margolis et a1 (2007) case control study (non melanoma skin cancer)
The results of this case-control study have shown that AD patients developing NMSC were not exposed more frequently to TCIs (tacrolimus or pimecrolimus) than those not developing NMSC (controls), suggesting that patients exposed to TCIs are not at increased risk to develop NMSC. However, the observational period for the cases in this study was not long enough considering the latency period of NMSC, and therefore the authors of this work have announced their intention to repeat the study within a few years after this publication as to accumulate a longer observational period. The MAH monitors the publication of the results of the planned repetition of the Margolis case control study on the risk of atopic dermatitis patients to develop NMSC after exposure to TCIs.
In parallel, the MAH has proposed to the CHMP the repetition of the Drug Utilization Cohort Studies (DUS), of which the first results were submitted in June 2007 and reviewed by the CHMP in

September 2007. The results for the repeated case-control study and both Drug Utilization Studies are expected at the end of 2010. The risk-benefit of Protopic ointment will be re-assessed again on the basis of these results.

Mechanistic in vitro study. "Tacrolimus effect on cutaneous T cell lymphoma lymphocyte and dendritic cells"
This mechanistic study was conducted and submitted to the CHMP in 2007 as part of the follow-up measures committed to the CHMP. The data from this study suggests the absence of increased proliferation of CTCL cells in the studied model when exposed to increasing concentrations of tacrolimus *in vitro*. Where these results are encouraging in the efforts to demonstrate the absence of an increased risk to develop CTCL in patients using Protopic ointment, a definitive translation to the clinical situation cannot yet be made. The MAH did not believe that these results do require further measures, however, other activities initiated to address overall risk for skin malignancy (e.g. APPLES study, DUS studies) would be utilized to investigate the CTCL risk.

Long-term EU epidemiological study (long-term effect on the skin with respect to malignancies)
In March 2006, the MAH committed to propose a European epidemiological study to assess the risk of development of skin malignancies. Accordingly, the MAH conducted, as an initial step, two Drug Utilization Studies in two well known European epidemiological institutions (GPRD and Pharmo Institute). As for the case-control study mentioned above, the exploratory analysis conducted in the frame of the DUS studies did not show an increased risk for the development of skin malignancies in patients exposed to TCIs (pimecrolimus, tacrolimus). The observational period was relatively short and therefore the MAH suggested in September 2007, to repeat the Drug Utilization Studies after a few years. The outcome of these new DUS' and the analysis for increased risk of cutaneous malignancy are expected at the end of 2010. No further measures are foreseen at this point in time.

APPLES study - prospective paediatric longitudinal observational study
The APPLES study is a follow-up measure requested by the CHMP to include European patients in an epidemiological study assessing the risk of lymphoma and skin malignancies in paediatric patients with atopic dermatitis exposed to Protopic ointment. The APPLES study planned for an observational period of 10 years for each enrolled paediatric patient, and therefore the availability of a final study report is expected by the end of 2018. The study analysis plan foresees an interim report by the end of 2013. In addition, the MAH is providing to the CHMP enrolment updates twice a year.

Long-term observational studies in Japan
The Japanese long-term observational studies will be assessed as other long-term safety studies through the routine pharmacovigilance procedures and PSUR during their execution and until their expected conclusion in 2015.

Regarding the detailed action plan for specific safety concerns the CHMP acknowledged the MAH comment that no further measures arising from the above five studies are foreseen at this point in time. With regard to the long-term EU epidemiological study, the need and feasibility of this study (rather than repetition of the DUSs) is currently under separate regulatory assessment. Dependant on the outcome of this assessment, the RMP may need to be further updated in this regard.

Risk Minimisation Plan
It has been shown that with the maintenance treatment there was less use of tacrolimus ointment versus the current recommended treatment in both adults and in children above 2 years of age. However, because of the fact that the theoretical risk of cutaneous malignancy and lymphoma cannot be ruled out and the importance to only threat the patients fulfilling the criteria for maintenance treatment the CHMP considered it necessary that the attention of the prescribers is drawn to the importance to respect these specific conditions when prescribing Protopic in maintenance therapy. This would be done through a DHPC letter that could also be used as a reminder of some of the important safety concerns as described in the RMP summary table. The MAH was therefore requested to commit to providing a DHPC to be reviewed by the CHMP (see letter of undertaking attached to this report).

Regarding Annex 7 of the RMP (other supporting data), a number of line listings of reports of malignancy reported to the MAH before 30th September 2007 has been presented. The MAH was therefore requested to provide an analysis of this data (to include patient exposure data, to provide context).

Following the CHMP request the MAH provided a response listing the 4 categories of malignancies reported.

Hodgkin's and Non-Hodgkin's lymphoma (n=38)

Overall, 38 cases of Hodgkin's and Non-Hodgkin's lymphoma have been reported in 38 patients in the period from 1998 to 30 September 2007. Of these, 2 cases were reported in clinical studies, 22 (58%) were spontaneous reports and 14 (37%) were Health Authority cases. The number of cases diagnosed is variable from year to year, but generally there have been several additional cases every year since the launches in Japan (1999), the USA (2001) and Europe (2002). Reporting of cases had been stable for several years until a peak in 2005. This was most likely as a result of regulatory actions conducted in the USA and Europe in relation to topical calcineurin-inhibitors and the associated publicity. Since then the number of diagnosed cases has decreased substantially where the number of cases reported has returned back to the level observed in 2004.

Twenty two (22) out of 38 cases (58%) were reported in North America (USA) and 8 (21%) in both Asia and in Europe (2 in UK, 2 in Spain, 2 in Finland and 1 each in Germany and Ireland). Thirty two (32) cases (84%) were reported in adults ≥ 18 years of age, of these 18 (47%) were in patients aged ≥ 50 years, and 14 patients where aged between > 18 and < 50 years; 3 patients (8%) where younger than 18 years at time of diagnosis, and age was not known for three cases. Twenty (20) cases (52%) were reported in male patients. For those patients where the information was available, the time elapsed from 1st application to diagnosis was highly variable ranging from a few months to several years. The majority of the patients are adults, with almost half of the cases being reported in patients older than 50 years.

CTCL, Sezary's syndrome, Mycosis Fungoides, T-cell lymphoma in skin biopsy (n=21)

Overall, 21 cases of lymphoma in the skin (CTCL, Sezary's syndrome, Mycosis Fungoides, T-cell lymphoma in skin biopsy) have been reported in 21 patients in the period from 1998 to 30 September 2007. From these, 6 were reported in clinical studies, 9 were spontaneous reports and 6 were Health Authority cases. The number of cases diagnosed is variable with few additional cases every year. Reporting has shown to be stable until 2005 with a peak in 2006 most likely due to the regulatory actions conducted in the USA and Europe in that year in relation to topical calcineurin-inhibitors. Fourteen (14) cases were reported in North America (USA), 1 in Asia (Japan) and 6 in Europe (3 in UK, 2 in France and 1 in Spain). Seventeen cases (81%) were reported in adults≥ 18 years of age, of these 11 (52%) were in patients aged ≥ 50 years, and 6 patients were aged between > 18 and < 50 years; 2 patients where younger than 18 years (16 and 15 years respectively) at time of diagnosis, and age was not known for two cases. Thirteen cases were reported in male patients (62%). For those patients where the information was available, the time elapsed from 1st application to lymphoma diagnosis was highly variable ranging from a few months to several years. Overall, the number of cases of CTCL reported remains low and stable over the last 10 years. The majority of the patients are elderly males with a long history of eczematous conditions, consistent with the population prone to develop CTCL.

Skin cancer cases (n=49)

Overall, 53 events of skin cancer have been reported in 49 patients in the period from 1998 to 30 September 2007. From these, 22 events were reported in clinical studies, 17 were spontaneous reports and 10 were from a Health Authority. As before, the number of cases diagnosed is variable from year to year. Reporting of cases had shown to be stable until 2005 with a peak in 2006, probably due to regulatory actions conducted in the USA and Europe and its associated media impact. Thirty four (34) cases were reported in America, 3 in Asia and 12 in Europe (3 in UK, 3 in France, 2 in Sweden, and 1 each in Germany, Norway, Ireland and The Netherlands). Forty four cases (90%) were reported in adults ≥ 18 years of age, 39 (79%) in patients aged ≥ 40 years, 3 patients where younger than 18 years at time of diagnosis, and age was not known for two cases. Twenty five cases were reported in male patients (50%). Time elapsed from 1st application to skin cancer diagnosis was highly variable ranging

from a few weeks to several years. Overall, the diagnosis of cases of skin malignancies remains low and stable over the last 10 years. The majority of the patients are aged > 40 years after which the risk for developing skin malignancies is known to be increased. The majority of reported cases are cases of SCC (Squamous Cell Carcinoma) and BCC (Basal Cell Carcinoma) in head, neck, face or limbs, regions with higher exposure to natural sunlight. Overall, the pattern of the patient's age and type of malignancy corresponds to what is known from the epidemiology of skin malignancies, particularly NMSC.

Other cancer cases (n=44)
Overall, 44 events of cancer other than lymphoma or skin cancer have been reported in 44 patients in the period from 1998 to 30 September 2007. From these, 20 were reported in clinical studies, 17 were spontaneous reports and 7 were Health Authority cases. The number of cases diagnosed increased over time in a regular manner consistent with the increasing exposure after launch in 2001 and 2002 in the USA and Europe respectively. In terms of case reporting, again a peak in 2006 was observed. Twenty six (26) cases were reported in America, 4 in Asia and 14 in Europe (2 in UK, 3 in France, 5 in Germany, 3 in The Netherlands and 1 in Spain). Thirty three cases (75%) were reported in adults ≥ 18 years of age, 18 (41%) in patients aged ≥ 50 years, 8 patients where children younger than 18 years, and age was not known for three cases. Twenty one cases were reported in male patients (48%). Also in this case time elapsed from 1st application to cancer diagnosis was highly variable ranging from a few weeks to several years. Overall, the age of the patients and the type of malignancy reported correspond well to what is expected from the normal population. From the 8 children reporting a malignancy, 4 were leukaemias. When comparing the number of cases diagnosed and reported for each type of malignancy to the overall exposure to the drug as presented in the current version of the RMP and the PSURs, the accrual of cases reported does appear to follow reasonably well the increase in overall exposure since marketing.

Overall, the MAH believed that for all 4 categories of malignancies presented, the number and pattern of reporting is in line with what could be expected from the normal population.

The CHMP acknowledged the MAH response and commented that the analysis requested related to tables 55, 56 and 57 of Annex 7 i.e. those involving lymphoma and skin cancers, although the MAH has also provided an analysis regarding malignancies other than skin and lymphomas. These reports would have been included and assessed in the clinical study reports and in the regular PSURs submitted. Risk of cutaneous malignancy and lymphoma are characterised as important potential risks and are subject to additional pharmacovigilance measures (expedited reporting of malignancies irrespective of causality and ongoing and completed post marketing studies as agreed follow-up measures). The SPC and PL contain information regarding risk of malignancy and post-marketing reports (causality not addressed in the SPC and neither confirmed nor refuted in the PL). The MAH was therefore requested to:

- Provide exposure data
- Clarify why reports of malignancy from clinical trials have not been reflected in the product information.
- Provide the CIOMS reports for the cases described (including reporter/ investigator assessment of causality).

In response, the MAH provided available information on exposure to tacrolimus as retrieved from the reviewed CIOMS forms. The review of CIOMS information on estimated treatment duration for reported cases of malignancy (lymphoma, CTCL, other skin malignancies) did not show a trend for an increased reporting of any of these malignancies with increasing treatment duration. Considered together, the MAH was of the opinion that, although sometimes scarce, the information available on treatment durations from reported cases of malignancies is consistent with the previous position of the MAH that it is likely that many of these events were either pre-existing lesions that became evident when the skin was cleared of AR, were cases of CTCL misdiagnosed as AD at the time of prescription, or represent events occurring at the background rate for the underlying disorder.

The MAH believed that the information available from treatment durations recorded from malignancy cases reported to the global safety database for Protopic do not support a causal link between treatment

duration/exposure and development of lymphoma or skin malignancy including CTCL, and does not provide evidence that prolonged treatment periods with Protopic translate into increased reporting of malignancy.

The CHMP agreed with the MAH conclusion.
Table 33 below summaries the Pharmacovigilance and Risk minimisation activities included in the version of the Protopic Risk Management Plan dated 21 January 2009.

Table 33: Summary of Pharmacovigilance and Risk Minimisation Activities

Safety Concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Important identified risks		
Application site pruritus/irritation/burning Paraesthesia Alcohol flushing Folliculitis/herpes simplex	Routine PV activities Additional PV activities: • None	Routine: All important identified risks are adequately addressed in the wordings included in SPC and PIL. SPC section 4.8: • In clinical studies approximately 50% of patients experienced some type of skin irritation adverse reaction at the site of application. Burning sensation and pruritus were very common, usually mild to moderate in severity and tended to resolve within one week of starting treatment. • Sensation of warmth, pain, paraesthesia and rash at the site of application were also commonly observed. • Alcohol intolerance (facial flushing or skin irritation after consumption of an alcoholic beverage) was common. • Patients may be at an increased risk of folliculitis, acne and herpes viral infections. Additional • None

Important potential risks		
Theoretical risk of cutaneous malignancy including Cutaneous T-cell lymphoma	Routine PV activities with: • Expedited reporting of all malignancies irrespective of causality • Follow-up of the reported cases of CTCL in paediatric patients under treatment with Protopic ointment. The follow-up will be provided a part of the PSUR obligations Additional PV activities: • Periodic review of newly reported malignancy cases • APPLES study (prospective paediatric longitudinal observational study), including maintenance treatment (EU only)	Routine: Potential risk is addressed in wording in SPC and PIL. SPC section 4.4: • The development of any new change different from previous eczema within a treated area should be reviewed by the physician. SPC section 4.8: • Post-marketing: cases of malignancies, including cutaneous and other types of lymphoma, and skin cancers, have been reported in patients using tacrolimus ointment (see section 4.4). Additional: • DHPC letter
Theoretical risk of other lymphoma	Routine PV activities with: • Expedited reporting of all malignancies irrespective of causality	Routine: Potential risk is addressed in wording in SPC and PIL. SPC section 4.4: • Lymphadenopathy was uncommonly (0.8%) reported in clinical trials. The majority of these cases related to infections (skin, respiratory tract, tooth) and resolved with appropriate antibiotic therapy. • Lymphadenopathy present at initiation of therapy should be investigated and kept under review. In case of persistent lymphadenopathy, the aetiology of the lymphadenopathy should be investigated. In the absence of a clear aetiology for the lymphadenopathy or in the presence of acute infectious mononucleosis, discontinuation of Protopic should be considered. • The development of any new change different from previous eczema within a treated area should be reviewed by the

		physician. SPC section 4.8: • Post-marketing: cases of malignancies, including cutaneous and other types of lymphoma, and skin cancers, have been reported in patients using tacrolimus ointment (see section 4.4).
	Additional PV activities: • Periodic review of newly reported malignancy cases • APPLES study (prospective paediatric longitudinal observational study), including maintenance treatment (EU only)	Additional: • DHPC letter
Important missing information		
Children below 2 years of age	Routine PV activities with: • Specific analysis of the reported ADRs in the PSUR Additional PV activities: • Annual monitoring and reporting of tacrolimus ointment use in children under 2 years of age according to the Protopic Follow-up Measures (FUM) scheme	Routine SPC section 4.2: • Protopic is not recommended for use in children below the age of 2 years until further data are available. Additional: • DHPC letter
Safety of maintenance treatment beyond 12 months (children above 2 years of age)	Routine PV activities with: • Specific analysis of ADRs of children who receive maintenance treatment for more than 12 months in PSUR	Routine: Treatment information is addressed in wording in SPC and PIL. SPC section 4.1 • Maintenance treatment of moderate to severe atopic dermatitis for the prevention of flares and the prolongation of flare-free intervals in patients experiencing a high frequency of disease exacerbations (i.e. occurring 4 or more times per year) who have had an initial response to a maximum of 6 weeks treatment of twice daily tacrolimus ointment (lesions cleared, almost cleared or mildly affected). SPC section 4.2: • After 12 months, a review of the patients' condition should be conducted by the physician and a decision taken whether to continue maintenance treatment in the

	Additional PV activities • None	absence of safety data for maintenance treatment beyond 12 months. In children, this review should include suspension of treatment to assess the need to continue this regimen and to evaluate the course of the disease. Additional: • DHPC letter

The CHMP considered that the proposed Pharmacovigilance and risk minimisation activities were sufficient. No additional risk minimisation activities apart from the DHPC letter were considered needed.

II. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

It is estimated that moderate-to-severe AD patients have frequent disease exacerbations and that they spend on average 112–192 days per year with active disease (Zuberbier et al, 2006). After discontinuation of treatment, AD flares commonly reoccur after approximately 14 days (Reitamo et al, 2002) therefore it would appear that this condition is not optimally managed.

The efficacy results of the CONTROL studies show that patients experienced fewer disease exacerbations, a longer time to their next disease exacerbation and longer disease-free periods. Although the safety of maintenance therapy with tacrolimus ointment has not been formally investigated beyond 12 months of treatment, studies conducted with the intermittent twice daily regimen for up to 4 years have no shown any evidence for development of lymphoma or CTCL.

It is known that in the early stages patches of CTCL resemble eczema, psoriasis, and contact dermatitis. It may also respond favourably to the topical treatments prescribed for these skin disorders. This is unfortunate as the disease may be missed or misdiagnosed as a benign condition and the patient may be untreated for years. CTCL is most likely discovered when a physician maintains a degree of suspicion about the disease, performs multiple skin biopsies, and provides close follow-up after the initial presentation. The MAH has shown that an intact stratum corneum is the rate limiting barrier to tacrolimus absorption and during a disease exacerbation (AD Flare) there is a 7 fold higher rate of skin absorption compared with normal skin. The MAH has also provided evidence that as skin heals the amount of tacrolimus absorption decreases over time and with the proposed maintenance regimen there is little or no skin accumulation of tacrolimus.

In relation to drug usage the control studies have shown that both adults and children used less tacrolimus ointment during a disease exacerbation when maintenance treatment was used versus the current regime (vehicle). While the amounts of tacrolimus ointment used during the study for both treatment regimens were comparable for adults, an increase amount was seen in children. However, this is not fully accurate as there was a higher drop out rate in patients treated with the currently approved regimen (vehicle) versus maintenance treatment therefore taking this into account the amount of tacrolimus ointment use per day during the DCP was calculated. It has been shown that with maintenance treatment there was less use of tacrolimus ointment (g/day) versus current recommended treatment. An additional study (FG-506-30) has concluded that 96% of tacrolimus ointment is cleared at 96 hours after the last application of the ointment, indicating that there was no sustained retention of tacrolimus in epidermis/dermis. As the maintenance treatment is proposed for once daily twice weekly no accumulation of tacrolimus would be expected to occur.

The MAH also provided an update on the clinical trials investigating long term safety which included an update from the APPLES study and the DUS. Neither of these studies has reported an increased rate of CTCL or lymphoma. The MAH has proposed to re-run the DUS as conducted in 2007, in two representative epidemiological databases in Europe to assess the risk of developing skin malignancies.

This repetition should ensure that patients included in the different cohorts have a minimum follow-up period of 5 years. In addition, the MAH has provided a thorough answer of the issues raised and examined and discussed the actual evidence to date for the risk of developing CTCL and lymphoma, the potential risks of tacrolimus exposure to both the skin and systemic compartments using both treatment regimens, given an update of ongoing and future studies.

The current licensed indications do not specify the frequency or duration of treatment as patients can be treated as often as they experience a flare. The purpose of this type II variation was to examine whether there is an increased risk with the proposed maintenance treatment versus the current licensed treatment regimen, as distinct from a full benefit risk assessment.

The current evidence suggests that exposure to tacrolimus will be less during maintenance treatment compared with the current licensed regimen as amount of tacrolimus used is less and absorption of tacrolimus is 7 fold lower with an intact stratum corneum compared with inflamed skin. It is also apparent that AD may commonly reflare 14 days after discontinuation of treatment. The proposed posology, of once daily for 2 days per week, will minimise skin exposure and accumulation of tacrolimus.

Currently there is no evidence of tacrolimus causing an immune system dysfunction. Taking the available evidence into consideration it does not appears that there is an increased risk (apparent or potential) with maintenance treatment versus the current treatment and overall it may be a safer way of treating patients as they appear to have lower tacrolimus exposure. It was the CHMP opinion that all of the available evidence supports the use of maintenance treatment for tacrolimus.

The CHMP therefore recommended that this variation is approvable and the amended changes proposed for the SPC are endorsed.

III. CONCLUSION

On 22 January 2009 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet.

Follow-up measures undertaken by the Marketing Authorisation Holder

As requested by the CHMP, the MAH agreed to submit the follow-up measures as listed below and to submit any variation application which would be necessary in the light of compliance with these commitments:

Area[1]	Description	Due date[2]
Clinical	Follow-up long-term paediatric patients under maintenance therapy with Protopic ointment, through the inclusion of these patients in the ongoing Prospective Pediatric Longitudinal Evaluation to Assess the Long-Term safety of Tacrolimus Ointment for the treatment of atopic dermatitis (APPLES study, FUM #032). Status of recruitment of patients using maintenance treatment will be included in the updates submitted currently to CHMP twice a year. The MAH will take appropriate actions (e.g., send letters to investigators to facilitate recruitment), in order to ensure that adequate proportion of patients on maintenance treatment are included in the study.	Twice yearly, starting in November 2009.

	Explore the feasibility of using the Scandinavian prescription and cancer registries for the follow up of children receiving maintenance treatment. Reporting on the feasibility to CHMP / EMEA.	May 2009
Clinical	To submit a Product Information in line with the draft EU SmPC guideline (EMEA/299527/2007) with the next variation affecting the annexes.	With next variation of PI.
Pharmacovigilance	Follow-up the reported cases of Cutaneous T-Cell Lymphoma in paediatric patients under treatment with Protopic ointment.	With the next PSUR
Pharmacovigilance	To provide a draft DHPC on the introduction of maintenance treatment therapy prior to commercial launch of this regimen. The deadline provided is an estimate , The letter would be submitted for review before distribution to HCPs.	Q3 2009 (speculative)
Pharmacovigilance	To provide an updated RMP, including information on ongoing and completed FUMs.	March 2009

1. Areas: Quality, Non-clinical, Clinical, Pharmacovigilance
2. Due date for the follow-up measure or for the first interim report if a precise date cannot be committed to.

IV. EPAR CHANGES

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope:
Extension of Indication to include 'maintenance treatment' further to completion of one study in adult patients (FG-506-06-40) and one in paediatric patients (FG-506-06-41). Sections 4.2, 4.4, 4.8 and 5.1 of the SPC and Sections 1, 2, 3 and 4 of the PL have been revised accordingly. In addition, Annex II has been updated to include the reference to version 4 of the EU RMP (dated 21 January 2009).

Summary / scientific discussion:

The CHMP variation Assessment Report will be published as part of the EPAR following review/deletion of confidential information.