THE EFFECTIVENESS AND COST-EFFECTIVENESS OF PIMECROLIMUS AND TACROLIMUS FOR ATOPIC ECZEMA

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ABOUT PENTAG

The Peninsula Technology Assessment Group is part of the Institute of Health and Social Care Research at the Peninsula Medical School. PenTAG was established in 2000 and carries out independent Health Technology Assessments for the U.K. HTA Programme and other local and National decision-makers. The group is multi-disciplinary and draws on individuals' backgrounds in public health, health services research, computing and decision analysis, systematic reviewing, statistics and health economics. The Peninsula Medical School is a school within the Universities of Plymouth and Exeter. The Institute of Health and Social Care Research is made up of discrete but methodologically related research groups, among which Health Technology Assessment is a strong and recurring theme. Projects to date include:

The Effectiveness and Cost-Effectiveness Of Imatinib (STI 571) in Chronic Myeloid Leukaemia: a Systematic Review (2002)

Screening for Hepatitis C Among Injecting Drug Users and in Genitourinary Medicine (Gum) Clinics: Systematic Reviews of Effectiveness, Modelling Study and National Survey of Current Practice (2002)

Systematic review of endoscopic sinus surgery for nasal polyps (2003)

Microwave and Thermal Balloon Endometrial Ablation for Heavy Menstrual Bleeding (in press)

The Effectiveness and Cost-Effectiveness of Imatinib for First Line Treatment of Chronic Myeloid Leukaemia in Chronic Phase (2003)

Do the Findings of Case Series Studies Vary Significantly According to Methodological Characteristics? (in press)

CONTRIBUTIONS OF AUTHORS

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CONFLICTS OF INTEREST

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The assessment report considers the effectiveness and cost effectiveness of pimecrolimus for mild to moderate atopic eczema and tacrolimus for moderate to severe atopic eczema compared to current standard treatment in adults and children.

1.2 Epidemiology and background

Atopic eczema (also known as atopic dermatitis) is a common, chronic, relapsing skin disease characterised by intense itching, dry skin, redness inflammation and exudation. Severity may vary widely. In the majority of cases, symptoms are mild, although in some, severe itching may lead to loss of sleep, and a range of impairments of quality of life.

Cumulative prevalence of 5-20% by the age of 11 has been estimated, with 60% occurring before the age of one. By adulthood, many will have grown out of the condition although may remain with a propensity for eczema later in life. Incidence of eczema has been increasing in recent years.

Most atopic eczema is managed in primary care with only a few severe or resistant cases referred to consultant dermatologists.

Current treatment is varied, with abundant use of emollients and active treatment with topical corticosteroids being the current mainstays of treatment. Numerous other approaches to preventing exacerbation of eczema (such as use of special clothing, dietary restrictions, avoidance of soaps etc.) and to treat dry itchy skin (wet wrapping, oil of evening primrose, light therapy etc.) are available, although evidence for many such treatments is lacking. There may be some consumer resistance to topical corticosteroid use, particularly over the long term and in children.

Two new topical immunosuppressants, pimecrolimus and tacrolimus, have recently been introduced for use in atopic eczema and are the subject of this assessment report.

1.3 Number and quality of studies, and direction of evidence

Electronic data bases were searched for published research on the clinical effectiveness and cost-effectiveness of topical pimecrolimus and tacrolimus in atopic eczema compared to current standard treatment (emollients and topical corticosteroids). In addition, bibliographies were searched for relevant publications and experts and the manufacturers of these agents approached for information.

The review includes eight RCTs of pimecrolimus [three of which were submitted on an in confidence basis], three in children [one of which was submitted on an in confidence basis] and five in adults [two of which were submitted on an in confidence basis] containing 1602 subjects (2601 including CIC data). The review includes ten RCTs of tacrolimus, four in children, five in adults and one containing both adults and children containing 4303 subjects. Of the pimecrolimus studies, four were in moderate to severe eczema which is not the licensed indication. All the tacrolimus trials were in those with moderate to severe eczema (the licensed indication), although one only included those with lichenified eczema.

1.3.1 Effectiveness Pimecrolimus

Three RCTs of pimecrolimus were provided as "commercial in confidence" by Novartis Pharmaceuticals UK Ltd.

Overall, the trial reports were of varying quality with methods of randomisation and blinding not stated or unclear in four out of eight.

Four RCTs compared pimecrolimus to vehicle (a placebo treatment consisting of the base cream or ointment without the active ingredient). One (two including CIC material) compared pimecrolimus to a potent topical corticosteroid in adults with moderate to severe eczema. [CiC information removed ……]No studies compared pimecrolimus to mild or moderate topical corticosteroids in patients with mild to moderate disease.

[CiC information removed ……]

[CiC information removed ……]

Pimecrolimus is more effective than vehicle according to global measures such as the Investigators Global Assessment, patient based measures such as number of flares and pruritus, and alternative treatment use i.e. the amount of additional topical corticosteroids needed to treat problem eczema. Quality of life is also improved more with pimecrolimus compared to vehicle. There is very little evidence available about pimecrolimus compared to topical corticosteroids. That which there is does not address the licensed population or potency of topical steroids.

1.3.2 Effectiveness of Tacrolimus

A total of 10 RCTs were included in the systematic review. The trials were of variable quality.

A range of populations and comparators were studied. Half of the RCTs compared tacrolimus with vehicle, two trials in children used a very mild potency topical corticosteroid and three in adults compared tacrolimus to potent topical corticosteroids.

Compared to vehicle, both 0.03% and 01% tacrolimus are more effective on global measures such as the Physicians Global Evaluation (PGE) and patient based measures such as pruritus score.

Compared to a very mild corticosteroid (1% hydrocortisone acetate) 0.03% tacrolimus is more effective in children as measured by a 90% or better improvement in the PGE.

Compared to potent topical corticosteroids (0.1% hydrocortisone butyrate and 0.12% betamethasone valerate) no significant difference in effectiveness is seen with 0.1% tacrolimus as measured by 75% or greater improvement in the PGE.

Minor application site adverse effects are common with tacrolimus. However, this did not lead to increased rates of withdrawal from treatment in trial populations.

1.3.3 Economic Evaluation

One published economic evaluation (of tacrolimus) was identified. This is of limited relevance to the U.K.

Industry submissions for pimecrolimus and tacrolimus were reviewed. The evaluation of tacrolimus did not calculate cost utility. The evaluation of pimecrolimus was restricted to a comparison with vehicle (placebo).

We developed a state transition (Markov) model to estimate cost-utility of tacrolimus and pimecrolimus separately, compared to current standard practice with topical corticosteroids (a) as first line treatment and (b) as second line treatment. The model was adaptable to investigate different treatment pathways for adults and children, for facial and non facial eczema and for mild to moderate and moderate or severe eczema. A total of eight cohorts of 1,000 patients each were therefore modelled.

For children, the model ran for 14 years (ages 2 to 16). For adults, the model ran for one year. The cycle length in all cases was 4 weeks.

Pimecrolimus appears unlikely to be considered a cost-effective treatment in mild to moderate eczema in adults or children compared to topical steroids. In all cases it costs more and confers fewer QALYs. However, the absolute differences in QALYs are small and these results are subject to uncertainty. Probabilistic analysis confirms the high degree of uncertainty in the data.

When compared to emollient alone, pimecrolimus becomes more likely to be considered cost effective if decision makers are willing to pay more than £20,000 for an additional QALY. At a willingness to pay of £30,000 per QALY the possibility that pimecrolimus is more cost effective is estimated to be 0.55.

Deterministic analyses of tacrolimus suggest it may be considered cost effective as a first-line option in moderate to severe facial eczema in adults and body eczema in children. However, these results are subject to great uncertainty. Stochastic analysis, which takes account of some of this uncertainty, shows no option (topical steroids or tacrolimus as first or second-line therapy) has a probability of being cost effective of greater than 50%, assuring decision makers are willing to spend £30,000 for an additional QALY.

The cost-effectiveness results should be interpreted with caution. Cost-effectiveness acceptability curves based on net benefit show that the probability of any of the regimens being the most cost effective is low – reflecting the considerable uncertainty in available empirical data. No conclusions can be confidently drawn about the cost-effectiveness of pimecrolimus or tacrolimus compared to active topical corticosteroid comparators.

LIST OF ABBREVIATIONS

AD	Atopic Dermatitis
ADASI	Atopic Dermatitis Area and Severity Index
ADSI	Atopic Dermatitis Severity Index
AEs	Adverse effects
BSA	Body Surface Area
BMV	Betamethasone-17-valerate
CDLQI	Children's Dermatology Life Quality Index
CEAC	Cost effectiveness acceptability curve
CI	Confidence Interval
CIC	Commercial in Confidence
CMH	Cochran-Mantel-Haenszel
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
FDA	Food and Drug Administration (USA)
FTU	Finger Tip Unit
IGA	Investigator global assessment
IgE	Immunoglobulin-E
ITT	Intent to treat
MAUC	Mean area under curve
m EASI	Modified Eczema Area and Severity index
NA	Not applicable
PGE	Physicians global evaluation
PI QoLIAD	Parent's index of Quality of Life Index – Atopic Dermatitis
QALY	Quality Adjusted Life Year
QoL	Quality of Life
QoLIAD	Quality of Life Index – Atopic Dermatitis
RCT	Randomised Controlled Trial
SCORAD	Severity Scoring of Atopic Dermatitis
TS	Topical corticosteroid
VAS	Visual Analogue Scale

DEFINITION OF TERMS

Adenoma	Benign epithelial tumour
Atopic dermatitis	Synonymous with atopic eczema
Atrophy	A wasting away – in this case, refers to thinning of the skin
Basophils	Granular white blood cells.
Cyclosporin	An immunosuppressive drug
Dander	Scurf from the coat or feathers of various animals
Desquamation	The shedding of skin in scales or flakes
Ectoderm	The outer of the three germ layers of the embryo that develops into epidermis and neural tissue.
Epidermis	The outer layer of the skin
Erythema	Redness of the skin caused by congestion of the capillaries.
Excoriation	Scratch marks on skin
Exudation	Weeping of the skin
Finger tip unit	A method of measuring the dose of steroid cream to be applied – approximately equivalent to 1g. A line of cream form the tip of the index finger to the top joint.
Folliculitis	Inflamed or infected hair follicles
Herpes simplex	Viral infection - cold sores
Immunophilins	A cellular protein that binds immunosuppressive drugs. Thought to interact with calcineurin.
Immunoglobulin	A protein produced by plasma cells to help with fighting infection.
Immunoglobulin E	An immunoglobulin associated with hypersensitivity reactions. Present in serum bound to mast cells and basophil white blood cells.
Induration	Abnormal hardness of the skin
Infiltration	Abnormal invasion of tissues by cells or fluid.
Lichenification	Overgrowth of the epidermis, resulting in the thickening of the skin with a leathery appearance
Macrolide	A group of antibiotics with a complex macrocyclic structure. They inhibit protein synthesis by blocking the 50S ribosomal subunit.
Mast cells	Cells contain much histamine and heparan and which in the skin are responsible for the reddening and weals response.
Molluscum contagiosum	A viral infection of the skin causing small dome shaped papules.
Modified Eczema Area and Severity index	As the EASI but excluding pruritus items.
Nasopharyngitis	Inflammation of the linings of the nose and pharynx, e.g. in the common cold.
Netherton's syndrome	A congenital skin condition causing widespread erythema and scaling.
Papulation	The formation of papules – small, circumscribed, superficial, solid elevations of the skin.
Prurigo nodularis	An eruption of hard nodules on the skin caused by rubbing and accompanied by itching.
Pruritus	Itching
Psoralens	A photo-sensitising plant extract.
Pyrexia	Fever
Striae	Silvery white lines in the skin, stretch marks.
Streptomyces	Genus of spore forming bacteria that grow in soil or water – a source of many antibiotics
Rule of nines	A method of estimating body surface area involved, by assigning values of 9 or 18% to body regions (e.g. head and neck = 9%, anterior thorax = 18%, posterior thorax = 18%, arms = 9%, legs = 18% each)
Telangiectasia	Permanent dilation of the blood vessels resulting in red patches on the skin.
T-lymphocyte	A white blood cell (T-cell) made in the thymus gland that co-ordinates immune response.
Varicella	Chickenpox

Vesiculobullous rash	Skin blisters

2 Aim

To assess the effectiveness and cost-effectiveness of pimecrolimus and tacrolimus for atopic eczema treatment relative to current standard treatments (emollients and topical corticosteroids).

3 Background

3.1 Description of the underlying health problems

3.1.1 Definition of atopic eczema

Atopic eczema (also known as atopic dermatitis) is a common chronic, relapsing skin disease. Sufferers are at increased risk of asthma or hay fever, and all three conditions share a similar hereditary background. This strong family tendency to hypersensitivity gives rise to the use of the word "atopic". Although elevated immunoglobin E (IgE) levels are considered a marker, in fact a proportion of those with this phenotype of eczema do not exhibit specific IgE antibodies to common environmental allergens.[1]

There is no single, definitive diagnostic test for atopic eczema. Identification therefore relies on assessing a variety of clinical features described by Hanifin and Rajka[2] and adapted by a UK working party.[3](www.nottingham.ac.uk/dermatology) According to these criteria, a person has atopic eczema if they show:

- An itchy skin condition (or report of scratching or rubbing in a child).

Plus three or more of:

- History of itching in the skin creases (bends of elbow, behind the knees, neck) or of the cheeks in child under 4.
- Personal or immediate family history of asthma or hayfever.
- Tendency towards dry skin.
- Visible flexural dermatitis (or cheeks, forehead and outer limbs in child under 4) as defined by a photographic protocol
- Onset in the first two years of life (not used in children under 4).

However, clinical features of atopic eczema may be highly variable in morphology, place and time. For example, the rash may be dry and thickened or weeping and eroded. It can affect the cheeks of infants and the skin creases of older children, and can be severe one day and quiescent a few days later.[4] Elements of the disease, such as papulation and redness, may be most apparent during acute exacerbations whilst dry skin and lichenification are more chronic features.[5] Lichenification with hyperpigmentation may be a particular problem in black skins.[6]

Atopic eczema is a distinct clinical type of eczematous reaction. The eczematous reaction pattern can occur in other forms of dermatitis, such as contact eczema (which itself may be caused by irritation from detergents or allergic contact eczema secondary to contact with specific contact allergens such as nickel), seborrhoeic eczema(caused by sensitivity to Pityrosporum yeasts), varicose eczema (associated with venous hypertension in the lower limbs) and discoid eczema (coin shaped lesions starting on the limbs).

3.1.2 Symptoms of atopic eczema

Atopic eczema is characterised by intense itching, dry skin, redness, inflammation and exudation[7] and is most prevalent in early childhood.[8] The severity may vary widely. In the majority of cases, symptoms are mild. Among 301 GP diagnosed cases of atopic eczema, 84% were classed as mild, 14% as moderate and 2% as severe[9]. Severe itching can lead to damage being done to the skin through scratching which can cause bleeding and secondary infection, and can lead to a thickening of the skin known as lichenification.[10] Itching may also lead to loss of sleep and this is seen in 10-30% of pre-school children and may be as high as 86% during flare ups.[11]

Infants usually first manifest head and facial (especially cheek) eczema, which is often very itchy, red, scaly and crusted.[6] This may then spread to the limbs and to the flexural surfaces of the elbows, knees and neck as the child gets older and often demonstrates papulation, rather than exudation. Adult eczema is often located on the hands,[10] face (especially forehead and periorbital areas) and flexural areas.[6]

Complications of eczema include staphylococcal, streptococcal and viral (such as herpes simplex, wart and molluscum contagiosum) infections.

3.1.3 Aetiology of atopic eczema

Atopic eczema has a complex aetiology which is not fully understood. It is genetically linked but environmental factors may cause its onset or existing symptoms to worsen. These include house dust mites, pet dander, pollen, tobacco, air pollution and low humidity.[8] Factors such as excessive use of soaps and other household irritants are also thought to aggravate the condition.[12] A possible suggested cause is a primary ectodermal defect that disturbs T-lymphocyte maturation.[13] Abnormal secretion of cytokines from T-lymphocytes is thought to be important in the creation of skin lesions.[14]

About 85% of patients have elevated immunoglobin E (IgE) levels.[15] This may play a role in atopic eczema through binding to basophils and mast cells and triggering the release of inflammatory mediators such as histamine.[15] It has also been suggested that polymorphisms within the gene for the β subunit of the high affinity IgE receptor (FCER1) on chromosome 11q12-13 may be linked to atopic eczema and asthma, but this is not considered proven.[6] *S. aureus* activates macrophages and T cells and appears to cause Ig-E mediated histamine release, worsening pruritus.[15]

3.1.4 Epidemiology of atopic eczema

A number of attempts to estimate the prevalence of eczema among children have been undertaken. It has been estimated that a cumulative prevalence of 15% and 20% is present by the age of 11 in developed countries.[16] In 60% of cases, onset is within the first year of life with 85% of cases onset is by five years old.[6] In adults, 65% of those having had atopic eczema as children will be clear of the condition by adulthood[1] although a propensity to eczema may remain which may manifest during adulthood as contact dermatitis or adult pattern atopic eczema.

Atopic eczema in childhood shows a reverse social class gradient, with higher prevalence in less deprived socio-economic groups.[8] Although results are not always consistent, more girls than boys are thought to develop eczema.[8] There is some evidence that while eczema is more common in developed countries, people moving to those areas from developing

countries may be at more risk. This has been shown in children of black Caribbean origin in London,[17] and in children from the Pacific Tokelau islands who migrated in New Zealand, and Chinese immigrants in Hawaii. However, a study of Asian children in the UK found no apparent difference in prevalence although Asian children were more likely to be referred to a dermatologist than their white counterparts.[8]

The risk of developing eczema is increasing in many countries, including Great Britain. A cohort study of all children born in England, Wales and Scotland over 7 days in 1958 and 1970 found eczema prevalent in 3.1% of those born in 1958, and of 6.4% in those born in 1970.[18] The authors also investigated various factors that might be linked to this rise. Taken together, changes between the cohorts in sex, birth weight, birth order, maternal age, breast feeding, maternal smoking during pregnancy and father's social class at birth did not seem to explain the observed rise in prevalence. Another study using a birth cohort of nearly 25,000 children from the West Midlands General Practice Research database has suggested that exposure to two or more courses of antibiotics *in utero* is associated with increased risk of doctor diagnosed asthma, eczema and hay fever.[19]

Older siblings appear to be associated with a protective effect[19] on the development of eczema, as do larger families.[10]

3.1.5 Eczema, severity of symptoms and impact on Quality of Life

Estimating Severity

There are several scales to assess the severity of atopic eczema. However, these are not standardised, and some may not have been properly tested.[5] This has led to difficulties in comparing results across studies.[5] [20]Reviews of these scales have been undertaken by Finlay in 1996[21], Charman and Williams in 2000[5] and Schiffner and colleagues in 2003.[22]

One of the commonly used scales of severity is from Rajka and Langeland, 1989[23] and is shown below in Table 1.

Table 1: Grading of Severity of atopic dermatitis (Rajka and Langeland 1989)[23]

I. Extent	
a) Childhood and adult phase Less than 9% of the body area Involvement evaluated to be more than score 1, less than score 3 More than approximately 36% of the body area involved	 1 2 3
b) Infantile phase Less than approximately 18% of the skin involved Involvement evaluated to be more than score 1, less than score 3 More than approximately 36% of the body area involved	 1 2 3
II. Course	
More than three months of remission during a year* Less than 3 months remission during a year* Continuous course	1 2 3
III. Intensity	
Mild itch, only exceptionally disturbing night's sleep Itch evaluated to be more than score 1, less than score 3 Severe itch, usually disturbing night's sleep	1 2 3
Score summation 3-4 = Mild 4.5-7.5 = Moderate 8-9 = Severe	

When in doubt, score 1.5 or 2.5 may be used

* May be adjusted in infants if onset was less than 1 year before grading

The Eczema Area Severity Index (EASI) is also commonly used in trials. This assigns proportionate body surfaces to the head and neck (10%), trunk (30%), upper extremities (20%) and lower extremities (40%) for those aged eight and over. For those aged 7 and under the proportions assigned are head and neck (20%), trunk (30%), upper extremities (20%) and lower extremities (30%). The area affected by inflammation (area of involvement not including dry skin) of each of the four body areas is given a numeric value 0-6 as shown below in Table 2. The head, trunk, upper and lower limbs are separately assessed for clinical signs of eczema erythema, infiltration/ papulation, excoriation and lichenification and given a score from 0 (none) to 3 (severe) with half points permitted (see Table 2). The EASI is then calculated as shown below with a maximum possible score of 72.[24] This combines clinical severity, measured as degree of erythema, infiltration, excoriation and lichenification, with proportion of body surface affected.

Table 2: Eczema Area and Severity Index (EASI)

EASI area of involvement	
0	No eruption
1	<10%
2	10-29%
3	30-49%
4	50-69%
5	70-89%
6	90-100%

Scoring clinical signs of EASI		
Erythema (E)		
0	None	
1	Mild	Faintly detectable erythema: very light pink
2	Moderate	Dull red, clearly distinguishable
3	Severe	Deep/dark red
Infiltration / papulation (I)		
0	None	
1	Mild	Barely perceptible elevation
2	Moderate	Clearly perceptible elevation but not extensive
3	Severe	Marked and extensive elevation
Excoriation (Ex)		
0	None	
1	Mild	Scant evidence of excoriation with no signs of deeper skin damage (erosion, crust)
2	Moderate	Several linear marks of skin with some showing evidence of deeper skin injury (erosion, crust)
3	Severe	Many erosive or crusty lesions
Lichenification (L)		
0	None	
1	Mild	Slight thickening of the skin discernible only by touch with skin markings minimally exaggerated
2	Moderate	Definite thickening of the skin with skin markings exaggerated so that they form a criss-cross pattern
3	Severe	Thickened indurated skin with skin markings visibly portraying exaggerated criss cross pattern

Calculating EASI score:

For aged 8 and over:

Head/ trunk	(E+ I + Ex + L) x area x 0.1
Trunk	(E+ I + Ex + L) x area x 0.3
Upper limbs	(E+ I + Ex + L) x area x 0.2
Lower limbs	(E+ I + Ex + L) x area x 0.4

EASI = sum of the above four areas

For aged 7 and under:

Head/ trunk	(E+ I + Ex + L) x area x 0.2
Trunk	(E+ I + Ex + L) x area x 0.3
Upper limbs	(E+ I + Ex + L) x area x 0.2
Lower limbs	(E+ I + Ex + L) x area x 0.3

EASI = sum of the above four areas

The Investigators Global Assessment (IGA) is a physician rating scale based on interpretation of signs of eczema (Table 3). This scale has not been validated, and it has

been suggested that the categories are vague (for example the distinction between "mild" and "just perceptible" erythema / papulation may be very difficult to make.)[25]

Table 3: Investigator's Global Assessment (IGA)

Score	Description
0 = Clear	No inflammatory signs of AD
1 = Almost Clear	Just perceptible erythema, and just perceptible papulation / infiltration
2 = Mild disease	Mild erythema and mild papulation / infiltration
3 = Moderate disease	Moderate erythema and moderate papulation / infiltration
4 = Severe disease	Severe erythema and severe papulation / infiltration
5 = Very severe disease	Very severe erythema and very severe papulation / infiltration with oozing / crusting

Finlay [21] reviewed 25 scales available in 1996. He noted that pruritus and consequent loss of sleep, the predominant symptoms of atopic eczema, were given a different emphasis in different scales. Weighting for pruritus in scales which provide a summary score, ranged from 7% to 33%. Finlay also discusses the problems of assessing long term disease activity. The degree to which individuals are affected by eczema may change quickly over quite short periods of time.

Charman and Williams (2000)[5] used an electronic database search to identify 13 scales in use from 1990 to 2000 and examined the extent to which these had been tested for validity, reliability, sensitivity to change and acceptability. For only one scale, the SCORAD index, were published data available for all these aspects. This scale was developed by the European Task Force on Atopic Dermatitis in 1993. It has shown sensitivity to change from cyclosporin, topical corticosteroids and UV-A therapy. It describes clinician assessment of the extent of disease using the rule of nines with six clinical features of disease intensity (assessed at a single, representative site), as well as a visual analogue score for itch and sleep loss completed by patients. However, some problems have been noted with intraobserver and interobserver reliability. Finlay also criticises the Severity Scoring of Atopic Dermatitis Index (SCORAD) as it combines observer and patients information, and is too complicated for routine use.[21]

A more recent systematic review by Charman and colleagues[26] found that 85/93 RCTs incorporated an objective measure of clinical signs. However, only 23 (27%) of these used a published severity scale, with the rest being modified scales or unnamed scales with no available validity or reliability data. The authors conclude that the wide variation of scales hinders evidence based practice, and also note that patient centred outcomes, such as QoL and effect of symptoms need to be given greater emphasis.[26]

In clinical practice, formal scales may not be used. Severity may be estimated from the extent of eczema, the localised severity and the disruption to life (for example sleep loss or prevention of work due to severe hand eczema) or some combination of these points for each individual case. Studies assessing inter-observer agreement have found this to be low for assessing the body surface involvement using the Rule of Nines[27] and using the Six Area, Six Sign Atopic Dermatitis severity score (SASSAD).[28] Low levels of agreement between clinicians using such scores suggest that objective assessment of the severity of eczema is difficult and that results using such measures should be interpreted with caution.

Estimating treatment effect

Changes in severity scores such as the EASI may be used to estimate the effect of treatment. Global assessments of change are also commonly used, such as the Physician's Global Evaluation (PGE) of clinical response. This estimates the percentage change in condition since the patient was last seen. (Table 4)

Table 4: Physicians Global Evaluation of treatment success

Affect on AD	% improvement
Cleared	100
Excellent Improvement	90-99
Marked Improvement	75-89
Moderate Improvement	50-74
Slight Improvement	30-49
No appreciable improvement	0-29
Worse	<0

Quality of life

Skin diseases can adversely affect sufferers' quality of life (QoL) as well as those of their family. Using the Stein and Riessman family questionnaire, an Australian study showed that the stresses on families of caring for a child with moderate to severe atopic eczema were significantly more than those experienced in caring for a child with insulin dependent diabetes-mellitus.[29] Carers describe feelings of guilt, exhaustion, frustration and helplessness.[30] Disturbed sleep and associated daytime tiredness and irritability affects both child and carers[31;32] with an estimated 1-2 hours of sleep lost by both each night.[29] An additional 2-3 hours a day is spent applying treatment.[29] A UK study of 30 families with children with eczema and 20 without, found children with eczema to have greater levels of clinginess, dependency and fearfulness. While fewer mothers of children with eczema had work outside the home.[33]

One qualitative study used latent content analysis to analyse the written accounts of 77 mothers caring for pre-school children with atopic eczema who had been referred to secondary care.[34] This study identified several areas of increased burden of care for the mothers of children with eczema. These included extra housework such as more frequent cleaning to minimise potential allergens, extra washing of clothes and bedding which were quickly soiled both by weeping and bleeding of eczema and by treatments, and restricted food choices with pressure to home-cook meals with limited ingredients. Added difficulties with normal activities were also described, such as problems changing clothes and undressing due to clothes sticking to the child's affected skin causing pain on removal or triggering fresh scratching episodes. Bathing may irritate the eczema, upsetting the child and offering renewed opportunities for scratching. Mothers also felt increased demands to entertain their children as they needed to be distracted from scratching; this was challenging as the children were often made irritable and distracted by itching.[34]

Children's emotional and social development may be affected. Older children may be embarrassed by their condition which can disrupt sporting activities.[30] Adolescents may be advised to avoid certain career areas that would involve prolonged wetness or exposure to irritants (e.g. hairdressing, catering, engineering, agriculture).

Dermatology specific scales

A very recent review of severity and QoL scores in atopic dermatitis by Schiffner and colleagues (2003) found 14 measures of illness severity and 17 measure of Quality of Life.[22]

These were identified through an electronic database search in late 2002. They found that SCORAD was by far the most commonly reported scale – giving 65 hits on MEDLINE compared to just five for the next most frequently reported scales (Atopic Dermatitis Area and Severity Index (ADASI) and Skin Intensity Score (SIS)). The review identified QoL data available for use of corticosteroids, tacrolimus and pimecrolimus, UVA/UVB combination, UVB narrowband, cyclosporin and the use of vehicle during acute flare ups. There were large differences in the treatment periods for different studies.[22] A clear improvement in QoL was shown after all treatments, but the use of different scales, variation in inclusion criteria and in the presentation of results precluded comparison between studies. One study of quality of life and steroid use[35] also assessed QoL after a treatment free follow up period and demonstrated a decrease in the QoL. The review authors suggest that this is an important aspect of establishing QoL in chronic relapsing illness such as atopic eczema. The authors suggest that fear of adverse effects is a neglected feature of current QoL measures in dermatology.

One trial[36] included in this review uses an Atopic Dermatitis Severity Index (ADSI). The review of severity scores by Schiffer and colleagues[22] only identifies this trial as using the ADSI score, and we were also unable to identify any more. The ADSI score asks clinicians to rate five items (erythema, excoriation, exudation, lichenification and pruritus) on a four-point scale none, mild, moderate and severe. These are translated into scores of 0-3 for each symptom, giving a total possible score of 15. The scale does not appear to have been validated, and we were unable to discover how score related to severity of atopic eczema. The included trial does state that a score of zero represents complete clearance and a score of two or one represents partial clearance.

One trial included in this review looked at the quality of life in families affected by atopic eczema using the Parent's Index of Quality of Life in Atopic Dermatitis (PIQoL-AD).[37] The same author developed the instrument using a needs based theoretical model, which states that the life quality is at its highest when most needs are met. Content was derived from qualitative interviews with European parents of children with atopic eczema. The PIQoL-AD scores range from 0 to 28 with higher scores indicating worse quality of life.

The Dermatology Life Quality Index (DLQI) was developed by Finlay and Khan[38] and is the most commonly used measure of quality of life in the studies included in this review. It consists of 10 questions which rate the disruption of various elements over the previous week. The questions ask about the affect of the skin condition over the last week:

1. How itchy, sore, painful or stinging has your skin been?
2. How embarrassed or self-conscious have you been because of your skin?
3. How much has your skin interfered with you going shopping or looking after your home or garden?
4. How much has your skin influenced the clothes you wear?
5. How much has you skin affected any social or leisure activities?
6. How much has your skin made it difficult for you to do any sport?
7. Has you skin prevented you form working or studying? How much of a problem has this been?
8. Has your skin created any problems with your partner or any close friends or relatives?
9. How much has your skin caused any sexual difficulties?
10. How much of a problem has the treatment for you skin been, for example by making your home messy or by taking up time?

Each of these questions is scored 0 (Not at all) to 3 (Very much). Finlay and Lewis-Jones also developed the Children's Dermatology Life Quality Index (CDLQI) and the Dermatitis Family Impact (DFI) questionnaire. For each scale a single summary score (higher scores

indicating worse conditions) is produced, which may make it difficult to assess, especially where one item has improved while another has worsened. The CDLQI is shown in Appendix 1.

A validation study of the DLQI translated into Spanish found that, despite sensitivity to overall changes in effect size, there were substantial floor effects (where results cluster at the bottom of the scale in this case due to similar, low levels of disease impact) in a population with mild and moderate eczema (or psoriasis) symptoms and there were small effect sizes seen on most dimensions of the scale.[39] Only the dimension of Symptoms and Perceptions showed substantial changes. The authors suggest that this dimension only might be useful in clinical trials.

Generic scales

A Swedish study by Lundberg and colleagues (1999)[40] examined quality of life (using DLQI and SF-36), health state utilities (obtained through a Visual Analogue Scale [VAS], time trade-off and standard gamble techniques) and willingness to pay in patients with dermatological conditions (psoriasis and atopic eczema). Utility values are from zero to one, where one represents a state of perfect health and zero represents a state of death. Scores of less than zero (i.e. a state considered to be worse than death) are also possible. The SF-36 elicits the impact illness or disease across eight health dimensions (physical activities, social activities, limitations in usual role, bodily pain, general mental health, limitations in usual role activities because of emotional problems, vitality (energy and fatigue), and general health perceptions) on a scale of 0 to 100 where zero is the worst imaginable health state and 100 is the best imaginable health state.

SF-36 scores and utility values from the dermatology group were compared Lundberg and colleagues[40] to general non-institutionalised population data for the country. The study included 366 adult patients aged 17-73 at a dermatology outpatient clinic. One hundred and thirty two patients (mean age 35) had atopic eczema and 70% of the sample overall had concomitant disease, most commonly asthma, allergy, cardiovascular disease and diabetes. No estimate of disease severity was provided for the sample. The population were asked to rate their eczema on a VAS anchored at 0 (calm) and at 100 (active). The mean on the day of questioning was 52.1, while an estimate of their condition when it was most active was 87.9 and when least active was 33.6.

People with atopic eczema and psoriasis scored lower on most dimensions of the SF-36 than the general Swedish population. For atopic eczema, scores of less than 70 were seen for Vitality (mean 56.97, SD 21.59), Bodily pain (mean 66.24, SD 39.16) and General Health Perceptions (mean 62.14, SD 24.23). General population scores for these dimensions were 68.8, 74.8 and 75.8 respectively.

On the DLQI mean total scores were 7.3 for atopic eczema and 5.9 for psoriasis (where 0 is the best score and 30 the worst).

Health state utilities were estimated using a rating scale, time trade off and standard gamble methods. For people with eczema (n=98), including those with concomitant diseases, results were 0.73, 0.93 and 0.98 with each method respectively. For patients with atopic eczema only (n=34), these figures were 0.77, 0.95 and 1.00. Differences were significant. Time trade off and standard gamble may be more difficult methods to understand and can result in more random measurement error than the rating scale. However, only the standard gamble method of estimating utility values elicits preferences about treatment and effect in the presence of uncertainty.

3.1.6 Economic Impact of Atopic Eczema

Emerson and colleagues estimated the cost of atopic eczema in pre-school children through information collected in a cross sectional survey of parents in 1995/96.[9] Total economic burden in the UK was estimated at £47 million (£30 million to the State). Estimated mean disease costs to the state were £79.59 per child over 12 months. Most costs were for consultations, generally with GPs at £28.62 mean annual cost and prescriptions (£22.03) mostly for emollients and bath preparations which accounted for almost four times as much spending as corticosteroids.[9]

Estimated annual costs to families were estimated at £28.94 per child – representing about one third of total disease costs. These costs were associated with changes to the home environment (such as need for cotton clothing, bedding covers etc.), purchase of over the counter medicine, transport costs, visits to homeopaths and salary loss.[9] A study of 10 severely affected adults in Scotland by Herd and colleagues in 1996 found an average personal cost of £325 over two months (maximum £1225, 75% of which was due to loss of salary.)[41]

3.2 Current treatment and service provision

Eczema is managed predominantly within primary care. A survey of parents with pre-school children who had atopic eczema found that only 6% of children were seen in secondary care.[9] Indications for referrals are shown below in Box 1. Patch testing may also be an indication for referral to see whether contact dermatitis has been induced, including by agents used to treat atopic eczema.

Lay treatments, including dietary restriction, may be tried by sufferers and parents at home.

Box 1: NICE Guidelines (under pilot): Indications for referral to a secondary care

**** Severe infection with herpes simplex (eczema herpeticum) is suspected.
*** The disease is severe and has not responded to appropriate therapy in primary care.
*** The rash becomes infected with bacteria (manifest as weeping, crusting, or the development of pustules), and treatment with an oral antibiotic plus a topical corticosteroid has failed.
** The rash is giving rise to severe social or psychological problems; prompts to referral should include sleeplessness and school absenteeism.
** Treatment requires the use of excessive amounts of potent topical corticosteroids .
* Management in primary care has not controlled the rash satisfactorily. Ultimately, failure to improve is probably best based upon a subjective assessment by the child or parent.
* The patient or family might benefit from additional advice on application of treatments (bandaging techniques).
* Contact dermatitis is suspected and confirmation requires patch-testing (this is rarely needed).
* Dietary factors are suspected and dietary control a possibility.
? The diagnosis is, or has become, uncertain.

Key:
**** immediate *** urgent ** soon * routine
? times will be discretionary and depend on clinical circumstances.

General supportive measures

Trigger factors, such as the use of soap and detergents should be avoided, using a dispersible cream as a substitute. Short nails are recommended to prevent too much damage being done through scratching. Cotton is advised to be worn next to the skin as other fabrics (wool for example) may be irritant although evidence for this approach is equivocal.[42] Extremes of temperature should also be avoided.[42]

Emollients

Emollient creams form a standard part of atopic eczema treatment. Theory for their use is based on their ability to provide a protective layer of lipids on the skin which slows water lost through evaporation, keeping the skin hydrated and preventing itching.[7] The film may also provide some protection against external irritants.[42] Generally the more oily the preparation, the better the emollient effect although there is a lack of evidence supporting the use of one type of emollient over another.[20] However, such creams or ointments can be very messy to use and there is a balance between effectiveness and acceptability. It is advised that emollients be applied at least twice daily, as well as after getting the skin wet, even when there are no symptoms.[7]

Topical Corticosteroids

Topical corticosteroids are the mainstay first line treatment for episodic worsening of eczema. These range in potency; from mild such as 1% hydrocortisone ointment to very potent, such as clobetasol propionate 0.05% (Dermovate®) for very severe cases. Potency is based on the ability to constrict blood vessels rather than clinical anti-inflammatory or skin thinning effect.[20] Application regimens may vary. Children may be treated in a “step up” approach (stepping up to a higher potency), and those who do not respond to 1%

hydrocortisone may try short term use of a more potent steroid preparation prescribed in primary care or after referral to secondary care. Adults may be started on a more potent steroid and have this reduced to a less potent preparation as symptom control is achieved.

A recent study in children with 18 weeks of follow up suggested that very short term application of a more potent steroid (three days of betamethasone valerate) is as effective and safe as a mild preparation such as hydrocortisone 1% for seven days.[43]

Following clearance of flares, two recent studies have also assessed the effectiveness of topical corticosteroids as a maintenance therapy, applied twice a week to recently healed lesions. Both studies suggest that relapse is less frequent than with vehicle alone.[44;45]

Corticosteroids are applied once or twice daily and the advantages of twice versus once daily application are the subject of a separate Technology Assessment Report for NICE.[46] Many dermatologists advise dosing using finger tip units (FTUs). One unit is a length of cream measured out from the last joint of the index finger to its tip and is assumed to be equal to 0.5g of cream.[47] This amount of cream is used to cover an area of eczema as big as two hand palms (i.e. an affected area equivalent to one palm would use half a fingertip of cream).[48] Corticosteroids are usually prescribed in "pulses" for example, use until the flare clears or for a maximum of two to four weeks.

Absorption is increased at certain sites, such as the face and the flexures. In particular there is a risk of permanent telangiectasia on the face and in general nothing stronger than 1% hydrocortisone is recommended here[42] although a moderate potency (such as Eumovate®) may be used in the short term. Long term use of even mild corticosteroids on the eyelids has been associated with the development of glaucoma.[42] In addition, care is recommended in using more potent preparations to treat breasts, abdomen, upper arms and thighs of adolescents - there is a danger that if striae form these may be permanent.[42]

Local adverse effects include the spread of untreated fungal infection, irreversible striae, prominent fine blood vessels, contact dermatitis, perioral dermatitis, worsening of acne and mild loss of skin pigmentation and skin thinning. Systemic adverse effects are rare and include suppression of the pituitary-adrenal axis (which may restrict growth) and Cushing's syndrome. In addition long term use can cause a reduction in responsiveness which may lead to escalation in dose or potency.[22]

There is some consumer resistance to the use of steroids.[42] It has been suggested that there is some confusion among consumers who fear that topical corticosteroids are subject to the same risks as anabolic steroids or oral corticosteroids.[49] The risk of adverse effects is related to the potency of the preparation, of which there is a wide range. If people with long standing eczema have been prescribed a wide variety of different corticosteroid preparations over the years, this may add to confusion about different potencies and indications for use.[50] Further, more different generic products may have different names, despite containing the same active ingredient, and may have different potency from a branded product, causing further confusion among users.[7]

A study of 200 adults and children with eczema attending a dermatological department in Nottingham showed than nearly three-quarters were worried about using steroid creams on their own or their children's skin. A third admitted some non-compliance with prescribed treatment.[49] The most common reason for concern was skin thinning (35%) followed by unspecified long-term effects (24%). Ten percent worried about absorption, and its effects on growth and development The same study showed that 31% of patients who had used hydrocortisone either didn't know the potency or believed this mild steroid to be strong or very strong.

Systemic Treatments

Systemic steroids may be used in some cases of severe eczema. They should be avoided during rapid adolescent growth.[42] Oral immunosuppressants, such as Azathioprine may also be used.

Other treatments

Numerous other treatments exist for eczema although the evidence for their effectiveness varies. Wet wraps – where a layer of emollients with or without corticosteroids is applied to the skin and wrapped with wet bandages, followed by dry bandages and left over-night, may be used in an attempt to maximise the effect of the treatment. Tar and ichthammol (a type of bitumen) maybe used as a cream, ointment or paste bandages or can be added to the bath. Oil of evening primrose oil can be taken orally or applied topically, diet may be restricted (especially dairy products and eggs) or alternative therapies, such as Chinese herbs, tried. The use of psoralens plus ultraviolet A (PUVA) may be effective although there is a risk of photo-ageing of the skin, and may increase the risk of skin cancer. Cyclosporin, an immunosuppressant, may be effective in severe treatment resistant cases, but carries the risk of hypertension, renal toxicity and a propensity for malignant disorders as well as headache and abdominal pain.[6] Azathioprine is an alternative immunosuppressant treatment in severe cases.

Secondary bacterial infections are treated with antibiotics orally, or in combination corticosteroid creams.

Evidence for current practice

A recent NHS HTA funded systematic review of treatments for eczema [20] found many RCTs about eczema treatment (n=1165) but only about a quarter (272) were finally included. The remaining 893 lacked appropriate data – in particular patient groups (i.e. it was unclear what type of eczema was present). Lack of appropriate outcome measures, especially patient centred measures and those deemed important by physicians, was also a problem. In general the authors found that the quality of reporting was poor. They found reasonable data to support the use of oral cyclosporin, topical corticosteroids, psychological approaches and UV light therapy. There was insufficient evidence to make recommendations on maternal allergen avoidance, oral anti-histamines, Chinese herbs, dietary restriction, house dust mite reduction, massage therapy, hypnotherapy, evening primrose oil, emollients, topical coal tar and topical doxepin.

There was RCT evidence that did not support the clinical benefit of avoiding enzyme washing powders, wearing cotton as opposed to soft weave synthetics, biofeedback, twice daily rather than once daily corticosteroid application, topical antibiotic / steroid combinations versus topical corticosteroids alone and antiseptic bath additives.

RCT evidence was not available at the time of this review on short burst potent topical corticosteroids treatment versus longer term milder steroid use, dilution of topical corticosteroids, oral prednisolone and azathioprine, salt baths, impregnated bandages, wet wrap bandages, water softening devices, allergy testing and different approaches to the organisation of care. An update of this Systematic Review will be available in Spring 2004.

An audit of eczema secondary care in the UK was undertaken by the British Association of Dermatologists (BAD) in 1997 to investigate adherence to guidelines issued by a BAD Working Party from 1992. All 187 departments were approached. Most reported that their department had access to dieticians (98%), patch testing (99%), trained nursing staff (93%), photochemotherapy (93%) and in-patient paediatrics (96%). However, only 57% reported

having wards staffed by nurses experienced in dermatology and only 52% included a request for treatment details to be brought by new patients to their first appointment. The audit also found wide regional variations.[51]

3.3 Description of the new interventions

3.3.1 Pimecrolimus

Pimecrolimus is an ascomycin derived immunosuppressant. It inhibits T-cell activation by blocking the synthesis and release of inflammatory cytokines. This is due to a high affinity to macrophilin-12 (FKBP-12) to which it binds, inhibiting calcineurin.[52] It inhibits interleukin-10 (Th2-type) cytokine synthesis in T cells and prevents the release of cytokines and mediators from mast cells after stimulation by IgE.

Pimecrolimus was specifically developed as a topical agent, although its exact mode of action in eczema is not known. A 1% cream preparation for use in atopic eczema (Elidel®, Novartis) was first licensed in the USA in 2000 and was introduced in the UK in 2003 for the treatment of mild to moderate atopic eczema in adults and children over the age of two.

The dose recommended by the manufacturer is twice daily application to affected areas for as long as signs and symptoms persist for up to six weeks, after which, if symptoms persist the patient should be re-evaluated.

The most common adverse effect is application site burning. Other reported common adverse effects (>5%) include headache, nasopharyngitis (common cold), flu, sore throat, viral infection, pyrexia, cough and headache although it is unlikely that pimecrolimus is causative for some of these. The long term effects of pimecrolimus on local immune response in the skin or incidence of skin cancers is not known. Animal studies in high dose oral pimecrolimus found increased risk for lymphoma, [53] thyroid adenoma and photocarcinogeneity.

Contraindications include pregnancy, infected lesions, viral infections (such as warts, chicken pox, herpes simplex), prolonged exposure to sunlight and artificial sunlight and Netherton's syndrome. The cream should not be applied to mucous membranes or eyes.

3.3.2 Tacrolimus

Tacrolimus (previously known as FK506) is an immunosuppressant agent derived from *Streptomyces tsukuba*. It has been available for several years for systemic use in, for example, transplant surgery. A topical treatment in the form of an ointment (Protopic®, Fujisawa) has been licensed in the UK since Spring 2002 for adults and children over the age of two with moderate to severe atopic eczema who are not responsive to conventional treatment.

Tacrolimus inhibits the activation of T-cells and in eczema is thought to exert this action through regulating the inflammatory response of skin mast cells and basophils.[15] Tacrolimus impairs histamine release from IgE-activated skin mast cells, reducing itching.[54] Tacrolimus forms complexes with immunophilins, binding proteins which then bind to and competitively inhibit the activity of calcineurin. This prevents regulation of the signal transduction pathways in T cells, and thus inhibits the transcription of genes for several cytokines, some

of which play a role in the patho-physiology of atopic eczema.[15] It has been suggested that tacrolimus also reduces *S. aureus* colonisation of the skin.[55;56]

Two strengths of ointment are available, 0.03% and 0.1%; the latter only recommended for use on adults. In both cases the manufacturer's recommended dose is twice daily application to dry skin for up to three weeks. In children, the dose is then reduced to once daily, whilst adults switch to 0.03% strength and continue twice daily. Currently, prescription in the UK is restricted to specialists although interpretation of this may vary locally with GPs in some areas initiating prescribing while in others this may be restricted to secondary care.

About half of all users will have some kind of skin irritation; very common adverse effects (>=10%) reported are burning, itching, redness flu-like symptoms, headache and skin infection.[15] Other common (>1%) effects are increased skin sensitivity and skin tingling, folliculitis, acne and herpes simplex infections. Drinking alcohol may cause the skin or face to become flushed and hot.[57]

Case reports have also identified rosacea-like granulomatous eruption[58] and Kaposi's varicelliform (eczema herpeticum)[59] in patients using tacrolimus.

When taken orally, tacrolimus has a number of well recognised adverse effects (including renal toxicity and blood vessel narrowing effects). The potential long term adverse effects of its topical use on the skin, immune system and other systems are not yet known. Topical use does result in some systemic exposure which is far below acute toxicity levels but the long term effects of this are unknown. Photocarcinogenicity animal studies have shown that the time to skin tumour formation is shortened by tacrolimus.[15]

Contraindications include pregnancy, infected lesions and exposure to long periods of sunlight or artificial sunlight. Those with rare skin diseases such as Netherton's syndrome in which the skin's barrier properties are affected may also be contraindicated due to increased risk of significant percutaneous absorption.[60] Vaccinations cannot be given during treatment and for some time afterwards – 28 days for live attenuated vaccines and 14 days for inactivated vaccines.[57]

3.3.3 Personnel and setting

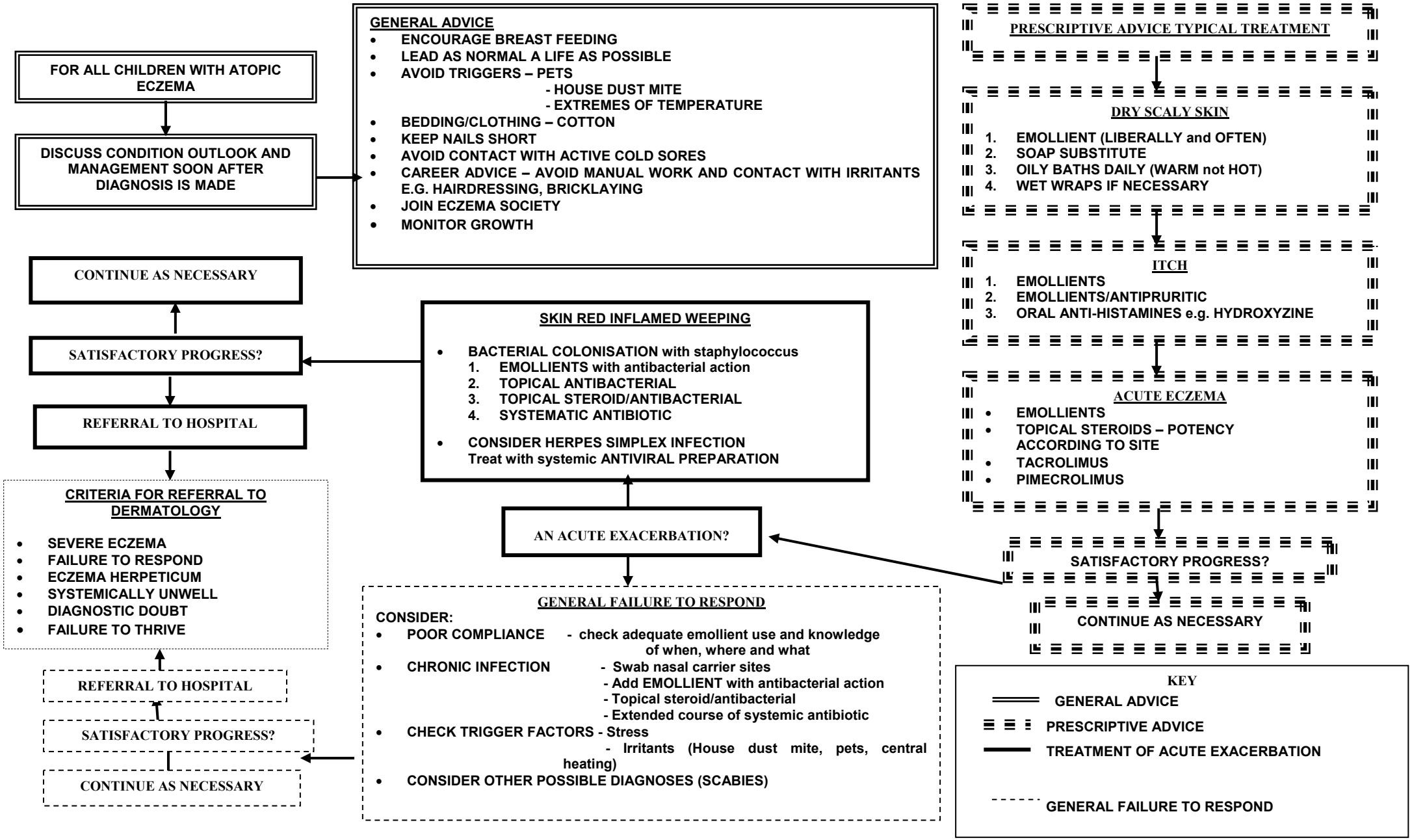
Information from Expert Advisory Group to this assessment suggests that there is considerable variation in the extent of primary care versus hospital based management. Most patients are managed in primary care, particularly as most eczema is mild in nature. Referral to secondary care may occur based on severe disease that is, disease resistant to even potent corticosteroids in adults, and moderately potent topical corticosteroids in children. Severity may also be related to the extent of disease and to the wider effect of eczema on personal, social and professional life. While some community based services may be able to offer training about wet wrapping for children, in other localities this is a hospital service. Current wording of the license for tacrolimus allows for its prescription by "dermatologists and physicians with extensive experience of atopic dermatitis with immunomodulating therapy". Some areas only recommend provision of tacrolimus from a secondary care setting while others permit GPs who are experienced with eczema to prescribe tacrolimus in primary care. Treatment such as phototherapy and systemic therapy are only offered in secondary care. Admission to hospital with eczema is very uncommon. In 2001-2002, there were 1093 hospital admissions in England for atopic dermatitis for a median stay of 4 days. 71% of these admissions were for children (aged<=15).[61]

As eczema is a chronic relapsing condition, ongoing treatment is required which may be varied and complex. A possible treatment pathway is shown in Figure 1. This treatment pathway was developed by Dr Sandra Campbell and the Eczema Pathway Team at the Royal Cornwall Hospital in Cornwall. There may be many local variations and this is presented as an example. This review concentrates on the details of the box on the right hand side of the diagram described as those with "acute eczema" which we refer to as "problem eczema" in this report and which may also relate to the terminology of "flares".

3.3.4 Anticipated costs

The anticipated costs of using tacrolimus and pimecrolimus in atopic eczema treatment will be influenced both by the relatively high costs of these drugs compared to topical corticosteroids and emollients, and also by the staffing implications – particularly whether they are provided in secondary or primary care.

Figure 1: Algorithm for treatment



4 Effectiveness of pimecrolimus and tacrolimus in atopic eczema

4.1 Research Questions

This technology assessment addresses two related questions regarding new immunosuppressants for atopic eczema:

- What is the effectiveness of pimecrolimus and tacrolimus for the treatment of atopic eczema?

- What is the cost-effectiveness of pimecrolimus and tacrolimus for the treatment of atopic eczema?

4.2 Methods

Methods for evaluating the effectiveness and cost-effectiveness of pimecrolimus and tacrolimus were specified *a priori* in the research protocol (See Appendix 2). This section reports the methods used to carry out the systematic review of existing evidence for effectiveness of pimecrolimus and tacrolimus. Methods for economic evaluation are reported in detail in section 5.1.

4.3 Review team and Advisory Group

The review was carried out by a review team comprising Dr Ken Stein, Ruth Garside, Emanuela Castelnuovo, Dr Martin Pitt, Dr Darren Ashcroft, Dr Paul Dimmock and Liz Payne.

In addition, an Expert Advisory Group provided advice during the assessment and comments on an early draft of the review:
Dr David Atherton, Consultant and Senior Lecturer in Paediatric Dermatology, Great Ormond Street Hospital for Children NHS Trust, London.
Dr David Gould, Consultant in Dermatology, Royal Cornwall Hospital, Cornwall
Dr Stephen Hayes, GP, Southampton, Hampshire
Dr Annabelle Hesford, GP, Taunton, Somerset.
Dr Rosemary Lever, Consultant in Dermatology, Royal Hospital for Sick Children, Glasgow and president of the British Society of Paediatric Dermatology,
Dr Andrew Warin, Consultant in Dermatology, RD&E Hospital, Exeter.
Prof. Hywel Williams, Foundation Professor of Dermato-Epidemiology, Centre of Evidence-Based Dermatology, University of Nottingham.

4.4 General methods

The methods of the review generally adhered to guidance laid out in methodological guidelines stated in the Centre for Reviews and Dissemination Report No. 4.[62]

4.4.1 Inclusion and exclusion criteria

Studies were included in the review if they fulfilled the following criteria:

Interventions:

(a) pimecrolimus for the treatment of mild to moderate atopic eczema
(b) tacrolimus for the treatment of moderate to severe atopic eczema.

Comparator:

Current standard treatment – topical corticosteroids in conjunction with emollients and emollients alone were considered as comparators.

Population:

Adults and children (aged two and over) with mild to moderate (pimecrolimus) or moderate to severe (tacrolimus) atopic eczema (the licensed indications).

Study design:

Systematic reviews or RCTs.

Exclusion

Populations without atopic eczema including those with a diagnosis of:

- Eczema secondary to other inherited or acquired disorders of immunodeficiency
- Seborrhoeic eczema
- Allergic or irritant contact eczema
- Nummular (discoid) eczema
- Fungal or parasitic skin infections
- Cutaneous T-cell lymphoma.

Study design:

- Non-randomised studies, case-control studies, case series or case reports.
- Studies on other types of eczema
- Studies in which insufficient details about baseline characteristics or methodology were given to allow quality assessment (e.g. conference abstract).
- Pre-clinical and biological experimentation in vitro, in animal models or in humans.
- Studies not reporting patient based outcomes.
- Studies not available in English.

Although the protocol suggested that systemic treatments would also be considered as comparators, strong clinical opinion was given that these were not appropriate comparators for pimecrolimus or tacrolimus and so have not therefore been considered as alternatives.

4.5 Assessment of the effectiveness of pimecrolimus and tacrolimus

4.5.1 Search Strategy

Electronic databases were searched for published studies and recently completed and ongoing research. Appendix 3 details the databases searched and the full search strategy. Bibliographies were also searched for further relevant publications. Experts in the field and the manufacturers of pimecrolimus and tacrolimus were asked to provide relevant information. Finola Delamere, Trial Co-ordinator of the Cochrane Skin Group, searched their Skin Registry for RCTs of Pimecrolimus or Tacrolimus against any comparator.

4.5.2 Identification of trials

Identification of relevant trials was made in two stages. Initially, the abstracts returned by the search strategy were examined independently by two researchers. Disagreements were resolved by discussion. Full texts of the identified studies were obtained. Two researchers (RG and EC) examined these independently for inclusion or exclusion and disagreements were resolved by discussion.

4.5.3 Data Extraction strategy

Data were extracted by one researcher (EC or RG) and checked by another (RG, EC or KS). Actual numbers were extracted where possible (see Appendices 5 and 6) and where necessary, analyses were recalculated on an intent to treat basis using the number of patients randomised as the denominator. Such analyses retain the minimisation of bias provided by randomisation but provide the most conservative estimates of effectiveness.

4.5.4 Quality assessment strategy

Assessments of RCT quality were performed using the indicators shown below. Results were tabulated and these aspects described.

Internal validity

Trial characteristics

- Appropriate methods of randomisation, avoiding selection bias.
- Appropriate allocation concealment, avoiding detection bias.
- Blind assessment of outcomes., avoiding detection bias
- Number of patients randomised, excluded and lost to follow up, avoiding attrition bias.
- Whether an intent to treat analysis was performed.
- Whether an appropriate power calculation was done.

External Validity

Study participants:

- Timing, duration and location of study.
- Age of participants.
- Co-morbidity.
- Inclusion criteria.

- Exclusion criteria.
- Concomitant treatment / wash out periods.
- Length of follow up.

External validity was judged according to the ability of a reader to consider the applicability of findings to a patient group in practice. Studies were given a rating of high generalisability if there was a detailed description of the exclusion criteria and patient group, medium if there was some description of exclusion criteria and population group and low if there was no description of exclusion criteria or patient group.

4.5.5 Methods of analysis

Study results were tabulated. Where statistical significance was not reported for differences in proportions, these were calculated by PenTAG at a 0.05 level using Confidence Interval Analysis software[63] and are presented in the text.

Meta-analyses were undertaken using random effects models for trials of similar intervention (for example tacrolimus versus topical corticosteroids) in order to estimate a weighted treatment effect across trials. A random effects model was used throughout in order to avoid the assumption of a single underlying treatment effect. Although this approach is more conservative it is less sensitive to underlying statistical heterogeneity. All meta-analyses were performed in the Cochrane Collaboration's Review Manager 4.2.2 (2003). Effectiveness on dichotomous outcomes was estimated with relative risk ratios (RR) and 95% confidence intervals (CI). Continuous outcomes were presented as standardised mean differences (SMD). Heterogeneity was tested using a χ^2 test with significant heterogeneity indicated by $p<0.05$. The analysis was stratified by age (adult or child), the nature of the intervention, and by duration of treatment.

The main outcome for trials of pimecrolimus was treatment success, measured as the proportion whose eczema was "clear" or "almost clear" (score 0-1) according to the Investigator's Global Assessment (IGA) compared to those who scored two or more. For tacrolimus a dichotomous outcome was created from reported results using the Physician's Global Evaluation (PGE) of 90% or better (the categories of "Clear" and "Excellent Improvement", score 0-1) compared to the rest.

Pruritus score was measured on a scale of 0 (none) to 3 (severe) and treatment success was assumed to mean no or mild pruritus (score 0-1).

The incidence of skin infections was analysed for tacrolimus using a combined rate for bacterial and viral infections as the presentation of data did not allow their separation. In pimecrolimus, results are presented separately for bacterial and viral infections. Incidence of skin burning was also analysed as this outcome was presented consistently across the trials.

4.6 Results of the systematic review: Quantity and quality of research available

4.6.1 Number and type of studies identified

A total of 232 papers were identified by the search strategy. Following examination of the abstracts, 17 full text articles on pimecrolimus and 17 on tacrolimus were obtained, details of

those meeting the inclusion criteria are described in Section 5.3 and Section 5.4. Full details of all data extracted from the included trials can be found in Appendix 5. A further three studies of pimecrolimus were provided in confidence by Novartis. RCTs used either an active comparator (topical corticosteroid) or "vehicle". Vehicle is the base of the cream or ointment being investigated but without the active ingredient and is applied in the same way (i.e. it is a placebo treatment).

4.7 Included RCTs of Pimecrolimus for Atopic Eczema

Table 5 gives details of the RCTs of pimecrolimus included in the review. Nine publications relating to eight RCTs of pimecrolimus are included, three in children and five in adults. *[Three of the studies have been provided on a commercial in confidence basis and are not discussed.]*

Table 5: Study Details: RCTs of Pimecrolimus

Study	Population	Sample size	Eczema severity	Definitions of eczema and severity	Intervention	Comparator	Recruitment dates	Setting	Length of treatment	Length of follow up
Eichenfield et al 2002[64]	Children 1-17	403	Mild to moderate	Williams et al IGA	Pimecrolimus 1% twice daily (n=267)	Vehicle (n=136)	Not stated	Multicentre	6 weeks	6 weeks
Whalley et al 2002 [37]	Children 2-8	241	Mild to moderate	Williams et al IGA	Pimecrolimus 1% twice daily (n=158)	Vehicle (n=83)	Not stated	11 centres in the USA	6 weeks	6 weeks
Wahn et al 2002[65]	Children 2-17	713	Mild	Williams et al IGA	Pimecrolimus 1% twice daily applied at first sign of itch, short term acute flare treatment with moderately potent TS (n=474)	Emollients, short term acute flare treatment with moderately potent TS (n=237)	July-Dec 1999	53 centres in 13 countries (Europe, Canada, South Africa, Australia)	12 months	53 weeks
CiC data removed										
Meurer et al 2002[67]	Adults	192	Moderate to severe	Rajka IGA	Pimecrolimus 1% twice daily to treat first signs of AD Acute flare treated with moderately potent TS (n=96)	Vehicle Acute flares treated with moderately potent TS (n=96)	Sept. 1999-June 2000	16 centres in Germany 12 University clinics, 1 dermatology clinic, 3 dermatology practices	24 weeks	24 weeks
CiC data removed										
Van Leent 1998[36]	Adults	34	ADSI >6	Hanifin and Rajka ADSI	Pimecrolimus 1% twice daily	Vehicle	March 1996 – Oct. 1996	Single academic dermatology clinic, Netherlands	3 weeks	3 weeks

Based on same population

	Study	Population	Sample size	Eczema severity	Definitions of eczema and severity	Intervention	Comparator	Recruitment dates	Setting	Length of treatment	Length of follow up
Based on same population	Luger et al 2001[69]	Adults	260	Moderate to severe	Hanifin and Rajka Hanifin and Langelend	Pimecrolimus 0.05% (n=42), 0.2% (n=46), 0.6% (n=42), 1% (n=45)	Vehicle (n=43) or betamethasone-17-valerate (high potency TS) (n=42)	Not stated	14 centres in Europe	3 weeks	3 weeks
	CiC data removed										

TS = Topical corticosteroids
IGA = Investigation Global Assessment
ADSI = Atopic Dermatitis Severity Index

Studies in Children

Three trial reports by Eichenfield and colleagues[64], Whalley and colleagues[37] and Wahn and colleagues [65] involved children and used vehicle as a comparator. The paper published by Eichenfield and colleagues[64] in fact combines the results of two separate trials of identical designs. These were reported individually in submissions to the FDA (as trials B505 and B307). Where data from the Eichenfield trials have been used in meta-analyses, results from B305 and B307 have been included separately. In addition, Eichenfield and colleagues give efficacy and safety data[64] while Whalley and colleagues report Quality of Life data for a subset of younger patients aged two to eight.[37] As only 9/403 patients (2.2%) in this trial were under the age of two, it was decided to include the study. The children treated in the study by Wahn and colleagues 2002[65] used topical corticosteroids to treat acute flares in both arms of the trial.

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Studies in Adults

Two trials, by Meurer and colleagues (2002) and Van Leent and colleagues (1998) compared pimecrolimus to vehicle in adults.[36;67] However, the study by Meurer and colleagues[67] also permitted the use of a moderately potent topical corticosteroid in both groups to treat acute exacerbations. Van Leent and colleagues 1998[36] compared twice daily and once daily application of pimecrolimus with vehicle. In the following effectiveness, safety and quality of life tables, results for twice daily application which is the current recommended treatment, are reported. Details of other results can be see in the data extraction tables in Appendix 5.

The study by Luger and colleagues 2001[69] in adults compared four potencies of pimecrolimus, with vehicle and with topical corticosteroids. As 1% pimecrolimus is the licensed treatment potency, this is the result reported in this section. Results against topical corticosteroids are shown in the following effectiveness and safety tables. However, where the relevant outcome and time period was appropriate for meta-analyses with other vehicle controlled studies, results of the vehicle group have been used. Details of other results can be seen in the data extraction tables in Appendix 5.

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In most trials the unit or randomisation and analysis was the patient. However, the study of pimecrolimus and vehicle in adults by Van Leent and colleagues 1998[36] allocated different treatments to each arm of the same patient.

Total studied population

A total of 1602 (range 34-713) patients (2601 including those from trials denoted 'confidential') were randomised in trials of pimecrolimus. Note that 241 patients in the pimecrolimus vs vehicle study by Whalley and colleagues (2002)[37] are a subset from the patients in the trials reported by Eichenfield and colleagues (2002). [64]

Indication for treatment

In the RCTs in children, Eichenfield and colleagues,[64] Whalley and colleagues[37] and Wahn and colleagues [65] used the criteria of Williams and colleagues to diagnose atopic eczema. [Commercial in confidence data removed ……
……] (See Section 3.3.1).

The study of pimecrolimus and topical corticosteroids and vehicle and topical corticosteroids by Wahn and colleagues 2002[65] was conducted in children with mild eczema (IGA scale), while the studies using vehicle alone as a comparator were conducted in children with mild to moderate eczema (also IGA scale). [Commercial in confidence data removed……..
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Of the studies of pimecrolimus in adults with atopic eczema, all used the criteria of Hanifin and Rajka for atopic eczema. Luger and colleagues (2001)[69] and Meurer and colleagues (2002)[67] included those with moderate to severe eczema (measured by the IGA and the Hanifin and Langeland criteria respectively). The study by Van Leent and colleagues (1998) included those who scored at least 6 on their ADSI scale (0-15) although it is unclear to which severity of eczema this relates.[36] [Commercial in confidence data removed……
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All these trials are presented in the following tables including those whose studied population was assessed to have moderate to severe eczema. This was a pragmatic decision. We were advised by the Expert Advisory Group that there is considerable overlap between the categories of eczema severity, with potential differing interpretations. In addition, given the limited amount of evidence for pimecrolimus compared to an active treatment, it was felt important to include the trials examining this comparison.

4.7.1 Quality of Pimecrolimus RCTs

Aspects of study quality are tabulated in Table 6 and Table 7. Full details of exclusion criteria are given in Appendix 5. These were largely similar, including such populations as pregnant and breast feeding women and those with acute skin infections.

Table 6: Methodological Details of Included Pimecrolimus Studies

	Study	Power calculation	Prospective recruitment	Consecutive Recruitment	Multi centre	Method of random-isation	Method of blinding	Main outcome measured blind / independently	ITT analysis?	General-isability	Conflicts of interest
Based on same population	Eichenfield et al 2002[64] P vs V Children	Yes	Not stated	Not clear	Yes	Not stated	Not clear – "double blind"	No	Yes	High	Yes
Based on same population	Whalley et al 2002[37] P vs V Children	Not stated	Not clear	Not clear	Yes	Not stated	Not stated	No	No	Low (but same population Eichenfield)	Yes
	Wahn et al 2002[65] P+TS vs V+TS Children	Yes	Yes	Not clear	Yes	2:1. Balanced within and between centres. Blocks of 6. Validated system that automates random assignment of treatment groups to randomised numbers.	Control group told to use emollient for same indication as intervention group. Described as double blind.	Not clear	Modified ITT - 2 patients excluded post-randomisation	High	Yes
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Table 6 (cont.)

Study	Power calculation	Prospective recruitment	Consecutive Recruitment	Multi centre	Method of random-isation	Method of blinding	Main outcome measured blind / independently	ITT analysis?	General-isability	Conflicts of interest
Meurer et al 2002[67] P+TS vs V+TS Adults	Yes	Yes	Not clear	Yes	Not stated	Vehicle same in appearance and odour as treatment, all site monitoring and data management personnel blinded	Yes	Yes	High	Yes
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Van Leent 1998[36] P vs V Adults	Not stated	Yes	No	No	Not stated	Plain packaging of treatments, assessor blind.	Yes	Yes	Medium	Yes
Luger et al 2001[69] P vs TS Adults	Not stated	Yes	Not clear	Yes	Not stated	Not clear – "double blind"	Not clear	Yes	High	None reported

Table 6 (cont.)

Study	Power calculation	Prospective recruitment	Consecutive Recruitment	Multic entre	Method of random-isation	Method of blinding	Main outcome measured blind / independently	ITT analysis?	General-isability	Conflicts of interest
Commercial in confidence data removed										

Table 7: Pimecrolimus Studies Sample Characteristics

	Mean age (SD)		% Male		% Caucasian			
	Intervention 1% pim.	**Control**	**Intervention 1% pim.**	**Control**	**Intervention 1% pim.**	**Control**	**Inclusion criteria**	**Eczema severity**
Eichenfield et al 2002[64] P vs V Children	6.8	6.6	52.4%	48.5%	-	-	Aged 1-17 Diagnosis by Williams criteria BSA >5% IGA score 2-3 Emollient used for at least 7 days before baseline	Mild to moderate (60.3% moderate plus 9.7% severe to very severe)
Whalley et al 2002[37] P vs V Children	4.0 (1.75)	3.8 (1.82)	53.2%	49.4%	-	-	Age 2-17 (this paper analyses a subset of Eichenfield aged 2-8) BSA >5% IGA 2-3	Mild to moderate
Wahn et al 2002[65] P+TS vs V+TS Children	8.0	7.9	47.3%	47.3%	-	-	Aged 2-17 BSA >=5% IGA >=2	Mild to very severe (19.4% severe / very severe)
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Meurer et al 2002[67] P+TS vs V+TS Adults	31.8 (+-11.1)	32.5 (+-10.78)	37.5%	42.7%	-	-	IGA score 3-4 BSA >5%	Moderate to severe (severe 32.3%)
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Based on same population

	Mean age (SD)		% Male		% Caucasian			
	Intervention 1% pim.	**Control**	**Intervention 1% pim.**	**Control**	**Intervention 1% pim.**	**Control**	**Inclusion criteria**	**Eczema severity**
Van Leent 1998[36] P vs V Adults	36 twice daily 29 1x daily	NA –arm not patient randomised	56.3% twice daily 38.9% 1x daily	NA – arm not patient randomised	-	-	BSA >1% of both arms	ADSI >6
Luger et al 2001[69] P vs TS Adults	28	BMV 32 V 33	24.0%	BMV 19 V 22	96.0	BMV 100 V 95	Aged 18 or over BSA affected 5-30%	Moderate to severe (severe 6.6%)
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1% pim. = 1% Pimecrolimus
ADSI = Atopic Dermatitis Severity Index
AE = Adverse effects
BMV = Betamethasone Valerate
BSA = Body Surface Area
IGA = Investigators Global Assessment
NA= Not applicable
P= Pimecrolimus
TS = Topical corticosteroids
V= Vehicle

Apart from one study, (Luger and colleagues 2001[69]) all the included trials stated potential conflicts of interest in that they and/or the authors were supported by the manufacturer of pimecrolimus.

Internal Validity

Selection Bias

Details of the methods employed by the RCTs of pimecrolimus are shown in Table 6. All included studies were randomised controlled trials. Four trials did not state the methods of randomisation used, the remaining trial appeared to have sound methods of randomisation.[65]

Detection Bias

Methods of ensuring allocation concealment are unclear in three studies that are described as "double blind" but with no further detail.[64;65;69] Attempts to protect blinding being broken post-randomisation through standardisation of packaging and treatment were shown in five studies [36;65;67]

The main outcome was measured independently in the three studies of adults [including one CiC and] Meurer and colleagues 2002,[67] and Van Leent and colleagues, 1998[36] while it was unclear if this was the case in the trial by Luger and colleagues 2001.[69]

Attrition Bias

Some withdrawal and lost to follow up was reported in all trials and was high in most. Details are shown in Table 8. [Commercial in confidence data removed …… …… …… …… ……] The study of pimecrolimus versus topical corticosteroids by Luger and colleagues[69] does not report attrition rates by treatment arm. [Commercial in confidence data removed …… ……]

Table 8: Reasons for attrition in pimecrolimus trials

	Reason for withdrawal (%)							
	Adverse effects		Lack of efficacy		Other reasons		Total	
	Int.	Cont.	Int.	Cont.	Int.	Cont.	Int.	Cont.
Eichenfield et al 2002[64] P v V Children	1.9	2.9	2.6	15.4	8.2	3.8	12.7	22.1
Whalley et al 2002[37] P v V Children	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	32.6	42.2
Wahn et al 2002[65] P+TS v V+TS Children	0	0	12.4	30.4	18.4	21.1	31.6	51.5
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Meurer et al 2002[67] P+TS v V+TS Adults	0	0	15.6	27.1	7.3	10.4	22.9	37.5
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Van Leent 1998[36] P v V Adults	-	-	-	-	-	-	20.6 overall	
Luger et al 2001[69] P v TS Adults	-	-	-	-	-	-	23.5 overall	
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Intention to Treat Analysis (ITT)

ITT analysis was performed by most studies. The quality of life study by Whalley and colleagues[37] is undertaken in a subset of patients form those in the Eichenfield and colleagues[64] trials, but details of selection are not given. Wahn and colleagues[65] [Commercial in confidence removed] use a modified ITT population excluded two patient who did not receive any treatment. This is unlikely to bias the results. [Commercial in confidence data removed ……]

Power calculation

Only three (five including CIC) studies reported a power calculation. These were based on IGA score,[64] number of flares,[65] [Commercial in confidence data removed ……] and use of topical corticosteroids.[67]

Of those not reporting a sample size calculation, Luger and colleagues[69] (pimecrolimus versus topical corticosteroids in adults) regarded change of EASI score as the primary outcome. Change in ADSI score was the primary outcome for Van Leent and colleagues[36] (pimecrolimus versus vehicle in adults).

External Validity

Study population features such as age, inclusion and exclusion criteria, and concomitant treatment are shown in Table 7. Studies were mostly short term. One trial in children had follow up to 12 months (Wahn and colleagues (2002)[65]) although this remains relatively short term in the context of a chronic condition. The other trials report in trials of six weeks.

In adults, the study of pimecrolimus and topical corticosteroids versus vehicle and topical corticosteroids included 24-week treatment and follow up (Meurer and colleagues 2002.[67]) The study of pimecrolimus and vehicle included 3 week treatment and follow up (Van Leent

et al, 1998[36]. The study by Luger and colleagues 2001[69] (pimecrolimus versus topical steroid) included 3 week treatment and follow up. [Commercial in confidence data removed ……]

External validity was categorised according to the adequacy of reporting of patient characteristics and inclusion and exclusion criteria. A high level of generalisability was given if the information was extensive enough to allow a clinician to decide whether the information was generalisible to patients in their clinical practice. In most cases, we judged generalisability as high. The study by Whalley and colleagues comparing pimecrolimus with vehicle was of low generalisability as it provided minimal patient characteristic details. However, these were given for the full combined sample as reported by Eichenfield and colleagues 2002.[64] The study of pimecrolimus versus vehicle by Van Leent and colleagues 2001[36] in adults only provided enough patient information to achieve a generalisability rating of medium.

Summary of the quality of pimecrolimus RCTs

- Four trials were carried out in children and five in adults. *[A three of the studies have been provided on a commercial in confidence basis and are not discussed.]*
- 8/9 the trials defined atopic eczema and its severity using recognised measures. [Commercial in confidence removed] Two trials in children were in mild to moderate disease. [Commercial in confidence removed……] In one trial it was not clear what the severity of the population was; they were included if they had an ADSI score of >6.
- 5/9 trials used vehicle as a comparator, [Commercial in confidence removed] compared pimecrolimus with topical corticosteroids. [Commercial in confidence data removed ……] This means that there is little evidence to help clinicians understand the place of pimecrolimus in current practice.
- Methods of randomisation were not stated in 5/9 trials.
- Methods of ensuring allocation concealment and blinding were unclear or inadequate in 4 trials.
- 2 trials did not report an ITT analysis, and 2 used a modified ITT population of those who received treatment.
- Attrition rates were high – varying from 12.7% to 32.6% in the treatment arms (median 23.2%) and 22.1% to 55.1% in the control arms.
- 7/9 trials received a generalisability rating of “high”.
- Only one trial did not report potential conflicts of interest.

4.8 Effectiveness of Pimecrolimus

Due to lack of data, it was not possible to undertake meta-analyses for the effectiveness of pimecrolimus compared to topical corticosteroids which is likely to be the most relevant clinical comparator in the majority of cases. It was possible to pool results for some outcomes reported in comparisons of pimecrolimus and vehicle (placebo). These are shown in Appendix 7 for interest. They show the efficacy of pimecrolimus measured by an IGA score of 0-1 at three and six weeks, avoidance of "flares" at six months, avoidance of topical corticosteroid use at six months and mild or absent pruritus at three and six weeks. Follow up times were chosen pragmatically, based on available data.

The remaining results have been tabulated and presented descriptively in this section. All trials are listed in all tables even if they do not provide data on a particular outcome. This is to provide consistency in the order of the trials listed and demonstrate the range and variability of outcomes used.

The study by Whalley and colleagues[37] reports only on quality of life in a subset of patients enrolled in the Eichenfield RCTs.[64] It has therefore been excluded from the following tables of effectiveness and is shown only in Table 11 which reports on quality of life.

Effectiveness measured by changes in IGA score

See Table 9.

IGA scores are reported by two studies in children. Eichenfield and colleagues[64] report more children treated with pimecrolimus show an improvement of at least one IGA point and an IGA score indicating that eczema was "clear" or "almost clear", than those treated with vehicle. ($p<0.05$ at six weeks, $p<=0.001$ at three weeks)

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In the trials in adults with moderate to severe eczema, Meurer and colleagues report that treatment success (defined as an IGA score of 2 or less – disease clear to mild) and improvement by at least one IGA score was significantly more frequent in those using pimecrolimus and topical corticosteroids compared to those using vehicle and topical corticosteroids ($p<0.001$).

Luger and colleagues 2001[69] do not report IGA in the published results. However, these data are reported (as study B202) in the FDA submission from Novartis. This shows that 11.1% of those treated with pimecrolimus were judged to have "clear" or "almost clear" eczema at three weeks compared to none of those treated with vehicle ($p=0.056$) and 50.0% of those treated with potent topical corticosteroids ($p<0.001$ compared to vehicle). Compared to pimecrolimus $p<0.05$ (95% CI –0.566 to -0.212; calculated by PenTAG).

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Effectiveness measured by number of flares

One study in children and two studies of adults reported on avoidance of flares (Table 9). There is no consistent definition of "flare". Wahn and colleagues[65] define a flare as a lesion judged to be "severe" using the IGA (IGA >=4). Meurer and colleagues[67] define a flare as the disease state requiring at least three days treatment with topical corticosteroids. [Commercial in confidence data removed ……

Wahn and colleagues 2002[65] report that significantly more of those receiving pimecrolimus and topical corticosteroids had not experienced a flare at six months and 12 months than those using vehicle and topical corticosteroids (p<0.001).

Meurer and colleagues 2002[67] reported that significantly more of those using pimecrolimus and topical corticosteroids had no flares by the end of study (24 weeks), compared to those using vehicle and topical corticosteroids (p<0.001).

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Effectiveness measured by disease control

Eichenfield and colleagues[64] report that more of those treated with pimecrolimus and than those treated with vehicle alone had their eczema "completely" or "well" controlled. (p<0.05, 95% CI 0.109, 0.310, calculated by PenTAG).

In their study of adults, Van Leent and colleagues report significantly more of those using pimecrolimus than those using vehicle had their atopic eczema totally cleared or partially cleared (p<0.001).

See Table 10.

Effectiveness measured by changes in EASI Score

In the paediatric studies, only Eichenfield and colleagues 2002 (pimecrolimus vs vehicle) report effectiveness in terms of change in EASI score. The change in EASI from baseline is –45% for those receiving pimecrolimus from a mean at baseline of 12.9 and –1% for those receiving vehicle from a mean at baseline of 12.7. This difference was significant (p<0.001). (Table 10)

Meurer and colleagues 2002[67] (pimecrolimus and topical corticosteroids versus vehicle and topical corticosteroids in adults) reports a 48.3% median reduction in EASI score for those using pimecrolimus and 15.9% in those using vehicle. This difference is significant (p<0.001) The actual average EASI score at 24 weeks was 5.7 for those in the pimecrolimus group compared to 8.8 for those in the vehicle group. At baseline these were 11.2 and 10.8 respectively. Difference at 24 weeks was statistically significant (p<0.001) although the differences in score are small and may not be clinically meaningful.

In the RCT of pimecrolimus versus topical corticosteroids in adults, Luger and colleague report a 47% reduction in median EASI for those using pimecrolimus and of 78% for those using topical corticosteroids, whereas no change was noted for those using vehicle only; mean EASI scores at baseline were 11.28, 10.28 and 10.12 respectively. Significance levels are not reported.

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See Table 10.

Effectiveness measured by change in ADSI

Changes in Atopic Dermatitis Severity Index (ADSI) were reported by Van Leent and colleagues 1998[36] who showed a greater mean reduction in ADSI on pimecrolimus compared to vehicle (p<0.01). (See Table 10)

Effectiveness measured by reduction in BSA affected

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Meurer and colleagues 2002,[67] report on the reduction in affected BSA in adults. Those treated with pimecrolimus and topical corticosteroids had significantly greater reduction in BSA affected than those treated with vehicle and topical corticosteroids (p<0.01).

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Concomitant use of topical corticosteroids and antihistamines

One study in children reports on the concomitant use of topical corticosteroids. Wahn and colleagues 2002[65] compared preventative use of emollients versus use of pimecrolimus at the first sign or symptom of flare, with both groups using moderately potent topical corticosteroids for the short term treatment of acute flares. In the pimecrolimus group, significantly more children had not used topical corticosteroids at six months compared to the control group. (p<0.05, 95% CI 0.183, 0.331, calculated by PenTAG). It should be noted that flares were counted as those of at least IGA 4. In normal practice it is unlikely that flares would be allowed to progress to this level of severity before initiating treatment with corticosteroids.

In adults, one study reported use of topical corticosteroids in patients with acute episodes ("flares") both in the pimecrolimus and the vehicle treated groups. Meurer and colleagues 2002[67] report that more patients using pimecrolimus avoided steroid use than patients using vehicle (p<0.001).

Wahn and colleagues 2002[65] reports on use of antihistamines by children in the study period. Statistical significance was not reported but was calculated and not significant (p<0.05, 95% CO -0.133, 0.019).

Table 9: Effectiveness of Pimecrolimus measures by IGA score or number of flares

	Improved by at least 1 IGA score %		IGA score (%)		IGA score 0-1 (clear – almost clear)		% patients without flares		Mean number of flares		Median time to first flare (days)	
	Interven-tion 1%	Control	Interven-tion 1%	Control	Interven-tion 1%	Control	Interven-tion 1%	Control	Interven-tion 1%	Control	Interven-tion 1%	Control
Eichenfield et al 2002[64] P vs V Children	59.9	33.1	-	-	B305 26.9 B307 27.0	B305 2.9 B307 11.8	-	-	-	-	-	-
Wahn et al 2002[65] P+TS vs V+TS Children	-	-	-	-	-	-	6 mnths 76 12 mnths 71	6 mnths 52 12 mnths 43	-	-		
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Meurer et al 2002[67] P+TS vs V+TS Adults	82.3	51.0	=<2 68.6	=<2 36.5	-	-	44.8	18.8	1.1	2.4	144	26
Commercial in confidence data removed												
Van Leent 1998[36] P vs V Adults	-	-	-	-	-	-	-	-	-	-	-	-
Luger et al 2001[69] P vs TS Adults	-	-	-	-	V 11.1	V 0.0 BMV 50.0	-	-	-	-	-	-
Commercial in confidence data removed												

[a] Moderate improvement or better, [b]Median number of relapses

NB: Data for IGA score of 0-1 taken from FDA submission

Table 10: Effectiveness of Pimecrolimus as measured by control of AD, EASI score, ADSI score and affected BSA

	AD Completely / well controlled (%)		Median % reduction in EASI		EASI score (95% CI)		Reduction in ADSI score (mean %)		Total BSA reduction (mean %)	
	Intervention 1%	Control	Intervention 1%	Control	Intervention 1%	Control	Intervention 1%	Control	Intervention 1%	Control
Eichenfield et al 2002[64] P vs V Children	60	39	45	1	-	-	-	-	-	-
Wahn et al 2002[65] P+TS vs V+TS Children	-	-	-	-	-	-	-	-	-	-
Commercial in confidence data removed										
Meurer et al 2002[67] P+TS vs V+TS Adults	-	-	48.3	15.9	5.7 (4.1-6.9)	8.8 (7.5-10.5)	-	-	48.4	20.5
Commercial in confidence data removed										
Van Leent 1998[36] P vs V Adults	93.8 [a]	12.5 [a]	-	-	-	-	79.1	10.3	-	-
Luger et al 2001[69] P vs TS Adults	-	-	47	BMV 78 V 0	-	-	-	-	-	-
Commercial in confidence data removed										

[a] Combined categories “Partially cleared” and “Totally cleared”

Table 11: Effectiveness of pimecrolimus as measured by days spent in remission, and use of corticosteroids or antihistamines

	Mean % days spent in remission at 12 months		% not using topical corticosteroids		Mean % days topical corticosteroids used		Use of antihistamines (%)	
	Intervention 1%	Control	Intervention 1%	Control	Intervention 1%	Control	Intervention 1%	Control
Eichenfield et al 2002[64] P vs V Children	-	-	-	-	-	-	-	-
Wahn et al 2002[65] P+TS vs V+TS Children	-	-	64.7	37.1	4.1	9.1	57.2	62.9
Commercial in confidence data removed								
Meurer et al 2002[67] P+TS vs V+TS Adults	-	-	49.0	21.9	14.2	37.2	-	-
Commercial in confidence data removed								
Van Leent 1998[36] P vs V Adults	-	-	-	-	-	-	-	-
Luger et al 2001[69] P vs TS Adults	-	-	-	-	-	-	-	-
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The results of patient based measures – quality of life and pruritus are shown in Table 12.

Effectiveness measured by change in Pruritus score

One publication [plus 1 CiC study] in children reports on pruritus. Eichenfield and colleagues[64] found that 57% of those using pimecrolimus had mild or absent pruritus compared to 34% in the control group. At baseline mild or absent pruritus was found in only 13% of those assigned to pimecrolimus treatment and 10% of those assigned to vehicle treatment. [Commercial in confidence data removed …… …… …… ……]

In adults, four studies report pruritus. Meurer records an average score on day 7 of 1.6 for those treated with pimecrolimus and topical corticosteroids and 2.5 for those treated with vehicle and topical corticosteroids (scale 0-4, baseline scores 2.5 and 2.4 respectively). Luger and colleagues reports that significantly fewer of those treated with pimecrolimus had mild or absent pruritus compared those treated with potent topical steroid ($p<0.05$, 95% CI – 0.531, -0.155, calculated by PenTAG). . [Commercial in confidence data removed …… …… …… …… ……]

See Table 12.

Quality of Life

Whalley and colleagues 2002[37] studied a subset of patients (aged 2-8 years) from the RCTs combined by Eichenfield and colleagues 2002[64] and reported on Quality of Life (QoL). The instrument used was the Parent's Index of QoL in Atopic Dermatitis. This consists of 28 statements to which parents of those with atopic eczema respond whether they are true or not. Scores range from 0-28 with a high score indicating poor quality of life. The mean score from parents of children using pimecrolimus was 6.1 and for parents of children using vehicle was 8.8 ($p=0.023$).

Meurer and colleagues 2002 report on change in two QoL measures: the Quality of Life Index – Atopic Dermatitis (QoLIAD) and the Dermatitis Life Quality Index (DLQI). The DLQI comprising 10 questions on symptoms and perceptions of disease, each of which is scored 0-3. The index is thus scored between 0 (best) and 30 (worst) QoL. The QoLIAD has 25 items to be answered "yes" (score = 1) or "no" (score =0). The score is expressed as a percentage of the maximum possible score of 25. Higher scores indicate poorer quality of life.

For both scores, a mean decrease in score is reported. For the QoLIAD, those using pimecrolimus had a mean reduction of 25.6%, compared to 7.4% for those using vehicle ($p=0.002$). For the DLQI, these mean decreases were 22.0% and 6.7% respectively ($p=0.01$).

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Table 12: Effectiveness of pimecrolimus as measured through changes in quality of life and pruritus

	Mean % decrease in QoLIAD score		Mean % decrease in DLQI score		Mean score Parent's Index of QoL in AD		Mild or absent pruritus %		Pruritus score	
	Intervention 1%	Control	Intervention 1%	Control	Intervention 1%	Control	Intervention 1%	Control	Intervention 1%	Control
Eichenfield et al 2002[64] P vs V Children							57	34	-	-
Whalley et al 2002[37] P vs V Children	-	-	-	-	6.1	8.8				
Wahn et al 2002[65] P+TS vs V+TS Children	-	-	-	-	-	-	-	-	-	-
Commercial in confidence data removed										
Meurer et al 2002[67] P+TS vs V+TS Adults	25.6	7.4	22.0	6.7	-	-	-	-	1.6	2.5
Commercial in confidence data removed										
Van Leent 1998[36] P vs V Adults	-	-	-	-	-	-	-	-	-	-
Luger et al 2001[69] P vs TS Adults	-	-	-	-	-	-	46.7	BMV 81.0 V 18.6	-	-
Commercial in confidence data removed										

Adverse effects

Full details of reported adverse effects are shown in the extraction tables in Appendix 5. Adverse effects were reported in different ways across the trials. In their combined trials in children, Eichenfield and colleagues 2002[64] report only adverse effects reported by at least 10% of patients in either group. Wahn and colleagues 2002[65] also report on the incidence of the most common adverse effects (>=10%) together with the incidence of bacterial and viral skin infections. Life table analysis was used to adjust for the differences in follow up for the two groups.

In adults, Luger and colleagues 2001[69] report only on the three most commonly experienced adverse effects (application site reactions, pruritus and worsening AD), together with a single figure recording all other adverse effects. Meurer and colleagues 2002[67] report only on local adverse effects - application site burning and bacterial, viral and fungal infections. Van Leent and colleagues 1998[36] report that there were no local adverse effects such as skin irritation. [Commercial in confidence data removed …… …… …… …… ……]

Minor local adverse effects are relatively common with up to 49.0% of participants reporting application site burning with pimecrolimus compared to 3.1%-35% in the vehicle groups and 10% with corticosteroids. Other localised adverse effects include pruritus, warmth, irritation and erythema.

[Commercial in confidence data removed …… …… …… …… …… …… ……]

Withdrawal due to adverse effects was reported in three trials and was between 1.9% and [CiC removed] with pimecrolimus and 2.9% with vehicle (See Appendix 5 for details). [Commercial in confidence data removed …… ……]

Pooled analysis of adverse effects

Data were available for meta-analysis of some aspects of adverse effects pimecrolimus compared to vehicle. Outcomes pooled were reported viral skin infections, bacterial skin infections and rates of skin burning. These are presented graphically in Appendix 7 as this is not the most clinically important comparator in most cases. Data on skin burning includes only reports of this name. No attempt has been made to combine categories of local skin irritation (such as redness, dryness, warmth etc.) as these are not reported consistently across trials. This data may therefore underestimate all types of localised skin irritation.

No significant difference between rates of bacterial infection and skin burning was found. The results for skin burning may be confounded by known irritants in the vehicle cream. A greater relative risk of viral skin infection was seen with pimecrolimus compared to vehicle (RR 1.97, 95% CI 1.21 to 3.19).

There were not enough data to pool results of trials with topical corticosteroids. [Commercial in confidence data removed ……]There may be a greater risk skin burning with pimecrolimus compared to potent topical corticosteroids (RR5.26, 95% CI 1.97 to 14.00), however, this data comes from a small trial, and the confidence intervals are very wide. [Commercial in confidence data removed ……]

Summary of effectiveness and safety of pimecrolimus

- Outcome measures in the included trials focussed on global assessment of clinical improvement such as IGA (4/8 trials), EASI (4/8trials), ADSI (1/8 trials), whether eczema was judged to be controlled (2/8 trials) and affected BSA (1/8 trials). In addition, patient centred outcomes such as pruritus (6/8 trials), flares (3/8) and use of concomitant corticosteroids (2/8) and time in remission (2/8) were also measured. 2/5 trials investigated quality of life using the QoLID, DLQI or patients' index of QoL in AD.
- Pimecrolimus is more effective than vehicle alone. This is the case for global measures such as the IGA score, patient centred measures such as pruritus score and number of flares and treatment issues such as the additional use of corticosteroids to treat flares. Quality of life is also improved for adults using pimecrolimus over vehicle. In the PIQoL no significant difference was seen. However, vehicle is not the key comparator for clinicians considering the place of pimecrolimus in practice.
- [Commercial in confidence data removed ……]
- Little evidence is available comparing the effectiveness of pimecrolimus and topical corticosteroids. One trial was included that reported on use of a high potency steroid betamethasone valerate s a comparator .[Commercial in confidence data removed] However, both trials were conducted in an adult population with moderate to severe eczema, which is not the licensed indication. .[Commercial in confidence data removed] ……
- [Commercial in confidence data removed……]
- Minor application site adverse effects were common with pimecrolimus and withdrawal due to adverse effects was between 1.9% and [CiC removed] compared to 2.9% with vehicle [Commercial in confidence data removed…]. No significant difference was seen in bacterial skin infection and skin burning between pimecrolimus and vehicle, although there may be a slightly greater risk of viral infection with pimecrolimus.

4.9 Included RCTs of Tacrolimus for Atopic Eczema

Details of the RCTs of tacrolimus are shown in Table 13. Twelve publications reporting on 10 trials of tacrolimus are included. Two are currently unpublished and were provided by Fujisawa* and one other trial has been published in Japanese and an English translation was provided by Fujisawa.

Studies in children

Two studies, by Bouguniewicz and colleagues and Paller and colleagues, are in children using vehicle as a comparator.[72;73]

Two trials in paediatric patients by Reitamo and colleagues (2002 and 2003),[74;75] consider tacrolimus against mild topical corticosteroids. One of these (by Reitamo and colleagues 2003) was provided by Fujisawa and is currently unpublished.

Studies in adults

Two publications in adults report on the same trial populations, with Hanifin and colleagues giving details of efficacy[76] and Soter and colleagues reporting on safety.[77] These publications combine the data from two RCTs in adults with identical protocols that were undertaken for the FDA (study 97-0-035 and study 97-0-036). Results of these trials are available separately from the FDA website. The study by Drake and colleagues study includes both adults (a subset of those investigated in the Hanifin trials) and children (a subset of those investigated in the Paller trials) with vehicle as the comparator.[78]

Four studies are in adults using vehicle as a comparator. These are by Granlund and colleagues, Hanifin and colleagues (who present the combined results of 2 RCTs), Ruzicka and colleagues and Soter and colleagues.[76;77;79;80]

Three trials in adults by Kawashima 1998, Reitamo and colleagues II (2002) and Petan and colleagues.[81-83] compare tacrolimus to potent topical corticosteroids. The latter is unpublished and was supplied by Fujisawa.[83] the trial by Kawashima has only been published in Japanese, but was supplied in translation by Fujisawa.

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Table 13: RCTs of tacrolimus*

Study	Population	Sample size	Eczema severity	Definitions of eczema and of severity	Intervention-Tacrolimus	Comparator	Recruitment dates	Setting	Length of treatment	Length of follow up
Boguniewicz et al 1998[72]	Children aged 7 to 16 years	180	Moderate to severe	Hanifin and Rajka	0.03%(n=43), 0.1% (n=49) 1% (n=44) twice daily	Vehicle (n=44)	Not stated	18 centres in USA	22 days	36 days
Reitamo et al 2002[74]	Children aged 2 to15 years	560	Moderate to severe	Hanifin and Rajka Rajka and Langeland	0.03% (n=189) 0.1% (n=186) twice daily	1% hydrocortisone acetate (mild potency) (n=185) twice daily	Not stated	27 centres in USA and Europe	3 weeks	5 weeks
Reitamo et al 2003[75]	Children aged 2 to 15 years	624	Moderate to severe	Hanifin and Rajka Rajka and Langeland	0.03% once daily (n=207) 0.03% twice daily (n=210)	1% hydrocortisone acetate (mild potency) twice daily (n=207)	Not stated	42 centres in 11 European countries	3 weeks	5 weeks
Granlund et al 2001[79]	Adults	14	Moderate to severe (lichenified)	Rajka and Langeland	0.1% (n=14)	Vehicle	Not stated	Not stated	2 weeks	1 month
Paller et al 2001[73]	Children aged 2 to 15 years	352	Moderate to severe	Hanifin and Rajka Rajka and Langeland	0.03% (n=117) 0.1% (n=118)	Vehicle (n=116)	August 1997 – June 1998	23 centres in USA	12 weeks	12 weeks
Drake et al 2001[78] (QoL)	Adults (aged 16+) and children (ages 2 to 15 years)	985	Moderate to severe	Rajka and Langeland	0.03%, 0.1% n not stated	Vehicle n not stated	Not stated	Multicentre USA	12 weeks	12 weeks
Hanifin et al 2001[76] (Efficacy)	Adults	632	Moderate to severe	Hanifin and Rajka Rajka and Langeland	0.03% (n=211) 0.1% (n=209) twice daily	Vehicle (n=212)	August 1997 to July 1998	41 centres in USA	12 weeks	14 weeks

Drake study based on patients form these trials

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Table 13 (continued)

Study	Population	Sample size	Eczema severity	Definitions of eczema and severity	Intervention - tacrolimus	Comparator	Recruitment dates	Setting	Length of treatment	Length of follow up
Soter et al 2001[77] (Safety)	Adults	632	Moderate to severe	Hanifin and Rajka Rajka and Langeland	0.03%(n=210) 0.1% (n=209)	Vehicle (n=212)	August 1997 to July 1998	41 centres in the USA	12 weeks	14 weeks
Kawashima 1998[81] (Fujisawa 108)	Adults	181	Moderate to severe	Hanifin and Rajka Rajka and Langeland	0.1% (n=89) twice daily	0.12% Betamethasone valerate (potent steroid) twice daily (n=92)	Unclear – project from June 1996-Feb. 1997	25 medical institutes in Japan	3 weeks	3 weeks
Ruzicka et al 1997[80]	Adults	215	Moderate to severe	Rajka and Langeland	0.03% (54), 0.1% (n=54) 0.3%(n=51)	Vehicle (n=54)	April 1995 to March 1996	16 centres in Europe	3 weeks	4 weeks
Petan et al 2003[83]	Adults	975	Moderate to severe	Hanifin and Rajka Rajka and Langeland	0.1% (n=488)	0.1% hydrocortisone butyrate (potent) to trunk and extremities, 1% hydrocortisone acetate (mild) to head and neck (n=487)	Not clear – from 10/11/2000	57 centres in Europe	6 months	6 months
Reitamo et al 2002 II[82]	Adults	570	Moderate to severe	Hanifin and Rajka Rajka and Langeland	0.03%(n=293) 0.1% (n=292)	0.1% hydrocortisone -17-butyrate twice daily (potent TS) (n=186)	Not stated	27 centres in Europe	3 weeks	5 weeks

Total population studied

A total of 4303 patients (range 14-985) were included in studies of tacrolimus. The papers by Hanifin and colleagues (2001)[76] and Soter and colleagues (2001)[77] report different aspects (efficacy and safety respectively) of the same trial in 632 patients. Drake and colleagues report on quality of life among 579 adults from the Hanifin trials[76] and 178 children and 145 toddlers from the Paller trial.[73]

Indication for treatment

All RCTs in children defined atopic eczema using the criteria of Hanifin and Rajka. Patients had moderate to severe eczema as defined by the Rajka and Langeland criteria in the trials by Paller and colleagues 2001,[73] Reitamo and colleagues 2002[74] and Reitamo and colleagues 2003[75]. Boguniewicz and colleagues 1998[72] state only that the Hanifin and Rajka criteria were used; the measure of severity used is not reported so it is not known how the population was defined as containing those with moderate to severe eczema.

Most trials in adult patients also used the Hanifin and Rajka criteria to define atopic eczema, the exceptions are Granlund and colleagues 2001[79] (tacrolimus versus vehicle) and Ruzicka and colleagues 1997,[80] (tacrolimus versus vehicle) who did not report diagnostic criteria, only severity criteria. The study population in Granlund and colleagues 2001 [79] was restricted to those with lichenified atopic eczema. All the studies in adults include patients with moderate to severe eczema as defined by the Rajka and Langeland criteria.

4.9.1 Quality of Tacrolimus RCTs

All of the included trials had potential conflicts of interest as all were financially supported by Fujisawa, the manufacturer of tacrolimus.

Details of aspects of quality are shown in Table 14 and patient characteristics and inclusion criteria are shown in Table 15. Full details of exclusion criteria can be found in Appendix 6.

Table 14: Methodological details of included tacrolimus RCTs*

Study	Power calculation	Prospective recruitment	Consecutive Recruitment	Multi centre	Method of random-isation	Method of blinding	Main outcome measured blind / independently	Loss to Follow up	ITT analysis?	General-isability	Conflicts of interest
Boguniewicz et al 1998[72] T vs V Children	Yes	Yes	Not stated	Yes	Centralised computer generated	Both ointments identical in appearance and packaging. All investigators, patients and sponsor were blind apart form staff preparing study medication.	Yes	11/136 Tacrolimus, 7/44 control	11 patients excluded after randomisation.	High	Yes
Paller et al 2001[73] T vs V Children	Not stated	Yes	Not stated	Yes	Stratified by age within each centre – no other details.	Investigator, patient, parent, study co-ordinator and other site personnel blind.	Yes	40/235 tacrolimus, 65/116 control	Yes	High	Yes
Reitamo et al 2002[74] T vs TS Children	Yes	Yes	Not stated	Yes	1:1:1. Central randomisation, stratified by age and centre	Described as double blind - Identical packaging.	Yes	34/375 tacrolimus, 20/185 TS	1 patient excluded post randomisation.	High	Yes
Reitamo et al 2003[75] T vs TS Children	Not stated	Yes	Not stated	Yes	1:1:1 stratified by age and centre	Described as double blind – separate identical tubes supplied for a.m. and p.m. application.	Not clear	26/207 once daily tacrolimus, 21/210 twice daily tacrolimus 41/207 TS	Stated that it is, but is based on all those receiving at least one study application – results also based on different denominators.	High	Yes

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Table 14 (cont.)

Study	Main outcome measured blind / independently	Power calculation	Prospective recruitment	Consecutive Recruitment	Multi centre	Method of random-isation	Method of blinding	Loss to Follow up	ITT analysis?	General-isability	Conflicts of interest
Granlund et al 2001[79] T vs V Adults	Yes	Not stated	Yes	No	Yes	1:1	Investigator, patients and study monitor blind to allocation.	Not stated	Not clear	Low	Yes
Drake et al 2001[78] T vs V Adults and children	Not stated	Not stated	Yes	Not stated	Yes	Not stated	Not stated	6-10% (no further detail)	No	Low	Yes
Hanifin et al 2001 (Efficacy)[76] T vs V Adults	Not clear	Not stated	Yes	Not stated	Yes	1:1:1 within each centre	Described as double blind – details not stated	113/423 tacrolimus 145/212 control	One excluded after randomisation.	High	Yes
Soter et al 2001[77] (Safety) T vs V Adults	Not stated	Not stated	Yes	Not stated	Yes	Not stated	Described as double blind – details not stated	113/423 tacrolimus 145/212 control	One 15 year old excluded from analysis, one excluded after randomisation.	Low	Yes
Kawashima 1998[81] (Fujisawa 108) T vs TS Adults	Yes	Not stated	Yes	Not stated	Yes	Central randomisation in permuted blocks of six.	Same sized tube used for both ointments.	11/89 tacrolimus 8/92 control	No – 19 patients not included in analysis	High	Yes

Based on same population

Table 14 (cont.)

Study	Power calculation	Prospective recruitment	Consecutive Recruitment	Multi centre	Method of random-isation	Method of blinding	Main outcome measured blind / independently	Loss to Follow up	ITT analysis?	General-isability	Conflicts of interest
Ruzicka et al 1997[80] T vs V Adults	Not stated	Yes	Not stated	Yes	1:1:1 stratified by centre	Investigators, patients and study monitors not aware of treatment assignment	Yes	21/159 tacrolimus 21/54 control	2 excluded after randomisation	Medium	Yes
Petan et al 2003[83] T vs TS Adults	Yes	Yes	Not sure	Yes	1:1 stratified by centre. Randomisation list centrally generated. Assigned to treatment sequentially.	Identical packaging – colour coded for head and neck treatment. Described as double blind	Yes	124/487 Tacrolimus 204/485 TS	3 excluded after randomisation plus outcomes report evaluable pts only even in ITT	High	Yes
Reitamo et al 2002 II[82] T vs TS Adults	Yes	Yes	Not sure	Yes	Block randomisation supplied to each centre by sponsor.	Identical packaging. Patients and investigators blind to allocation.	Yes	44/384 Tacrolimus 17/186 TS	1 excluded after randomisation	High	Yes

Table 15: Tacrolimus Studies: Sample Characteristics*

	Mean age (SD)			% Male			% Caucasian				
	Intervention		Cont.	Intervention		Cont.	Intervention		Cont.	Inclusion criteria	Eczema severity
	0.03%	0.1%		0.03%	0.1%		0.03%	0.1%			
Boguniewicz et al 1998[72] T vs V Children	10.1	10.8	10.4	41.9	42.9	40.9	55.8	77.6	61.4	Age 7 to 16, Affected BSA 5-30%, Menstruating women using reliable contraception.	Moderate to Severe (severe 17.6%)
Paller et al 2001[73] T vs V Children	63.2% aged 2-6 years 36.8% aged 7-15 years	58.5% aged 2-6 years 41.5% aged 7-15 years	62.1% aged 2-6 years 37.9% aged 7-15 years	47.0	48.3	45.7	65.0%	65.0%	67.2%	2-15 years of age Moderate to severe eczema BSA affected 10-100%	Moderate to Severe (Severe 61.5%)
Reitamo et al 2002[74] T vs TS Children	7.6 (4.4)	7.2 (3.9)	7.2 (4.0)	40.2	51.6	51.4	74.1	77.4	81.1	Aged 2-15 years BSA affected >5% <60%	Moderate to severe (severe 44.5%)
Reitamo et al 2003[75] T(1x,2x) vs TS Children	6.7 (3.9)	6.9 (4.2)	7.2 (4.1)	48.3	45.2	51.7	83.1	81.9	86.5	Aged 2-15 years BSA affected 5%-100% Written consent from guardian Adherence to wash out rules	Moderate to severe (severe 46.6%)
Drake et al 2001[78] T vs V Adults and children	For adults 39 years For children 9 years For toddlers 3 years			Approx. half			Approx. two-thirds			Adults (>15 years), Children (5-15 years), Toddlers (2-4 years)	Moderate to severe (approx. half the adults and 2/3 toddlers)
Granlund et al 2001[79] T vs V Adults	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Moderate to severe

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Table 15 (cont.)

	Mean age (SD)			% Male			% Caucasian				
	Intervention		Cont.	Intervention		Cont.	Intervention		Cont.	Inclusion criteria	Eczema severity
	0.03%	0.1%		0.03%	0.1%		0.03%	0.1%			
Hanifin et al 2001 (Efficacy)[76] T vs V Adults	37.9 (13.8)	39.3 (14.5)	38.5 (14.0)	45.0	40.7	44.8	68.2	66.5	66.0	Aged 16 years and over BSA affected 10-100%	Moderate to severe (severe 56.2%)
Soter et al 2001 (Safety)[77] T vs V Adults	38.0 (13.7)	39.3 (14.5)	38.5 (14.0)	44.8	40.7	44.8	68.1	66.5	66.0	Age 16 years and over BSA affected 10-100%	As for Hanifin et al
Kawashima 1998[81] (Fujisawa 108) T vs TS Adults	-	25.9 (5.7)	26.3 (7.6)	-	43.6	64.3	-	-	-	Age 16 years and over Patient who could be treated with 5g or less of ointment per application to trunk and extremities (head, neck, face, hands and feet were excluded sites)	Moderate to severe (severe 54.7%)
Ruzicka et al 1997[80] T vs V Adults	30 (12)	28 (9)	29 (11)	48	41	48	96	94	98	Age 13 to 60 years 200-1000cm^2 non contiguous area of trunk, extremities, face and neck. At least 200cm^2 on neck or extremities.	Moderate to severe

Based on same population

Table 15 (cont.)

	Mean age (SD)			% Male			% Caucasian				
	Intervention		Cont.	Intervention		Cont.	Intervention		Cont.	Inclusion criteria	Eczema severity
	0.03%	0.1%		0.03%	0.1%		0.03%	0.1%			
Petan et al 2003[83] T vs TS Adults	-	32.1 (11.6)	32.9 (12.0)	-	46.2	46.2	-	95.3	97.1	Aged 18 and over Patient capable of understanding purposes and risks of the trials and gives written consent Patient agrees to and is able to comply with study requirements and attend clinic for scheduled visits Women of child bearing potential agree to practice effective birth control during study and 28 days after. On day 1 blood screening parameters normal Comply with washouts.	Moderate to severe (severe 42.6%)
Reitamo et al 2002 II[82] T vs TS Adults	31.1 (11.5)	32.4 (11.4)	30.8 (10.3)	43.5	42.9	46.8	94.8	96.3	97.8	Aged 16-70 years BSA >5%	Moderate to severe (severe 52.8%)

Internal Validity

Selection Bias

The trials vary in the amount of detail given the methods of randomisation but in the five where details are given,[72;74;81-83] randomisation methods seem sound.

Detection bias

Methods of ensuring allocation concealment are unclear in four studies where they are simply labelled "double blind".[74;76;83] and not stated in one case.[81] Attempts to protect blinding from being broken post randomisation through standardising packaging and treatment were made in five cases.[74;75;81-83]

In trials in adults, it is unclear or not stated whether the main outcome was measured blind in the studies reported by Drake and colleagues 2001[78], Hanifin and colleagues[76] and Soter and colleagues 2001[77] (all tacrolimus versus vehicle). All other studies do report main outcome measured by investigators blind to allocation group.

Attrition bias

This section reports on the numbers of patients who did not complete the study period due to withdrawal for any reason (adverse effects, withdrawal of consent, lack of efficacy, etc.), loss to follow up or protocol violation. These are collectively referred to as participants lost to follow up. Full details of reasons for loss to follow up can be seen in the data extraction tables in Appendix 6. Main reasons for withdrawal are shown in Table 16. Withdrawal rates in the vehicle arms of trials is noticeably high, primarily due to lack of efficacy or consequent need for treatment prohibited by protocol. Drake and colleagues did not give details of attrition, but state that 6-10% of patients were lost to follow up.

Table 16: Reasons for attrition in trials of tacrolimus*

	Reason for withdrawal (%)									
	Adverse effects		Prohibited therapy use		Lack of efficacy		Other reasons		Total	
	Int.	Cont.	Int.	Cont.	Int.	Cont.	Int.	Cont.	Int.	Cont.
Boguniewicz et al 1998[72] T vs V Children	2.9	4.5	0	0	0.7	9.1	3.7	2.3	8.1	15.9
Paller and colleagues 2001[73] T vs V Children	3.8	7.8	0	0	3.8	38.8	9.4	8.6	17.0	56.0
Reitamo et al 2002[74] T vs TS Children	1.6	2.2	0	0	1.1	3.8	6.4	4.9	9.1	10.8
Reitamo et al 2003[75] T vs TS Children	2.6	2.9	0	0	1.4	8.2	7.3	8.7	11.3	19.8
Granlund et al 2001[79] T vs V Adults	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
Hanifin et al 2001[76] T vs V Adults	5.7	12.3	0	0	10.5	44.8	10.5	11.3	26.7	68.4
Ruzicka et al 1997[80] T vs V Adults	4.6	9.3	0	24.1	4.6	0	4.0	5.5	13.2	38.9
Kawashima 1998[81] T vs TS Adults	0	0	1.1	2.2	0	0	11.2	6.5	12.3	8.7
Petan et al 2003[83] T vs TS Adults	2.1	3.3	2.7	2.7	10.7	25.6	10.0	5	25.5	42.1
Reitamo et al 2002 (II)[82] T vs TS adults	3.9	1.6	1.3	1.1	0.8	1.1	5.5	5.3	11.5	9.1

Intent to treat (ITT) analysis

Most trials use a modified intent to treat analysis, where patient not receiving at least one application of study treatment were (between one and 11 patients excluded) excluded.[72;74;76;80;82;83] In one trial it is unclear whether ITT has been used.[79] One trial states that a modified ITT analysis has been used but appears to base individual outcomes on different denominators.[75] One trial does not use ITT.[81]

Power calculation

In children, two trials against vehicle report sample size calculation, Boguniewicz and colleagues 1998,[72] and Reitamo and colleagues 2002[74], as do both trials of tacrolimus versus topical corticosteroids. The remaining two trials do not report power calculations. In adults, two trials of tacrolimus both versus topical corticosteroids by Petan and colleagues and Reitamo and colleagues,[82;83] report a sample size calculation, the remaining studies do not.

External Validity

Length of treatment and follow up

Reported aspects of study population such as age. Severity of eczema and race are shown in Table 15. Duration of studies was mostly short term, with all studies of children following treatment of three weeks. One adult study followed treatment of six months[83] and one of three months.[76] The remainder evaluated treatment of two-three weeks.

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External validity was categorised according to the level of detail given in studies about patient characteristics, and inclusion and exclusion criteria. Thus, a high level of generalisability was given if the information provided was extensive enough for a practitioner to be able to judge whether the information was generalisable to their practice. All the trials in children had a high level of generalisability.

In adults, Drake and colleagues 2001[78] and Granlund and colleagues 2001[79] (both tacrolimus versus vehicle) were categorised as having low generalisability. This was also true for Soter and colleagues 2001[77] (tacrolimus versus vehicle) although the companion paper to those by Soton and colleagues and Drake and colleagues by Hanifin and colleagues 2001[76] was rated as having high generalisability. Ruzicka and colleagues 1997[80] (tacrolimus versus vehicle) was given a generalisability rating of medium. All three studies of tacrolimus versus topical corticosteroids (Kawashima 1998,[81] Reitamo and colleagues 2001 (II)[82] and Petan and colleagues 2003[83]) were given generalisability ratings of high.

Summary of the quality of tacrolimus RCTs

- 8/10 trials used a recognised measure to define atopic eczema and 9/10 to define the severity of eczema in the study populations.
- 5/10 trials were of tacrolimus versus vehicle. 2/10 were of tacrolimus versus mild topical corticosteroid in children and 3/10 were of tacrolimus versus potent topical corticosteroids in adults (one of the latter used a mild TS on delicate areas).
- Methods of randomisation were not stated or unclear in 5/10 trials.
- Methods of blinding were not stated or unclear in 5/10 trials.
- Only one trial reports ITT analysis. In other trials a modified ITT population is used excluding between one and 11 patients who did not receive treatment after randomisation - the impact of this is likely to be limited.
- Attrition rates were high, in the treatment arms ranging from 8.0% to 26.7% (median 11.5%) and from 8.0% to 68.4% (median 19.8%) in the control arms. One study did not report attrition.
- 1/10 trials received a generalisability rating of low. The papers by Soter and colleagues and Drake and colleagues were also of low generalisability. However, these papers reported on the safety and QoL aspects of the same trial from which Hanifin and colleagues had reported effectiveness. The report by Hanifin had high generalisibility as it provided full details of the population characteristics
- All included trials reported potential for conflicts of interest.

4.10 Effectiveness of Tacrolimus

Effectiveness is estimated using a range of measures (see

Table 17 to Table 21). Some papers do not state actual figures but present results graphically (See Appendix 6 for details). Where this is the case, data have been extracted from the graphs and therefore may be subject to inaccuracies. Such data are presented in the following tables with no decimal places to avoid spurious accuracy.

Boguniewicz and colleagues 1998[72] provide details of treatment with 0.3% as well as 0.03% and 0.1% tacrolimus. Outcomes with 0.3% tacrolimus are recorded in the data extraction tables (Appendix 6) but not presented in the following tables as this is not the licensed treatment potency. The study by Drake and colleagues 2001[78] reports on quality of life for a subgroup of patients in the trials by Hanifin and colleagues and Paller and colleagues. This study is reported only in Table 21. Soter and colleagues 2001[77] report on safety aspects, and Hanifin and colleagues 2001[76] on the effectiveness of the same trials so these trials are reported only in the relevant tables. The study by Petan and colleagues 2003[83] provides six month and three month follow up data. Three month data are reported in the following tables, while the six month data are included in the accompanying text where appropriate. The exception is adverse effects data which are based on six month follow up data.

Pooled analyses

Data were available for meta-analysis for two outcomes comparing tacrolimus with active comparator. Follow up times were chosen pragmatically, based on available data (see Table 17). At three weeks, there was information about the effectiveness of 0.03% tacrolimus in children compared to mild topical corticosteroids measured by at least 90% improvement on the Physician's Global Evaluation (PGE, "Cleared" to "excellent improvement") (Figure 2). Tacrolimus 0.03% is more effective than mild topical corticosteroids in paediatric moderate to severe eczema (RR 2.56 95% CI 1.95, 3.36)

Effectiveness of 0.1% tacrolimus in adults compared to potent topical corticosteroids was also available for an improvement of at least 75% on the PGE ("Cleared" to "Marked improvement"). Differences in outcome measures are due to the way in which results were presented in the original papers Figure 3. Tacrolimus 0.1% is not more effective than potent topical corticosteroids in moderate to severe eczema (RR1.08 95% CI 0.97, 1.21)

An attempt was made to pool data on PGE at three weeks from the studies by Ruzicka and colleagues 1997[80] and Boguniewicz and colleagues 1998[72]. This related to PGE scores of 75% and over ("Marked improvement" to "cleared" at three weeks. However, when tested, these studies displayed marked statistical heterogeneity (I^2 = 85.4%, p=0.009) and so this meta-analysis has not been presented.

It was also possible to pool other outcomes relating to trials of tacrolimus and vehicle. These have not been presented as this is not the most clinically relevant comparator in the majority of cases. These, together with meta-analyses comparing 0.1% and 0.03% tacrolimus are available from the authors on request.

Figure 2: Forest plot showing at least 90% on PGE in children with moderate to severe atopic eczema after three weeks treatment with 0.03% tacrolimus or 1% hydrocortisone acetate (control) *

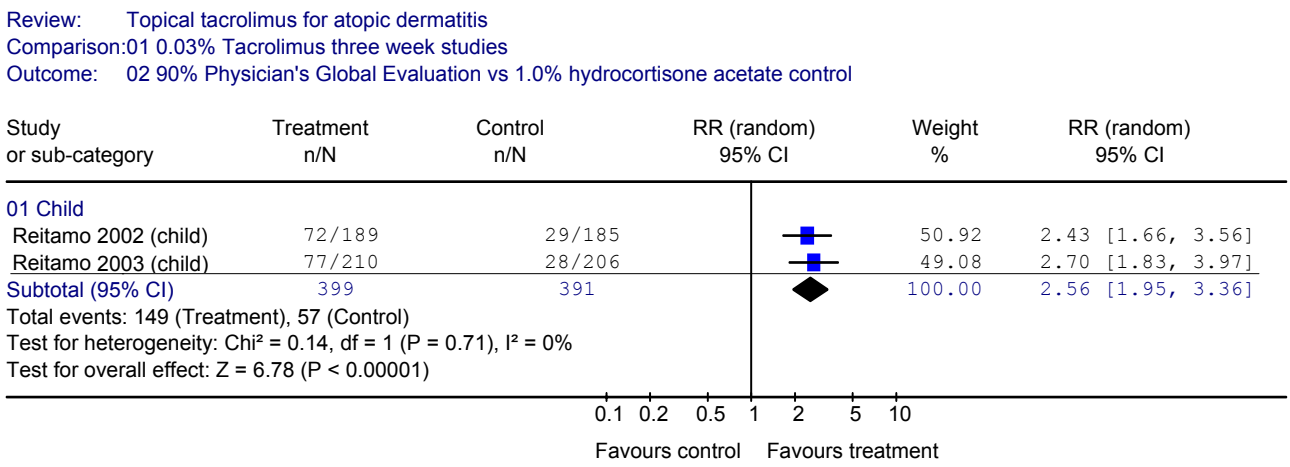
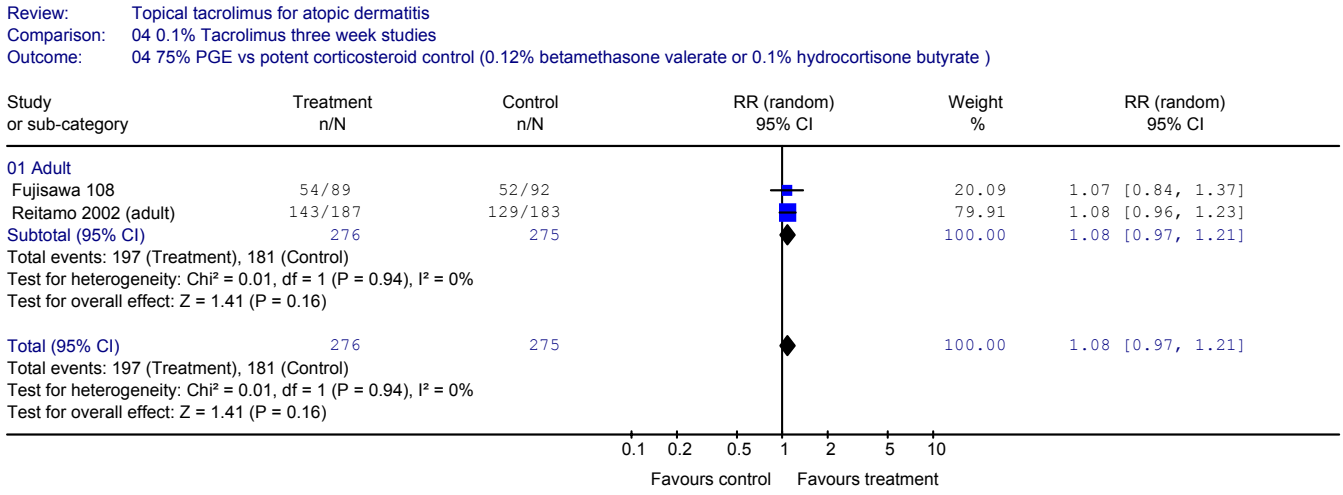


Figure 3: Forest plot showing at least 75% PGE in adults with moderate to severe atopic eczema after treatment for three weeks with 0.1% tacrolimus or potent topical corticosteroids



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The remaining results were not presented across trials in a way that permitted meaningful meta-analyses and have been tabulated and presented descriptively below.

Effectiveness measured by Physician's Global Evaluation

Clinical improvement as measured by Physician's Global Evaluation (PGE) is reported by all RCTs of tacrolimus reporting effectiveness. Results are shown in Table 17. PGE is a seven point scale evaluating treatment success from "Worse" to "Cleared". See Table 4 page 26 for details. PGE classifications "Cleared", "Excellent" and "Marked" improvement have been combined. Some studies report all categories separately and these can be seen in Appendix 6.

All trials in children reported effectiveness as measured by the PGE. Tacrolimus 0.03% and 0.1% was found to be more effective than vehicle using the PGE categories of "clear" to "marked improvement" by Boguniewicz and colleagues 1998[72] ($p<0.007$) and Paller and colleagues[73] ($p<0.001$).

Kawashima 1998[81] report on a 5-point global scale – "cured", "markedly improved", "moderately improved", "Slightly improved" and "no change". The figures reported in Table 17 refer to those who were "cured or "Markedly improved". No significant difference between tacrolimus and potent topical corticosteroid was found at 3 weeks.

Pooled results for 0.03% tacrolimus compared to mild topical corticosteroids in children are shown at the beginning of this chapter.

All the RCTs of adults reported effectiveness relating to PGE. Granlund and colleagues 2001[79] report that all patients using 0.1% tacrolimus were judged to have had eczema cleared or demonstrated a marked improvement compared to none of those using vehicle.

Significantly more patients were found to have "clear" to "marked improvement" in their eczema after treatment with tacrolimus than with vehicle by Hanifin and colleagues 2001[76] ($p<0.001$ for 0.1% versus vehicle and $p=0.041$ for 0.03% versus vehicle) and Ruzicka and colleagues 1997 [80] ($p<0.001$ for 0.1% vs vehicle). More treatment success measured at least 90% improvement from baseline PGE was also reported by Hanifin and colleagues 2001[76] ($p<0.001$ for both tacrolimus potencies versus vehicle).

Pooled results for 0.1% tacrolimus compared to potent topical corticosteroids in adults are shown at the beginning of this chapter.

Effectiveness measured by affected BSA

Results for changes in affected body surface area are shown in Table 17.

One trial in children reported change in affected BSA by treatment. Reitamo and colleagues 2002[74]reports a greater mean decrease in affected BSA in those using 0.03% tacrolimus ($p<0.05$, 95% CI 0.199, 0.391, calculated by PenTAG), and in those using 0.1% tacrolimus ($p<0.05$, 95% CI 0.359, 0.541, calculated by PenTAG) compared to mild topical corticosteroids.

Three trials in adults report median decrease in affected BSA was greater with tacrolimus compared to vehicle. Granlund and colleagues 2001[79] (significance not reported), Hanifin

and colleagues 2001[76] (differences between vehicle and both potencies of tacrolimus p<0.001) and Petan and colleagues 2003[83] (p<0.001).*

Effectiveness measured by changes in EASI

Results for changes in EASI or mEASI score of patients, are shown in Table 17. EASI has a maximum score of 72. Improvement in mEASI score was reported in all four RCTs of tacrolimus in children and both potencies of tacrolimus showed greater improvement than vehicle (Boguniewicz and colleagues 1998,[72] p<0.001; Paller and colleagues 2001.[73] p<0.001) Both potencies of tacrolimus also showed greater improvement than mild topical corticosteroids (Reitamo and colleagues 2002[74] p<0.001; Reitamo and colleagues 2003,[75] (p<0.001).

Three trials in adults report on changes in EASI or mEASI score, although none give baseline scores. Hanifin and colleagues 2001[76] report greater mean improvement in EASI of with tacrolimus compared to vehicle (p<0.001).

Differences in improvement in EASI score between 0.1% tacrolimus and potent topical corticosteroids were not significant, but differences between 0.03% tacrolimus and potent topical corticosteroids were significant (p<0.05), with corticosteroids showing greater improvement according to Reitamo and colleagues 2002 (II)[82] However, Petan and colleagues 2003[83] report greater median improvement in EASI in those treated with 0.1% tacrolimus compared to those treated with topical corticosteroids (mild on face, potent on body) (p<0.001 at 3 months, also significant at 4 and 6 months).

Effectiveness as measured by head and neck score

Two trials of tacrolimus in children report on improvement in head and neck score. Like the EASI, this consisted of the sum of the physician's assessment for clinical signs, each on a scale of 0 (absent) to 3 (severe).

Boguniewicz and colleagues 1998[72] report that the mean percentage improvement was better with 0.03% and 0.1% tacrolimus, compared to vehicle (p<0.001).

Reitamo and colleagues 2002[74] report on the median improvement in mean area under the curve of mEASI for the head and neck only. This is improved by 62.5% in those treated with 0.03% tacrolimus, 75.2% in those treated with 0.1% tacrolimus and 43.3% in those treated with mild topical corticosteroids. Significance levels were not reported.

Effectiveness measured through patient global assessment.

Effectiveness as measured through patient reports of "feeling better" is reported by two trials in children and one in adults (see Table). A seven point scale of "much better" to "much worse" was used.

Boguniewicz and colleagues 1998[72] report that more of those treated with 0.03% and 0.1% tacrolimus felt "better" or "much better" compared to those treated with vehicle (p<=0.025).

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Reitamo and colleagues 2003[75] report that more of those treated once and twice daily with tacrolimus reported feeling "better" or "much better" compared to those treated with mild potency topical corticosteroids. Significance not reported but calculated by PenTAG p<0.05 (for once daily tacrolimus 95% CI –0.256, -0.687; for twice daily tacrolimus 95% CI –0.407, -0.236).*

0.1% tacrolimus was reported to show more patients feeling "better" or "much better than topical corticosteroids (mild on the face, potent on the body) by Petan and colleagues 2003[83] at three months (p<0.0012) and this difference remained significant after 6 months of follow up. They also reported the same measure in relation to head and neck eczema only, again, more of those treated with 0.1% tacrolimus reported feeling "better" or "much better" compared those treated with topical corticosteroids. Significance levels were not reported but calculated by PenTAG p<0.05 (95% CI –0.330, -0.210).

Eczema recurrence after clearing

One study in children reports on eczema recurrence after clearing as seen at follow-up two weeks later. Boguniewicz and colleagues 1998[72] report that recurrence was higher in those treated with 0.03% tacrolimus and vehicle (p<0.05, 95% CI 0.0245, 0.404) but no t significantly different for 0.1% tacrolimus and vehicle (95% CI –0.0364, 0.321 - Significance levels are calculated by PenTAG).

Effectiveness measured by level of pruritus

Levels of pruritus and sleep disturbance reported by the included trials are shown in Table 18.

Three of the studies of children report a separate score for pruritus on a 10cm visual analogue scale (VAS) where 0 was "no itch" and 10 "the worst itch imaginable". Improvement in score before and after treatment is reported. Boguniewicz and colleagues 1998[72] report that those treated with 0.03% tacrolimus had a mean improvement in pruritus score of 3.9 (median 88.7% improvement from 5.7 at baseline), those treated with 0.1% tacrolimus had a mean improvement in pruritus score of 3.2 (median 73.6% improvement from 4.9 at baseline) and those treated with vehicle alone improved by a mean score of 1.8 (50.5% median improvement from 5.4 at baseline). The difference in scores between tacrolimus and vehicle was significant for mean percentage improvement in score (p=0.027)

Paller and colleagues 2001[73] report greater median improvement in pruritus score in both the 0.03% and the 0.1% tacrolimus groups compared the group treated by vehicle alone (p<0.001). Baseline values were not given.

Reitamo and colleagues 2003[75] reported a mean improvement in pruritus score of 3.0 (from 6.3) in those treated with once daily tacrolimus, 2.6 (from 6.1) in those treated with twice daily tacrolimus and 3.1 (from 6.2) in those treated with topical corticosteroids. Significance not reported. They also reported patient assessment of sleep quality. On a 10cm visual analogue scale (VAS) where 10 was "good sleep", a score of 7.5 was reported in those treated with once daily tacrolimus (from 5.9 at baseline), 8.1 in those treated with twice daily tacrolimus (from 5.6 at baseline) and 7.0 in those treated with topical corticosteroids (from 5.6 at baseline). Significance levels were not reported.

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Two trials in adults report pruritus. Granlund and colleagues 2001 report an 80% median improvement in pruritus score in those treated with 0.1% tacrolimus compared to none of those in the vehicle only group. Significance levels were not reported.

Petan and colleagues 2003[83] report itch assessment at 3 months for those treated with 0.1% tacrolimus to be 1.6 (improvement in median of 4.8) compared to 2.3 in the group treated with topical corticosteroids regimen (improvement in median of 4.1). At baseline median values were 6.4 in both groups. Significance levels were not reported. In addition, the authors investigated sleep quality using a patients VAS of 10cm, where 0 represented "slept badly" and 10 "slept well". For those treated with 0.1% tacrolimus, the median sleep assessment was 9.1 (improvement in median of 3.4) and for those treated by topical corticosteroids regimen, 8.4 (improvement in median of 2.6). Again, significance levels were not reported. *

Tacrolimus effectiveness measured by signs and symptoms score.

Reported decrease (improvement) in the Signs and Symptoms Score for aspects of atopic eczema – oedema, erythema, excoriation, lichenification, oozing and scaling, is shown in Table 20

One study of children, by Paller and colleagues 2001[73] reports on the decrease in signs and symptoms. For all signs and symptoms, oedema, erythema, excoriation, lichenification, oozing and scaling, both 0.03% and 0.1% tacrolimus resulted in significantly greater percentage improvement in score than vehicle ($p<0.001$).

Two trials in adults report on the decrease in signs and symptoms score. Hanifin and colleagues 2001[76] reported that for oedema, erythema, excoriation, lichenification, oozing and scaling, both 0.03% and 0.1% tacrolimus resulted in significantly greater percentage improvement in score than vehicle ($p<0.001$) while for oedema, excoriation and scaling 0.1% tacrolimus also showed significantly greater improvement than 0.03% tacrolimus. ($p<0.05$)

Petan and colleagues 2003[83] report median decreases in sign and symptom scores from the PGE. Significance levels are not reported, although appear to be greater for topical corticosteroids compared to tacrolimus for all signs except erythema (Table 20).

Kawashima reports on a variation of signs and symptoms scores. All items are scored on a scale of 0 (none) to 4 (severe). Items examined were: Erythema, swelling, papule, prurigo nodularis, lichenification, desquamation, erosion, incrustation, itching. Results are shown in Appendix 6. No significant differences between tacrolimus and potent topical corticosteroids were found for any of these outcomes.

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Table 17: Effectiveness of Tacrolimus as measured by PGE, affected BSA and EASI score*

Study	PGE – Cleared to marked improvement (%)			>=90% improvement in PGE (%)			Mean % decrease in affected BSA			Median % decrease in affected BSA			Mean % Improvement EASI score			Mean improvement EA sco		
	0.03%	0.1%	Cont.	0.03%	0.1%	Cont.	0.03%	0.1%	Cont.	0.03%	0.1%	Cont.	0.03%	0.1%	Cont.	0.03%	0.1%	Co
Boguniewicz et al 1998[72] T vs V Children	69	67	38	-	-	-	-	-	-	-	-	-	72 [a]	77 [a]	26 [a]			
Paller et al[73] 2001 T vs V Children	56.5	56.0	15.7	-	-	-	-	-	-	-	-	-	-	-	-	-14.0	-15.0	-2
Reitamo et al 2002[74] T vs TS Children	63.1	73.8	32.8	38.1	49.1	15.7	-	-	-	60	75	30	75[b]	82[b]	37[b]	-	-	
Reitamo et al 2003[75] T(1x,2x) vs TS Children				27.8	36.7	13.6	-	-	-	-	-	-	66.7[c]	76.7 [c]	47.6 [c]	-	-	
Granlund et al 2001[79] T vs V Adults	-	100	0	-	-	-	-	-	-	-	45.6 [d]	2.9 [d]	-	-	-	-	-	
Hanifin et al 2001 (Efficacy)[76] T vs V Adults	46.2	57.0	13.8	27.5	36.8	6.6	19	24	5	-	-	-	-	-	-	-11.7	-14.4	-2

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Table 17 (cont.)

Study	PGE – Cleared to marked improvement			>=90% improvement in PGE (%)			Mean decrease in affected BSA			Median % decrease in affected BSA			Mean % in Improvement EASI score			Mean improvement EASI sco		
	0.03%	0.1%	Cont.	0.03%	0.1%	Cont.	0.03%	0.1%	Cont.	0.03%	0.1%	Cont.	0.03%	0.1%	Cont.	0.03%	0.1%	Co
Kawashima 199881 (Fujisawa 108) T vs TS Adults	-	60.7	56.5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Ruzicka et al 1997[80] T vs V Adults	59	81	10	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Petan et al 2003[83] T vs TS Adults (3mnth)	-	62.9	40.7	-	-	-	-	-	-	-	81.9	71.4	-	82.1`	75.0`	-	-	
Reitamo et al 2002 II[82] T vs TS Adults	57.9	76.9	70.9	-	-	-	-	-	-	60	76	77	71 [b]	82 [b]	83 [b]	-	-	

[a] Mean percentage improvement in mEASI
[b] Median % improvement in mEASI score
[c] Median % improvement in EASI score
[d] Reduction in area of symptomatic skin

PGE = Physician's Global Evaluation

0.03% = 0.03% Tacrolimus ointment

0.1% = 0.1% Tacrolimus ointment

Cont. = Control treatment

TS = Topical cprtoicposteroids

Table 18: Effectiveness of Tacrolimus as measured by improvement in head and neck eczema, feeling better and recurrence*

Study	Mean % improvement in head and neck score			% Patients feeling "better" or "much better"			% patients feeling head and neck is "better" or "much better"			Recurrence after clearing (2 weeks FU)		
	0.03%	0.1%	Cont.	0.03%	0.1%	Cont.	0.03%	0.1%	Cont.	0.03%	0.1%	Cont.
Boguniewicz et al 1998[72] T vs V Children	65	83	-2	76	91	52	-	-	-	72	81	75
Paller et al 2001[73] T vs V Children	-	-	-	-	-	-	-	-	-	-	-	-
Reitamo et al 2002[74] T vs TS Children	62.5*	75.2*	43.3*	-	-	-	-	-	-	-	-	-
Reitamo et al 2003[75] T(1x,2x) vs TS Children	-	-	-	66.7	82.9	50.2	-	-	-	-	-	-
Granlund et al 2001[79] T vs V Adults	-	-	-	-	-	-	-	-	-	-	-	-
Hanifin et al 2001 (Efficacy)[76] T vs V Adults	-	-	-	-	-	-	-	-	-	-	-	-

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Kawashima 1998[81] (Fujisawa 108) T vs TS Adults	-	-	-	-	-	-	-	-	-	-	-	-

Table 18 (cont.)

Study	Mean % improvement in head and neck score			% Patients feeling "better" or "much better"			% patients feeling head and neck is "better" or "much better"			Recurrence after clearing (2 weeks FU)		
	0.03%	0.1%	Cont.	0.03%	0.1%	Cont.	0.03%	0.1%	Cont.	0.03%	0.1%	Cont.
Ruzicka et al 1997[80] T vs V Adults	-	-	-	-	-	-	-	-	-	-	-	-
Petan et al 2003[83] T vs TS Adults	-	-	-	-	63.9	45.2	-	61.7	36.8	-	-	-
Reitamo et al 2002 II[82] T vs TS Adults	-	-	-	-	-	-	-	-	-	-	-	-

* Median improvement in Mean Area under Curve (MAUC) of mEASI score for head and neck only

Table 19: Tacrolimus effectiveness as measured by pruritus score and sleep quality*

Study	Median (* mean) improvement in pruritus score (10cm VAS)			Median % improvement in VAS pruritus score			Assessment of pruritus (10cm VAS)			Patients assessment of sleep quality (10cm VAS)		
	0.03%	0.1%	Cont.	0.03%	0.1%	Cont.	0.03%	0.1%	Cont.	0.03%	0.1%	Cont.
Boguniewicz et al 1998[72] T vs V Children	3.9*	3.2*	1.8*	88.7	73.6	50.5	-	-	-	-	-	-
Paller et al 2001[73] T vs V Children	3.9	3.9	0.8	-	-	-	-	-	-	-	-	-
Reitamo et al 2002[74] T vs TS Children	-	-	-	-	-	-	-	-	-	-	-	-
Reitamo et al 2003[75] T(1x,2x) vs TS Children	3.0*	2.6*	3.1*	-	-	-	-	-	-	7.5	8.1	7.0
Granlund et al 2001[79] T vs V Adults	-	-	-	-	80	0	-	-	-	-	-	-
Hanifin et al 2001 (Efficacy)[76] T vs V Adults	-	-	-	-	-	-	-	-	-	-	-	-
Kawashima 1998[81] (Fujisawa 108) T vs TS Adults	-	-	-	-	-	-	-	-	-	-	-	-

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Table 19 (cont.)

Study	Median improvement in pruritus score (10cm VAS)			Median % improvement in VAS pruritus score			Assessment of pruritus (10cm VAS)			Patients assessment of sleep quality (10cm VAS)		
	0.03%	0.1%	Cont.	0.03%	0.1%	Cont.	0.03%	0.1%	Cont.	0.03%	0.1%	Cont.
Ruzicka et al 1997[80] T vs V Adults	-	-	-	-	-	-	-	-	-	-	-	-
Petan, et al 2003[83] T vs TS Adults	-	4.1	4.8	-	-	-	-	1.6	2.3	-	9.1	8.4
Reitamo et al 2002 II[82] T vs TS Adults	-	-	-	-	-	-	-	-	-	-	-	-

Table 20: Effectiveness Tacrolimus: Decrease in signs and symptoms score *

	% decrease in signs and symptoms score																	
	Oedema			Erythema			Excoriation			Lichenification			Oozing			Scaling		
	0.03	0.1	Cont.	0.03	0.1	Cont.	0.03	0.1	Cont.	0.03	0.1	Cont.	0.03	0.1	Cont	0.03	0.1	Cont.
Boguniewicz et al 1998[72] T vs V Children	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Paller et al 2001[73] T vs V Children	0.7	0.8	0.2	0.8	0.8	0.2	0.7	0.9	0.2	0.8	0.7	0.2	0.5	0.5	0	0.9	0.1	0.3
Reitamo et al 2002[74] T vs TS Children	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Reitamo et al 2003[75] T(1x,2x) vs TS Children	-	-	-	--	-	--	-	-	--	-	-	-	-	-	-	-	-	-
Granlund et al 2001[79] T vs V Adults	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hanifin et al 2001 (Efficacy)[76] T vs V Adults	0.7	0.9	0.1	0.8	0.9	0.2	0.7	0.8	0.1	0.7	0.8	0.2	0.3	0.4	0	0.8	1.0	0.3
Kawashima 1998[81] (Fujisawa 108) T vs TS Adults	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

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Table 20(cont.)

	% decrease in signs and symptoms score																	
	Oedema			Erythema			Excoriation			Lichenification			Oozing			Scaling		
	0.03	0.1	Cont.	0.03	0.1	Cont.	0.03	0.1	Cont.	0.03	0.1	Cont.	0.03	0.1	Cont	0.03	0.1	Cont.
Ruzicka et al 1997[80] T vs V Adults	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Petan, et al 2003[83] T vs TS Adults	-	2.3*	2.9*	-	3.0*	2.2*	-	1.8*	2.2*	-	2.1*	2.5*	-	0.8*	1.1*	-	1.4*	1.9*
Reitamo et al 2002 II[82] T vs TS Adults	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

*Actual decrease, not proportion

Quality of life

Only two papers report on quality of life measures following treatment with tacrolimus. Drake and colleagues report separately on adults (aged16 and over), children (aged 5-15) and toddlers (aged 2-4) for those treated with tacrolimus and those treated with vehicle. The participants were drawn from the trial samples used by Hanifin and colleagues and Paller and colleagues. The QoL measures used are the Dermatology Life Quality Index (DLQI) the Children's Dermatology Life Quality Index (CDLQI - completed by children with help from parents/guardians) and a modified version of this; the CDLQI (Toddlers) which was completed by parents or guardians. All these measures relate to experience in the previous week. Results are shown in Table 21. Affects of eczema at baseline are shown in the data extraction sheets in Appendix 6. However, only combined categories for those affected "very much", "a lot" and "a little" compared to those affected "not at all" are reported, so it is not possible to assess the level of change over time.

Among adults treated for atopic eczema, significant differences for QoL were found overall and across all measurement dimensions (symptoms and feelings, daily activities, leisure, work/school, personal relations, treatment) for both potencies of tacrolimus compared to vehicle (p=0.000). In addition, most individual dimensions were significantly better with 0.1% tacrolimus compared to 0.03% tacrolimus (symptoms and feelings p=0.006, daily activities p=0.003, leisure p=0.01, work/school p=0.006, personal relations p=0.025) and overall (p=0.003).

Among children significant differences between 0.1% tacrolimus and vehicle (p=0.000-0.024) were found overall and for all dimensions (symptoms and feelings, leisure, school or holiday, personal relationships, sleep, treatment) while for 0.03% tacrolimus all were significant (p=0.000-0.02) with the exception of the personal relationships dimension where the difference was not significant. No significant differences were found between 0.1% and 0.03% tacrolimus.

Among toddlers, differences overall and across all dimensions were significant (p=0.000) for 0.1% tacrolimus versus vehicle and for 0.3% tacrolimus versus vehicle (p=0.000-0.001). No significant differences between 0.1% and 0.03% tacrolimus were found.

Petan and colleagues 2003[83] include limited reports on the changes in QoL as measured by the DLQI for patients treated with tacrolimus of a topical corticosteroid regimen (TS). The only reported data are improvement from baseline in overall total score. This was 66.7% for those using 0.1% tacrolimus and 58.5% for those using TS regimen at 3 months and 74.3% and 69.2% at 6 months respectively. Significance levels were not reported. *

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Table 21: Effectiveness and Tacrolimus – Quality of Life in adults*

	Reduction in DLQI score at end of treatment																				
	Symptoms and feelings			Daily activities			Leisure			Work / school			Personal relationships			Treatment			Total score		
Total score	**0.03**	**0.1**	**Cont.**	**0.03**	**0.1**	**Cont.**	**0.03**	**0.1**	**Cont.**	**0.03**	**0.1**	**Cont.**	**0.03**	**0.1**	**Cont**	**0.03**	**0.1**	**Cont.**	**003**	**0.1**	**Cont.**
Drake et al 2001[78] T vs V Adults	33.7	41.1	10.4	20.9	28.4	6.0	21.9	28.6	7.3	22.0	31.8	5.7	10.2	15.1	0.6	13.3	14.8	3.1	21.1	27.1	5.6
Petan, J. et al 2003 (Fujisawa 108)[83] T vs TS Adults																			-	66.7	58.5

	Reduction in CDLQI at end of treatment																							
	Symptoms and feelings			Activities			Leisure			School/ holidays			Personal relationships			Treatment			Sleep			Total score		
Total score	**0.03**	**0.1**	**Cont.**	**0.03**	**0.1**	**Cont**	**0.03**	**0.1**	**Cont**	**0.03**	**0.1**	**Cont**	**0.03**	**0.1**	**Cont**	**0.03**	**0.1**	**Cont.**	**0.03**	**0.1**	**Cont.**	0.03	0.1	Cont
Drake et al 2001[78] T vs V Children	36.4	35.9	12.5	-	-	-	18.2	17.8	8.4	17.5	21.9	5.2	11.3	15.8	5.6	35.0	34.7	7	-	-	-	24.4	24.1	8.1
Drake et al 2001[78] T vs V Toddlers	41.2	42.8	8.5	20.1	26.5	4.3	-	-	-	-	-	-	-	-	-	38.3	44.6	20.2	43.4	45.7	10.2	30.8	35.6	7.9

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Adverse effects

The different papers report adverse effects in different ways. Full details of reported adverse effects can be seen in the data extraction tables in Appendix 6. Of those conducted in children, Boguniewicz and colleagues 1998[72] (tacrolimus vs vehicle) reported only application site adverse effects. Reitamo and colleagues 2002[74] reported adverse effects experienced by at least 4 patients in either treatment group (~2%). Reitamo and colleagues 2003[75] report averse effects affecting at least 2% of any treatment group as well as herpes infections and serious adverse effects (including those unlikely to be related to treatment).* Granlund and colleagues 2001[79] do not report on adverse effects experienced by participants in their tacrolimus versus vehicle trial. Hanifin and colleagues 2001[76] report on efficacy, while Soter and colleagues 2001[77] present adverse effects from the same trial. This paper presents comprehensive data on adverse effects.
Paller and colleagues 2001[73] report 12 week adjusted incidence rates for application site adverse effects and infections. Petan and colleagues 2003[83] report on all adverse effects, both those possibly related and those unrelated to treatment.

Kawashima 1998[81] reports on skin "irritations" and infections.

Reitamo and colleagues 2002 (II)[82] report adverse effects affecting at least 5 patients in any patient group (~3%), serious adverse effects that could have been associated with treatment and infections.

Ruzicka and colleagues 1997[80] report overall adverse effects and the three most common adverse effects.

Withdrawal due to adverse effects was reported in al trials and occurred in 1.6%-5.7% of those treated with tacrolimus compared to 4.5%-12.3% of those treated with vehicle and 1.6%-3.3% of those treated with topical corticosteroids.

Pooled analyses

For the primary comparator of topical corticosteroids, data were available for meta-analyses on rate of infection and skin burning. The nature of the reported data made it impossible to separate infection rates into bacterial and viral skin infections. No difference was seen in the rate of overall skin infection rates of those treated with 0.03% or 0.1% tacrolimus and topical corticosteroid (Figure 4 and Figure 5).

Data on reported skin burning is shown in Figure 6 and Figure 7 . No attempt was made to combine other aspects of local skin irritation (such as redness, flaking, warmth etc) as there was no consistent way that these were reported. This may underestimate the amount of overall local skin irritation. For both potencies of tacrolimus and in adults and children, there was more skin burning in the tacrolimus arms of the trials (0.03% tacrolimus RR 4.17, 95% CI 3.36 to 5.18; 0.1% tacrolimus RR 3.49, 95% CI 2.33 to 5.24).

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Figure 4: Forest plot of skin infection rates in patients treated with 0.03% tacrolimus and topical corticosteroids*

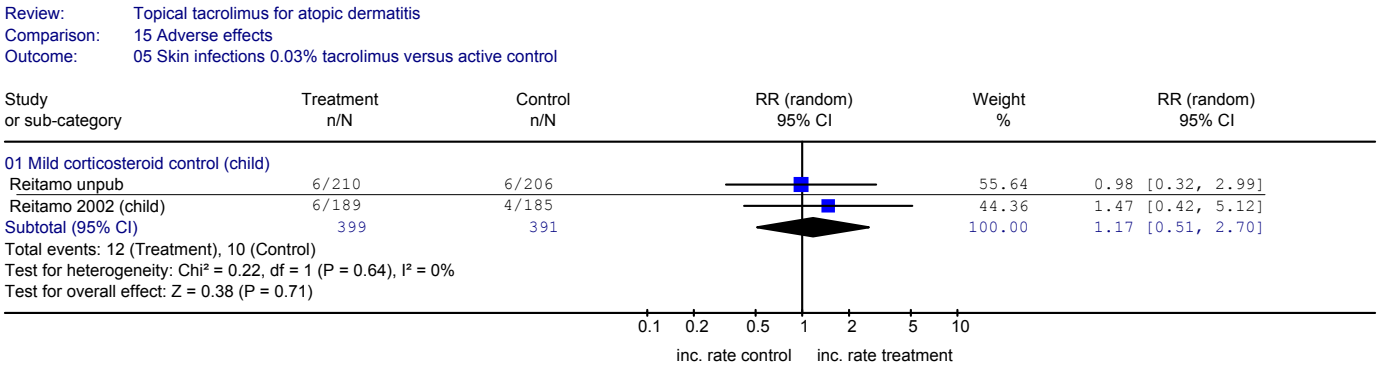

Figure 5: Forest plot of skin infection rates in patients treated with 0.1% tacrolimus and topical corticosteroids

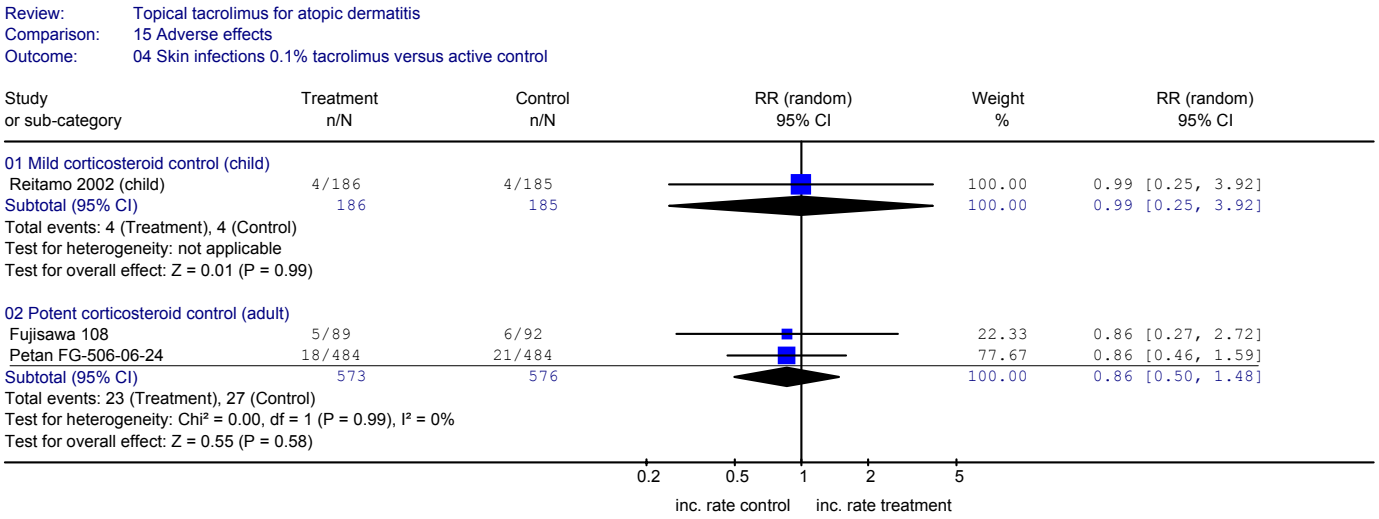

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Figure 6: Forest plot showing rates of skin burning in those treated with 0.03% tacrolimus and topical corticosteroids*

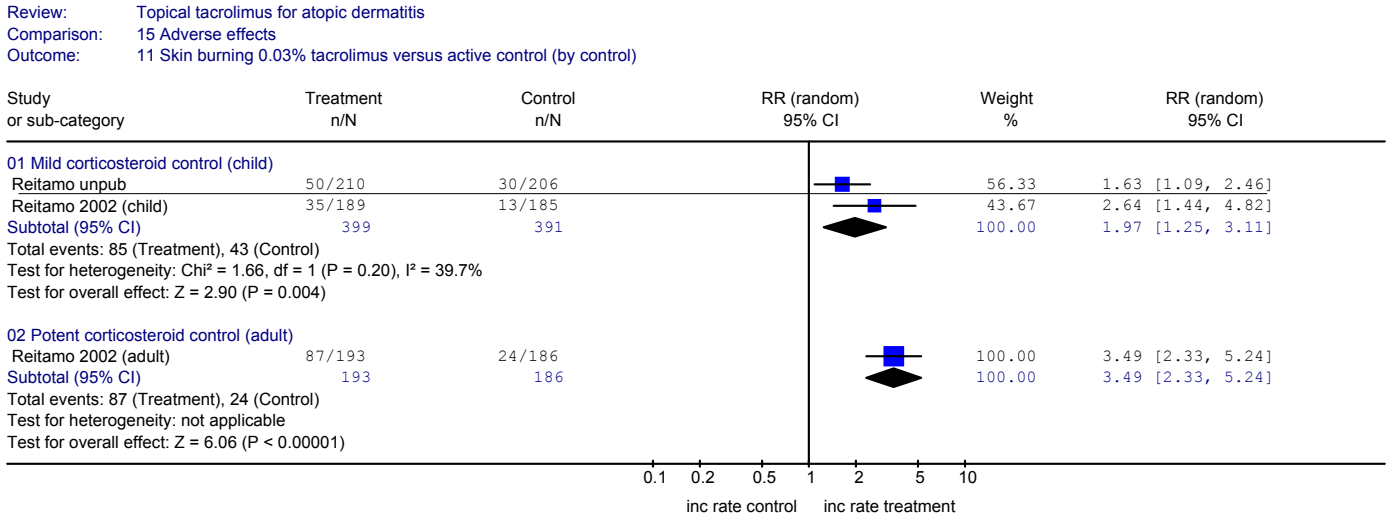
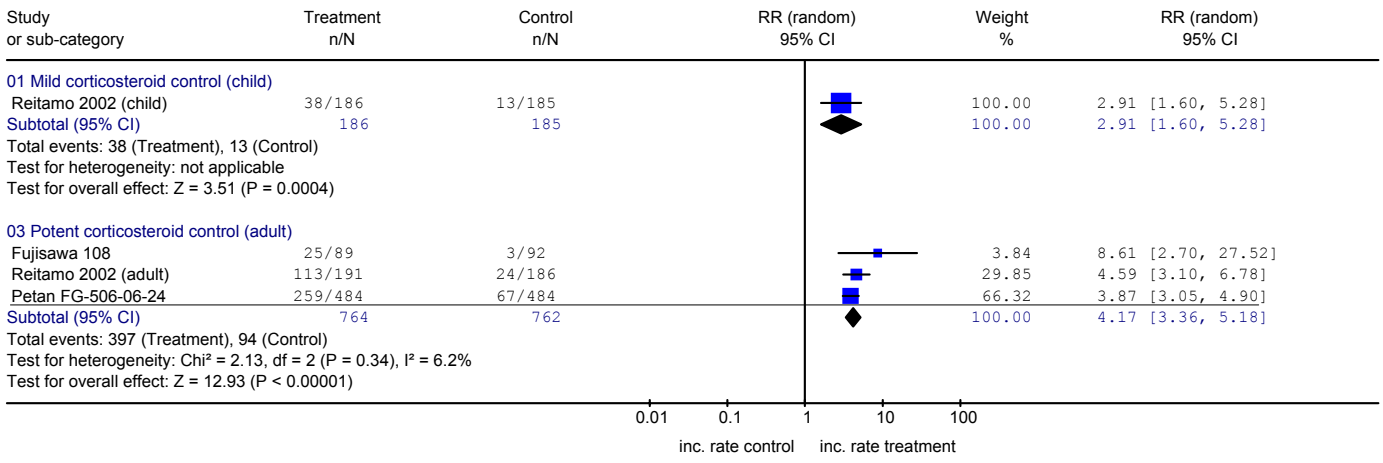


Figure 7: Forest plot showing rates of skin burning in those treated with 0.1% tacrolimus and topical corticosteroids



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Summary of effectiveness of tacrolimus

- Outcome measures focussed on global assessment of clinical improvement such as PGE (10/10 trials), EASI (7/10 trials), affected BSA (3/10 trials) and disease recurrence after clearing (1/10). Some trials also reported individual signs and symptoms scores (4/10). Clinical improvement of head and neck eczema was reported separately by 2/10 trials, while patient assessment of improvement in that area was reported in 1/10 trial. Trials also reported patient assessment of improvement (3/10), pruritus (5/10) and sleep quality (2/10). Quality of life was reported using the DLQI in adults (2/10 trials) and CDLQI in children (1/10 trial).

- Compared to vehicle alone, 0.1% and 0.03% tacrolimus were more effective in treating AD. This was the case for global measures such as >90% improvement PGE and patient centred measures such as change in pruritus score.

- Little evidence (3/10 trials) is available comparing tacrolimus to an appropriate (moderate to high) potency topical corticosteroid.

- 0.03% tacrolimus was more effective than a mildly potent topical steroid cream (1% hydrocortisone acetate) at three weeks using the measure of PGE >=90% improvement.

- Treatment with 0.1% tacrolimus did not produce significantly different results to potent steroids (0.1% hydrocortisone butyrate and 0.12% betamethasone valerate) after three weeks using PGE >=75% improvement, or other measures of global improvement.

- Comparisons of 0.1% tacrolimus with 0.03% tacrolimus are unclear. At three weeks, 0.1% tacrolimus is more effective than 0.03% tacrolimus according to 75% or better improvement with PGE and improvement in mean area under the curve for mEASI. This is not the case using the more stringent measure of 90% or better PGE improvement.

- At 12 weeks, differences were not significant according to effectiveness as measured by 75% or better improvement of PGE, change in EASI score, affected area of BSA, pruritus and patients assessment of disease control. However, 0.1% tacrolimus appeared to be significantly better according to a measure of 90% or better control on the PGE.

- Application site adverse effects such as site burning are more common with tacrolimus than controls. However, withdrawal rates due to adverse effects for tacrolimus and topical steroids are similar and low, at 3-6%, although there is a higher maximum withdrawal rate reported with tacrolimus. No difference in infection rates with tacrolimus and topical corticosteroids have been reported in trials to date.

5 Cost effectiveness of Pimecrolimus and Tacrolimus

5.1 Research Question

This technology assessment has two aims: to assess the effectiveness and the cost-effectiveness of pimecrolimus and tacrolimus for atopic eczema. This chapter addresses the second of these questions.

There are three main sections to this chapter; firstly, a systematic review of existing published literature was undertaken and the study identified critiqued. Secondly the economic model devised by PenTAG is described and the results presented. Based on the advice of clinical experts, the main comparator is topical corticosteroids. Subsidiary to this is an analysis of pimecrolimus compared to vehicle, in line with our protocol, although this will be relevant to only a very small population of people resistant to topical corticosteroid use. Finally, two submissions from industry were provided to the National Institute for Clinical Excellence by the makers of pimecrolimus (Elidel®, Novartis) and tacrolimus (Protopic®, Fujisawa) and these submissions were used by the assessment team in a number of ways. Firstly, they were examined for additional data which met the inclusion criteria for the systematic review of effectiveness or the economic model. Secondly, the economic evaluations they provided were appraised using the framework proposed by Sculpher and colleagues for decision analytic models (See section 5.6 and Appendix 8). Finally, a brief comparison of the model produced by PenTAG and those supplied by the technology sponsors was undertaken.

5.2 Systematic review of cost effectiveness

5.2.1 Search Strategy and Critical Appraisal Methods

Electronic databases were searched for published cost-effectiveness, cost-utility and cost-benefit studies of pimecrolimus or tacrolimus compared to corticosteroids, vehicle or both for treatment of mild to severe eczema cost-effectiveness studies of pimecrolimus and tacrolimus in atopic eczema. Appendix 3 details the databases and the full search strategy. We also looked for cost analyses that may inform the model. A total of 21 studies of costs, cost-effectiveness and quality of life were obtained in full text form. Of these, only one[84] was a relevant cost-effectiveness study. Most of the other studies were cost of illness studies (n=10) from the USA,[85] the UK,[9;41;86;87] Australia,[29;31;88] New Zealand,[89] and the Netherlands.[90] The framework published by Sculpher and colleagues was used as a framework for critical appraisal. [91]

5.2.2 Assessment of published cost-effectiveness study (tacrolimus vs topical steroids)

Ellis and colleagues[84] assessed the cost per disease controlled day (DCD) of treating adults with moderate to severe atopic eczema with tacrolimus or high potency topical corticosteroids in the USA.

Appendix 8 gives additional details on the appraisal of Ellis and colleagues, alongside evaluations included in the technology sponsor submissions to NICE.

Ellis and colleagues[84] compared the cost effectiveness of tacrolimus with two regimens (2 or 4 week duration) of topical corticosteroids in adults. The evaluation uses a Markov model and includes a realistic range of treatment options with tacrolimus and steroids used in first line therapy. Second line therapy with mid-potency topical steroids and oral antibiotics is included but no other systemic therapies are considered.

Effectiveness data came from selected short term trials (Hanifin and colleagues,[76] Paller and colleagues,[73] and an unspecified internal report from Fujisawa), one of which was carried out in children.[76] The total follow up for the two published studies was 12 weeks and no details were reported on methods for extrapolating data to the one year horizon of the model.

The effectiveness of the comparator was obtained from a literature review conducted on electronic sources (Medline), methods for which were not reported in detail. The effectiveness of topical steroids was adjusted (-15%) to incorporate loss of efficacy in applications subsequent to first burst of treatment. This correction was based on the judgement of the authors without further justification. No adjustment was considered for tacrolimus. Second line treatment was assumed to be ineffective although this assumption was relaxed in the sensitivity analysis. Cost effectiveness is expressed by comparison of average cost effectiveness ratios, which is inappropriate. Incremental results were recalculated from data given in the published paper and are shown in Table 22.

Table 22: Summary of results by Ellis and colleagues

Treatment	Average cost-effectiveness ratio	ICER
High potency topical corticosteroids – 2 weeks course	$9.8/DCD	Tacrolimus dominates corticosteroids 2-weeks course Corticosteroids 4-weeks course dominate tacrolimus
High potency topical corticosteroids – 4 weeks course	$6.8/DCD (min $5.85, max $7.59)	
Tacrolimus	$6.97/DCD	

Only direct medical costs were included, with resource consumption based on assumptions or trial data. Consumption of tacrolimus was assumed to be equal to that of corticosteroids (17.5gr/week) and appears low compared to estimates from the same trials (i.e. 4.1-4.5 g/day tacrolimus, 6.3-7.4 g/day steroids) or other trials (for example. 8.6-9.8 g/day, Boguniewicz[72]. Resource use was realistically valued with unit costs obtained from standard US sources. The base year for costs is not stated.

Uncertainty was addressed in a limited way. One two-way sensitivity analysis was reported in the 4-week corticosteroids strategy, with the effectiveness of second line therapy varied in the range from 0% to 100%, and costs from $0 to $300. Corticosteroids were considered more cost-effective than tacrolimus if the total cost of second line therapy was comprised between $120 (in the case of 0% efficacy of second line therapy) and $210 (in the case of 100% efficacy).

The failure of Ellis and colleagues to value potential credible differences in resource consumption between tacrolimus and corticosteroids might explain the sensitivity of their results to changes in the treatment pathways, concluding that tacrolimus is dominant if corticosteroids are used for 2 weeks and steroids are dominant if used for 4 weeks.

The analysis has significant methodological flaws and is of limited relevance to the UK.

5.3 PenTAG Cost-utility model

5.3.1 Structure of PenTAG cost-effectiveness model – active comparator

A state transition (Markov) model was developed by the authors in Microsoft Excel. The structure was informed by the expert advisory group. The primary purpose of the model was to analyse the cost-effectiveness of different treatment options involving pimecrolimus and tacrolimus for atopic eczema. Specifically, the model compares the cost and health state utility for pimecrolimus and tacrolimus against established treatment with topical corticosteroids. Several alternative approaches to using the new technologies are considered. Pimecrolimus and tacrolimus are not compared to each other. Pimecrolimus is also compared against no treatment to model the less common situation where steroids are completely contra-indicated. The base case assesses costs in 2003 and takes the perspective of the NHS.

Initially, a generic Markov model was developed which aimed to capture all the various stages within the treatment of eczema with topical corticosteroids and immunosuppressants. This is shown in Appendix 11. Due to differences in treatment options and costs, this was simplified to produce eight separate models each of which relates to treatment options in different cohorts of people with eczema. This also accommodates the licensed indications of tacrolimus (moderate to severe eczema) and pimecrolimus (mild to moderate eczema). Other indications of pimecrolimus and tacrolimus are not considered. The eight cohorts modelled are:

- Children with Mild to Moderate facial eczema
- Children with Mild to Moderate body eczema
- Children with Moderate to Severe facial eczema
- Children with Moderate to Severe body eczema

- Adults with Mild to Moderate facial eczema
- Adults with Mild to Moderate body eczema
- Adults with Moderate to Severe facial eczema
- Adults with Moderate to Severe body eczema

“Facial eczema” in this section refers to eczema on the face or other sensitive areas such as armpits, groin etc. Treatment options in these areas are affected by concerns about the risk of local adverse effects, particularly skin thinning, from topical corticosteroids. “Body eczema” in this section refers to eczema on all other areas of the body.

Children are those aged 2-16 and adults aged over 16. For adults, cost-effectiveness over one year is modelled, while for children, cost effectiveness over 14 years (childhood) is modelled to incorporate the possibility of disease resolution. Results are appropriately discounted (costs 6%, benefits 1.5%).

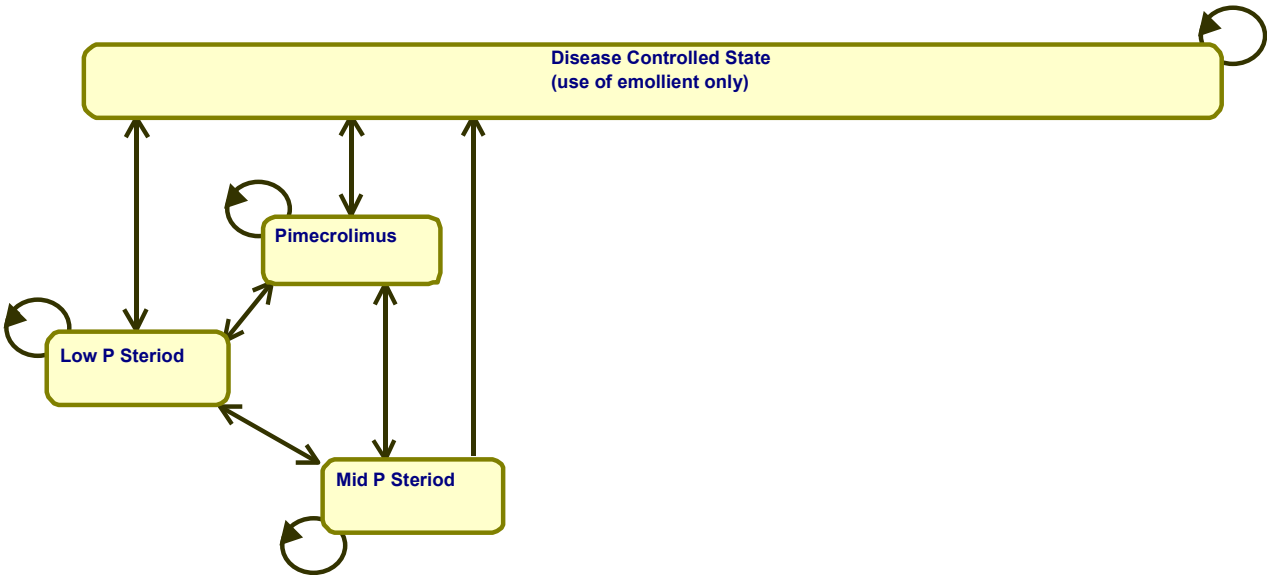
For each of these eight cohorts, the cost effectiveness of three treatment pathways are compared:

1. No new immunosuppressants (treatment with topical corticosteroids only, current standard treatment – baseline)
2. New immunosuppressants (pimecrolimus in mild to moderate eczema, tacrolimus in moderate to severe eczema) as second line treatment, topical corticosteroids as first line treatment.
3. New immunosuppressants as first line treatment with topical corticosteroids as second line treatment.

An example of the Markov models used is shown below in Figure 8. This is the model of adults with mild to moderate facial eczema. The main components of the influence diagram are treatment states (shown as boxes) and transitions (shown as arrows).

"Disease controlled state" refers to non-problematic eczema, where skin is managed with emollients alone. When the skin is not controlled and becomes problematic (through itch, redness etc.) it is treated initially with topical corticosteroids or immunosuppressants (pimecrolimus in the case of mild to moderate facial eczema in the example shown below).

Figure 8: Influence diagram for adults with mild to moderate facial eczema



Possible movements between states are shown as arrows in the influence diagram above. Transition probabilities are associated with each of these and arrow heads indicate possible transition directions. These govern the likelihood of a patient moving from one treatment state to another. The transition probabilities thus have a critical impact in determining the modelled outcome. Transition probabilities are taken from the effectiveness literature. They are set at a level between zero and one, where a value of zero renders a transition redundant whilst a level of one renders it a certainty.

Transitions between states occur at the end of each model cycle. A cycle time of four weeks has been chosen to represent the appropriate decision interval of the model. It is assumed that treatment with corticosteroids will not be for the full four weeks but for up to two weeks within this time period, and it is costed accordingly. After each period of four weeks patients move between states. Patients who have previously had their eczema controlled may find it becoming problematic and needing treatment – they will move to one of the treatment states. Three possible outcomes of treatment are possible:

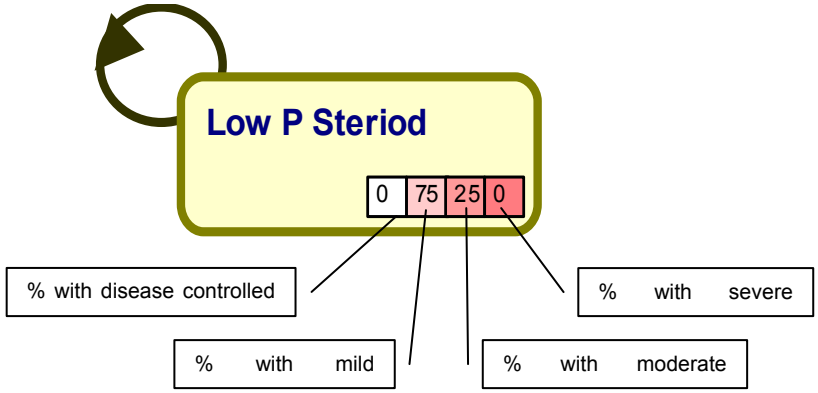
- Treatment is effective – move to disease controlled state.
- Treatment is partially effective – continue with another cycle of treatment
- Treatment is not effective – move to another active treatment.

The option to continue with another course of treatment immediately is possible for all treatments except high potency topical corticosteroids where a break is assumed between the first and second cycle of treatment (see models for body and adult eczema below). Recycling within a treatment state in this way is represented by the circling arrow in the model diagram.

Each treatment state has an associated cost and health state utility which are used to evaluate the key outcome measures from the model.

Within the model, treatment states rather than disease states are used. In order to capture levels of eczema severity within each treatment state a severity matrix is incorporated into the model which maps each treatment to four levels of eczema severity – Controlled, Mild, Moderate and Severe.

Figure 9: Example of eczema severity within each treatment state



For each treatment state a percentage of patients falling within each of the four levels of severity is assessed and represented by the matrix as shown in Figure 9 (darker background shading for increasing levels of severity). The utility values associated with each treatment state are adjusted accordingly. The weakness of this method is that the proportion of people with mild, moderate or severe eczema who are treated by, for example, low potency topical corticosteroids, has to be estimated as there are no published data on this point. Input from the advisory group was therefore sought. This affects the utility values attached to the treatment states in uneven ways, so for example, it has been assumed that 50% of adults receiving tacrolimus treatment will have moderate eczema and 50% will have severe eczema. In comparison, of adults treated with high potency topical corticosteroids, only 25% have moderate eczema, and 75% have severe eczema. The utility value of the treatment state "High Potency Topical Corticosteroids" is thus lower than the treatment state for "Tacrolimus" which may bias against the immunosuppressants. We have investigated the implications of this approach in sensitivity analyses.

Clinical assumptions

It is assumed that all patients in the model have received general advice, support and education about the correct use of emollients and active treatments, as well as how to avoid exacerbating eczema.

It has been assumed that emollients and bath oils are used extensively throughout treatment of atopic eczema in addition to any active treatments. We have not therefore included the costs of these. This will underestimate the cost saving made for children who enter the "non-recurrence" state and who will no longer need emollients.

Wet wraps have not been included in the model as there is variation in how wet wraps are used (e.g. over emollients or corticosteroids) and currently evidence of their effectiveness is lacking.

All patients are assumed to be suitable for all the treatments modelled and to use them correctly – the data informing transition probabilities is based on clinical trial data, not general use.

There is a disease relapse rate of 50% per cycle in patients who initially had their disease controlled after treatment.[84] This estimate from the published cost-effectiveness study of tacrolimus was confirmed by expert opinion that an average of a flare a month is likely.

We have used an amalgamated treatment state for systemic treatments and phototherapy. Based on clinical opinion, we have assumed that 70% of people have their condition controlled after one cycle of use. The remaining 30% undergo a further treatment cycle.

5.3.2 Childhood models

For children, all patients are aged 2 when they enter the model which then runs for 14 years (182 cycles), until the cohort is 16 years old. The child models support the possibility of resolution of eczema – shown by a "non recurrence" state which occurs in around 65% of sufferers by the age of 16. Once in this state in the model, no further eczema occurs (i.e. it is a "sink" state). This is independent of severity of eczema and treatment options.

None of the childhood models include systemic treatments (cyclosporin or systemic corticosteroids) or UV therapy. We took this step to simplify the models. Exclusion of the very small number of children who are likely to progress to systemic therapy is unlikely to introduce significant bias.

The different models of eczema in children are described in detail below.

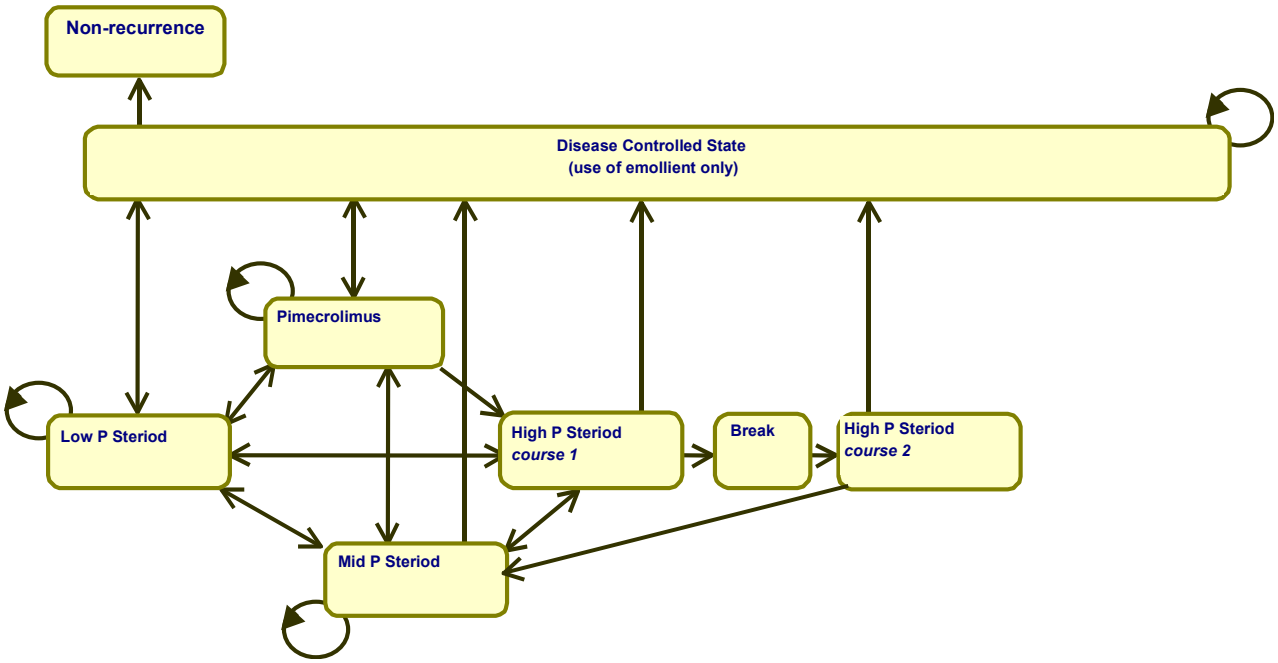
1. Children with mild to moderate eczema

Children with mild to moderate eczema do not use mid or high potency corticosteroids as a first line treatment; a step up approach is used. Tacrolimus is not used for mild to moderate eczema. Systemic treatments are not used for mild to moderate eczema.

(a) Children with mild to moderate body atopic eczema (pimecrolimus vs low/mid/high potency topical corticosteroids)

The state transition model for children with mild to moderate body eczema is shown below in Figure 10. Note that there is a break between cycles of treatment with high potency topical corticosteroids to prevent continuous use.

Figure 10: Influence diagram for children with mild to moderate body eczema



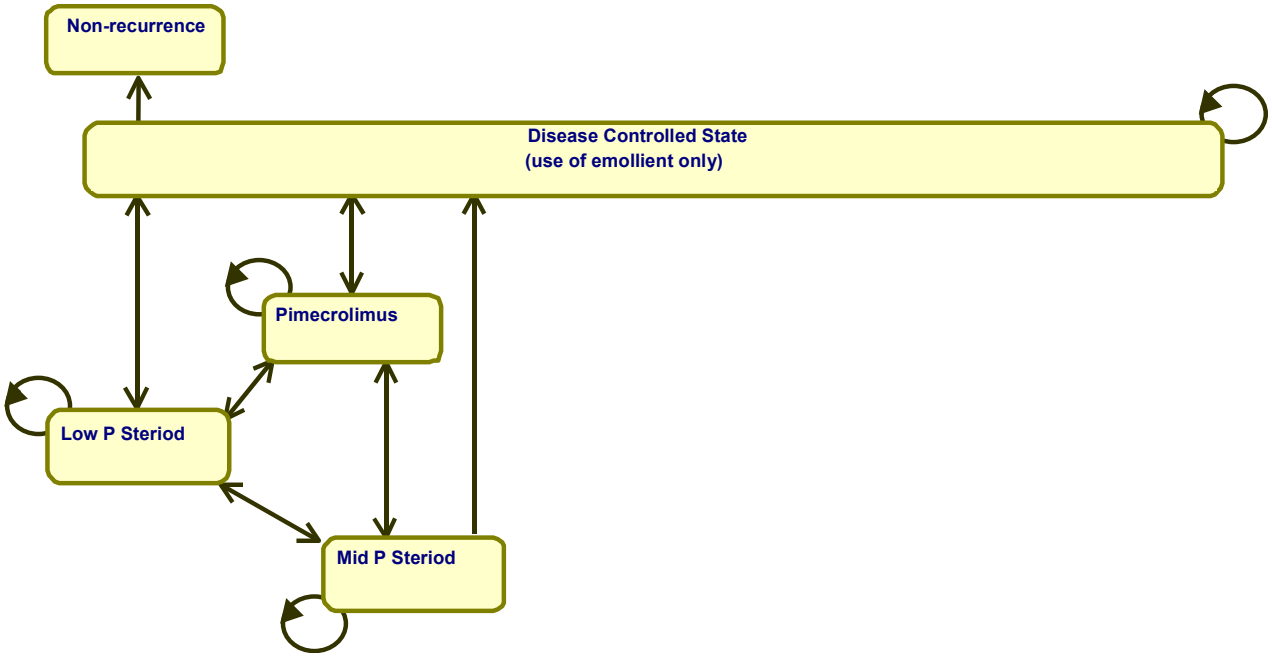
The three treatment pathways compared are:

1. Baseline – pimecrolimus is not a treatment option. Children with problem eczema receive low potency topical corticosteroids, stepping up to mid or high potency topical corticosteroids if this fails.
2. Children with problem eczema receive low potency topical corticosteroids. If this fails they step up to mid potency topical corticosteroids, or receive pimecrolimus, stepping up to high potency steroid if required.
3. Children with problem eczema receive pimecrolimus. If this fails they receive low or mid potency topical corticosteroids if this fails, stepping up to high potency steroid if required.

(b) Children with mild to moderate facial atopic eczema (pimecrolimus vs low/ mid/potency topical corticosteroids)

The state transition model for children with mild to moderate facial eczema is shown in Figure 11. High potency corticosteroids are not a treatment option.

Figure 11: Influence diagram for children with mild to moderate facial eczema



The three treatment pathways compared are:

1. Baseline – pimecrolimus is not a treatment option. Children with problem eczema receive low potency topical corticosteroids, stepping up to mid potency topical corticosteroids if this fails.
2. Children with problem eczema receive low potency topical corticosteroids. If this fails they either step up to mid potency topical corticosteroids, or receive pimecrolimus.
3. Children with problem eczema receive pimecrolimus. If this fails they receive low or mid potency topical corticosteroids.

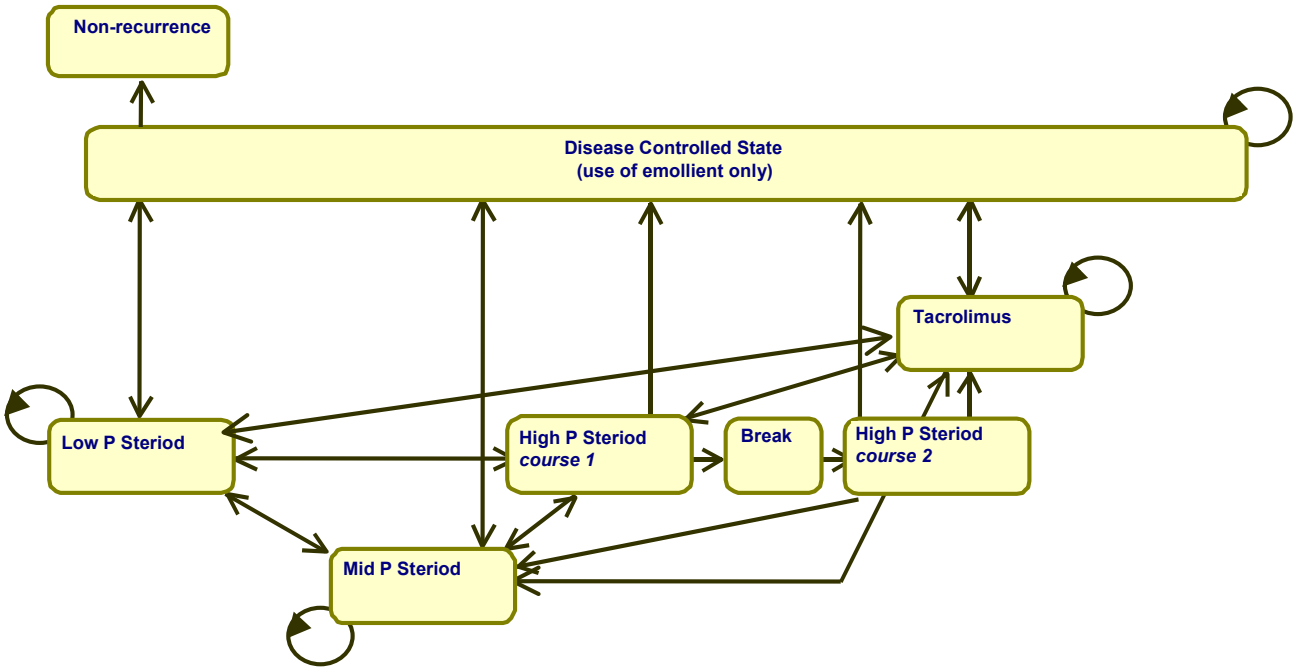
2. Children with moderate to severe atopic eczema (tacrolimus vs low/mid/high potency topical corticosteroids)

Pimecrolimus is not used in moderate to severe eczema. Use of systemic treatments for children were not modelled. This was because of the very small numbers of children receiving such treatment.

(a) Children with moderate to severe body eczema

The state transition model for children with moderate to severe body eczema is shown in Figure 12. First line treatment with high potency topical corticosteroids is not a treatment option.

Figure 12: Influence diagram for children with moderate to severe body eczema



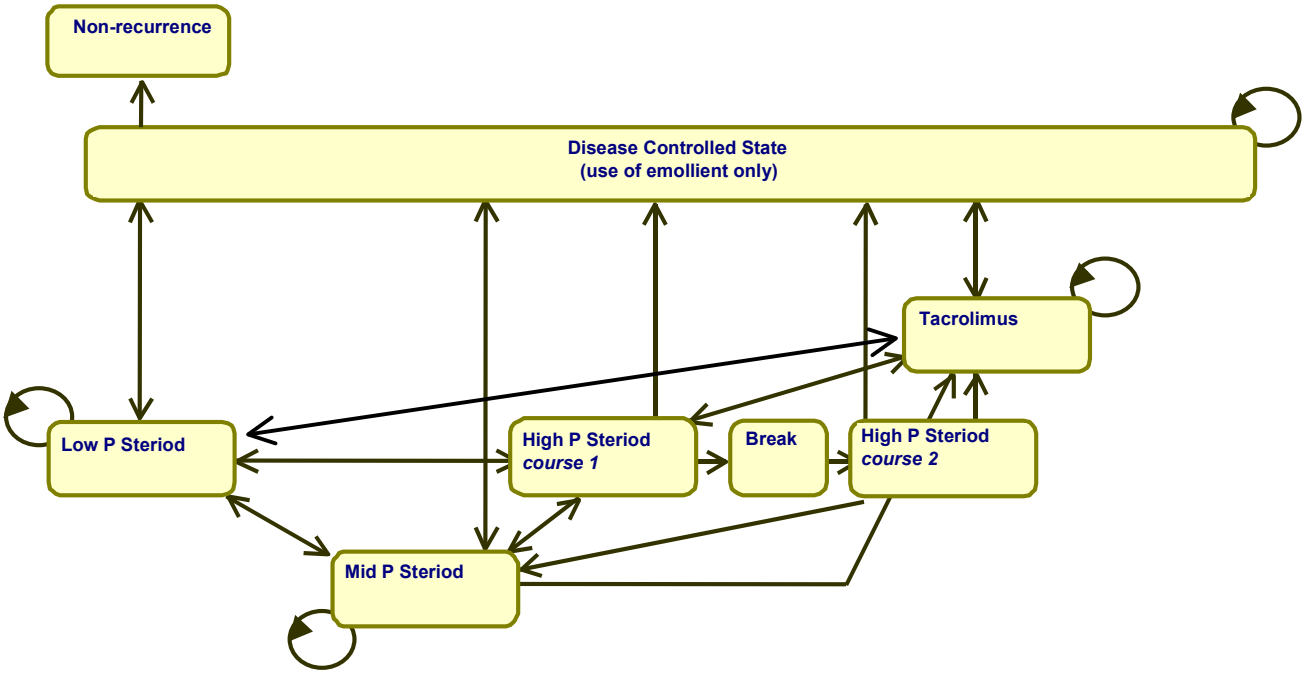
Treatment pathways compared are:

1. Baseline –tacrolimus is not a treatment option. Children with problem eczema receive low or mid potency topical corticosteroids, stepping up to mid or high potency topical corticosteroids if this fails.
2. Children with problem eczema receive low or mid potency topical corticosteroids. If this fails they step up to mid or high potency topical corticosteroids, or receive 0.03% tacrolimus.
3. Children with problem eczema receive 0.03% tacrolimus. If this fails they receive low potency topical corticosteroids, stepping up to mid or high potency topical corticosteroids if necessary.

(b) Children with moderate to severe facial atopic eczema (tacrolimus vs low/mid/high potency topical corticosteroids)

The state transition model for children with moderate to severe body eczema is shown below in Figure 13. First line treatment with high potency topical corticosteroids is not a treatment option.

Figure 13: Influence diagram for children with moderate to severe facial eczema



The three treatment pathways compared are:

1. Baseline – tacrolimus is not a treatment option. Children with problem eczema receive low or mid potency topical corticosteroids, stepping up to mid or high potency topical corticosteroids if this fails.
2. Children with problem eczema receive low or mid potency topical corticosteroids. If this fails they step up to mid or high potency topical corticosteroids, or receive 0.03% tacrolimus.
3. Children with problem eczema receive 0.03% tacrolimus. If this fails they receive low potency topical corticosteroids, stepping up to mid or high potency topical corticosteroids.

5.3.3 Adult models

The adult model runs for one year (13 cycles). Non recurrence (resolution of eczema) is not possible in the adult model.

The different adult models are described in detail below.

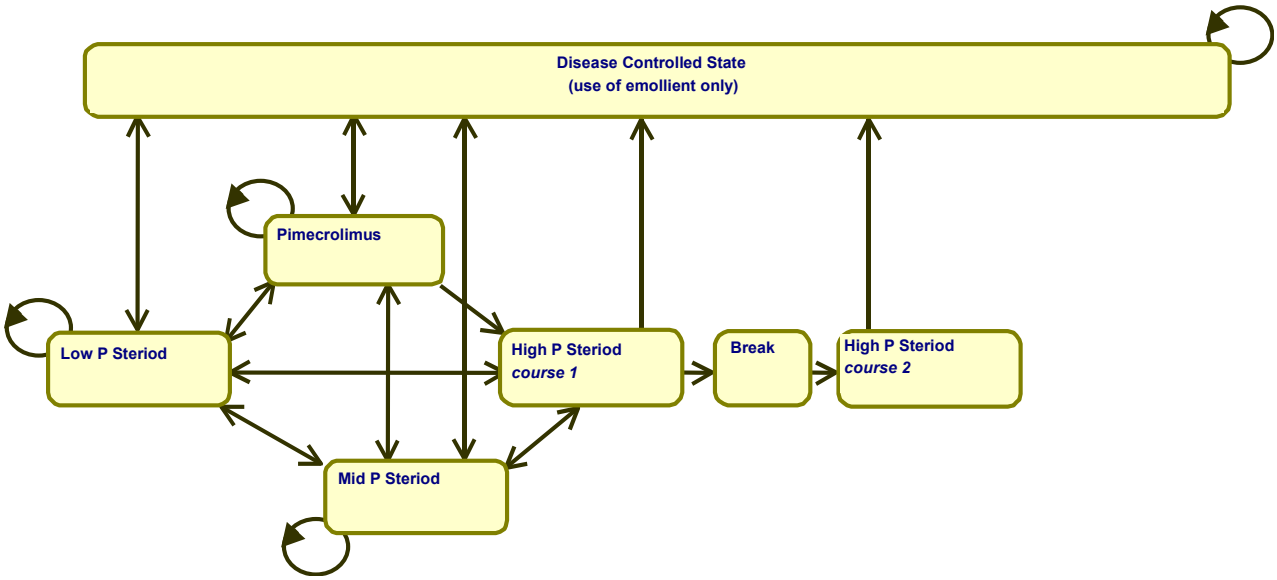
3. Adults with mild to moderate eczema (pimecrolimus vs low/mid/high potency topical corticosteroids)

First line treatment with mid and high potency corticosteroids is not a treatment option. Tacrolimus is not used in mild to moderate eczema.

(a) Adults with mild to moderate body eczema

The state transition model for adults with mild to moderate body eczema is shown below in Figure 14. First line treatment with mid and high potency corticosteroids are not a treatment option.

Figure 14: Influence diagram for adults with mild to moderate body eczema



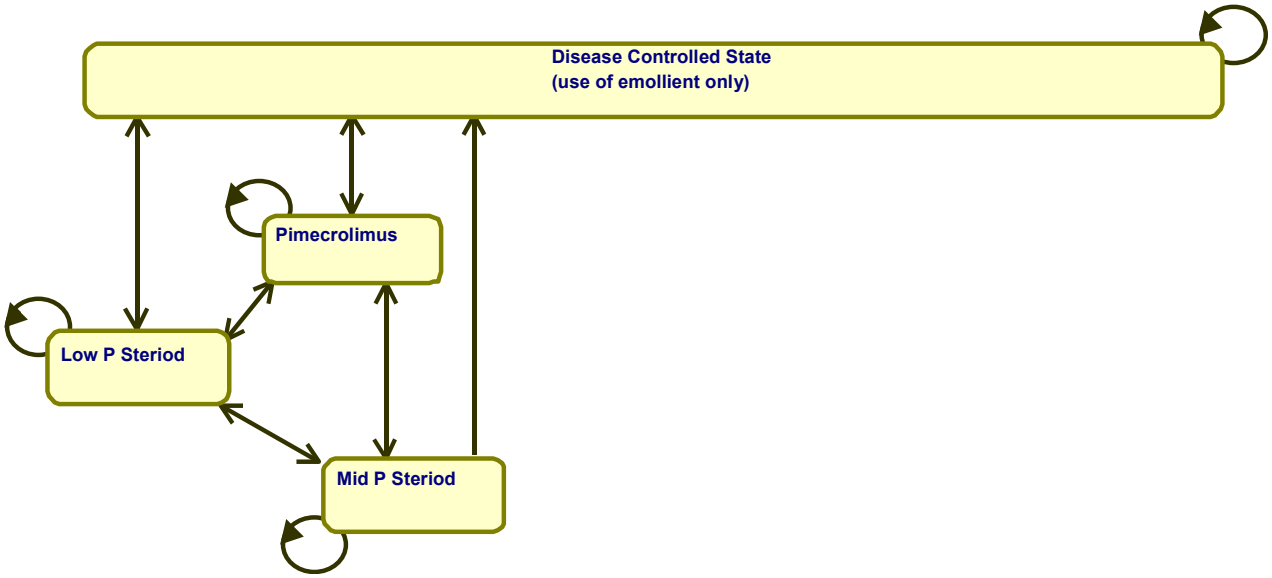
The three treatment pathways compared are:

1. Baseline – pimecrolimus is not a treatment option. Adults with problem eczema receive low potency topical corticosteroids, stepping up to mid or high potency topical corticosteroids if this fails.
2. Adults with problem eczema receive low potency topical corticosteroids. If this fails they step up to mid potency topical corticosteroids, or receive pimecrolimus.
3. Adults with problem eczema receive pimecrolimus. If this fails they receive low or mid potency topical corticosteroids if this fails.

(b) Adults with mild to moderate facial eczema (pimecrolimus vs low/mid potency topical corticosteroids)

The state transition model for adults with mild to moderate facial eczema is shown below in Figure 15. High potency corticosteroids are not a treatment option.

Figure 15: Influence diagram for adults with mild to moderate facial eczema



The three treatment pathways compared are:

1. Baseline – pimecrolimus is not a treatment option. Adults with problem eczema receive low potency topical corticosteroids, stepping up to mid potency topical corticosteroids if this fails.
2. Adults with problem eczema receive low potency topical corticosteroids. If this fails they step up to mid potency topical corticosteroids, or receive pimecrolimus.
3. Adults with problem eczema receive pimecrolimus. If this fails they receive low or mid potency topical.

4. Adults with moderate to severe atopic eczema

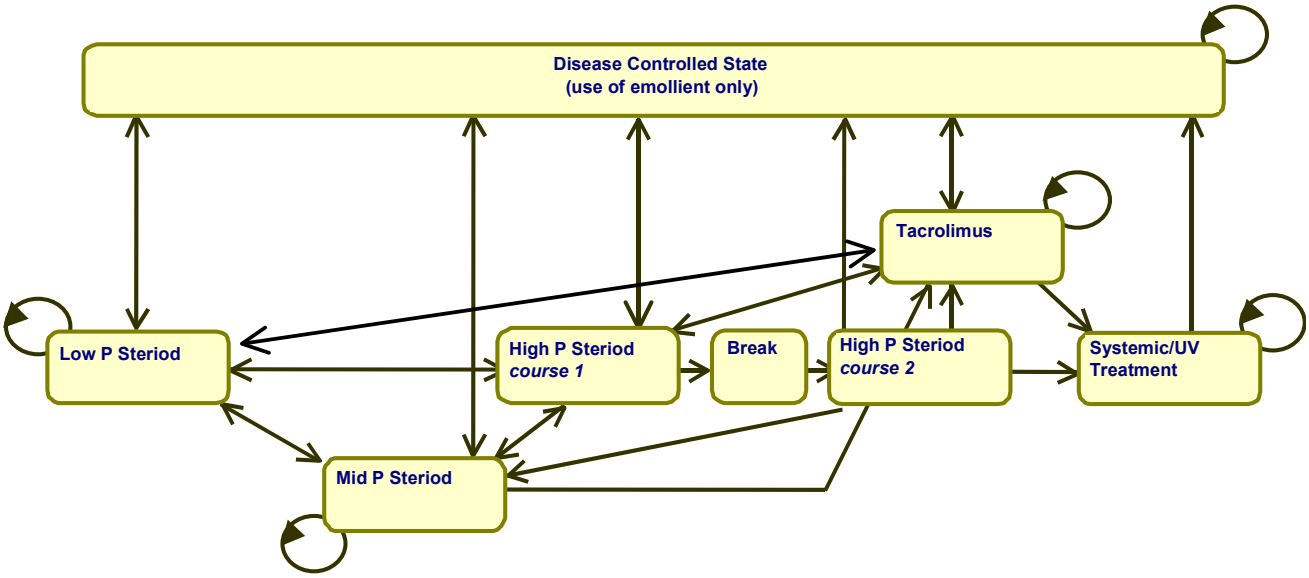
Pimecrolimus is not a treatment option for moderate to severe eczema.

Adults with moderate to severe atopic eczema may receive systemic treatments (cyclosporin or systemic corticosteroids) or phototherapy if they fail to respond to high potency topical corticosteroids or tacrolimus. These treatments have been aggregated into one treatment state. Once receiving these treatments, they will either have their eczema controlled after one cycle or continue treatment for a further cycle.

(a) Adults with moderate to severe body eczema (tacrolimus vs low/mid/high potency topical corticosteroids with systemic treatment option)

The state transition model for adults with moderate to severe body eczema is shown in Figure 16.

Figure 16: Influence diagram for adults with moderate to severe body eczema



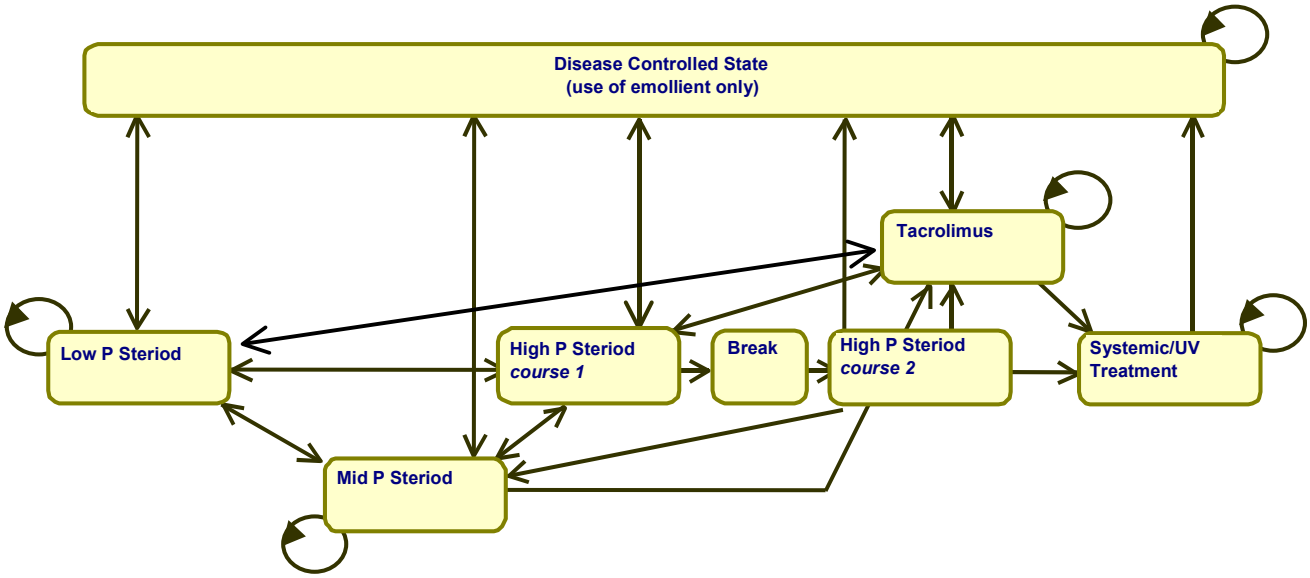
The three treatment pathways compared are:

1. Baseline – tacrolimus is not a treatment option. Adults with problem eczema receive low, mid or high potency topical corticosteroids, stepping up to mid or high potency topical corticosteroids if this fails.
2. Adults with problem eczema receive low, mid or high potency topical corticosteroids. If these fail they either step up to mid or high potency topical corticosteroids, or receive 0.1% tacrolimus.
3. Adults with problem eczema receive 0.1% tacrolimus. If this fails they receive low, mid or high potency topical corticosteroids.

(b)Adults with moderate to severe facial eczema (tacrolimus vs low/mid/high potency topical corticosteroids with systemic treatment option)

The state transition model for adults with moderate to severe facial eczema is shown in Figure 17.

Figure 17: Influence diagram for adults with moderate to severe facial eczema



The three treatment pathways compared are:

1. Baseline – tacrolimus is not a treatment option. Adults with problem eczema receive low, mid or high potency topical corticosteroids, stepping up to mid or high potency topical corticosteroids if this fails.
2. Adults with problem eczema receive low, mid or high potency topical corticosteroids. If these fail they step up to mid or high potency topical corticosteroids, or receive 0.1% tacrolimus.
3. Adults with problem eczema receive 0.1% tacrolimus. If this fails they receive low, mid or high potency topical corticosteroids.

5.3.4 Structure of PenTAG cost-utility model – emollient comparison

In a small number of cases, those with mild to moderate eczema may be unable, or unwilling to use active treatment. Their topical treatment options are therefore very limited. We have evaluated the cost-effectiveness of using pimecrolimus compared to emollients only, with moderate potency topical corticosteroids used as a "rescue therapy" for all patients with uncontrolled "problem" eczema. Two Markov models, based on the generic model for eczema, were designed to examine two cohorts of patients:

- Children with mild to moderate eczema
- Adults with mild to moderate eczema

For these models, no distinction was made between face and body eczema which were assumed to be treated in the same way.

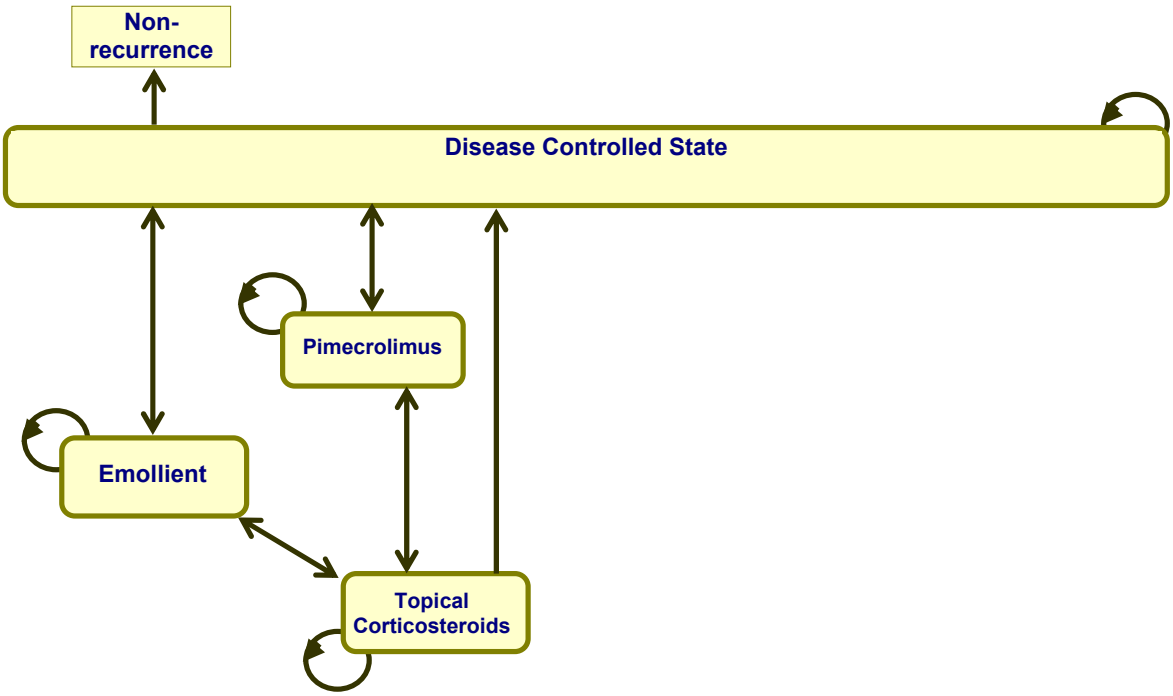
The basic structure of the model (cycle length, model duration etc.) is the same as for the models comparing active treatments.

On eczema becoming problematic, patients are treated either with pimecrolimus or continue to use emollients only. If this is effective the patient returns to the disease control state. If a moderate improvement is seen, the patient continues to use the initial treatment. If eczema shows no improvement, the patient will receive rescue therapy with a moderately potent topical corticosteroid.

Children with mild to moderate eczema (emollient comparator)

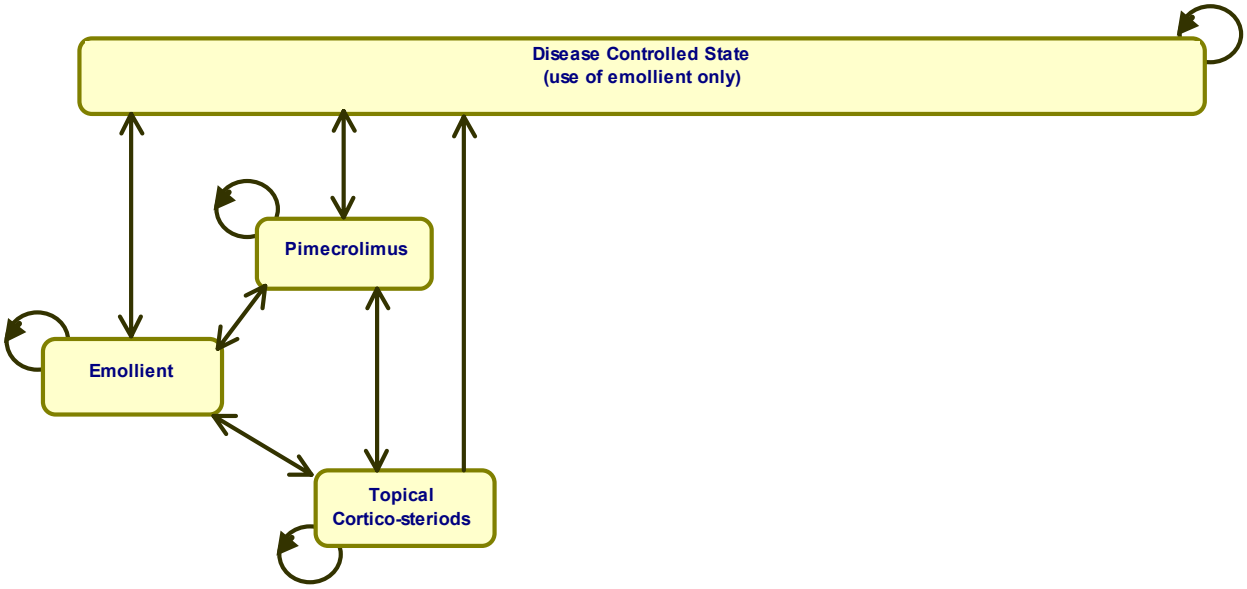
The state transition model for children with mild to moderate eczema unable or unwilling to use topical corticosteroids as a standard treatment is shown in Figure 18. Children may grow out of eczema ("non-recurrence") in the same way to the childhood models comparing pimecrolimus and steroids.

Figure 18: Influence diagram for children with mild to moderate eczema (emollient comparator, Model 5)



Adults with mild to moderate atopic eczema (emollient comparator)

Figure 19: Influence diagram for adults with mild to moderate eczema (emollient comparator, Model 6)



5.3.5 Data sources used in the cost-effectiveness models

Parameters included

The following parameters were included in the models.

- The proportion of those treated with each treatment regimen who achieve disease control, achieve partial control and continue the same treatment for another cycle, or fail treatment and receive a different treatment.

- Utility values associated with mild, moderate or severe atopic eczema. Within each treatment state, the proportion of patients with each severity of eczema is accounted for.

- The costs associated with each state (including cost of consultation in primary or secondary care and cost of prescribed treatment).

Sources of estimates

In populating the model, a hierarchy of evidence was used. Firstly, data from a good quality systematic review was sought (including data obtained as part of this report's effectiveness assessment). If these data were not available then data from a good quality individual RCT were sought. Where these were not available, large prospective, observational studies conducted in the UK were used. Finally, if no published evidence could be found, the opinion of clinical experts was sought. Values used in the models are reported in the next section. This section outlines our approach and describes data sources.

Source of transition probabilities

Effectiveness of pimecrolimus is based on a pooled analyses in this technology assessment of IGA scores of 1 (almost clear) or 0 (Clear) (see Figure 41). It is assumed that the success at four weeks (cycle length) will be the same as success at three weeks.

Effectiveness for topical corticosteroids and tacrolimus are based on RCT estimates from this technology assessment of physicians global evaluation of at least 90% ("cleared" to "excellent improvement") which has been assumed to be equivalent to the IGA score of 0-1.

As data for low potency topical corticosteroids in this population are not available as an IGA or PGE score, only as an EASI score, we have assumed low potency topical corticosteroids in mild to moderate eczema are as effective as high potency topical corticosteroids are in moderate to severe eczema.

Patients achieving a 50% improvement (moderate improvement) on the Physician's Global Evaluation after a cycle of treatment will continue to use the treatment for another cycle. Data for this are taken from individual RCTs.

Failure with any treatment means not achieving at least 50% improvement (moderate improvement) on the Physician's Global Evaluation. Where a treatment fails, a number of treatment options may be possible. We have used estimates from the expert advisory group to show what proportion of patients failing with a treatment would progress to different further treatment options.

Source of Utility Values

We have been unable to identify ideal utility data for use in the cost utility model. Such data would present the preferences of the general public in relation to health states associated with eczema in children and adults. In the absence of ideal data, several approaches have been used taken from published data, industry submissions, clinical input and a pilot "utility panel". The impact of different data sources on this element of the analysis was explored through sensitivity analyses.

Our literature search identified only one published study reporting utility values associated with eczema. Lundberg and colleagues carried out a survey of 132 patients with atopic eczema in Sweden and measured health status using a range of generic, disease specific and preference based approaches.[40] The severity of eczema was not measured using clinical severity scales such as the EASI but the mean DLQI score was 7.3, which is close to the mean value reported by Finlay in a study of DLQI in people with severe eczema as measured using the Rajka and Langeland criteria (mean DLQI 7.9).[21] No information is given on the distribution of DLQI scores. Utilities were measured using visual analogue scales (VAS), time trade off and standard gamble techniques. As expected, utility values varied by method of elicitation.

In addition to this published paper, estimates for utility in eczema were provided in the Novartis industry submission to NICE. Brazier and Stevens developed a preference based measure of quality of life in atopic dermatitis based on the Parents' Index of Quality of Life (PIQoL) which includes 45 items, 12 of which concern the impact of atopic eczema on the child. Following analysis of the 12 child centred questions, four were chosen to form the basis for a descriptive system involving 12 health states: (1) She can't join in some activities with other children (2) She is very moody (3) She cannot be comforted (4) She sleeps badly most nights. Two levels for each of these four items were established (i.e. responses yes or no), giving a total of 16 possible health states. The standard gamble method was then used to elicit preferences regarding the health states from a population sample taken from 16

sample points around England. Attempts were made to balance the sample to the population according to the 1991 census although a comparison between the sample and the national population for age group, ethnicity, gender and socio-economic statues are not reported. 150 people completed the valuation element of the study, in which they were asked to imagine they were a child in the relevant state. This survey yielded the values used in the main Novartis economic analysis. The relationship between PIQoL and IGA was established (but not reported in detail) and therefore utilities associated with IGA states estimated. Mean utility values for each IGA state were not reported and we therefore estimated utilities for mild, moderate and severe eczema from the utility associated with decrements across the four items used by Brazier and Stevens. Mild eczema was taken as the average of the median scores associated with none or one decrement, moderate eczema as the average of the median scores for two or three decrements and severe eczema as the average of the median scores for three or four decrements.

Appendix 8 of the Novartis submission reports a study carried out in Germany and Switzerland by the Medical Economics Research Group in which the EQ5D was used to measure health status in 267 people with atopic eczema. Values are given for very mild, mild, moderate and severe "flares" in eczema with corresponding values for post-flare states. Utilities associated with EQ5D states were estimated from a German population sample.

Appendix 7 of the Novartis submission reports on a patient preference study carried out by the Duke Clinical Research Institute based in the USA in 3,539 adults recruited across the internet. Five health state scenarios were developed (methods unclear) and valued using VAS. Scores were converted to utilities using an appropriate power function (utility score =1-(1-VAS score)$^{\alpha}$), giving values for mild, mild/moderate, moderate, moderate/severe and severe eczema.

We developed scenarios describing mild, moderate and severe eczema in adults using the six domains of the Dermatitis Life Quality Index (DLQI). In 1996, Finlay measured quality of life in 92 adults in the UK with severe atopic dermatitis (8 or 9 by Rajka and Langeland's criteria[23]) using the DLQI.[21] Statements in the scenario were developed using, as much as possible, the wording of the DLQI and following the distribution of domain scores reported in the Finlay study. Scenarios for moderate and mild eczema were developed by scaling down the statements in the severe scenario, while retaining the overall distribution of severity between domains. Scenarios were checked for clinical validity by two consultant dermatologists and presented to members of the Utility Panel.

The Utility Panel is a pilot collaborative project between PenTAG, the University of Southampton and the University of Sheffield. The project is funded by NHS R&D and the Health Technology Board for Scotland and aims to evaluate an approach to obtaining utilities for health states from the general public. A small initial panel of 15 lay people has been established in Exeter and trained in the standard gamble method. The members of the group meet regularly to value health state scenarios, usually developed from disease specific measures of quality of life, thereby providing an opportunity to respond to the needs of decision analytic modellers carrying out cost utility analyses. The project is currently moving to its second stage in which a larger panel will carry out valuations using the internet, with the possibility of a much larger, representative panel being established in the future. As the project is both a pilot and at an early stage, the results have been used with caution and with appropriate investigation of uncertainty in modelling. Due to the small numbers of members involved, median values are reported.

We also asked the eight members of the Expert Advisory Group (EAG) for the project to estimate the degree of impairment of quality of life experienced by people with mild, moderate or severe eczema using (a) a visual analogue scale and (b) the descriptive system

of the EQ5D. Four members of the EAG responded. Due to the small numbers involved, median values are reported.

A summary of the values available is shown in Table 23.

Table 23: Summary of utility values for different severity's of atopic eczema derived from different sources

Source Severity	Lundberg *et al*	Brazier & Stevens	MERG	Duke*	Utility Panel	EAG – EQ5D	EAG – VAS
Very mild	-	-	0.89	-	-	-	-
Mild	-	0.8625	0.76	0.9970	0.985	0.691	0.945
Mild to moderate	-	-	-	0.9876	-	-	-
Moderate	-	0.69	0.71	0.9571	0.875	0.689	0.780
Moderate to severe	-	-	-	0.8971	-	-	-
Severe	0.73 (VAS) 0.93 (TTO) 0.98 (SG)	0.59	0.60	0.8052	0.675	-0.154	0.505

using α=2.4 in the power function to convert VAS to utilities

In the cost utility models for children we used the values reported by Brazier and Stevens. These are the only available estimates for utility in childhood eczema and preferences were elicited from a UK population sample. Despite the limitations of this study, these provide the best available estimates.

Neither the MERG nor the Duke data are ideal estimates for adults as both studies used non-UK populations. We therefore used the estimates from the Utility Panel for adults. The values from the study by Lundberg and colleagues have several disadvantages. Firstly, the relationship between disease severity and utility is not clear. Given the similarity in mean DLQI score between the Lundberg and Finlay samples the utility values are surprisingly high. Secondly, the study was carried out in a non-UK sample of patients with eczema. Finally, utilities are available for only one state.

The values from the Expert Advisory Group were not used for several reasons. Firstly, using the EQ5D, values for mild and moderate eczema were similar whilst the rating for severe eczema received a rating of less than zero for three of the four respondents. This corresponds to a state that is worse than death, which is unlikely for this condition and is inconsistent with other estimates of utility. Secondly, there is very little relation between the scores given on the VAS scale and those using the EQ5D as a descriptive framework and applying population utilities.

One further limitation of all the available data relates to the wide variety of eczema that might be regarded as "severe". For example, eczema on the hands that has a profound effect on a person's ability to undertaken normal domestic, social or professional activities might be regarded as severe, due to the disability it causes, despite its limited extent. Likewise, extensive, very itchy eczema may also be regarded as severe. The same utilities are used regardless of which part of the body is affected or the extent of effect. It is likely that there will be some difference in utility on this factor, although the size of that difference could be small. It is not possible to explore these potential differences given available data. In addition, the utility values are based on the severity of eczema only and do not take into account any adverse effects of treatment. Given that topical corticosteroids are generally well tolerated, while immunosuppressants have common, though mild application site effects, this may over estimate the utility of immunosuppressants.

Aspects of care in the model

It is assumed that all patients with mild to moderate eczema (and therefore all treatment in the pimecrolimus models) would be treated in primary care.

It is assumed that 50% of tacrolimus prescriptions are provided in primary care and the rest in secondary care. According to the expert advisory group there is variation about where tacrolimus is supplied, with some localities supporting primary care supply and others maintaining secondary care supply.

It is assumed that 80% of potent corticosteroids are prescribed in primary care and 20% in secondary care.

It is assumed that all systemic treatments are undertaken in secondary care.

Resource use

Types of topical corticosteroids used have been based on commonly used preparations. There is likely to be variation between patients and nationally. Costs have been varied in sensitivity analyses.

Amount of topical corticosteroid used on the face and on the body has also been taken from local guidelines. Costs of topical corticosteroids have been calculated based on the costs of the treatment, the amount of treatment required for different body areas and the duration of treatment.

Costs of treating infections and other adverse effects have not been included in the studies. There is no evidence of different incidence of infections between the different treatment pathways and incidence is low in all cases. We have therefore assumed that this is cost neutral. This is a limitation of the model and we have varied the costs of treatment in sensitivity analyses to explore costs uncertainties.

While cycle length is four weeks, reflecting a reasonable amount of time between consultations, treatment with topical corticosteroids is not normally constant for such as long period of time. This is handled by costing only two weeks continual treatment with topical corticosteroids in each treatment state per cycle.

It is usually assumed that topical corticosteroid treatment requires twice daily application. However, a recent systematic review suggested that there was little, if any benefit to twice daily over once daily topical corticosteroid use.[20] We have therefore run the economic model with both.

As no equivalent data is available from the UK, frequency of visits to primary and secondary care was taken from a study of 48 children with atopic eczema in Australia,[29] data from which was confirmed by the Expert Panel. These have been adjusted to take account of the proportion of treatment provided in primary and secondary care stated above.

Discounting

Costs were discounted at 6% and benefits at 1.5% in accordance with HM Treasury Guidance. The effect of new guidance, discounting both costs and benefits at 3.5% was also explored.

5.3.6 Dealing with uncertainty

One way sensitivity analysis

One way sensitivity analyses were undertaken to establish which estimates have the greatest impact on the incremental cost utility for pimecrolimus and tacrolimus. The sensitivity analyses focussed on:

- Effectiveness of tacrolimus and pimecrolimus
- Effectiveness of topical corticosteroids
- Balance of prescription within primary and secondary care
- Cost of creams / ointments.
- Utility values for controlled, mild, moderate and severe eczema

Probabilistic Simulation

A probabilistic Monte Carlo simulation was developed to explore the impact on cost effectiveness of parameter uncertainty in the underlying model inputs. In the stochastic approach, the Markov model is run for 1000 trials with key input values randomly drawn from probability density functions for each trial. In these simulated trials, values were sampled for utilities, costs, and transition probabilities using the following distributions.

- Utility Values – sampled from a beta distributions since these values are bounded on the 0-1 scale (assuming positive values). Alpha and beta parameters for the distribution were derived using standard formula from the observed means (Table 23) and standard deviations. Standard deviations were calculated using the pooled data from Brazier supplied in the Novartis industry submission.

- Cost Values – sampled from lognormal distributions (to represent the essentially positive skewed nature of cost data). Parameter values for mean were derived from aggregated cost data (Table 32). Standard deviation was estimated using author's assumptions about the variance in the amount of resources used for each treatment regimen.

- Transition Probabilities – sampled from beta distributions since these probabilities are bounded by 0-1 limits. Alpha and beta parameters were derived using standard formula from mean and standard deviation measures. Mean values were based on clinical outcome data (Table 9 and Table 17). Standard deviation was derived from author's assumptions based on an assessment of the likely variability in outcome.

Results are presented graphically.

5.4 Data used in the model

Table 24 below shows the data for probability of transition between states, together with the source of the data used and the justification for using this source. The table header "Disease controlled" refers to the probability that problematic eczema will be controlled in each cycle. The table header "moderate improvement" refers to probability that problematic eczema will show improvement but not be controlled after one cycle of treatment, and will lead to a further cycle of treatment being undertaken.

Where results are reported at week three, we have assumed that this will be the same as at four weeks. The transitions used for facial eczema come from the trial by Petan and colleagues[83] and IGA score is reported at 3 months. Other outcomes are reported after

each month. As the results are similar at months one and three for other outcomes (for example tacrolimus improved eczema by 60%+ in 73.8% of patients at month one, and 72.6% of patients at month three[83]) we have assumed that IGA score will also be similar at month one. We have not used pooled data for tacrolimus because the pooling was not possible across the most appropriate outcome. We have therefore relied on data from individual trials.

Table 24: Effectiveness data used for transition probabilities

Disease controlled – body	Value	Source	Justification
Pimecrolimus in mild to moderate eczema	0.249	Pooled estimate for IGA 0-1 at 3 weeks (Figure 41).	Pooled data from RCTs. Best available evidence.
Low potency corticosteroid in mild to moderate eczema	0.52	Assumption that effectiveness is the same as high potency TS in moderate to severe eczema.	No data available in comparable population available for this. Expert group consulted.
Low potency topical corticosteroid in moderate to severe eczema	0.147	Pooled estimate for PGE 90%+ improvement at three weeks (Figure 2)	Pooled data from RCTs. Best available evidence.
Mid potency topical corticosteroid in mild to moderate eczema	0.6	Assumption. Estimate based on evidence for low and high potency corticosteroids	No data available in comparable population. Expert group consulted.
Mid potency topical moderate to severe eczema	0.35	Assumption. Estimate based on evidence for low and high potency corticosteroids	No data available in comparable population. Expert group consulted.
0.1% Tacrolimus in moderate to severe eczema in adults	0.374	PGE 90%+ improvement at 3 weeks from Reitamo 2002 (II)[82]	Large, good quality RCT (n=570) in adults with relevant outcome.
0.03% Tacrolimus in moderate to severe eczema in children	0.385	PGE 90%+ improvement at three weeks from Reitamo 2002[74]	Large, good quality RCT (n=560) in children with relevant outcome.
High potency topical corticosteroid in moderate to severe eczema	0.52	PGE 90%+ improvement at 3 weeks from Reitamo 2002 (II)[82]	Large, good quality RCT (n=570) in adults with relevant outcome.
High potency topical corticosteroid in mild to moderate eczema	0.7	Assumption. Estimate based on evidence for low and high potency corticosteroids	No data available in comparable population. Expert group consulted.
Emollient only use	0.057	Pooled data for IGA 0-1 at three weeks (Figure 41)	Best available data.
Systemic treatment for severe eczema	0.7	Clinician estimate	No data available in comparable population Best estimate for 4 weeks treatment
Moderate improvement (IGA 3) – requiring second course - body			
	Value	**Source**	**Justification**
0.03% tacrolimus in moderate to severe eczema (adults)	0.154	Hanifin 2001[76]	Large, combined RCTs (n=632) in adults reporting PGE scores separately
0.03% tacrolimus in moderate to severe eczema (children)	0.171	Reitamo 2002[74]	Large good quality RCT in children (n= 560) reporting PGE scores separately
0.1% tacrolimus in moderate to severe eczema (adults)	0.157	Hanifin 2001[76]	Large, combined RCTs (n=632) in adults reporting PGE scores separately
0.1% tacrolimus in moderate to severe eczema (children)	0.115	Reitamo 2002[74]	Large good quality RCT in children (n= 560) reporting PGE scores separately
1% pimecrolimus in mild to moderate eczema	0.59	Eichenfield 2002	Large combined RCTs (n=403) reporting IGA score separately
Low potency topical corticosteroids in mild atopic eczema	0.18	Assume values for low potency TS in mild eczema same as for high potency in severe eczema	No data available. Expert group consulted.

(Cont.)

Mid potency topical corticosteroids in moderate atopic eczema	0.18	Assume effectiveness in moderate eczema same as for high potency in severe eczema	No data available, Expert group consulted
High potency topical corticosteroids in severe atopic eczema	0.183	Average of results in Petan 2003[83] and Reitamo 2002[74]	Large RCTs (n=975, n=560) reporting relevant PGE score.
Emollient only use	0.478	Weighted average for IGA 3 from Eichenfield[64] and Luger[69]	Large RCTs with IGA presented separately.
Disease controlled - face			
Tacrolimus 0.1%	0.632	90% + IGA Petan 2003[83]	Large RCT (n=975) reporting IGA scores and results for face and body separately.
Mild TS	0.350	90% + IGA Petan 2003[83]	Large RCT (n=975) reporting IGA scores and results for face and body separately.
Moderate improvement – continue for another cycle - face			
Tacrolimus 0.1%	0.080	50-75% IGA Petan 2003[83]	Large RCT (n=975) reporting IGA score separately and for face alone
Mild TS	0.172	50-75% IGA Petan 2003[83]	Large RCT (n=975) reporting IGA score separately and for face alone

The transition probabilities shown in Table 24 show successful treatment (eczema controlled), and partially successful treatment that will lead to another cycle of the same treatment being undertaken. The remainder of patients will be treatment failures. For these patients a change of active treatment is likely. However, a range of different treatment options that may be given. For example, failure of mild potency topical corticosteroids on mild to moderate facial eczema ,may result in a prescription of mid potency corticosteroids or pimecrolimus. We asked the expert advisory group for views on the proportion of people failing with a particular treatment who would be offered each further treatment option. Options were obtained both for the baseline scenario in which new immunosuppressants are not a treatment option, and for situations where pimecrolimus or tacrolimus could be offered. In order to simplify the model, only one immunosuppressant was available in each model, therefore pimecrolimus is available as a treatment option in the models of moderate to severe eczema and tacrolimus is available in the models of mild to moderate eczema. We did not establish different sets of assumptions for subsequent treatment options in adults and children after treatment failure. The results are shown in Table 25 to Table 30.

Table 25: Likelihood of patients being offered different treatment options having failed a treatment for moderate to severe facial eczema (immunosuppressants available).

Treatment options	Value
Failed treatment with high potency topical corticosteroids	
Tacrolimus	0.9
Systemic treatments	0.1
Failed treatment with mid potency topical corticosteroids on the face	
Tacrolimus	0.8
High potency topical corticosteroids	0.2
Failed treatment with low potency topical corticosteroids	
Tacrolimus	0.85
Mid potency topical corticosteroids	0.1
High potency topical corticosteroids	0.05
Failed treatment with tacrolimus	
Low potency topical corticosteroids	0.4
Mid potency topical corticosteroids	0.3
High potency topical corticosteroids	0.3

Table 26: Likelihood of patients being offered different treatment options having failed a treatment for moderate to severe body eczema (immunosuppressants available).

Treatment options	Value
Failed treatment with high potency topical corticosteroids	
Tacrolimus	0.4
Alternative topical corticosteroid	0.5
Systemic treatments	0.1
Failed treatment with mid potency topical corticosteroids	
Tacrolimus	0.1
High potency topical corticosteroids	0.9
Failed treatment with low potency topical corticosteroids	
Tacrolimus	0.1
Mid potency topical corticosteroids	0.3
High potency topical corticosteroids	0.6
Failed treatment with tacrolimus	
High potency topical corticosteroids	0.7
Mid potency topical corticosteroids	0.2
Systemic treatment	0.1

Table 27: Likelihood of patients being offered different treatment options having failed a treatment for mild to moderate facial eczema (immunosuppressants available).

Treatment options	Value
Failed treatment with high potency topical corticosteroids	
Low potency topical corticosteroids	0.7
Systemic treatments	0.3
Failed treatment with mid potency topical corticosteroids	
Pimecrolimus	0.8
High potency topical corticosteroids	0.2
Failed treatment with low potency topical corticosteroids	
Pimecrolimus	0.85
Mid potency topical corticosteroids	0.1
High potency topical corticosteroids	0.05
Failed treatment with pimecrolimus	
Low potency topical corticosteroids	0.5
Mid potency topical corticosteroids	0.4
High potency topical corticosteroids	0.1

Table 28: Likelihood of patients being offered different treatment options having failed a treatment for mild to moderate body eczema (immunosuppressants available).

Treatment options	Value
Failed treatment with high potency topical corticosteroids	
Alternative high potency corticosteroid	0.9
Systemic treatments	0.1
Failed treatment with mid potency topical corticosteroids	
High potency topical corticosteroids	0.8
Pimecrolimus	0.2
Failed treatment with low potency topical corticosteroids	
Pimecrolimus	0.1
Mid potency topical corticosteroids	0.3
High potency topical corticosteroids	0.6
Failed treatment with pimecrolimus	
Low potency topical corticosteroids	0.1
Mid potency topical corticosteroids	0.4
High potency topical corticosteroids	0.5

Table 29: Likelihood of patients being offered different treatment options having failed a treatment for mild to moderate facial eczema (immunosuppressants not available).

Treatment options	Value
Failed treatment with high potency topical corticosteroids	
Low potency topical corticosteroids	0.7
Systemic treatments	0.3
Failed treatment with mid potency topical corticosteroids	
High potency topical corticosteroids	0.8
Alternative mid potency topical steroid	0.2
Failed treatment with low potency topical corticosteroids	
Mid potency topical corticosteroids	0.9
High potency topical corticosteroids	0.1

Table 30: Likelihood of patients being offered different treatment options having failed a treatment for mild to moderate body eczema (immunosuppressants not available).

Treatment options	Value
Failed treatment with high potency topical corticosteroids	
Alternative high potency corticosteroids	0.9
Systemic treatments	0.1
Failed treatment with mid potency topical corticosteroids	
High potency topical corticosteroids	0.2
Different mid potency topical steroid	0.8
Failed treatment with low potency topical corticosteroids	
Mid potency topical corticosteroids	0.4
High potency topical corticosteroids	0.6

Table 31: Utility values used in the economic model

Health State	Utility	Source	Justification
Non recurrence of eczema (children only)	1	Assumption	Utility values for children not available. Assume that once eczema does not recur, children have a value that is similar to perfect health.
Disease controlled (emollient only used) children	0.98	Assumption	Utility values for children not available. Assume that need for continued preventative measures will cause small decrease in health state – more difficulty than for adults.
Disease controlled (emollient only used) adults	0.99	Assumption	Utility values for adults with DCS not available. Assume that need for continued preventative measures will cause small decrease in health state.
Mild atopic eczema in children	0.8625	Brazier and Stevens, Novartis submission	Only available estimate of utility in children with eczema
Moderate atopic eczema in children	0.69	Brazier and Stevens, Novartis submission	Only available estimate of utility in children with eczema
Severe atopic eczema in children	0.59	Brazier and Stevens, Novartis submission	Only available estimate of utility in children with eczema
Mild atopic eczema in adults	0.985	Utility panel	UK non- patient values for adults.
Moderate atopic eczema in adults	0.875	Utility panel	UK non- patient values for adults.
Severe atopic eczema in adults	0.675	Utility panel	UK non- patient values for adults.

Table 32: Costs used in the economic model

Item	Cost	Source	Justification
DRUG COSTS			
Cost of tacrolimus 0.03% (Protopic®, Fujisawa)	60 g = £36.94	http://www.BNF.org (accessed 7/10/03)	Standard UK prices
Cost of tacrolimus 0.1% (Protopic®, Fujisawa)	60 g = £41.04	http://www.BNF.org (accessed 7/10/03)	Standard UK prices
Cost of pimecrolimus 1% (Elidel®, Novartis)	60 g = £37.41	http://www.BNF.org (accessed 7/10/03)	Standard UK prices
Cost of mild topical corticosteroids			
Hydrocortisone 1% (non proprietary)	15 g = 37p	http://www.BNF.org (accessed 7/10/03)	Standard UK prices
Cost of moderately potent topical corticosteroids			
Clobetasone butyrate 0.05% (eg Eumovate®)	100 g = £5.68	http://www.BNF.org (accessed 7/10/03)	Standard UK prices
Cost of potent topical corticosteroids			
Betamethasone valerate 0.1% (eg Betnovate®)	100 g = £4.35	http://www.BNF.org (accessed 7/10/03)	Standard UK prices
Cost of emollients (for emollient comparator model)			
Emollients	0.001	http://www.BNF.org (accessed 7/10/03)	Standard UK data
SYSTEMIC TREATMENT COSTS			
Cyclosporin	£109.20	Fujisawa submission	Best available UK estimate.
UV treatment	£76.86	Fujisawa submission	Best available UK estimate
PERSONNEL COSTS			
9.36 minute GP consultation	£14	Unit Costs of Health and Social Care[92] Cost without qualification costs, and direct staff costs	Standard UK prices
Dermatology outpatient consultation	£60	Unit Costs of Health and Social Care[92]	Standard UK prices
Dermatology inpatient day costs	£232	Unit Costs of Health and Social Care[92]	Standard UK prices

Table 33: Other assumptions used in the model

Assumption	Value	Source	Justification
Number of GP visits (annually) – mild eczema	4.0	Survey of 48 Australian children in outpatient clinics Su et al 1997[29]	No UK data available. Expert panel consulted.
Number of GP visits (annually) – moderate eczema	7.0	Survey of 48 Australian children in outpatient clinics Su et al 1997[29]	No UK data available. Expert panel consulted.
Number of GP visits (annually) – severe eczema	11.7	Survey of 48 Australian children in outpatient clinics Su et al 1997[29]	No UK data available. Expert panel consulted.
Number of consultant visits (annually) – mild eczema	2.7	Survey of 48 Australian children in outpatient clinics Su et al 1997[29]	No UK data available. Expert panel consulted.
Number of consultant visits (annually) – moderate eczema	3.2	Survey of 48 Australian children in outpatient clinics Su et al 1997[29]	No UK data available. Expert panel consulted.
Number of consultant visits (annually) – severe eczema	6.5	Survey of 48 Australian children in outpatient clinics Su et al 1997[29]	No UK data available. Expert panel consulted.
Amount of treatment used per cycle		Exeter RD&E guidelines for amount of corticosteroids used. Assume pimecrolimus and tacrolimus are the same. Amounts halved for child model.	Based on advised amounts to be prescribed for correct use of corticosteroids. No data for tacrolimus and pimecrolimus but likely to be similar..
Face	30g		
Hands	60g		
Scalp	60g		
Arms and legs	200g		
Body	200g		
Groin and perineum	30g		
Average affected BSA in moderate to severe eczema (adults)	33%	Mean amount reported by included RCTs	Best estimate available for relevant populations.
Average affected BSA in moderate to severe eczema (children)	23%	Mean amount reported by included RCTs	Best estimate available for relevant populations.
Average affected BSA in mild to moderate eczema (adults)	17%	Mean amount reported by included RCTs	Best estimate available for relevant populations.
Average affected BSA in mild to moderate eczema (children)	25%	Mean amount reported by included RCTs	Best estimate available for relevant populations.

5.5 Baseline results of cost effectiveness: active comparator

Cost effectiveness was estimated for each of the eight population groups separately. For each, incremental cost effectiveness ratios were calculated for the new topical immunosuppressant drugs as first line treatment and as second line treatment compared to current standard practice of topical corticosteroids alone. In the tables below, all results from the models have been rounded to whole numbers.

5.5.1 Cost effectiveness in Children

The total costs for the modelled cohort of 1000 children with mild to moderate atopic eczema after 14 years are shown in Table 34 and Table 35. Table 34 shows the cost-utility analysis for children with eczema on the body (non-sensitive areas i.e. not on the face etc.) while Table 35 shows the costs utility analysis for children with atopic eczema affecting sensitive areas such as the face. It should be remembered that these results take no account of the underlying parameter uncertainty, which is assessed in Section 5.4.2.

Table 34: Summary of cost utility analysis for pimecrolimus in children with mild to moderate body eczema (model 1a)

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (Cost/QALY)
No pimecrolimus	355,513	11,845	-	-	-
Pimecrolimus – second line	435,649	11,823	80,136	-22	Corticosteroid dominates
Pimecrolimus – first line	1,797,962	11,705	1,442,449	-140	Corticosteroid dominates

Table 35: Summary of cost utility analysis for pimecrolimus in children with mild to moderate eczema facial eczema (model 1b)

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (Cost/QALY)
No pimecrolimus	248,468	11,866	-	-	-
Pimecrolimus – second line	423,184	11,715	174,716	-151	Corticosteroid dominates
Pimecrolimus – first line	723,812	11,736	475,344	-130	Corticosteroid dominates

In mild to moderate eczema affecting face and body, pimecrolimus costs more and confers slightly fewer QALYs, although these numbers are very small indeed given that they are for the whole cohort over the 14 years of the model. As would be expected, using pimecrolimus as a second line treatment is not as expensive as using it as a first line treatment but in neither case would it be cost-effective based on point estimates alone. The similarity in cumulative benefits between strategies emphasises the importance of taking parameter uncertainty into account and we consider the deterministic analyses to be relatively uninformative.

The cost utility analysis for children with moderate to severe eczema is shown in Table 36. The costs utility analysis for children with moderate to severe eczema on sensitive areas such as the face is shown in Table 37. Again, these results take no account of underlying uncertainty in the data.

Table 36: Summary of cost utility analysis for tacrolimus in children with moderate to severe body eczema (Model 2a)

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (Cost/QALY)
No tacrolimus	956,466	10,850	-	-	-
Tacrolimus – second line	1,209,393	10,868	252,927	18	14,175
Tacrolimus – first line	2,446,337	11,015	1,489,871	164	9,083

Table 37: Summary of cost utility analysis for tacrolimus in children with moderate to severe facial eczema (Model 2b)

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (Cost/QALY)
No tacrolimus	624,102	10,997	-	-	-
Tacrolimus – second line	1,129,347	10,996	505,244	-1	Corticosteroid dominates
Tacrolimus – first line	1,737,132	11,028	1,113,030	31	35,669

For children with moderate to severe body eczema, the cost effectiveness of tacrolimus is in the range likely to be considered by decision makers as acceptable as first and second line treatment. In children with moderate to severe facial eczema, tacrolimus may be considered cost effective as first line treatment but not as second line treatment. This anomaly is due to the very similar levels of QALYs conferred by the different treatment regimen. Again, considering these are modelled over ten years for a cohort of 1000, the differences are marginal and the deterministic analysis is insufficient.

The similarity in expected benefits across treatment options in almost all cases, with both new immunosuppressants, raises the likelihood of alternative conclusions given plausible variation in input values.

5.5.2 Sensitivity analyses for child models

One way sensitivity analyses for a range of input values were used to examine the uncertainty associated with individual inputs. These were expressed as a percentage change in the cost per QALY for each of the three treatment options (corticosteroids only, immunosuppressant as first line, immunosuppressant as second line treatment) against base case outputs. The effect of changes in input values is shown independently for each of the three possible treatment options. Graphs are shown in Appendix 13. In these deterministic analyses, all models appeared to be particularly sensitive to the values for the cost of immunosuppressants. In addition, separate models showed sensitivity (>10% change in cost per QALY from baseline) for the inputs shown with a tick (✓) in Table 38.

Table 38: Results of one way sensitivity analyses of economic models for children

	Mild/moderate body eczema	Mild/moderate facial eczema	Moderate/severe body eczema	Moderate/severe facial eczema
Utility value for Non-recurrence	x	x	x	x
Utility value for disease controlled state	x	x	x	x
Utility value for mild eczema	x	x	N/A	N/A
Utility value for moderate eczema	x	x	x	x
Utility value for severe eczema	N/A	N/A	x	x
% high potency topical corticosteroids prescribed in secondary care	x	N/A	✓	x
% tacrolimus prescribed in secondary care	N/A	N/A	✓	✓
Cost of low potency corticosteroids	✓	x	x	x
Cost of moderate potency topical corticosteroids	x	x	x	x
Cost of high potency topical corticosteroids	x	N/A	x	x
Cost of pimecrolimus	✓	✓	N/A	N/A
Cost of tacrolimus	N/A	N/A	✓	x
% patients with disease controlled with pimecrolimus treatment	x	x	N/A	N/A
% patients with disease controlled with tacrolimus treatment	N/A	N/A	x	x
% patients with disease controlled with low potency topical corticosteroids	✓	✓	x	✓
% Patients with disease controlled with moderate potency topical corticosteroids	x	x	✓	x
% patients with disease controlled with high potency topical corticosteroids	x	N/A	x	x
Moderate control with low potency topical corticosteroids requiring a second course	x	x	x	x
Moderate control with moderate potency topical corticosteroids requiring a second course	x	x	x	x
Moderate control with high potency topical corticosteroids requiring a second course	x	N/A	x	x
Moderate control with pimecrolimus requiring second course	✓	✓	N/A	N/A
Moderate control with tacrolimus requiring a second course	N/A	N/A	x	x

Stochastic analyses

Probabilistic analyses were also undertaken. Outputs from Monte-Carlo simulation are shown graphically below (Figure 20 to Figure 27). For each population cohort, these illustrate the cost-effectiveness outcomes for the 1000 trials under the three treatment options (i.e. steroid only, immuno-suppressant second line, immuno-suppressant first line). Cost effectiveness acceptability curves (CEACs) have also been calculated for each population cohort which demonstrates, at different levels of willingness to pay for an additional QALY, the probability that each option is the most cost effective.

For children with mild to moderate body atopic eczema (Model 1a), the simulation of 1000 trials shows that similar benefits are likely to be achieved with pimecrolimus for greater costs than topical corticosteroids in most simulations if pimecrolimus is used as a first line treatment, and similar costs if it is used as a second line treatment (Figure 20). The acceptability curves show that steroid only regimens are most likely to be cost-effective at all levels of willingness to pay. However, the probability is low (less than 50% above £5000). Pimecrolimus as first line treatment is least likely to be cost effective at all levels of willingness to pay. Results are similar for children with mild to moderate facial eczema (Model 1b), although there is greater overlap in costs between the three treatment regimens in the simulation model (Figure 22). The acceptability curve (Figure 23) shows steroid only regimens most likely to be cost effective at all costs, although the probability is again low (less than 50% over £5000 per QALY). These figures and associated CEACs demonstrate the high level of uncertainty in the analyses.

For children with moderate to severe body atopic eczema (Model 2a), the simulation again shows that similar benefits accrue on first line tacrolimus treatment for greater costs than alternatives in most simulations (Figure 24). Second line tacrolimus and corticosteroids only show more overlap with a tendency for greater expense with second line tacrolimus. The acceptability curves show that steroid only regimens are most likely to be cost-effective up to a willingness to pay of £10,000, and then first line tacrolimus is most likely to be cost-effective at levels above this. However, the probability is low (less than 40% above £10,000) and similar for the three regimens (Figure 25). For children with moderate to severe facial eczema (Model 2b), there is greater overlap in costs between the three regimens in the simulation model (Figure 26). Corticosteroids show the lowest costs and first line tacrolimus the highest. The willingness to pay graph (Figure 27) shows topical corticosteroid only regimens most likely to be cost effective at low costs (up to £8000), and above this very similar probabilities that all three regimens are the most cost effective. These findings reflect the high level of uncertainty in the analyses.

Figure 20: Simulation output (1000 trials) for cost-effectiveness for pimecrolimus treatment for children with mild to moderate body eczema (Model 1a)

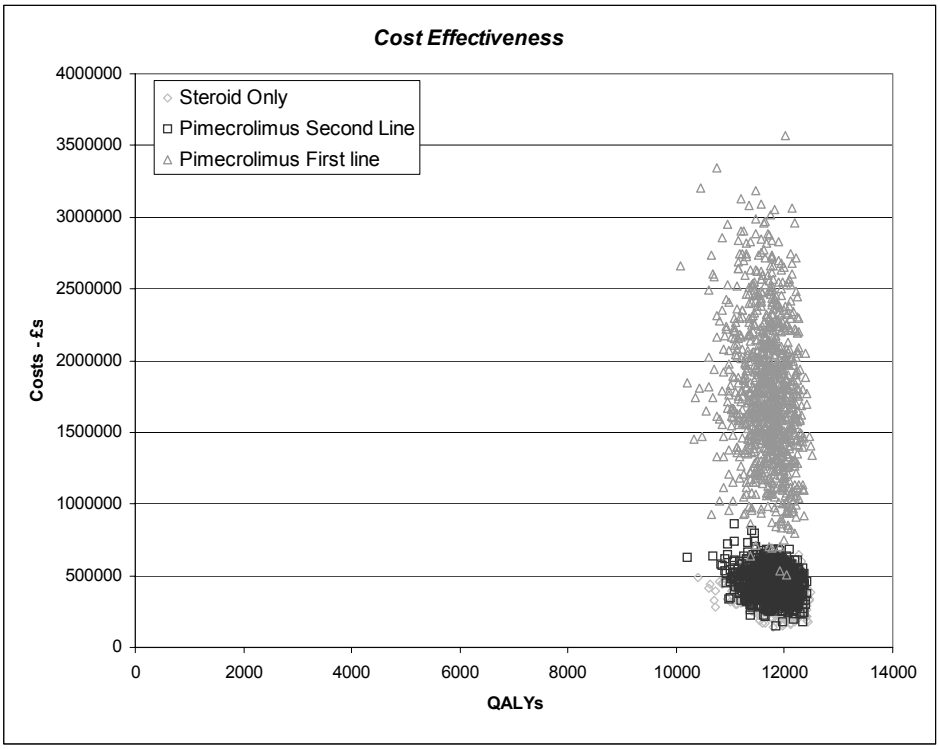


Figure 21: Simulation output (1000 trials) showing the probability of pimecrolimus being cost-effective at various amounts of willingness to pay for an additional QALY (Model 1a)

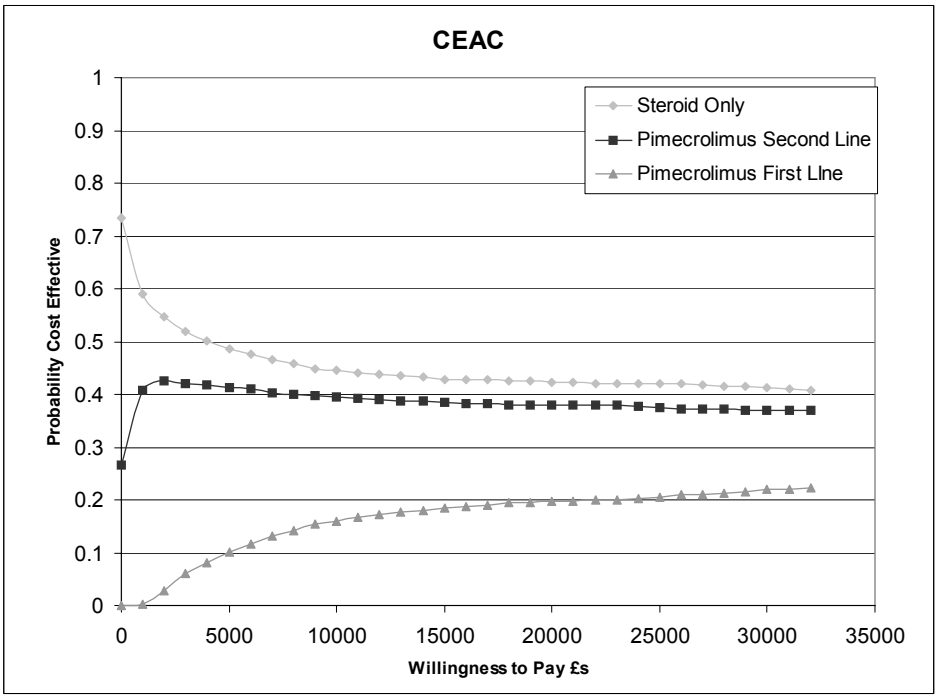


Figure 22: Simulation output (1000 trials) for children with mild to moderate facial eczema (Model 1b)

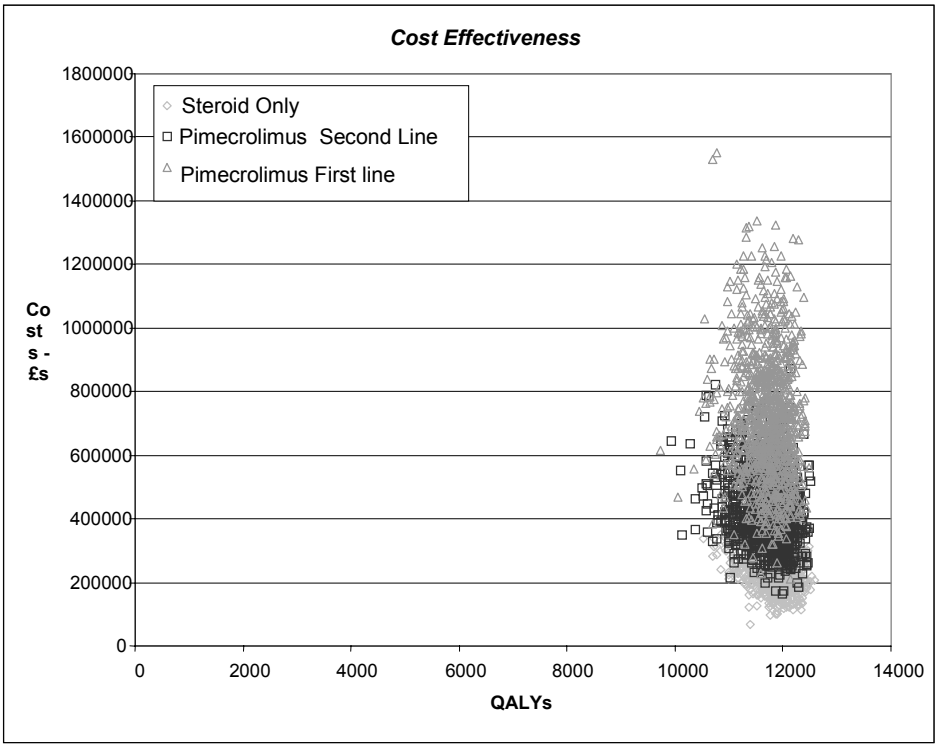


Figure 23: Simulation output (1000 trials) showing probability of pimecrolimus for children with mild to moderate facial eczema being at cost-effective different levels of willingness to pay for an additional QALY (Model 1b)

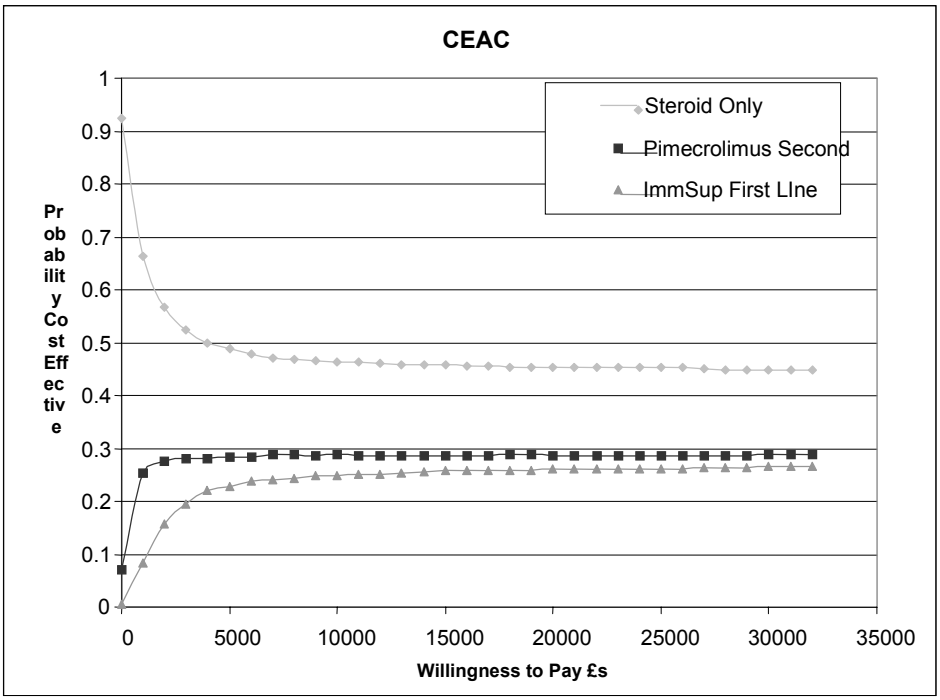


Figure 24: Simulation output (1000 trials) of cost-effectiveness of tacrolimus in children with moderate to severe body eczema (Model 2a)

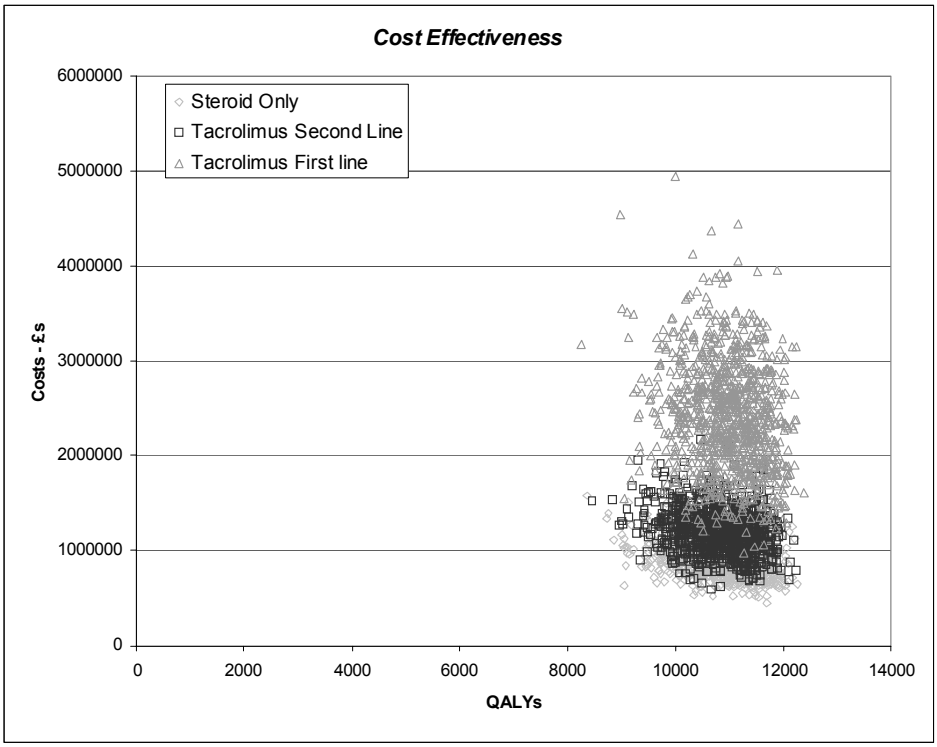


Figure 25: Simulation output (1000 trials) for showing the probability that tacrolimus is cost effective in children with moderate to severe body eczema at various levels of willingness to pay (Model 2a)

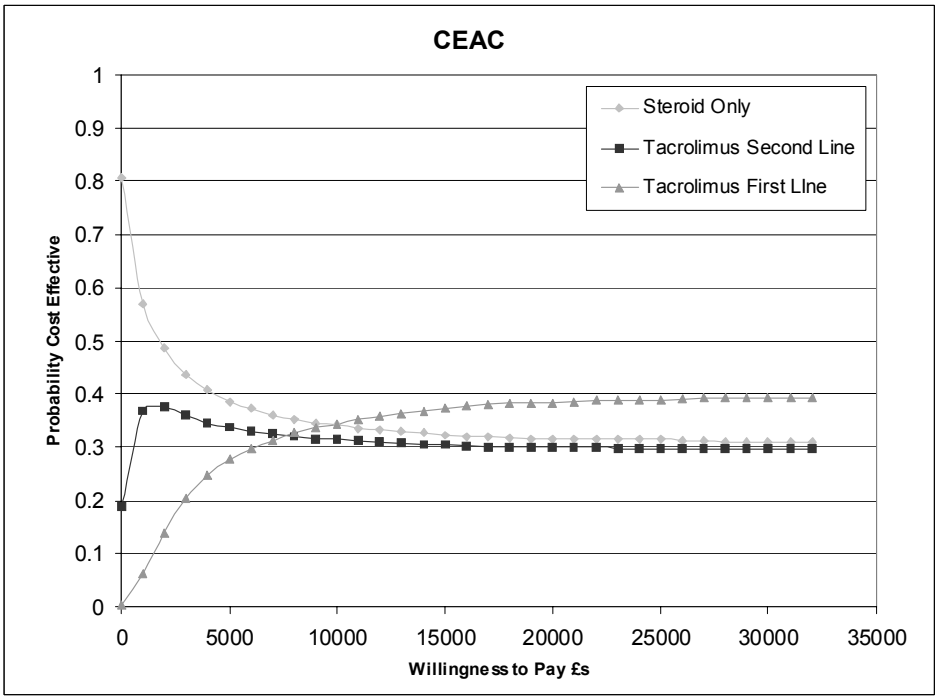


Figure 26: Simulation output (1000 trials) for tacrolimus in children with moderate to severe facial eczema (Model 2b)

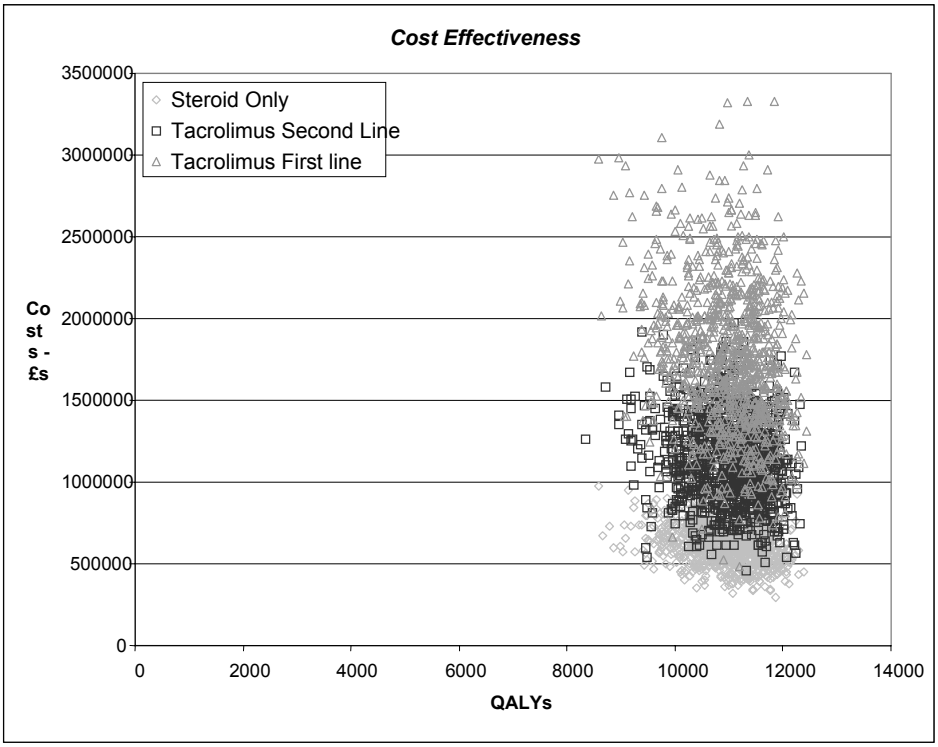
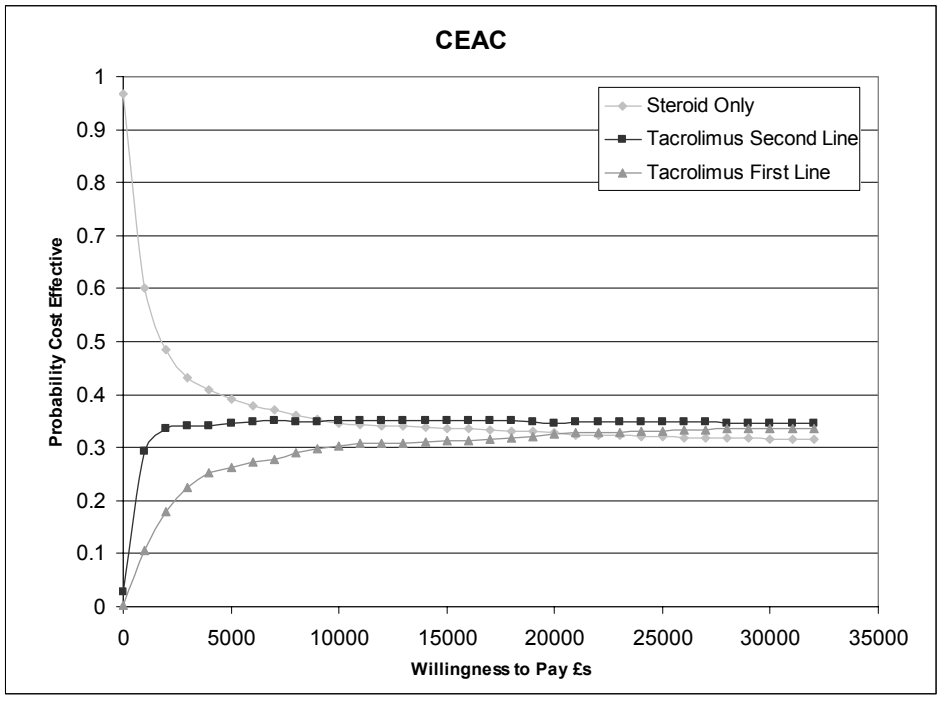


Figure 27: Simulation output (1000 trials) showing the probability that tacrolimus is cost-effective win children with moderate to severe facial eczema at various levels of willingness to pay for an additional QALY. (Model 2b)



5.5.3 Cost effectiveness in Adults with Atopic Eczema

The total costs for the modelled cohort of 1000 adults with mild to moderate atopic eczema after one year are shown in Table 39 and Table 40. Table 39 shows the cost-utility analysis for adults with mild to moderate eczema on non sensitive areas (i.e. not on the face etc.) while Table 40 shows the cost utility analysis for adults with mild to moderate atopic eczema affecting sensitive areas such as the face. These results take no account of the underlying uncertainty in the data, which is assessed in Section 5.4.4.

Table 39: Summary of cost utility analysis for pimecrolimus in adults with mild to moderate body eczema (Model 3a)

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (Cost/QALY)
No pimecrolimus	50,940	968	-	-	-
Pimecrolimus – second line	84,800	965	33,860	-3	Corticosteroid dominates
Pimecrolimus – first line	361,229	966	310,289	-2	Corticosteroid dominates

Table 40: Summary of cost utility analysis for pimecrolimus in adults with mild to moderate eczema on facial eczema (Model 3b)

Treatment	Total costs (£)	Total QALYs	Incremental costs(£)	Incremental QALYs	ICER (Cost/QALY)
No pimecrolimus	39,392	968	-	-	-
Pimecrolimus – second line	70,584	961	31,193	-6	Corticosteroid dominates
Pimecrolimus – first line	135,441	967	96,049	0	Corticosteroid dominates

In mild to moderate eczema affecting the body and face, pimecrolimus costs more and confers marginally fewer QALYs, although these numbers are negligible given that they are for the whole cohort over the one year of the model. As would be expected, using pimecrolimus as a second line treatment is not as expensive as using it as a first line treatment but in neither case does it appear to be cost-effective compared to standard practice using topical corticosteroids. However, the deterministic analysis alone is, in our view, insufficient to inform policy given the similarities in benefits.

The cost utility analysis for adult with moderate to severe eczema is shown in Table 41. The costs utility analysis for adults with moderate to severe eczema on sensitive areas such as the face is shown in Table 42. Again, these results take no account of the underlying uncertainty in the data.

Table 41: Summary of cost utility analysis for tacrolimus in adults with moderate to severe body eczema (Model 4a)

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (Cost/QALY)
No tacrolimus	265,452	868	-	-	-
Tacrolimus – second line	284,521	861	19,069	-7	Corticosteroid dominates
Tacrolimus – first line	755,367	875	489,915	7	68,428

Table 42: Summary of cost utility analysis for tacrolimus in adults with moderate to severe facial eczema (Model 4b)

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (Cost/QALY)
No tacrolimus	131,375	875	-	-	-
Tacrolimus – second line	202,462	874	71,087	-2	corticosteroid dominates
Tacrolimus – first line	326,615	892	195,240	16	11,882

For adults with moderate to severe body eczema, tacrolimus does not seem to be cost-effective as first or second line treatment – as second line treatment it costs more and confers marginally fewer QALYs, while as a first line treatment, it confers slightly greater benefits at a cost of £69,988 per QALY which is likely to be above the expected level of willingness to pay. In both cases, the difference in QALYs is anyway negligible given that this is for the whole cohort over one year. In adults with moderate to severe facial eczema, tacrolimus appears cost effective as first line treatment (at £11,882 per QALY) but not as second line treatment. This anomaly is due to the very similar levels of QALYs conferred by the different treatment regimens. Again, considering these are modelled over one year for a cohort of 1000, the differences in QALYs are negligible and the deterministic analysis relatively uninformative without taking uncertainty into account.

5.5.4 Sensitivity analyses for adult models

One way sensitivity analyses were used to examine the uncertainty in the models. These were expressed as a percentage change in cost per QALY for each of the three treatment options (corticosteroids only, immunosuppressants as first-line treatment, immunosuppressants as second line treatment) and the resultant graphs are shown in Appendix 13. All models appeared to be sensitive to the cost of new immunosuppressants. In addition, specific models showed sensitivity (>10% change in cost per QALY from baseline) for those inputs shown with a tick (✓) in Table 43.

Table 43: Results of one way sensitivity analyses of economic models for adults

	Mild/moderate body eczema	Mild/moderate facial eczema	Moderate/severe body eczema	Moderate/severe facial eczema
Utility value for disease controlled state	x	x	x	x
Utility value for mild eczema	✓	✓	N/A	N/A
Utility value for moderate eczema	x	x	x	✓
Utility value for severe eczema	N/A	N/A	x	x
% high potency topical corticosteroids prescribed in secondary care	x	N/A	x	✓
% tacrolimus prescribed in secondary care	N/A	N/A	x	✓
Cost of low potency corticosteroids	✓	x	x	x
Cost of moderate potency topical corticosteroids	x	x	x	x
Cost of high potency topical corticosteroids	x	N/A	x	x
Cost of pimecrolimus	✓	✓	N/A	N/A
Cost of tacrolimus	N/A	N/A	✓	✓
% patients with disease controlled with pimecrolimus treatment	x	x	N/A	N/A
% patients with disease controlled with tacrolimus treatment	N/A	N/A	x	x
% patients with disease controlled with low potency topical corticosteroids	✓	✓	x	x
% Patients with disease controlled with moderate potency topical corticosteroids	x	x	x	x
% patients with disease controlled with high potency topical corticosteroids	x	N/A	✓	x
% patients with disease controlled with systemic treatment	N/A	N/A	x	x
Moderate control with low potency topical corticosteroids requiring a second course	✓	x	x	x
Moderate control with moderate potency topical corticosteroids requiring a second course	x	x	x	x
Moderate control with high potency topical corticosteroids requiring a second course	x	N/A	x	x
Moderate control with pimecrolimus requiring second course	✓	✓	N/A	N/A
Moderate control with tacrolimus requiring a second course	N/A	N/A	x	x

Stochastic analyses

Probabilistic analyses were also undertaken. Outputs from Monte-Carlo simulations are shown graphically below (Figure 28 to Figure 35). For each population cohort, these illustrate the cost-effectiveness for the 1000 trials under the three treatment options (i.e. topical corticosteroid only, tacrolimus as second line treatment, tacrolimus as first line treatment). Cost effectiveness acceptability curves have also been produced for each population cohort.

For adults with mild to moderate body eczema, the simulation of 1000 trials shows that similar benefits accrue on first line pimecrolimus treatment for greater costs in almost all simulations (Figure 28). Second line pimecrolimus shows greater overlap with corticosteroid only regimens but shows higher costs in many situations. There is a ceiling effect with the QALYs because of the proximity of utility values to one, which causes the apparent line to the right of this graph. The CEACs show that steroid only regimens are most likely to be cost-effective at all levels of willingness to pay. However, the probability is low at moderate levels of willingness to pay (less than 50% from £15,000) (Figure 29). First line tacrolimus is unlikely to be considered cost effective, with a probability of only 20% at £30,000 and less than this at lower levels of willingness to pay. Results are very similar for adults with mild to moderate facial eczema (Model 3b), although there is greater overlap in costs for the three treatment regimens in the simulation model (Figure 30). The ceiling effect is again visible. The CEAC (Figure 31) shows topical corticosteroid only regimens most likely to be cost effective at all costs, although again the probability is low at moderate levels of willingness to pay (less than 40% over £15,000 per QALY). These figures and associated CEACs confirm the high level of uncertainty in the analyses.

For adults with moderate to severe body atopic eczema (Model 4a), in the simulation of 1000 trials a similar pattern is shown. Similar benefits accrue on first line tacrolimus for greater costs in almost all simulations (Figure 32). Second line tacrolimus and topical corticosteroid only treatment show similar costs and benefits. The willingness to pay curves show that steroid only regimens are most likely to be cost-effective up to a willingness to pay of about £22,000. Above this, first line tacrolimus is more likely to be cost effective. However, the probability is low (less than 50% at £5,000, falling to less than 40% at £14,00) (Figure 33). For adults with moderate to severe facial eczema (Model 4b), there is greater overlap in costs of the three regimens in the simulation model (Figure 34). The willingness to pay graph (Figure 35) shows topical corticosteroid only regimens most likely to be cost effective up to £8000, with tacrolimus then cost-effective as first line treatment. Again, the probability is low (less than 45% at all levels of willingness to pay). These figures and associated CEACs again demonstrate the high level of uncertainty in the analyses.

Figure 28: Simulation output (1000 trials) for cost-effectiveness of pimecrolimus in adults with mild to moderate body eczema (Model 3a)

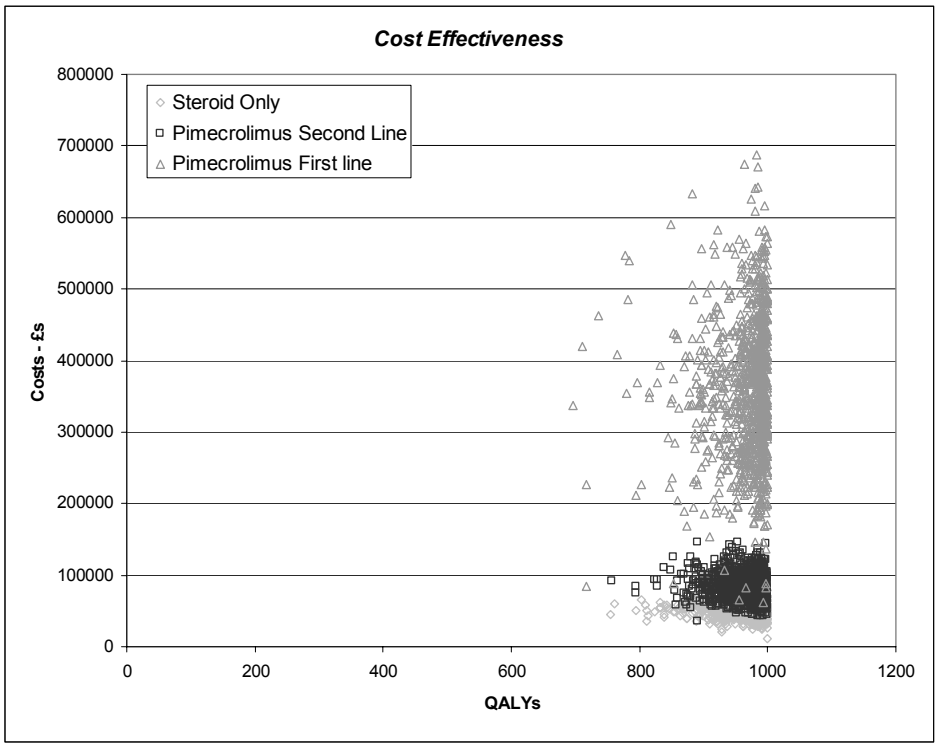


Figure 29: Simulation output showing the probability of pimecrolimus being cost effective in adults with mild to moderate body eczema at various levels of willingness to pay (Model 3a)

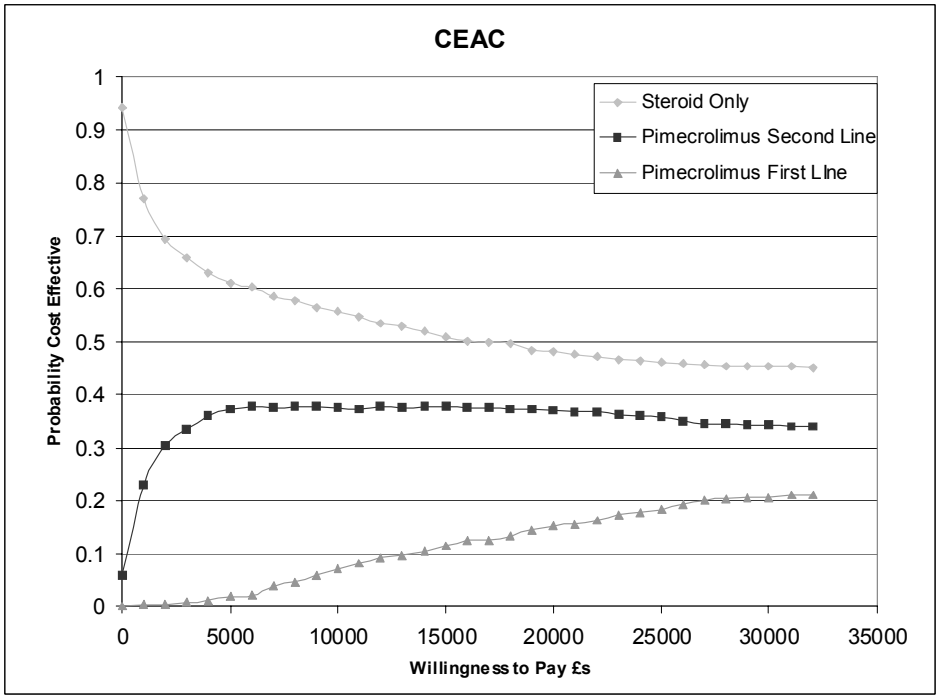


Figure 30: Simulation output (1000 trials) for cost-effectiveness of pimecrolimus in adults with mild to moderate facial eczema (Model 3b)

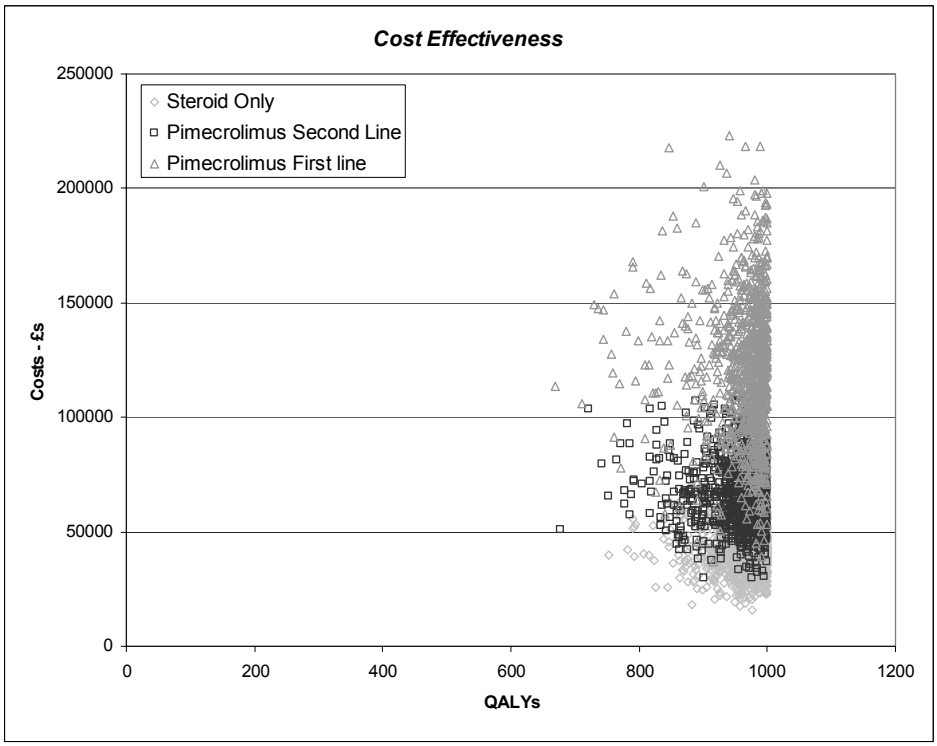


Figure 31: Simulation output (1000 trials) showing the probability that pimecrolimus is cost effective in adults with mild to moderate facial eczema at various levels of willingness to pay. (Model 3b)

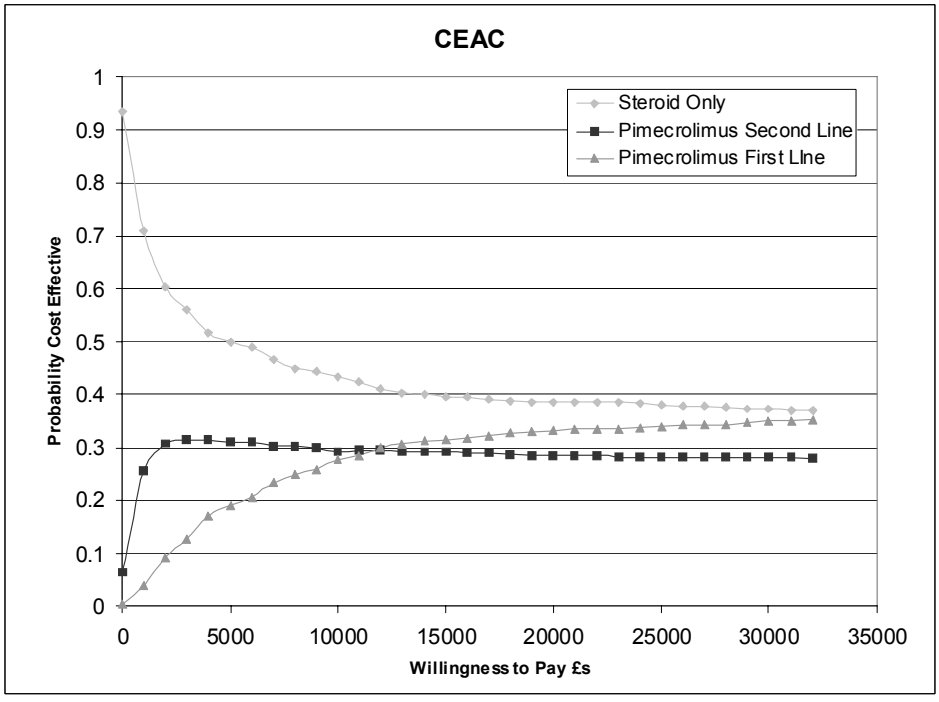


Figure 32: Simulation output (1000 trials) of cost-effectiveness of tacrolimus in adults with moderate to severe body eczema (Model 4a)

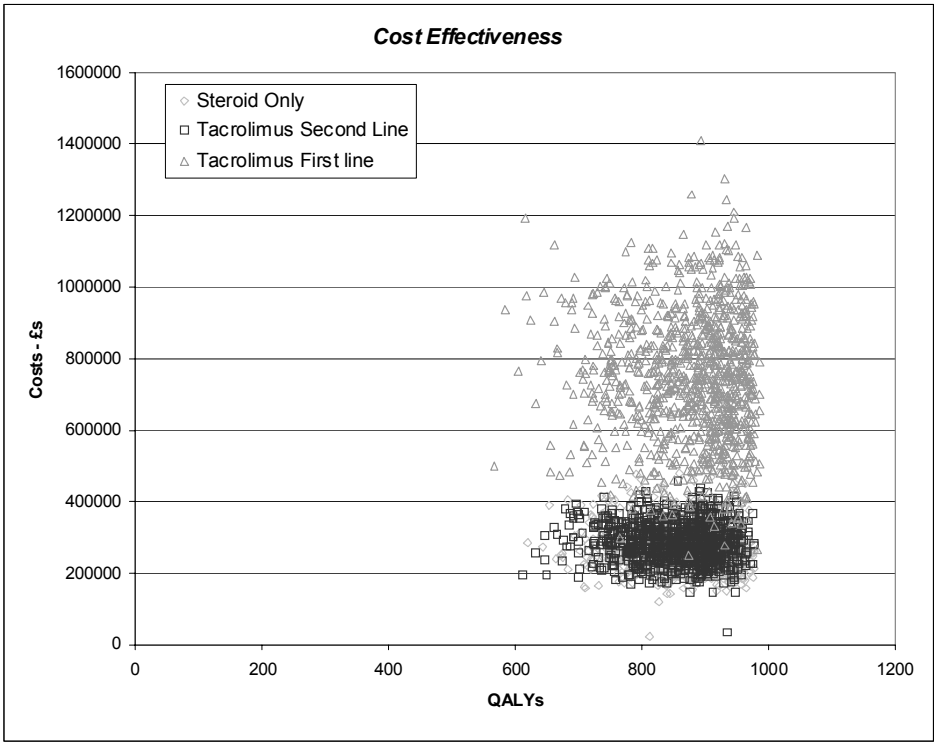


Figure 33: Simulation output (1000 trials) showing the probability that tacrolimus is cost effective in adults with moderate to severe body eczema at various levels of willingness to pay (Model 4a)

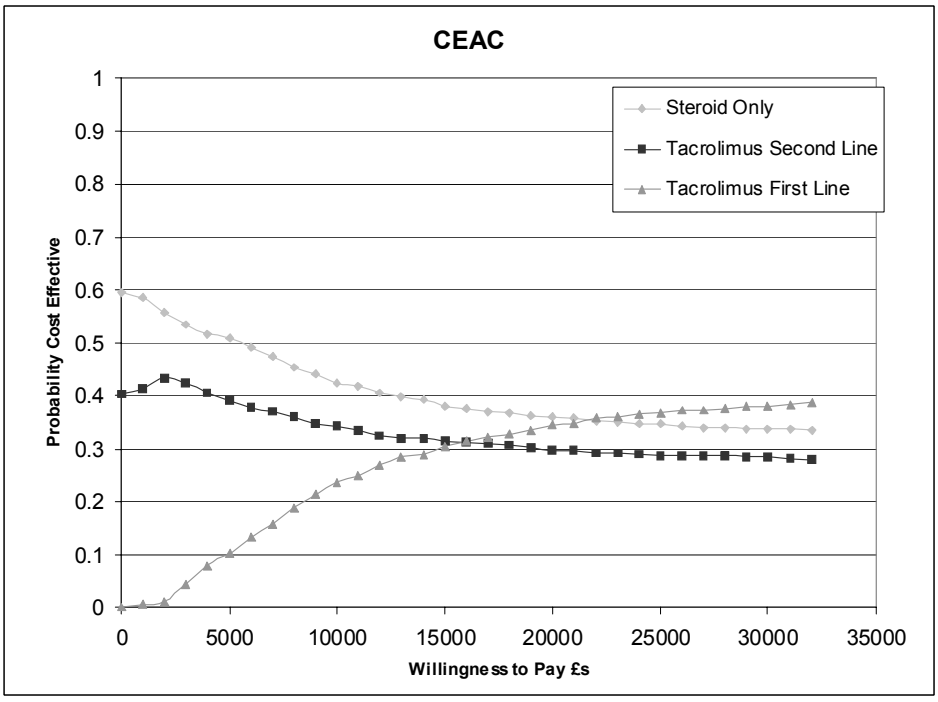


Figure 34: Simulation output (1000 trials) showing cost effectiveness of tacrolimus in adults with moderate to severe facial eczema (Model 4b)

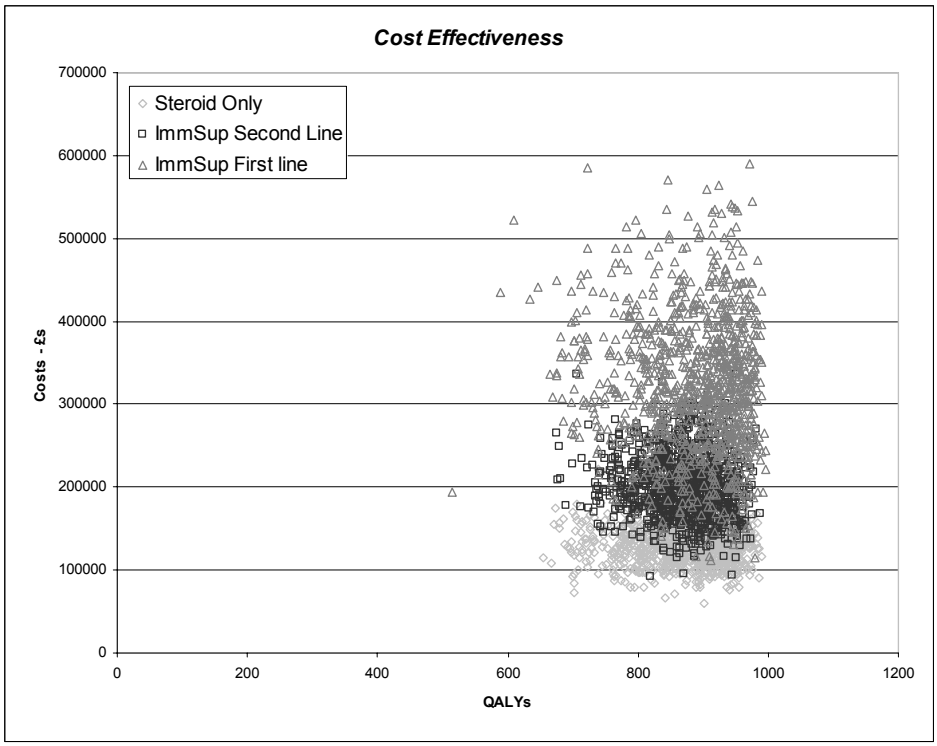
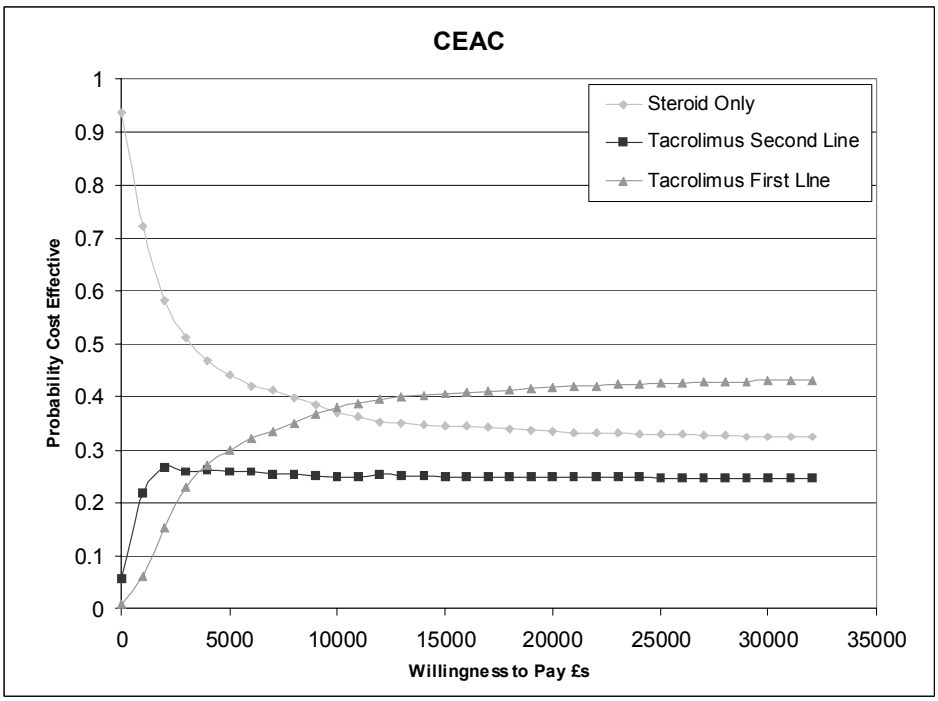


Figure 35: Simulation output (1000 trials) showing the probability that tacrolimus is cost effective in adults with moderate to severe facial eczema at various levels of willingness to pay (Model 4b)



5.5.5 Baseline results of cost-effectiveness model for emollient comparator

Cost effectiveness for pimecrolimus versus emollients was estimated separately for adults and children with mild to moderate atopic eczema.

Cost effectiveness of pimecrolimus versus emollient in children

The total costs of the modelled cohort for 1000 children with mild to moderate eczema over 14 years are shown in Table 44. Pimecrolimus is cost effective, accruing more QALYs at greater cost. However, the absolute different in QALYs is small over the whole cohort for 14 years and clearly subject to uncertainty.

Table 44: Summary of cost utility for pimecrolimus compared to emollient in children with mild to moderate eczema (Model 5)

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (Cost/QALY)
Emollients	409,253	11,556	-	-	-
Pimecrolimus	1,874,149	11,707	1,464,896	151	9,684

Cost effectiveness of pimecrolimus versus emollient in adults

The total costs of the modelled cohort for 1000 adults with mild to moderate eczema over one year are shown in Table 45. Pimecrolimus is cost effective, accruing more QALYs at greater cost. However, the absolute different in QALYs is very small and subject to uncertainty.

Table 45: Summary of cost utility for pimecrolimus compared to emollient in children with mild to moderate eczema (Model 6)

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (Cost/QALY)
Emollients	66,439	855	-	-	-
Pimecrolimus	375,691	874	309,253	19	16,646

Sensitivity analyses for emollient comparator models

One way sensitivity analyses for a range of input parameters were used to examine the uncertainty in the adult and child models for pimecrolimus versus emollient. These were expressed as a percentage change in the cost per QALY for each of the two treatment options (pimecrolimus with topical corticosteroid rescue therapy, and emollients with topical corticosteroids rescue therapy). Results are shown in Table 46 where a change from the baseline of 10% or more is shown with a tick (✓). The models are sensitive to the costs and effectiveness of pimecrolimus. The adult model is also slightly sensitive to the cost of corticosteroid cream. The results are presented graphically in Appendix 13.

Table 46: One way sensitivity analysis for pimecrolimus versus emollients (models 5 & 6)

	Mild/moderate eczema in children	Mild/moderate eczema in adults
Utility value for disease controlled state	x	x
Utility value for mild eczema	x	x
Utility value for moderate eczema	x	x
Cost of moderate potency topical corticosteroids	x	✓
Costs of emollients	x	x
Cost of pimecrolimus	✓	✓
% patients with disease controlled with pimecrolimus treatment	x	x
% Patients with disease controlled with moderate potency topical corticosteroids	x	x
% patients with disease controlled with emollients	x	x
Moderate control with moderate potency topical corticosteroids requiring a second course	x	x
Moderate control with pimecrolimus requiring second course	✓	✓
Moderate control with emollients a second course	x	x

Stochastic analyses

Probabilistic analyses were also undertaken. Outputs from the Monte-Carlo simulation are shown graphically below. For the adult and children population cohorts, these illustrate the cost-effectiveness outcomes for 1000 trials under the two treatment options (pimecrolimus with topical corticosteroid rescue therapy, and emollients with topical corticosteroids rescue therapy). Cost effectiveness acceptability curves have also been calculated. Results for the child model (Model 5) are shown in Figure 36 and Figure 37 and results for the adult model (Model 6) are shown in (Figure 38 and Figure 39.

For children with mild to moderate eczema (Model 5), the simulation of 1000 trials shows that the spread of QALY values goes lower with emollients, although values are similar, while in virtually all cases, pimecrolimus is more expensive (Figure 36). The CEACs show that emollient only is likely to be more cost effective at low levels of willingness to pay (up to £10,000 per QALY) while pimecrolimus is more likely to be cost effective above this. The probabilities are similar however, (55%:45%) even at high levels of willingness to pay. This reflects the uncertainty within the model.

For adults with mild to moderate eczema (Model 6), the simulation shows a similar spread of QALY values with both treatments, while in virtually all cases, pimecrolimus is more expensive (Figure 38). The willingness to pay curves show that vehicle is likely to be more cost effective up to £20,000 per QALY while pimecrolimus is more likely to be cost effective above this. The probabilities are similar however, (55%:45%) even at high levels of willingness to pay. This reflects the uncertainty within the model.

Figure 36: Simulation output (1000 trials) for the cost effectiveness of pimecrolimus compared to emollients in children (Model 5)

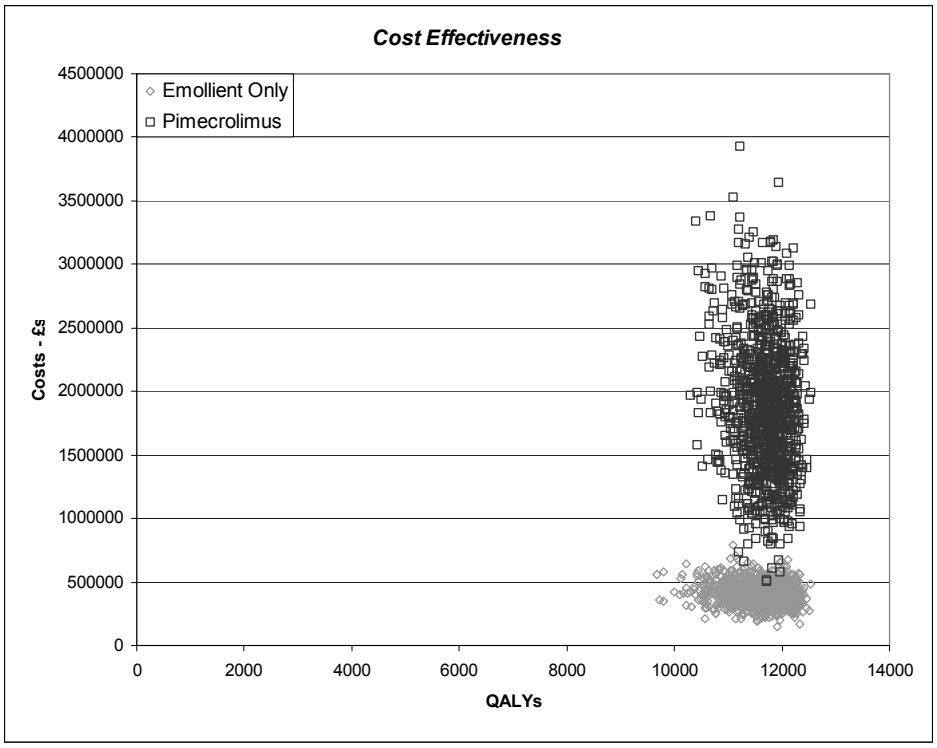


Figure 37: Simulation output (1000 trials) showing the probability of pimecrolimus compared to emollients in children being cost-effective at various amounts of willingness to pay (Model 5)

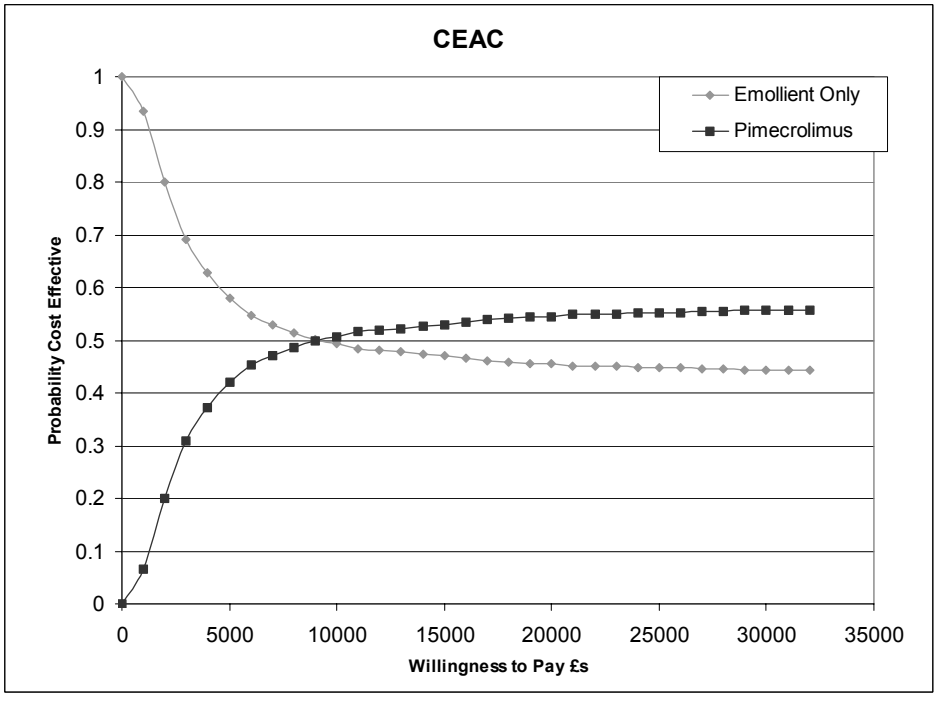


Figure 38: Simulation output (1000 trials) for the cost effectiveness of pimecrolimus compared to emollients in adults (Model 6)

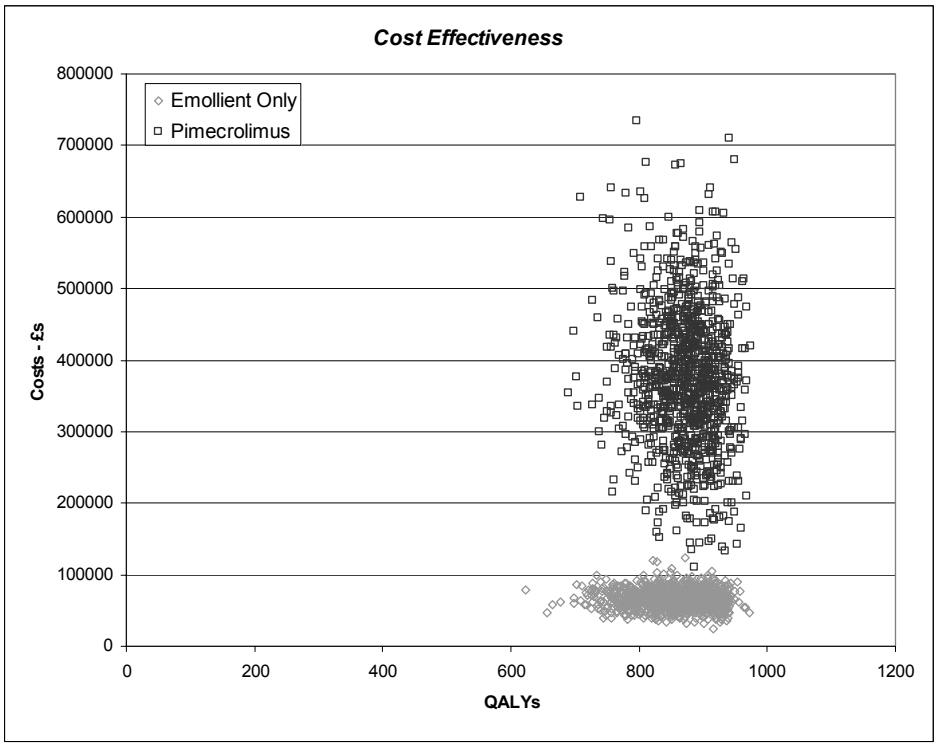
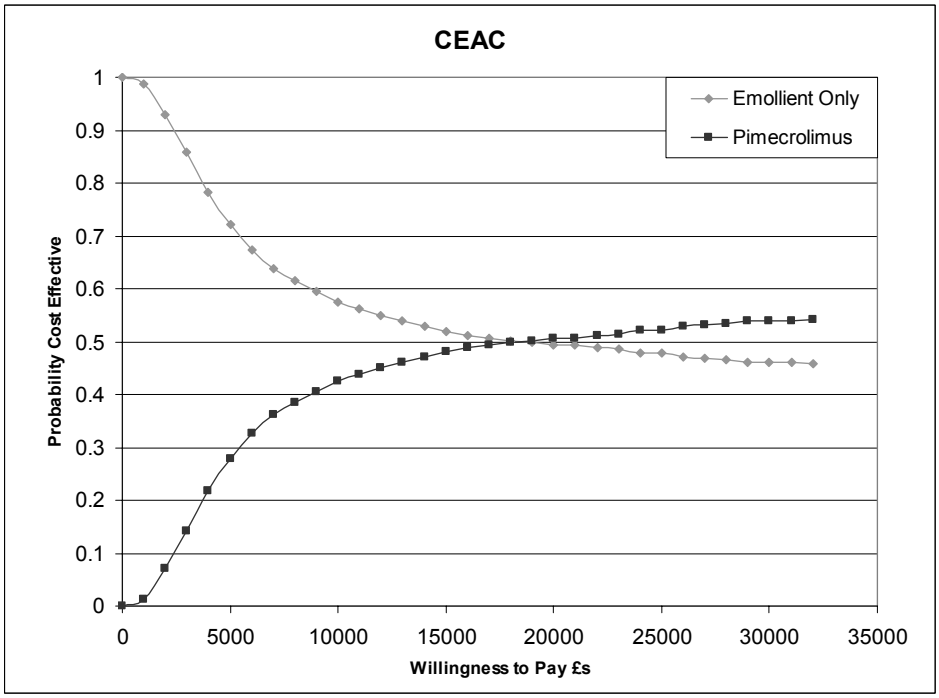


Figure 39: Simulation output (1000 trials) showing the probability of pimecrolimus compared to emollients in children being cost-effective at various amounts of willingness to pay (Model 6)



5.6 Models supplied by technology sponsors to NICE

As part of their industry submissions to NICE, both Fujisawa and Novartis provided information about the cost-effectiveness models they had produced. These were critiqued using the Sculpher framework and the results of this are shown in Appendix 8. This section describes the main aspects of these models.

5.6.1 Novartis evaluation of pimecrolimus

The Novartis model uses a Markov approach based on four states of progressive severity. Cycle length is one week and the model runs for one year. Patients are classified in state IGA 0/1 (remission), IGA 2 (mild), IGA 3 (moderate) and IGA 4/5 (severe eczema). Cost effectiveness is modelled separately in children and adults. The base year used for estimating costs is 2003 and the model takes the perspective of the NHS.

The model represents the current licensing indications for pimecrolimus in mild and moderate patients, but considers pimecrolimus against emollients, making it relevant to only a small minority of patients. The model allows corticosteroid use only in patients with IGA scores of 4/5. This is also unlikely to reflect clinical practice, where topical steroids are likely to be introduced at an earlier stage in progression of severity in the majority of cases.

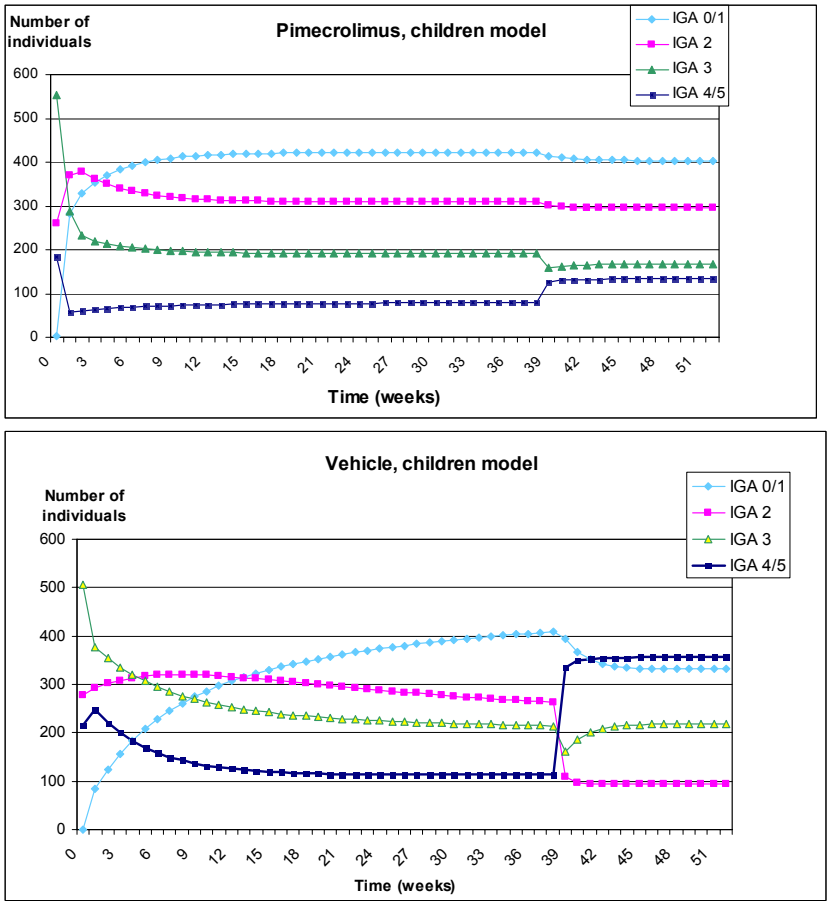
The effectiveness of pimecrolimus compared to vehicle was estimated from two randomised controlled trials (Wahn and colleagues[65] and Meurer and colleagues[67]). Transition probabilities were calculated from trial data with least squared estimation, and then compared back to trial data. No comparisons with other independent data or model were reported.

An important limitation of the model lies in its method to extrapolate effectiveness data beyond month 6. In the children model, two separate sets of transition probabilities have been used, one for the first 9 months of the model and another for the period 10-12 months. The effect of this is to introduce a step-change in model outputs at week 39, demonstrated by a large shift of patients from states IGA0/1, 2 or 3 to IGA 4/5 introduced in both arms, when approximately 5% (pimecrolimus) and 25% (vehicle) shift to treatment with steroids (Figure 40).

Although unclear from the documentation supplied, the use of two transition probability matrices appears to be undertaken because the original calculated matrix failed the chi-squared test for validity during the period week 39 to week 52. This is shown in the Novartis model and appears to be due to a large influx of patients occurring at week 52, when all patients were recalled, regardless of whether they had previously dropped out.

Such a step change would be highly unlikely. The impact of this change in probabilities is likely to change of the cost-effectiveness ratio in favour of Pimecrolimus, since it (a) increases the differential advantage of pimecrolimus in utilities (by increasing the numbers of patients in IGA state 4) and (b) decreases the difference between the cost of pimecrolimus and vehicle by reducing the numbers of patients on vehicle in sates IGA 2 and 3. The size of this bias is unknown.

Figure 40: Showing effect on number of children in each disease state after data extrapolation



The model includes credible estimates of direct medical care costs (intervention and other drugs, outpatient and primary care consultations, hospital admissions). Some are measured in the trials (consumption of cream or emollients and concomitant treatment), with additional data retrieved from published literature. In the absence of more directly relevant information, data from an Australian study were used for frequency of clinic visits (Su et colleagues[29]). These were adjusted to the UK setting by halving the frequency of visits to account for differences between resource allocation in the UK and Australia. An alternative set of resource consumption data was based on expert opinion, specifically, the number of physicians visits for each IGA class used in the model (named "assumed visit costs" in the model). Resources are valued using appropriate sources for current unit costs in the UK (Netten[92] and the BNF). Despite the lack of published estimates of healthcare costs for eczema, it is likely that the resources estimated provide a reasonable alternative to primary costing studies.

The model incorporates utilities for each IGA severity state, derived from three studies, for adults (MERG) and for children (Duke and Brazier). The methods and results of these studies are described fully in Section 5.3.5, "Sources of Utility Values" as they were considered for inclusion in the PenTAG model.

Results of Novartis model

The economic evaluation concludes that pimecrolimus is cost-effective compared to vehicle with an ICER of £24,489 in children and £27,350 in adults.

These two ICERs are calculated using adjusted costs from the Su study for the children model and costs based on expert opinion for the adults model. Utilities are from the Brazier and Stevens study for children and from the MERG study for adults.

Sensitivity analyses of Novartis model

The model includes a range of sensitivity analyses, both one-way analyses on point estimates of each key parameter and, limited to utilities and costs, probabilistic sensitivity around central estimates (Appendix 9). Sensitivity analysis was not performed on effectiveness; a limitation of the analyses.

One-way sensitivity analysis show that the ICER for children decreases using utilities from the Duke studies (£16,524-£19,226) and increases using resource consumption obtained from expert opinion (£40,927). In the adult model, the ICER increases using utilities from the Duke study (£36,426-£42,661) and the Brazier Study (£49,323).

The most favourable ICERs for the adult model are found in the range of estimates pertaining to the base case (min £21,766 - max £36,149), with the extreme estimates reported for the treatment of head and neck body areas and lower limbs respectively. Estimates are moderately sensitive to utility values and to a slightly lesser extent, on costs. However, most estimates are between £22,000 and £50,000 per QALY.

In the children model, the base case estimate appears to be towards the high end of the range of values provided. More favourable ICERs are found in the treatment of the trunk (dominates under all utility profiles), with the worst estimates corresponding to the 'assumed resource consumption' profile.

The ICER is sensitive to the pattern of resource utilisation, increasing as non-drug costs decrease in proportion to total costs. In fact, the smallest ICERs are found under the scenario of resource consumption described by Su and colleagues, where the cost of visits is a high proportion of total costs and is similar for the intervention and the comparator, thus reducing the relative (%) difference in total costs.

Probabilistic sensitivity was carried out for the children model only, using a Gamma distribution for the cost of the cream and a Beta distribution for utilities. Assuming a maximum willingness to pay of £30,000/QALY, the probability of the ICER being below the threshold value is 0.6, with dominance in 20% of the cases. There is a probability of around 0.2 that the ICER will be over £100,000. No probabilistic analysis was undertaken for the adult model.

In summary, this is a reasonably sound cost utility model based on a Markov process. In particular, important efforts have been taken to overcome uncertainty regarding the utility associated with health states in eczema. However, there are limitations. The model does not compare pimecrolimus to topical steroids, which we believe to be a more appropriate comparison in the majority of cases. Bias may have been introduced in the application of transition probabilities in the children model. The potential impact of uncertainty has not

been consistently addressed between adult and children models and between important parameters (i.e. no sensitivity analysis based on effectiveness data).

5.6.2 Fujisawa model for tacrolimus

The industry submission by Fujisawa, compares tacrolimus to corticosteroids in children and adults with moderate to severe eczema.

The model includes four states of progression of eczema (cleared or virtually cleared, moderately controlled, uncontrolled and flare) and main treatment options (first and second line therapy, including light therapy, systemic immunosuppressants, wet wraps, antibiotics). The progression between states is based on a set of assumptions and estimates described clearly. The relevant comparator is usual care i.e. topical steroids for all severity states.

The model adopts a semi-Markov approach, organised in four arms (corticosteroids in moderate or severe eczema, tacrolimus in moderate or severe eczema). In a semi-Markov model, individuals enter a severity arm and cannot move to another severity arm for the rest of the follow-up, whilst they can move across states within that branch at each cycle. Each arm is run in cycles of 3 weeks for a total of 27 weeks (adults) or 15 weeks (children), corresponding to the duration of follow-up in the trials from which effectiveness estimates were derived (Petan[83] (adults) and Reitamo (children).[74]

The authors provided an extension of the model up to 51 weeks (scenario 2), populated with effectiveness estimates obtained from experts for both intervention and comparator. This aimed to represent routine practice more closely than trial data. A fifth arm is added in the adult model, cyclosporin in severe eczema.

Costs were estimated with a bottom-up approach, including medical direct costs (drugs, laboratory tests and diagnostic procedures, GP and specialist consultations, ward admissions by type and length of stay) and workdays lost. Base year for costs is not stated.

Resource consumption for drugs and concomitant treatment was directly measured in the trial. The model includes drug use of 18.5 g/week (tacrolimus) for moderately severe patients and 35.5 g/week for severe patients, with some use (5-12 g/week) included in disease controlled states after clearance. The cost of corticosteroids is calculated by a similar method, based on a variety of agents, for both treatment and maintenance. Other resource use data were estimated from an expert panel of dermatologists, based on a questionnaire identifying patient profiles for each severity state. The physician was asked to fill in a resource utilisation table for first line and second line therapy. Unit costs were obtained from standard UK sources with base year 2003.

The outputs of the model are measured in disease-free days and total costs. The authors also include a measure of quality of life directly obtained from scores from the Dermatology Quality of Life Index, calculated for adults. This is not attempted for children.

The main limitation of the model lies in the high probability assigned to receiving second-line therapy in both the children and the adult model. In the adult model, patients have a high probability of switching to second-line therapy both in moderate patients (2%-12% of patients per cycle for tacrolimus and 7-29% for corticosteroids) and in severe patients (6%-22%, tacrolimus and 9%-45%, corticosteroids). This leads to high numbers of patients receiving such treatment. The percentages in the children model are 8%-15% (tacrolimus 0.03%), 3%-8% (tacrolimus 0.1%) and 7%-24% (corticosteroids) in the moderate population and 4%-

18% (tacrolimus 0.03%), 1%-16% (tacrolimus 0.1%) and 9%-37% (corticosteroids). The basis for these assumptions is not clear.

The effect of such high proportions of individuals in second line therapy is that costs are accrued with no additional effectiveness. The corticosteroid arms show higher numbers of patients receiving second line treatment in all cases.

Another limitation of the analysis is in the definition of perspective. Costs were calculated including workdays lost, justified on the pragmatic availability of reliable estimates. Strictly speaking, these should be excluded from the NHS perspective. Cost estimates are provided net of workdays lost for the base case, but the remaining analyses and the sensitivity analysis include this element.

A third important limitation to this model is in the method used to summarise results, since average cost-effectiveness ratios are used throughout the model.

Fujisawa model results: Adults

The conclusion is that tacrolimus is superior to topical corticosteroids. In the adult model, tacrolimus had a higher proportion of virtually cleared patients in both moderate and severe eczema, and with similar treatment cost. However, patients treated with tacrolimus suffered from a higher number of flares, explained by longer time spent in first line treatment. These conclusions applied with and without inclusion of workdays lost, and to both scenarios. In particular, the exclusion of workdays lost seems to have an impact on the magnitude of the average cost-effectiveness analysis conducted by the authors of the model, but it seems unlikely to have an impact on the final results when analysed in terms of incremental cost-effectiveness.

Scenario 2 suggested that cyclosporine was superior to tacrolimus.

Table 47: Baseline results from Fujisawa model for adults

Results Including workdays lost			
Moderate eczema			
		Average cost-effectiveness ratio	Incremental cost-effectiveness ratio (based on cost per DCD)§
Scenario 1	Tacrolimus	£10.90 /DCD £136.44/DLQI	Tacrolimus dominates §
	Topical corticosteroids	£17.19 /DCD £164.36/DLQI	
Scenario 2	Tacrolimus	£10.88/DCD	ICER £6.18/DCD §
	Topical corticosteroids	£11.46/DCD	
Severe eczema			
Scenario 1	Tacrolimus	£49.83/DCD £471.11/DLQI	Tacrolimus dominates§
	Topical corticosteroids	£106.69/DCD £614.31/DLQI	
Scenario 2	Tacrolimus	£59.04/DCD	Tacrolimus vs. corticosteroids: ICER £26.76/DCD §
	Topical corticosteroids	£62.54/DCD	
	Cyclosporine	£31.12/DCD	Cyclosporin vs. tacrolimus: ICER £4.84/DCD§
Results excluding workdays lost			
Moderate eczema			
Scenario 1	Tacrolimus	£9.01 /DCD £112.87/DLQI	Tacrolimus dominates §
	Topical corticosteroids	£13.14 /DCD £125.66/DLQI	
Scenario 2	Tacrolimus	£8.44/DCD	ICER £7.2/DCD §
	Topical corticosteroids	£8.59/DCD	
Severe eczema			
Scenario 1	Tacrolimus	£26.80/DCD £253.41/DLQI	Tacrolimus dominates §
	Topical corticosteroids	£55.93/DCD £322.04/DLQI	
Scenario 2	Tacrolimus	£35.60/DCD	Tacrolimus vs. corticosteroids: ICER £15.8/DCD §
	Topical corticosteroids	£37.75/DCD	
	Cyclosporine	£20.91/DCD	Cyclosporine vs. tacrolimus: ICER £7.4/DCD§

DCD: disease controlled days

§ Incremental cost-effectiveness ratios were recalculated within this TAR based on total costs and effectiveness provided in the model report.

Fujisawa results: children

The authors concluded that tacrolimus was superior to corticosteroids in the children model, with more disease-free days in the tacrolimus 0.1% group in moderate eczema and more disease-free days in tacrolimus 0.03% in the severe group. The authors explained this with the small number of individuals cleared in the first 3 weeks in the tacrolimus 0.1% group compared to tacrolimus 0.03%. However it should be noted that differences in both effectiveness and costs of tacrolimus compared to topical steroids are very small therefore resulting in unstable cost-effectiveness ratios.

Table 48: Baseline results for Fujisawa for children

Moderate eczema			
		Average cost-effectiveness ratio	Incremental cost-effectiveness ratio §
Scenario 1	Tacrolimus 0.03%	£26.07/DCD	Tacrolimus 0.03% vs. corticosteroids: corticosteroids dominates Tacrolimus 0.1% vs. corticosteroids ICER £16.41 Tacrolimus 0.1% vs Tacrolimus 0.03%: Tacrolimus 0.1% dominates
	Tacrolimus 0.1%	£20.04/DCD	
	Topical corticosteroids	£20.7/DCD	
Scenario 2	Tacrolimus	£10.16/DCD	tacrolimus vs. corticosteroids: ICER £3.31
	Topical corticosteroids	£11/DCD	
Severe eczema			
Scenario 1	Tacrolimus 0.03%	£68.09/DCD	Tacrolimus 0.03% vs. corticosteroids: ICER £18.10 Tacrolimus 0.1% vs. corticosteroids: dominates Tacrolimus 0.1% vs Tacrolimus 0.03%: Tacrolimus 0.03% dominates
	Tacrolimus 0.1%	£100.92/DCD	
	Topical corticosteroids	£86.17/DCD	
Scenario 2	Tacrolimus	£39.21/DCD	Tacrolimus vs. corticosteroids: ICER £16.11
	Topical corticosteroids	£41.72/DCD	

DCD: disease controlled days

§ Incremental cost-effectiveness ratios were recalculated within this TAR based on total costs and effectiveness provided in the model report

Sensitivity analyses in the Fujisawa model

Extensive one-way sensitivity analyses were conducted on both costs and effectiveness (See Appendix 10). Based on average cost-effectiveness ratios, the adult model was shown to be sensitive to workdays lost, consultations and hospitalisation (for severe eczema only).

Crucial effectiveness values were:

- the proportion of patients continuing treatment following moderate improvement after the first cycle (both moderate and severe eczema);
- the percentage of patients having no flares after clearance (moderate only);
- the percentage of patients having clearance at the end of the first cycle (moderate only).

The children model was sensitive to the cost of consultations, medications (moderate eczema) and hospitalisation (severe eczema). For probabilities critical variables were the percentage of patients having clearance at the end of the first cycle, the proportion of patients continuing treatment in case of moderate improvement after the first cycle and for patients with moderate improvement after the 1st cycle, the percentage of patients having clearance after the second cycle and percentage of patients experiencing no flares.

In summary, the Fujisawa model has a reasonably sound structure, and compares tacrolimus to topical steroids. Effectiveness data are based on the results of randomised trials of short-term duration, whilst a longer-term model is provided based on data collected from an experts panel. Although valid measures of cost effectiveness, the outputs of the

analysis do not permit comparison of tacrolimus with other technologies and the original analysis has several methodological flaws, particularly the use of average cost effectiveness ratios. Since differences in costs between tacrolimus and corticosteroids are driven by the occurrence of second-line therapy, the costs of topical corticosteroids are likely to be over estimated compared to those of tacrolimus, with a possible impact on cost-effectiveness ratios.

Summary Comparison of Fujisawa, Novartis and PenTAG models

A summary table and analysis of the industrial submissions in the context of the PenTAG model presented in this report are given below in Table 49 and main outcomes in Table 50. At the outset however, the following key observations should be made.

- The Novartis model is focussed on the use of pimecrolimus versus emollient and therefore presents no analysis which directly compares the use of pimecrolimus to corticosteroids.
- The Fujisawa model provides a cost-effectiveness analysis in terms of disease free days rather than Quality Adjusted Life Years to assess different treatment alternatives. This makes it difficult to directly compare the outputs of this model with the PenTAG model.

Table 49: Summary of industry and PenTAG models

Study	Fujisawa	Novartis	PenTAG
Intervention and comparator	Tacrolimus vs. topical corticosteroids (moderate eczema) Tacrolimus vs. corticosteroids and cyclosporin (severe eczema)	Pimecrolimus vs. emollients (mild and moderate eczema)	Pimecrolimus vs. topical corticosteroids (mild and moderate eczema) Tacrolimus vs. topical corticosteroids (moderate and severe eczema) Pimecrolimus vs. emollients (mild and moderate eczema)
Study type	Cost Effectiveness Analysis	Cost Utility Analysis	Cost Utility Analysis
Population	Adults (moderate to severe) Children (moderate to severe)	Adult (mild to severe) Children (mild to severe)	Adults (mild to moderate) Adults (moderate to severe) Children (mild to moderate) Children (moderate to severe)
Perspective	NHS Personal and Social Service	NHS	NHS
Model Type	Semi-Markov	Markov	Markov
Time Horizon	15 weeks (scenario 1, children) 27 weeks (scenario 1, adults) 51 weeks (Scenario 2)	1 year	Adults one year Children 14 years (age 2 to 16)
Cycle length	Three weeks	One Week	Four weeks
Country	UK	UK	UK
Definition of effectiveness	Disease Free Days	QALYs	QALYs
Main outcome measure	Cost Effectiveness Ratio	Incremental Cost Effectiveness Ratio	Incremental Cost Effectiveness Ratio
Probabilistic analysis ?	Not undertaken	Monte Carlo Markov chain Simulation	Monte Carlo Markov chain Simulation
Type of sensitivity analysis	One-way sensitivity Tornado analysis	One-way sensitivity Probabilistic simulation	One-way sensitivity Probabilistic simulation
Notes on sensitivity analysis	Probabilistic Simulation not used	Probabilistic analysis does not vary transition probabilities	
Model State types (disease vs state)	Disease states referenced against treatment.	Disease Severity states (using IGA scores)	Treatment states referenced against severity levels

Table 50: Summary of Main Outputs in models

PenTAG Model			
Comparison	**Population**	**Body Area**	**ICER (cost/QALY)**
Pimecrolimus 1st line vs Corticosteroids (CS)	Children & Adults	Facial & Body	CS dominates
Pimecrolimus 2nd line vs Corticosteroids (CS)	Children & Adults	Facial & Body	CS dominates
Tacrolimus 1st line vs Corticosteroids (CS)	Children	Facial	£35669
Tacrolimus 2nd line vs Corticosteroids (CS)	Children	Facial	CS dominates
Tacrolimus 1st line vs Corticosteroids (CS)	Children	Body	£9083
Tacrolimus 2nd line vs Corticosteroids (CS)	Children	Body	£14175
Tacrolimus 1st line vs Corticosteroids (CS)	Adults	Facial	£11882
Tacrolimus 2nd line vs Corticosteroids (CS)	Adults	Facial	CS dominates
Tacrolimus 1st line vs Corticosteroids (CS)	Adults	Body	£68428
Tacrolimus 2nd line vs Corticosteroids (CS)	Adults	Body	CS dominates
Pimecrolimus 1st line vs Emollient 1st line	Children	General	£9684
Pimecrolimus 1st line vs Emollient 1st line	Adults	General	£16646

Novartis - Model			
Comparison	**Population**	**Body Area**	**ICER (cost/QALY)**
Pimecrolimus 1st line vs Emollient 1st line	Children	General	£19016
Pimecrolimus 1st line vs Emollient 1st line	Adults	General	£27350

Fujisawa – Model (clinical trial data)			
comparator	**Population**	**Severity**	**Inc. Cost per Disease Controlled Day**
Tacrolimus 1st line vs Corticosteroids (CS)	Children	moderate	CS Dominates
Tacrolimus 1st line vs Corticosteroids (CS)	Children	severe	£18.1
Tacrolimus 1st line vs Corticosteroids (CS)	Adults	moderate	Tacrolimus Dominates
Tacrolimus 1st line vs Corticosteroids (CS)	Adults	severe	Tacrolimus Dominates

The ICER given by Pimecrolimus is higher than that calculated by PenTAG, however, when Novartis ran the model with the same data from Su et al as used in the PenTAG model, results were more similar (See Appendix 9 for sensitivity analyses in the Novartis model). PenTAG has assumed that costs such as emollients and treatment for infections were cost neutral and did not include them in their cost calculations. The effect of including such additional costs is to dilute the treatment cost differences of immunosuppressants and topical corticosteroids.

It is not possible to directly compare the results of the Fujisawa model and the PenTAG models due to the differing outcomes used (disease free days and utilities respectively.) However, PenTAG never finds tacrolimus to dominate corticosteroids.

Summary of economic analyses

One published cost effectiveness analysis of tacrolimus was identified. It has significant methodological flaws and is less relevant to the NHS than the model supplied by Fujisawa.

- The Novartis model of pimecrolimus concludes that the new immunosuppressant is likely to be more cost effective than treatment with emollient alone in terms of cost utility. No comparison to steroids is included, which we believe is more clinically relevant. Although analysis of uncertainty is incomplete, probabilistic sensitivity analysis suggests the probability of the ICER being below £30,000 per QALY is only 0.6 in children.

- The Fujisawa model of tacrolimus does not calculate cost utility and so comparison with other technologies is difficult. Although the value of outcomes is difficult to judge, results suggest that tacrolimus may be considered a cost effectiveness alternative to steroids. However, this result is driven by the small calculated difference in costs between tacrolimus and topical corticosteroids than we consider likely.

- The PenTAG model demonstrates a large degree of uncertainty in about the cost effectiveness of pimecrolimus and tacrolimus in first or second line use compared to topical corticosteroids.

- In all cases we estimate immunosuppressant regimens to be more costly than alternatives and differences in benefits to be small and subject to considerable uncertainty.

- Taking into account the extensive uncertainty in underlying parameters, the probability that either pimecrolimus or tacrolimus are more cost effective than steroids at levels of willingness to pay which have been demonstrated by NHS decision makers in the past, is not high.

- The comparison of pimecrolimus to emollients alone examines a clinical situation which we believe is not currently common i.e. steroids are completely contraindicated or unnacceptable. Although the ICER is lower, as would be expected, in this comparison than against an active comparator, the probability that pimecrolimus is more cost effective at levels of willingness to pay that appear to be acceptable to the NHS is not high (0.55)

6 Cost implications for the NHS

Estimating cost-impact for the NHS of adopting the new topical immunosuppressants is hampered by a number of important uncertainties. Firstly, it is uncertain how many children and adults suffer from atopic eczema in the UK. The cumulative prevalence in children by the age of 11 has been estimated at between 15% and 20%,[16] but as onset may be at any age (although the majority occurs by the age of 5) we do not how this onset is distributed and this is further complicated by the fact that eczema spontaneously resolves childhood cases. Estimates from the Health Survey of England (2001) found that 16% of men and 10% of women had ever suffered from eczema. A prevalence study of 9786 patients in a rural UK practice found point prevalence of visible eczema to be 11.1% in children up to the age of 15 and 2.3% in adults over that age.[93]

The position of the new treatments among existing treatment options is also currently unclear. Is pimecrolimus posed as an alternative to topical corticosteroids, or emollient? Should the place of tacrolimus be considered as a second line treatment after failure of corticosteroids (and if so of what strength?) or as a first line treatment for those who are unwilling or unable to use topical corticosteroids? In any case, what proportion of emollient or topical corticosteroids use might be expected to be replaced, or added to?

There are also questions of appropriateness of population – are adults or children more suitable for topical immunosuppressants? May the new treatment be most appropriate only for certain types of eczema (facial eczema for example)? Adoption of the new treatments among these specific subgroups would affect the amount of agent used and the subsequent budget impact.

The vast majority of eczema (84%) has been estimated to be of mild severity, with 14% being moderate and 2% being severe.[9] Changes in the topical treatment of mild to moderate eczema will therefore have much greater impact than changes to the topical treatment of moderate to severe eczema.

Given these uncertainties, it seems most appropriate to look initially at the absolute cost differences between treatments. This approach assumes that all other treatment costs – such as amount of cream used, number of visits to physicians, incidence and treatment of adverse affects such as infections etc. are the same, regardless of treatment.

Currently, atopic eczema is likely to be treated by emollients and topical corticosteroids. The cost per gram of these treatment is small. The BNF shows that standard emollients treatments cost 1p or less per gram. Steroids cost 3p-14p per gram with most commonly used preparations costing 6p or less. By contrast, pimecrolimus costs 59p per gram, and tacrolimus costs 62p-68p. In other words the new treatments are at least 10 times more expensive than most commonly used corticosteroids, and four times more expensive than the most expensive. As yet, there is no evidence about the amount of pimecrolimus or tacrolimus needed compared to the amount of topical corticosteroids although it is reasonable to assume that amounts used would be similar.

None of the published trials of pimecrolimus records the amount of cream used by participants. In our model we estimated amount use through guidelines for topical corticosteroids and average affected body area reported in trials. Amounts of tacrolimus used was reported by three trials in children[72;73;76] and one in adults.[83] Patients in the Boguniewicz trial were restricted to those who could be treated with 10g or less of cream per day, so this may underestimate use in a non-restricted population. It is unknown what, if any, differences there may be between a general population's use of treatment compared to

that in a monitored trial population. Results for various estimates of topical preparation use are shown below.

Table 51: Estimated average amount of topical agent used per day

Source	Population	Severity	Mean cream used per day
Boguniewicz et al[72]	Children	Moderate to severe	2.6g
Paller et al[73]	Children	Moderate to severe	4.4g
Hanifin et al[76]	Children	Moderate to severe	4.6g
PenTAG	Children	Mild to moderate	2.5g
	Children	Moderate to severe	2.5g
Petan et al[83]	Adults	Moderate to severe	2.3g
PenTAG	Adults	Mild to moderate	3.5g
	Adults	Moderate to severe	6.8g

There are some limitations in all of these estimates. However, using a minimum and maximum estimate of the cost of corticosteroids and the amount of cream used, the added cost of using pimecrolimus instead of topical corticosteroids per patient over one year is estimated below. We have assumed no discount would be available on the lost price for pimecrolimus or tacrolimus.

Table 52: Additional cost of pimecrolimus compared to corticosteroids per patient per year.

	Low estimate	Moderate estimate	High estimate
Cost of pimecrolimus per g (£)	0.59	0.59	0.59
Cost of steroid (per g)	0.03	0.06	0.14
Difference in cost (per g)	0.59	0.56	0.48
Amount of agent used (g per day)	2.5	4.4	6.8
Amount used per year (g)	912	1606	2482
Cost pimecrolimus (£/yr)	538	948	1464
Cost corticosteroid (£/yr)	27	96	347
Additional cost for pimecrolimus	£511	£852	£1117

Table 53: Additional cost of tacrolimus compared to corticosteroids per patient per year.

	Low estimate	Moderate estimate	High estimate
Cost of tacrolimus per g (£)	0.62	0.62	0.62
Cost of steroid (per g)	0.03	0.06	0.14
Difference in cost (per g)	0.59	0.56	0.48
Amount of agent used (g per day)	2.5	4.4	6.8
Amount used per year (g)	912.5	1606	2482
Cost tacrolimus (£/yr)	566	996	1539
Cost corticosteroid (£/yr)	27	96	347
Additional cost for tacrolimus	£538	£900	£1192

As a rough estimate of the impact on Primary Care Trust (PCT) covering 150,000 people (the average size of PCTs in the South West Region), we assumed that a point prevalence of eczema of 13.4% based on a prevalence study in the UK in 1996.[93] This suggests 20,100 people per PCT requiring eczema treatment. Of these, we assume that 91% (18,291) have mild to moderate eczema and 9% (1,809) have moderate to severe eczema. The table below shows the low and high estimates of the additional cost of treatment

assuming that immunomodulators replace different percentages of topical corticosteroid creams. Clearly this estimate must be viewed as speculative.

Table 54: Estimate of additional spending in a PCT at different levels of pimecrolimus uptake

Percentage of people with eczema switching to receive pimecrolimus	1%	2%	5%	10%
Total number of people treated	183	366	915	1829
Low cost estimate for additional cost (£)	93,513	187,026	467,565	934,619
High cost estimate for additional cost (£)	204,411	408,822	1,022,055	2,042,993

Table 55: Estimate of additional annual spending in a PCT at different levels of tacrolimus uptake

Percentage of people with eczema switching to receive tacrolimus	1%	2%	5%	10%
Total number of people treated	18	36	90	181
Low cost estimate for additional cost (£)	9,684	19,368	48,420	97,378
High cost estimate for additional cost (£)	21,456	42,912	107,280	215,752

7 Discussion

7.1 Main Results

Atopic eczema is a common condition in childhood, which may persist into adulthood. Current treatment regimens rely on education, consistent and liberal use of emollients and active treatment with various potencies of topical corticosteroids when eczema is problematic, these may be combined with bandaging (wet wraps). More severe and persistent cases may also be treated systemically.

While topical corticosteroids are effective, there are concerns about their use, especially more potent preparations for children. Adverse effects can include skin thinning and they may be less suitable for long-term use on sensitive areas such as the face. However, careful use of topical steroids is considered by most clinicians to be appropriate and safe in eczema.

7.1.1 Clinical effectiveness

We have carried out a systematic review of the effectiveness of pimecrolimus compared to vehicle and topical corticosteroids in mild to moderate atopic eczema, and of tacrolimus compared to vehicle and topical corticosteroids in moderate to severe atopic eczema.

Pimecrolimus

This assessment included six publications relating to five trials as two of these reported different aspects (effectiveness and quality of life) of the same trial. There were two trials conducted in children and three conducted in adults. *A further three studies have been provided on a commercial in confidence basis and are not discussed*

Four trials used vehicle as a comparator and only one trial compared pimecrolimus with topical corticosteroids.

Four trials did not state, or had unclear or inadequate methods of randomisation and blinding. Duration of follow up was three to 53 weeks. Attrition rates were high: 12.7% to 51.5%. High levels of attrition were especially noted for lack of efficacy.

Pimecrolimus is more effective than vehicle at treating atopic eczema. However, vehicle is a placebo and is not the relevant comparator in clinical practice.

A comparison with topical corticosteroids is the most appropriate in most cases. However, data were limited for this comparison to one published study [69] with only three weeks' follow up. Greater effectiveness with potent corticosteroids was shown, however, this comparison is unlikely to inform most clinical decisions where the place of pimecrolimus could be as an alternative or adjunct to low potency topical corticosteroids. In addition, the population studied had moderate to severe eczema, whilst pimecrolimus is indicated in mild to moderate disease.

Most of the trials reported on clinician measures of effectiveness such as the IGA and EASI. Two of the trials reported on quality of life (QoL). Each reported different measures of QoL, and only one in children looked at the effect on the family through the Parents' Index of QoL. Quality of life was not reported in the trial comparing pimecrolimus with topical

corticosteroids. Better QoL after using pimecrolimus compared to vehicle was reported by both parents of children using mean Parent's Index of QoL with eczema and adult patients using reduction in both the QoL Index of AD and the Dermatology Life Quality Index (DLQI).

Levels of adverse effects do not appear to be significantly different with pimecrolimus compared to other treatments. However, the absolute numbers are small and the trials may not be powered to identify such differences. Levels of drop out for adverse effects, which may give an indication of severe adverse effects, were not high, or very different between pimecrolimus and its comparators.

Tacrolimus

There were 12 trial reports of RCTs involving tacrolimus. Two of these reported on different aspects (effectiveness and safety) of the same trial, while another reported on quality of life in a subset drawn from two RCTs. There were therefore a total of 10 trials included - four trials which reported on tacrolimus use in children and six in adults.

Five trials (two in children and three in adults) used vehicle as a comparator. Two trials in children compared tacrolimus to a mild topical corticosteroid. Three trials compared tacrolimus to a potent topical corticosteroids in adults, one of these also used a mild topical corticosteroid on the face and neck.

Half the trials (5/10) described did not state methods of randomisation or gave methods that were unclear or inadequate. The same was true for descriptions of treatment allocation and blinding.

Follow up periods range from three to 24 weeks and attrition rates were high, ranging from 8% to 68.4%.

Pooled results show that both 0.03% and 0.1% tacrolimus are more effective in treating moderate to severe eczema than vehicle. However, as with pimecrolimus, vehicle is not the most appropriate comparator to inform clinical practice.

Pooled results from treatment with topical corticosteroids show that in children, mild topical corticosteroids were less effective than 0.03% tacrolimus on a global measure of clinical evaluation (PGE). Significantly more patients treated with tacrolimus were rated as having "excellent improvement" or better (>=90% improvement). However in adults, the same measure was only available for meta-analysis on the basis of "marked improvement" or better (>=75% improvement"). In this case, no significance difference between treatment with potent topical corticosteroids and 0.1% tacrolimus was seen.

Most trials (8/10) include both 0.03% and 0.1% tacrolimus. It is therefore possible to compare the effectiveness of these two potencies of treatment in meta-analysis. Again, the results are somewhat unclear. At three weeks of follow up, it appears that 0.1% tacrolimus is more effective than 0.03% tacrolimus based on an improvement of PGE of 75% or more, as well as improvement in mean area under the curve. However, this is not the case using a PGE measure of 90% improvement or better.

At 12 weeks, more patients treated with 0.1% tacrolimus improved by at least 90% (PGE) than patients treated with 0.03% tacrolimus. However, a significant difference was seen on the basis of other measures such as 75% or better improvement according to the PGE, change in EASI score, and affected BSA, nor in patients centred measures such as pruritus score or patient assessment of disease control.

Two trials report on Quality of Life (QoL). One, comparing 0.03% and 0.1% tacrolimus to vehicle reports on values for adults and children based on the Dermatology Life Quality Index (DLQI) in adults and the Children's DLQI in children and toddlers. Most dimensions were significantly better after treatment with tacrolimus than treatment with vehicle. One study of 0.1% tacrolimus compared to topical corticosteroids in adults also reported quality of life in adults. However, this is only reported as an improvement from baseline. Significance levels are not reported though tacrolimus has slightly greater improvement at both 3 and 6 months.

The evidence base for pimecrolimus and tacrolimus does not, therefore, provide a particularly clear basis for clinical and policy decisions. Although trials have some methodological limitations (particularly high levels of attrition) both agents appear superior to vehicle. Since most people with eczema can be treated with steroids, given appropriate education, support and monitoring, this is the most important comparator to inform possible changes in clinical practice. The evidence base in this regard is limited and sometimes contradictory.

7.1.2 Costs and cost-effectiveness

Compared to topical corticosteroid based regimens, either as a first or second line treatment, pimecrolimus is unlikely to be considered a cost-effective option in any of the child or adult scenarios with mild to moderate body or facial eczema. However, findings are associated with considerable uncertainty. One way sensitivity analyses suggests that the analysis is particularly sensitive to the cost of pimecrolimus, and also to the effectiveness of low potency topical corticosteroids. Our model is based on one possible approach to corticosteroid treatment and the inputs for effectiveness are not based on good quality data. In all pimecrolimus models, differences in accumulated QALYs were small. Probabilistic analyses showed that topical corticosteroid regimens were more likely than regimens including pimecrolimus to be cost effective at all levels of willingness to pay. The probability that corticosteroid regimens were more effective was relatively low in all cases.

Despite BNF cautions regarding the use of corticosteroids stronger than mild preparations on the face or in other sensitive areas, clinical advice is that more potent corticosteroids are used as a treatment option in these sites. The use of corticosteroids as a comparator is therefore valid in most cases.

For the small population unable or unwilling to use topical corticosteroids, pimecrolimus was shown to be more cost-effective than emollient regimens (rescue therapy with corticosteroids was permitted in both arms) at a cost of £9,684 per QALY in children and £16,646 per QALY in adults. However, these results are subject to considerable uncertainty and the probability that pimecrolimus would be cost effective is not substantially greater than the corresponding probability for steroids where decision makers are willing to pay more than £20,000 to achieve an additional QALY. Where decision makers are not willing to pay this amount, steroids are increasingly likely to be more cost effective as willingness to pay falls.

For tacrolimus, results of the model suggest that tacrolimus may be cost effective as first line treatment in children with moderate to severe eczema on the face or body, and as second line treatment of the body. However, while the cost effectiveness acceptability curves (CEACs) show that tacrolimus as first line therapy is more likely than other regimens to be cost effective above a willingness to pay of about £10,000 per QALY, the probability is low (less than 40%) and similar to the probability that the other regimens are cost-effective. In the moderate to severe facial eczema CEAC for children, all three treatment regimens

converged at about £10,000 suggesting all are equally likely to be the most cost effective. Absolute differences in QALYs conferred by the different treatment regimens are small.

In adults, baseline case results suggest that tacrolimus offers more QALYS for more money (£68,428 per QALY on the body and £11,882 per QALY on the face) and may be cost effective on facial eczema depending on the willingness to pay. However, the results should be viewed with considerable caution, as absolute differences in QALYs are negligible and probability of tacrolimus being cost effective is low at all levels of willingness to pay in both body and facial eczema.

Given the large amount of uncertainty in the cost effectiveness analyses, we cannot say with confidence whether or not topical immunosuppressants for atopic eczema are cost-effective. However, it should be borne in mind that the new drugs are much more expensive than corticosteroids (£0.61-0.68 per gram, compared to £0.03-£0.15).

There may be sub-groups of eczema sufferers who would benefit from use of new immunosuppressants, for example, those who have become resistant to the treatment effects corticosteroids, thereby requiring very regular use with attendant risk of skin thinning. It should be borne in mind that the effects of similar long term use of topical immunosuppressants is not yet known.

Compared to emollients with corticosteroids used as a rescue therapy only, pimecrolimus is cost effective in both adults and children (at £9684 / QALY and £16,646 / QALY respectively.) However, this is likely to be relevant to only a minority of eczema sufferers.

7.2 Assumptions, limitations and uncertainties

7.2.1 Quality of available data

Many trials do not report how they approached randomisation and allocation concealment, aspects of study design that are known to have an effect on estimated treatment effect. In addition, it may be difficult to maintain blinding post randomisation given that topical immunosuppressants have commonly reported application site reactions.

Length of follow up is short for most papers. Eczema is a chronic relapsing condition that may require many years of treatment. At the moment, there are very few long term data. This may be particularly important for adverse effects. Currently, the effects of very long-term use of topical immunosuppressants are unknown, including whether tachyphylaxis may be a problem with the new agents as well as with corticosteroids.

Two trials have been combined in each of the published papers by Eichenfield and colleagues 2002[64] and Hanifin and colleagues 2002.[76] No full explanation is given in the published papers. However, data from the original trials is given separately in reports to the FDA or EMEA by the manufacturers. Using results from these separate trials in the meta-analysis, it can be seen that differences in effectiveness as measured by the IGA score between pimecrolimus and vehicle which are reported in the paper by Eichenfield and colleagues 2002[64] are non-significant in one of these trials when reported separately. However, given the similarity of the trials it is appropriate to combine the results to increase power.

7.2.2 Populations studied

Clinical trials may not represent clinical realities – for example the wash out periods required for other treatments, including topical corticosteroids, may not be realistic in clinical practice.[94] In addition, many of the included trials excluded people with clinical skin infection, and infected lesions are contraindicated for both pimecrolimus and tacrolimus. In reality, skin infection is common with atopic eczema, particularly with more severe eczema.

Although pimecrolimus is licensed for use in patients with mild to moderate eczema, two studies in adults, by Meurer and colleagues 2002 and Luger and colleagues 2001[67;69] were conducted in adults with moderate to severe eczema and may not be transferable to those with mild to moderate eczema. This is particularly important in the trial by Luger and colleagues, which compares pimecrolimus to a potent topical steroid.

7.2.3 Appropriateness of comparisons

Assessment of topical immunosuppressants is hampered by the lack of relevant comapartor data, especially for pimecrolimus. Most of the trials of pimecrolimus and tacrolimus used vehicle as a comparator in line with UK and European drug licensing requirement to demonstrate efficacy. However, such studies are unlikely to assist clinicians in their decision about where to place these new treatments within an already complex algorithm of possible treatments.[25] As well as topical corticosteroids, it would be useful to know how effective immunosuppressants are compared to treatments such as wet wraps, particularly in extensive eczema in children. A recent systematic review suggested that the vehicle "placebo" effect is relatively high, accounting for as much as 30% of improvement[20] and this has been shown in some studies included in this review. Expert opinion stresses the importance of correct and consistent use of emollient in controlling atopic eczema, especially in milder cases.

It has also been questioned whether allocating patients (especially children) with severe eczema to an inactive treatment is ethical[25] when active alternatives are known to exist. High attrition rates were shown in the trials further increasing uncertainty.

Patterns of topical corticosteroids use vary, largely because there is little conclusive evidence to indicate the best patterns of use.[20] Different practitioners may adopt a "step up" or a "step down" approach to management. In addition, current evidence suggests that a few days application of a higher potency steroid may be as effective as a longer course of mild corticosteroid in mild to moderate eczema.[95] Once a day application may be as effective as twice daily application (currently under review for the NICE programme). Such variation of prescribing practice has yet to be fully studied but could have implications for the cost-effectiveness of topical corticosteroids and alternative treatment options.

7.2.4 Measurement of treatment success

Measures used to assess the effectiveness of treatment may be problematic (as discussed in Section 3.1.6). Few trials included measures of patient assessment of success or quality of life.

In trials the primary outcome measure was a clinician estimate of improvement such as the IGA or PGE. Such scales have not been tested for validity, reliability, sensitivity to change. However, a simple method of assessing the affected body surface area of patients with

atopic eczema using the rule of nines was found to have poor inter-rater reliability[27] and it is possible that global assessments of improvement may similarly be of limited reliability.

There is also inconsistency in the definition of the different expressions of eczema, described variously as “flares”, “problematic eczema”, exacerbations” and so on. These categories are often subjective and not clearly described leading to uncertainty around whether or not similar states are being described.

In some trial reports, it is unclear why median values are reported where means would appear to be more appropriate. The effect of this is unknown.

There were relatively high rates of attrition from many of the included trials. This was especially true in the vehicle control arms. It is possible that there are high levels of expectation about the effectiveness of eczema treatment through topical corticosteroid experience that are not met by a placebo treatment alone. The withdrawals may lead some detection bias in intention to treat analyses although this is likely to be small.

7.2.5 Costs

Costs of treatments for atopic eczema include consultation costs in primary and secondary care as well as the costs of treatment. The number of visits made by those with atopic eczema to primary and secondary care is uncertain, and we could only find data from Australia to inform the model, which may not accurately reflect activity in the UK. In our cost-effectiveness models, the majority of treatment costs are accounted for by the cost of consultations. This has the effect of lessening the incremental costs between the treatment options and may bias in favour of the more costly new treatments.

In addition, costs of secondary care consultations are much higher than those in primary care and overall costs, particularly in the tacrolimus models, will change if the balance of consultations between primary and secondary care alters. Currently, tacrolimus is licensed for prescription by ”dermatologists and physicians with extensive experience of atopic dermatitis with immunomodulating therapy”. This has been interpreted differently in different localities and may change over time as more GPs gain experience of using topical immunosuppressives or in the event of a change in the licensing.

7.2.6 Key Modelling Challenges

The main challenges surrounding the modelling of eczema relate to data limitations, uncertainty of assessment measures used, and wide range of legitimate variation in the treatment pathway. In relation to the Markov model developed for our assessment, the following issues are highlighted as presenting specific problems.

Treatment pathways and transitions

Limitations in the published data and inherent variability in the treatment of eczema present difficulties in accurately determining the transition probabilities for the model. Previous studies have relied on panel judgements and assumptions to populate many of these aspects in the model. We have also had to use clinician opinion to establish what alternative treatment may be offered where initial treatment is unsuccessful. Clinical practice varies and these assumptions are uncertain. Given this, it was essential to include comprehensive sensitivity analysis across the range of modelled variables.

While wet-wrapping may be often used to treat children with extensive or very itchy eczema, we did not include this in our model. This was due to a lack of clarity about where wet-wrapping fits in the overall treatment pathways, as well as lack of data about costs and effectiveness. We also excluded systemic treatments from the child models, due to the very small number of children receiving this. These are acknowledged limitations of our model.

Utility levels

Whilst the method of relating treatment states to eczema severity via a four-way matrix (as described in Section 5.1.1) simplifies the representation of severity within the model, there are issues about the mapping of severity to treatment states (i.e. what percentages to use in the model). Also the use of just four levels of severity remains quite a coarse measure (although it may be all that is practicable and sufficient for modelling outcomes). More importantly however eczema severity is not a direct measure of utility. The relation of severity to utility in eczema presents particular challenges, compounded by the wide variety of methods and metrics used to measure severity in eczema and to elicit preferences.

We have not explored the impact of varying disease severity mix in treatment states. Also, the fundamental limitation of the Markov approach (lack of memory) means that as the model is run, the severity mix in a given treatment state does not change as a result of patients with partial response recycling.

Cost levels

Assessment of costs for different treatment states is prone to a large level of variability. Factors such as amount of ointment used, frequency of use, varying adherence to treatment regime all impact on the overall costs associated with treatment states. No UK data was available for the number of visits to a primary or secondary care practitioner and the Australian values used may not be appropriate to this setting.

Cycle Time

The selection of four weeks as the cycle time within the Markov model is open to question although there seems some consensus that this is acceptable. One alternative considered a two weekly cycle interval to reflect a minimus length of courses of treatment. We have tried to allow for the fact that topical corticosteroids are not used for as long as four weeks through costs adjustment.

Markovian assumption

A recognised limitation of Markov models is that transition to a new state cannot be influenced by the previous pathway taken to reach the current state. This is important for eczema treatment since previous treatment often influences future options and suggests a role for simulation modelling in this area.

7.3 Research Recommendations

- Good quality RCTs and further economic analysis of pimecrolimus in adults and children compared to appropriate potencies of topical corticosteroids in mild to moderate eczema are needed.
- Further large good quality RCTs of tacrolimus in adults and children compared to appropriate potencies of topical corticosteroids in moderate to severe eczema are needed.

- Data on long term use of immunosuppressants, particularly the incidence and nature of adverse effects.
- There is a dearth of information about the normal treatment patterns and consultations for eczema, including health service utilisation, for sufferers in the UK. Observational studies are needed to provide basic information about this patient group.
- Randomised controlled trials of the effects of different potencies of topical corticosteroids and different treatment regimens.
- Randomised controlled trials of the effects of wet-wrapping in children are required.
- Researchers and clinicians should try to reach a consensus about how to measure treatment success in treatments of atopic eczema, informed by further research into the reliability of methods of measurement.
- Further studies using general population estimates of utility values for the various severities of eczema would be helpful for future cost-utility analyses.
- Given the limitation of the Markov model for such chronic relapsing conditions, further modelling using other techniques (such as Discrete Event Simulation) are required.
- The role of clinician and patient education in supporting the appropriate use of topical steroids should be investigated further.

8 Conclusions

There is limited evidence from a small number of RCTs that pimecrolimus is more effective at controlling mild to moderate eczema than vehicle. Evidence is lacking for the effectiveness of pimecrolimus against steroid preparations in patients with the relevant severity of atopic eczema, which would form the usual alternative option in most clinical practice.

Preliminary modelling analyses suggests that pimecrolimus is unlikely to be cost effective compared to topical corticosteroids in the treatment of adults and children with mild to moderate eczema of the face or body. However, levels of uncertainty are high.

The evidence base for the use of tacrolimus in moderate to severe eczema is also limited, though more extensive than that for pimecrolimus. At both 0.03% and 0.1% concentrations, tacrolimus appears to be more effective than vehicle. There is little evidence comparing tacrolimus to appropriate potencies of topical corticosteroids. Tacrolimus appears to be more effective than mild potency topical corticosteroids in controlling moderate to severe eczema although this is not the most clinically relevant comparator. No significant difference was shown between tacrolimus and potent steroid preparations, although this may be due to inadequate power in the studies carried out to date. There is some evidence that 0.1% tacrolimus is more effective than 0.03%, although the results are not striking and sometimes contradictory findings.

Our Markov modelling study suggests that tacrolimus may be cost effective compared to topical corticosteroids in the treatment of children with moderate to severe eczema of the face or body. However, levels of uncertainty are high, and it is not possible to draw conclusions with confidence based on available data. The Markov approach is hampered in eczema by the wide range of treatment ordering options.

Short term side effects of treatment with both pimecrolimus and tacrolimus are relatively common but mild. Experience of very long term use of these topical agents is lacking and so the risk of rare but more serious side effects remains unknown.

9 Appendices

9.1 Appendix 1: Children's Quality of Life questionnaires

CHILDREN'S DERMATOLOGY LIFE QUALITY INDEX

Hospital No
Name:
Age:
Address:

Diagnosis:

Date:

CDLQI SCORE: ☐

The aim of this questionnaire is to measure how much your skin problem has affected you OVER THE LAST WEEK. Please tick ✓ one box for each question.

1.	Over the last week, how **itchy**, **"scratchy"**, **sore** or **painful** has your skin been?	Very much ☐ Quite a lot ☐ Only a little ☐ Not at all ☐
2.	Over the last week, how **embarrassed** or **self conscious**, **upset** or **sad** have you been because of your skin?	Very much ☐ Quite a lot ☐ Only a little ☐ Not at all ☐
3.	Over the last week, how much has your skin affected your **friendships**?	Very much ☐ Quite a lot ☐ Only a little ☐ Not at all ☐
4.	Over the last week, how much have you changed or worn **different** or **special clothes/shoes** because of your skin?	Very much ☐ Quite a lot ☐ Only a little ☐ Not at all ☐
5.	Over the last week, how much has your skin trouble affected **going out**, **playing**, or **doing hobbies**?	Very much ☐ Quite a lot ☐ Only a little ☐ Not at all ☐
6.	Over the last week, how much have you avoided **swimming** or **other sports** because of your skin trouble?	Very much ☐ Quite a lot ☐ Only a little ☐ Not at all ☐
7.	Last week, was it **school time?** → **If school time**: Over the last week, how much did your skin affect your **school work**?	Prevented school ☐ Very much ☐ Quite a lot ☐ Only a little ☐ Not at all ☐
	OR	
	was it **holiday time?** → **If holiday time**: How much over the last week, has your skin problem interfered with your enjoyment of the **holiday**?	Very much ☐ Quite a lot ☐ Only a little ☐ Not at all ☐
8.	Over the last week, how much trouble have you had because of your skin with other people **calling you names**, **teasing**, **bullying**, **asking questions** or **avoiding you**?	Very much ☐ Quite a lot ☐ Only a little ☐ Not at all ☐
9.	Over the last week, how much has your **sleep** been affected by your skin problem?	Very much ☐ Quite a lot ☐ Only a little ☐ Not at all ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been?	Very much ☐ Quite a lot ☐ Only a little ☐ Not at all ☐

Please check that you have answered EVERY question. Thank you.

9.2 Appendix 2: Research Protocol

FINAL DRAFT PROTOCOL: THE EFFECTIVENESS AND COST-EFFECTIVENESS OF PIMECROLIMUS AND TACROLIMUS FOR ATOPIC ECZEMA

A. Details of the research team

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Dr. Ken Stein, Senior Lecturer in Public Health, Peninsula Technology Assessment Group (LEAD)
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Ms Liz Payne, Information Specialist, Southampton Health Technology Assessment Centre

B. Full title of research question

What is the effectiveness and cost-effectiveness of pimecrolimus and tacrolimus for atopic eczema relative to current standard treatments.

C. Clarification of research question and scope

Atopic dermatitis (or eczema) is a skin condition characterised by inflammatory lesions of very varied manifestations including redness, dryness, itching, thickening of the skin and scaling. Lesions may be limited to small isolated patches resolving within a short time or can evolve into widespread persistent disease or recurrent flares, sometimes complicated by bacterial or viral skin infections. Objective measurement of eczema severity is difficult. Standard measurement scales exist (such as the Atopic Dermatitis Severity Index, ADSI, and many others)[96] encompassing the extent of areas affected and the intensity or spectrum of symptoms, including erythema (redness), pruritus (itching), exudation (weeping), excoriation (peeling) and lichenification (skin thickening).

Although a chronic, non-fatal condition, eczema causes considerable distress and costs to patients and carers, including itching and sleep disturbances, the need for special clothing, frequent use of messy ointments and emollients, and often restriction of sports activities and social interaction with consequent risk of stigma and isolation.[97]

Atopic eczema is likely to be determined at least in part by genetic susceptibility, triggered by a range of environmental factors such as irritants, temperature, infections, stress, clothing and allergies to house dust mite,, some foods and pollen. Its prevalence has increased considerably over the last 30 years, for reasons that are unclear, and currently effects about 6.5% of the population each year.[98] Eczema affects 5-15% of children in school age,[97] with 60% of cases starting within the first year of life and 85% within five years.[99] Most children present a mild form, with spontaneous remission within childhood in 40-60% of the cases.[99] Adults account for a third of the cases[4] and generally present with more severe disease.

Eczema management mostly occurs in primary care, and includes a combination of preventative measures with topical treatment. Patients are advised to avoid contacts with allergens, such as detergents, wool, lanolin, select clothing and to reduce house dust mite,

often in association with food restrictions or supplementation and prolongation of breast-feeding in infants.[3;4]

Topical treatment frequently relieves symptoms and may facilitate remission or clearance of eczema. Many patients are recommended abundant use of skin moisturisers or emollients. Standard treatment also includes corticosteroids[3;100;101] of mild potency for maintenance therapy or high potency to treat flares. Despite the introduction of newer, safer corticosteroids,[101] concerns around potential local and systemic side effects of corticosteroids (such as skin atrophy, disfiguring striae (lines on the skin) or telangiectasia (redness), adrenal suppression and growth retardation[100]) still remain in many patients and parents, especially regarding long-term use.[102] Such concerns may hamper adherence to treatment, especially in paediatric or mild cases, whilst the balance between potential benefits and discomfort and risk to the patient is yet little studied. Corticosteroids should also be use with great caution in certain delicate areas of skin such as the eyelids.

The recent introduction of advanced immunosuppressive therapy (calcineurin inhibitors) is thought to offer potential enhanced effectiveness and tolerability.[103]

- Tacrolimus (FK506) is a macrolide compound derived from Streptomyces Tsukubaensis.[104]

- Pimecrolimus is a macrolactam and the parent compound to a class of semi-synthetic derivatives for topical use, including SDZ ASM 981.[101;105]

Their relevance for eczema is similar and resides in the potential to inhibit T-cell activation interrupting the process between T-cell ligation, binding to macrophilin-12 and forming a complex which blocks the inhibition cytokine gene transcription. A second mechanism seems to reduce symptomatic pruritus, by inhibiting the release of histamine and inflammatory mediators and blocking activation of IL-3 and IL-5 cytokine genes. Thirdly, the stimulation of autologous lymphocytes regulated by Langerhans cells is inhibited.[101]

Compared to corticosteroids, pimecrolimus and tacrolimus may offer a better side-effect profile, with marked reduction of skin atrophy,[104] yet proof of higher efficacy in controlling pruritus in children and adults has not been clarified.

Limited knowledge has been collated on the effect of available treatments on disease progression and on sustainability of response. It is believed that pimecrolimus and tacrolimus might be effective in decreasing relapse and occurrence of flares in the long term. Tacrolimus may also offer a more acceptable therapy, with faster efficacy and better tolerability compared to other immunosuppressants, such as azathioprine, cyclosporine, methotrexate, phosphodiesterase inhibitors or interferon Gamma.[106]

There is limited pre-existing work on the effectiveness of pimecrolimus and tacrolimus. A previous HTA review[4] on treatment for eczema includes a brief overview on pimecrolimus and tacrolimus treatments; at that time evidence was limited to two small trials of effectiveness and one pre-clinical trial.

Pimecrolimus cream (Elidel, 1%, Novartis) was first licensed in 2000 by the FDA and in Japan, and was introduced in the UK in 2003 for acute treatment of mild to moderate atopic eczema, including flares in adults and children over the age of two. The recommended dose is twice daily until symptoms clear.

Tacrolimus cream (Protopic, 0.03%, Fujisawa) was registered in the EC in February 2002 for topical use and licensed in the UK in March/April 2002 for adults and children (over the age of two) with moderate to severe atopic eczema where other treatments have failed. 0.1% tacrolimus is only licensed for use in adults. The recommended dose is twice daily application until symptoms clear and for a further week afterwards. Currently it is advised that treatment with tacrolimus be initiated by a specialist.

For both treatments, exposure to excessive UV light should be avoided.

Scope

This technology assessment aims to ascertain clinical and cost effectiveness of pimecrolimus in the treatment of mild and moderate atopic eczema, and tacrolimus in the treatment of moderate to severe atopic eczema. For both drugs, adult and child (over the age of two) populations will be assessed. All randomised trials of pimecrolimus versus any emollient or topical corticosteroids will be included. All randomised trials of tacrolimus versus topical corticosteroids, short courses of systemic corticosteroids, other immunosuppressives or phototherapy will be included.

A cost-utility analysis will be carried out if sufficient data are available from the literature, or other sources. If a well designed cost-utility analysis is already available and required data is available, this will form the basis for the assessment of cost-effectiveness.

Intervention

Pimecrolimus cream (1%) (Elidel®, Novartis) for mild to moderate atopic eczema.

Tacrolimus ointment (0.03% and 0.1%) (Protopic®, Fujisawa) for moderate to severe atopic dermatitis unresponsive or intolerant of standard treatment.

Comparator

Current standard treatment - regular emollient used in conjunction with topical corticosteroids in mild to moderate atopic eczema and topical corticosteroids, short courses of systemic corticosteroids, other immunosuppressives or phototherapy in moderate to severe atopic eczema.

Populations of interest

Children (over the age of two) and adult patients recruited in primary care clinics or specialised dermatology clinics. Patients with mild to moderate eczema and patients with moderate to severe eczema.

- Inclusion criteria

Participants with a primary diagnosis of atopic eczema as made by a physician or using defined criteria such as those described by the UK working party.[107]

- Exclusion criteria

Studies will be excluded if patients with the following characteristics are not reported separately:

Eczema secondary to other inherited or acquired disorders of immunodeficiency
Seborroic dermatitis
Allergic or contact eczema
Nummular (discoid) dermatitis
Fungal or parasitic skin infections
Cutaneous T-cell lymphoma

Outcomes

The review will be focussed on patient centred outcomes.

- Effectiveness: Immediate response rates (using standardised measures of improvement, symptoms and/or severity scales), sustained response rates, avoidance of flares.
- Duration of treatment, changes in therapy
- Adverse effects (including deterioration of symptoms, skin atrophy, systemic toxicity, treatment withdrawal, incidence of local skin infections)
- Quality of life: Patients and parents' perceived quality of life.
- Cost effectiveness (cost-effectiveness analyses only)

Patient preferences

Where available, information on the treatment preferences of patients and caregivers will be extracted from included trials.

Time perspective

Follow up of at least three weeks.

D. Review and report methods

Search strategy

A preliminary search has established that no systematic reviews on this topic have yet been completed. A search strategy will be developed for the electronic databases shown below. For the question of effectiveness, publications that describe trials comparing pimecrolimus to emollients and topical corticosteroids, and those comparing tacrolimus to topical corticosteroids, short courses of systemic corticosteroids, other immunosuppressives or phototherapy will be sought. Only studies with an experimental design and a comparison group will be considered for inclusion.

The search will be performed in:

- Electronic databases, including Medline PubMed, Embase, The Cochrane Library (including Cochrane Systematic Reviews Database, Cochrane Controlled Trials Register, Cochrane Skin Group Specialised Registrar), Science Citation Index, Web of Science Proceedings, DARE, NHS EED, HTA databases;
- Trial registers in the UK (National Research Register), Current Controlled Trials, US (Clinical Trials.gov) Canada;
- Bibliographies
- Contacting research groups and industry
- Websites of patients' self-help groups (for example The National Eczema Society)

Two researchers will independently assess relevance of the abstracts retrieved and full texts of these papers will be obtained. Two researchers will then independently assess whether these trials fulfil the inclusion criteria.

Inclusion

RCTs or systematic reviews of pimecrolimus or tacrolimus compared to corticosteroids, emollients or both for treatment of mild to severe eczema;

Non randomised evidence may be considered if it gives the best estimates of a required parameter (for example adverse effects or patient preferences) or where RCT data is scanty or uninformative.

Cost-effectiveness, cost-utility and cost-benefit studies of pimecrolimus compared to corticosteroids, vehicle or both for treatment of mild to moderate atopic eczema, and of tacrolimus compared to topical corticosteroids, short courses of systemic corticosteroids, other immunosuppressives or phototherapy for treatment of moderate to severe atopic eczema will be included.

Exclusion

Non-randomised studies, case-control studies, case series, case reports
Studies only available as abstracts
Animal models
Pre-clinical and biological experimentation in vitro or on humans;
Studies not reporting patient relevant outcomes;
Studies on patients with secondary eczema or on non-eligible patients
Studies not published in English

Data extraction

Data will be extracted by one researcher and checked by a second researcher, with differences resolved by consensus.

Quality assessment

The methodological quality of included RCTs and systematic reviews will be assessed using the criteria reported in the NHS CRD Report No. 4. Cost-effectiveness or cost-utility studies will be assessed following the methodology reported in Drummond (BMJ).

Methods of analysis/synthesis

Meta-analysis will be performed if sufficient randomised evidence is located of reliable homogeneity. Otherwise, a tabulated description of the available evidence will be presented and discussed.

The meta-analysis will use a fixed effects method if there is sufficient homegenity. Analyses will be based on intenet to treat data. Sources of heterogeneity will be identified and their impact explored. Sub-group analysis will be specified prior to meta-analysis, and be based on further examination of the papers to be included.

Estimation of effectiveness, quality of life, costs and cost-effectiveness or cost-utility

Cost data will be extracted from published work, NHS costs and industry submission as appropriate. If insufficient data are retrieved from published sources, costs will be derived from individual Trusts or groups of Trusts. Costs will be discounted at 6% and benefits at 1.5%. Both costs and discount will be tested for sensitivity.

If possible, an independent cost-utility model will be developed to determine cost-effectiveness and cost-utility of treatment with pimecrolimus and tacrolimus compared to emollients and corticosteroids. Ideally, the model will consider treatment, relapse, for a sufficiently long period (1 year) and if sufficient data are available, longer-term outcomes and costs (clearance of symptoms or eradication of eczema). However, if insufficiently robust data are available, an alternative short-term model may be constructed encompassing intermediate outcomes.

E. Handling industry submission

Information provided by the industry will be included in the report when meeting our inclusion criteria (RCTs) and for information on costs.

A critique of any industry models submitted will be undertaken. The extent of the detail in this critique will depend on the number and size of the industry submissions.

Any "commercial in confidence" data taken from the industry submissions will be underlined and the source identified in the assessment report.

F. Project management

Timetable

Initial draft protocol: 15th July 2003
Final draft protocol: 5th August 2003
Progress report: 31st October 2003
Initial draft report to peer review: 15th December 2003 (tbc)
Final draft report: 26th January 2004

Competing interests

None

External reviewers

A panel of reviewers is currently being formed. The panel will act as expert resource to guide the review process. At least two independent reviewers will be identified as peer reviewers of the initial draft report.

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9.3 Appendix 3: Search Strategy

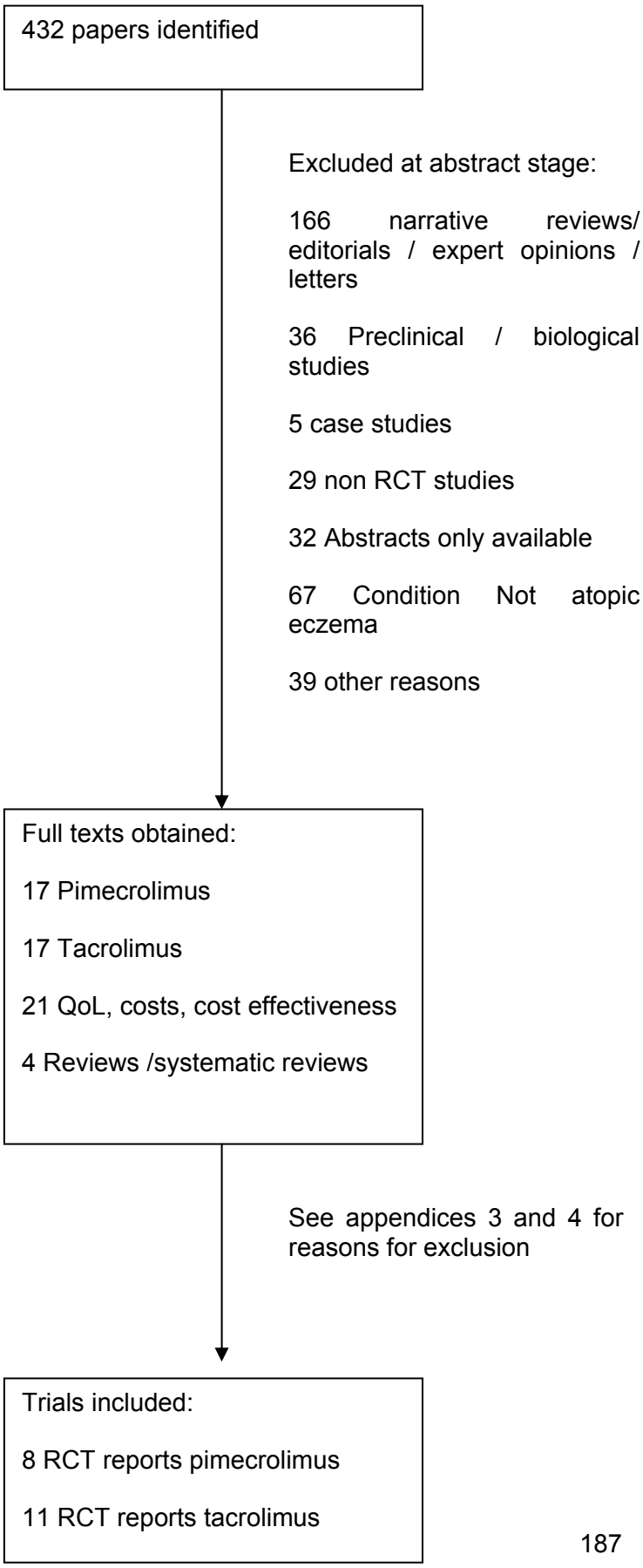
Databases and years searched and date searched	Strategies
Cochrane Library – CSRD – Issue 2, 2003 (18/7/2003)	1. tacrolimus 2. pimecrolimus 3. elidel 4. protopic 5. tsukubaenolide 6. 1 or 2 or 3 or 4 or 5 7. dermatitis 8. eczema* 9. 7 or 8 10. 6 and 9
Cochrane Library – CENTRAL – Issue 2, 2003 (18/7/2003)	1. tacrolimus 2. pimecrolimus 3. elidel 4. protopic 5. tsukubaenolide 6. 1 or 2 or 3 or 4 or 5 7. dermatitis 8. eczema* 9. 7 or 8 10. 6 and 9
Cochrane Skin Group Specialised Register	
Medline (OVID) 1966-2003, July Week 2 (18/7/2003)	1 Randomized Controlled Trials/ (29510) 2 randomized controlled trial.pt. (177801) 3 Random Allocation/ (49058) 4 Double-Blind Method/ (74777) 5 Single-Blind Method/ (7414) 6 controlled clinical trial.pt. (63767) 7 1 or 2 or 3 or 4 or 5 or 6 (301855) 8 clinical trial.pt. (362214) 9 exp Clinical Trials/ (148184) 10 clinical trial$.ti,ab. (72033) 11 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).ti,ab. (71443) 12 random allocation.ti,ab. (559)

	13 randomi#ation.ti,ab. (6801) 14 (randomi#ed adj4 trial$).ti,ab. (55341) 15 8 or 9 or 10 or 11 or 12 or 13 or 14 (477254) 16 7 or 15 (504426) 17 TACROLIMUS/ (5699) 18 tacrolimus.ti,ab. (2739) 19 pimecrolimus.ti,ab. (48) 20 elidel.ti,ab. (11) 21 protopic.ti,ab. (13) 22 tacrolimus.rw. (6195) 23 17 or 18 or 19 or 20 or 21 or 22 (6890) 24 Skin Diseases, Eczematous/ (33) 25 exp Eczema/ (5133) 26 Dermatitis/ (4341) 27 Dermatitis, Atopic/ (7636) 28 eczema.ti,ab. (5503) 29 excema.ti,ab. (7) 30 24 or 25 or 26 or 27 or 28 or 29 (18426) 31 dermatitis.ti,ab. (20037) 32 30 or 31 (31396) 33 23 and 32 (193) 34 16 and 33 (77) 35 limit 34 to human (75) **36 limit 35 to english language (72)**
Embase (OVID) 1980-2003, Week 28 (18/7/2003)	1 tacrolimus.ti,ab. (2865) 2 pimecrolimus.ti,ab. (64) 3 elidel.ti,ab. (12) 4 protopic.ti,ab. (16) 5 Tsukubaenolide/ (12149) 6 tacrolimus.tn. (431) 7 elidel.tn. (62) 8 protopic.tn. (89) 9 tsukubaenolide.tn. (3) 10 Pimecrolimus/ (186) 11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 (12310) 12 Dermatitis/ (5254) 13 eczema.ti,ab. (4469) 14 excema.ti,ab. (6) 15 ECZEMA/ (4365) 16 Atopic Dermatitis/ (7375) 17 12 or 13 or 14 or 15 or 16 (17322) 18 dermatitis.ti,ab. (18086)

	19 12 or 13 or 14 or 15 or 16 or 18 (27099) 20 11 and 19 (456) 21 Randomized Controlled Trials/ (76204) 22 Random Allocation/ (6812) 23 Double-Blind Method/ (48438) 24 Single-Blind Method/ (4273) 25 exp Clinical Trials/ (276817) 26 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).ti,ab. (67271) 27 random allocation.ti,ab. (448) 28 randomi#ation.ti,ab. (5845) 29 (randomi#ed adj4 trial$).ti,ab. (49847) 30 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 (339671) 31 20 and 30 (139) 32 limit 31 to human (138) **33 limit 32 to english language (122)**
Premedline (OVID) 17/7/2003 (18/7/2003)	1 [TACROLIMUS/] (0) 2 tacrolimus.ti,ab. (224) 3 pimecrolimus.ti,ab. (15) 4 elidel.ti,ab. (4) 5 protopic.ti,ab. (2) 6 [tacrolimus.rw.] (0) 7 1 or 2 or 3 or 4 or 5 or 6 (231) 8 [Skin Diseases, Eczematous/] (0) 9 [exp Eczema/] (0) 10 [Dermatitis/] (0) 11 [Dermatitis, Atopic/] (0) 12 eczema.ti,ab. (101) 13 excema.ti,ab. (0) 14 8 or 9 or 10 or 11 or 12 or 13 (101) 15 dermatitis.ti,ab. (395) 16 14 or 15 (465) 17 7 and 16 (17) 18 limit 17 to english language (12) 19 from 18 keep 1-3,5,7-12 (10) 20 from 18 keep 11-12 (2) (selected non-animal by scanning) **21 12 refs downloaded**
PubMed not searched - Premedline instead – see above)	
Science Citation Index 1981-2003	(tacrolimus or pimecrolimus or elidel or protopic or tsukubaenolide) and (dermatitis or excema or eczema)

(24/7/2003)	
Web of Science Proceedings 1990-2003 (24/7/2003)	(tacrolimus or pimecrolimus or elidel or protopic or tsukubaenolide) and (dermatitis or excema or eczema)
DARE (Cochrane Library Issue 2, 2003) (18/7/2003)	1. tacrolimus 2. pimecrolimus 3. elidel 4. protopic 5. tsukubaenolide 6. 1 or 2 or 3 or 4 or 5 7. dermatitis 8. eczema* 9. 7 or 8 10. 6 and 9
HTA database (CRD databases) (24/7/2003)	tacrolimus or pimecrolimus or elidel or protopic or tsukubaenolide
NRR (National Research Register) (24/7/2003)	1. tacrolimus 2. pimecrolimus 3. elidel 4. protopic 5. tsukubaenolide 6. 1 or 2 or 3 or 4 or 5 7. dermatitis 8. eczema* 9. 7 or 8 10. 6 and 9
Current Controlled Trials http://controlled-trials.com/ (24/7/2003)	tacrolimus or pimecrolimus or elidel or protopic or tsukubaenolide
Clinical Trials.gov http://clinicaltrials.gov/ (24/7/2003)	tacrolimus 18 refs pimecrolimus or elidel or protopic or tsukubaenolide 0 refs
FDA website http://www.fda.gov/cder/approval/index.htm	Tacrolimus, Protopic Pimecrolimus, Elidel

9.4 Appendix 4 : Flow chart of included studies



9.5 Appendix 5: Data extraction sheet for pimecrolimus

Reference and Design	Intervention	Subjects	Outcome measures
▪ *Author:* ▪ Eichenfeld et al 2002 ▪ *Study design:* 2 RCTs ▪ *Recruitment dates:* Not stated ▪ *Setting:* Multicentre - details not stated	▪ *Treatment:* Pimecrolimus 1% twice daily ▪ *Comparator* Vehicle ▪ *"Wash out" period* Phototherapy or systemic therapy within 1 month from baseline; Topical therapy within 7 days System antibiotics within 2 weeks ▪ *Concomitant treatment* Not stated ▪ *Length of treatment* 6 weeks ▪ *Safety levels* End of treatment samples taken for haematology, urinalysis, serum chemistries	▪ *Total number of patients: 403 (267 Intervention, 136 control)* ▪ *Eczema definition:* Williams et al 1994 ▪ *Eczema severity:* Mild to moderate (IGA) ▪ *Inclusion criteria:* 1-17 years Diagnostic criteria of Williams BSA >5% IGA score 2 or 3 (mild or moderate disease) Receiving emollient for at least 7 days before baseline ▪ *Exclusion criteria:* Significant concurrent disease Pregnancy or nursing .	▪ *Primary and secondary outcome measures used:* Treatment success Extent of disease Pruritus Disease control Adverse effects ▪ *Method of assessing outcomes:* IGA (by investigator at day 8, 15, 22, 29, 43, score of 0-1 = treatment success) EASI pruritus assessment (score 0 = no scratching itching, to 3 = bothersome itching scratching), AD disease control as assessed by patients or caregivers for the last 7 days (0=complete disease control to 3 = uncontrolled disease) AE – through physical tests, measures of vital signs and physical examination. ▪ *Length of follow up:* 6 weeks

Results:	Pre Intervention	Post Intervention	Pre Comparison	Post comparison	P-value (Difference between groups)
▪ *Amount of ointment used*	Not stated				
▪ *Participant characteristics:* Age mean Males	 6.8 140 (52.4%)		 6.6 62 (48.5%)		

Results from the 2 trials combined in this publication are reported separately in the FDA submission as trials B305 and B307. Methodological details are the same as reported in the published paper. Below, data used separately in meta-analyses this review are recorded.

▪ *Symptoms* Clear / Mild (IGA) Moderate (IGA) Severe Very Severe Improved by at least 1 IGA score Maintained baseline score Worsened Cleared by day 8 TBSA mean (range) EASI mean EASI median (range) EASI change from baseline Pruritus – none or mild AD not well controlled Complete/good control	80 (30%) 161 (60.3%) 23 (8.6%) 3 (1.1%) 26.1% (1-95) 12.9 9.2 (1-52) 13% >80% 12%	34.8% 59.0% 59.9% 36% 4.1% 12% - 45% 57% 60%	43 (31.6%) 78 (57.4%) 11 (8.1%) 4 (2.9%) 25.5% (1-96) 12.7 10.2 (2-72) 10% >80% 18%	18.4% 33% 33.1% 47.1% 19.9% 2.2% -1% 34% 39%	P<=0.05 P<0.001 P<0.001
▪ *QoL*	Not stated				
▪ *Recurrence*	Not stated				
▪ *Adverse effects* Overall URTI Headache Cough Nasopharingitis Site burning		44% 14.2% 13.9% 11.6% 10.1% 10.4%		42.6% 13.2% 8.8% 8.1% 7.4% 12.5%	

Methodological comments

- *Prospective* Not stated
- *Consecutive patients enrolled* Not stated
- *Method of Randomisation:* Ratio 2:1
- *Blinding:* Not clear – but described as "double blind".
- *Unit of randomisation and analysis:* Patient
- *Power calculation?* Sample size of 198 gives 95% power to detect 25% difference in proportions at 5% significance level
- *All patients given same intervention?* Yes
- *Loss to follow up?* 34 (11.2%) in intervention, 30 (25%) in control - 7 in intervention and 21 in control group discontinued due to unsatisfactory therapeutic effect and 1.9% intervention, 2.9% control due to adverse effects
- *Method of data analysis:* 2 RCTs – data pooled for analysis. ITT; Cochrane Mantel Haenszel Test stratified by centre; General linear methods for EASI scores with baseline scores and centre as covariates.

General comments

- *Generalisability:* High
- *Main outcome measured blind/independently:* Not clear
- *Inter-centre variability*: Stratification of results by centres
- *Conflicts of interest*: Research supported by Novartis Pharmaceuticals Corp. LE and AL are consultants to Novartis and Fujisawa; MB received trial grants from Novartis; RL received a research grant from Novartis; RC and KM are employees of Novartis

Reference and Design	Intervention	Subjects	Outcome measures
▪ *Author:* Van Leent et al 1998 ▪ *Study design:* RCT – double blind, placebo controlled, right and left arm comparison "proof of concept" ▪ *Recruitment dates:* 25/4/96 – 1/10/96 ▪ *Setting:* Academic dermatology clinic (one-site) (n=20) plus non clinic patients who heard or read about the trial (n=18).	▪ *Treatment:* Pimecrolimus 1% once or twice a day ▪ *Comparator* Placebo (Vehicle) ▪ *"Wash out" period* Phototherapy or systemic therapy: 1 month Antibiotics or topical therapy: 2 weeks Antihistamines: 1 week Radiation therapy, systemic therapy with cytostatics or inmmunosuppressive drugs: 24 weeks ▪ *Concomitant treatment* 1% hydrocortisone acetate on lesions other than intervention sites (once daily) ▪ *Length of treatment* 21 days ▪ *Safety levels* Haematologic, clinical chemistry and urinalysis. Blood levels of pimecrolimus were > recommended 0.1ng/mL in 2 cases - one 2 hrs after first application 2.39ng/mL; one 6 hrs after day 11 application 0.22ng/mL	▪ *Total number of patients:* 34 (18 once daily and 16 twice daily) ▪ ▪ *Eczema definition:* Hanifin and Raika criteria ▪ *Eczema severity:* ADSI >6, with difference <1 between arms ▪ *Inclusion criteria:* BSA >1% of both arms ▪ *Exclusion criteria:* Acute skin infection	▪ *Primary and secondary outcome measures used:* Reduction in disease severity ▪ *Method of assessing outcomes:* Changes in ADSI score on days 0, 4, 11, 21. Modification of standard grading according to Hanifin ▪ *Length of follow up:* 21 days

Results:	Pre Intervention	Post Intervention	Pre Comparison	Post comparison	P-value
▪ *Participant characteristics* Age; once daily Age; twice daily Male; once daily Male; twice daily	 36 29 9/16 7/18				
▪ *Amount of ointment used*	Not stated				
▪ *Symptoms* ADSI mean; twice daily ADSI mean; once daily Partially cleared; twice daily Once daily Totally cleared Twice daily Once daily	 7.72 8.06	ADSI reduction 79.1% 37.7% 12/16 3/18 3/16 0/18	 7.78 8.13	ADSI reduction 10.3% 6.2% 2/16 0/18 0/16 0/18	 P<0.01 P not reported
▪ *QoL*	Not stated				

▪ *Recurrence*	Not stated				
▪ *Adverse effects*	None reported				

Methodological comments

- *Prospective?* Yes
- *Consecutive patients enrolled?* No
- *Method of Randomisation* Not reported. Not clear either how patient was allocated to daily or twice daily group or how arm was chosen for active or placebo treatment.
- *Unit of randomisation and analysis* Arm?
- *Blinding:* Not clear – described as double blind. Packaging of ointments plain and labelled "left" and "right". Assessment of efficacy made by single investigator blind to treatment.
- *Power calculation?* Not reported
- *All patients given same intervention?* Two interventions compared, once and twice daily topical applications
- *Loss to follow up?* 7 patients; 5 due to exacerbation or infection on placebo arm, 2 for other reasons. An additional 3 recruited but not randomised.
- *Method of data analysis:* ITT. Matched paired t-tests and rank-sum tests for difference in treatment effects; Survival techniques were used to analyse time to clearance and to partial clearance.

General comments

- *Generalisability:* Medium
- *Main outcome measured blind/independently:* Yes
- *Inter-centre variability:* N/a
- *Conflicts of interest*: Study funded by Novartis Pharma AG

Some items estimated from graph presentation.

Reference and Design	Intervention	Subjects	Outcome measures
▪ *Author:* Whalley et al 2002 ▪ *Study design:* 2 RCTs followed by open label clinical trial ▪ *Recruitment dates:* Not stated ▪ *Setting:* 11 centres in the US	▪ *Treatment:* Pimecrolimus 1% ▪ *Comparator* Vehicle ▪ *"Wash out" period* Not stated ▪ *Concomitant treatment* Not stated ▪ *Length of treatment* 6 weeks RCT plus 6 months open lable ▪ *Safety levels* Not stated	▪ *Total number of patients:* 403 total; only patients over 8 were included; QoL scores were available for 241 of 278 patients (158 Intervention, 83 control) ▪ *Eczema definition:* Williams diagnostic criteria ▪ *Eczema severity:* IGA score 2 or 3 (mild to moderate) ▪ *Inclusion criteria of the original study:* BSA >5% Age 2-17 years (this paper section analysis parents of those aged 2-8) ▪ *Exclusion criteria:* Not stated	▪ *Primary and secondary outcome measures used:* QoL ▪ *Method of assessing outcomes:* Parent's Index of QoL in AD questionnaire administered to parents (IGA, pruritus scores - not reported) ▪ *Length of follow up:* 6 weeks RCT (6 months open label – all patients switched to intervention after 6 weeks.)

Results:	Pre Intervention N=158	Post Intervention N=132	Pre Comparison N=83	Post comparison N=61	P=value
▪ *Participant characteristics:* Males Mean age (SD)	 84 (53.2%) 4.0 (1.75)		 41 (49.4%) 3.8 (1.82)		
▪ *Amount of ointment used*	Not stated				
▪ *Symptoms*	Not stated				
▪ *QoL* Mean (SD) Median (Q1-Q3) No difference in mean scores at 6 months when all have transferred to pimecrolimus	 9.4 (6.04) 8.0 (5-13)	 6.1 (5.89) 4.5 (2-9)	 8.8 (6.91) 7.0 (3-13)	 7.5 (7.82) 5 (1-12)	Tac vs vehicle P=0.023
▪ *Recurrence*	Not stated				
▪ *Adverse effects*	Not stated				

Methodological comments

- *Prospective?* Unclear
- *Consecutive patients enrolled?* Unclear
- *Method of Randomisation:* Not stated
- *Method of blinding:* Not stated
- *Unit of randomisation and analysis:* Patients
- *Power calculation?* Not stated
- *All patients given same intervention?* Yes
- *Loss to follow up?* 48 patients at 6 weeks(26 intervention, 22 control*),* 80 (45 intervention, 35 placebo at 6 months) no QoL data available on a further 37 patients.
- *Method of data analysis*: Only over 8s reported on, cases with up to 20% missing data were included, Repeated measurement t tests for treatment within group; generalised linear model techniques used to test differences in treatment with centre and treatment as covariates; Association between PIQoL, IGA and pruritus tested with Spearman rank correlation coefficients.

General comments

- *Generalisability:* Low – only age and sex reported.
- *Main outcome measured blind/independently:* No
- *Inter-centre variability: Not stated*
- *Conflicts of interest*: The study was funded by Novartis Pharma AG, JH and DvA are employees of Novartis

Reference and Design	Intervention	Subjects	Outcome measures
▪ *Author:* Meurer et al 2002 ▪ *Study design:* RCT – double blind, parallel group ▪ *Recruitment dates:* 09/1999 to 06/2000 ▪ *Setting:* 12 University clinics, 1 dermatology clinic and 3 dermatology practices in Germany	▪ *Treatment:* Pimecrolimus 1% twice daily, to treat first signs of AD and prevent a flare, acute flares treated by prednicarbate 0.25% cream (Dermatop) for max 14 days followed by 7 days pimecrolimus treatment. ▪ *Comparator* Vehicle Acute flares treated by prednicarbate 0.25% cream (Dermatop) for max 14 days ▪ *"Wash out" period* PUVA UVA or systemic corticosteroids 3 months before; topical therapies or systemic antibiotics, 2 weeks; systemic steroids for non AD indications, 1 month ▪ *Concomitant treatment* Emollient, cetirizine (anti-histamine) ▪ *Length of treatment* 24 weeks ▪ *Safety levels* Not stated	▪ *Total number of patients:* 192 (96 intervention, 96 controls) ▪ *Eczema definition:* Rajka criteria ▪ *Eczema severity:* Moderate to severe ▪ *Inclusion criteria:* IGA score 3 or 4 (moderate to severe) BSA >5% ▪ *Exclusion criteria:* Pregnancy, lactation, women in gestational age not using reliable contraception; Patients requiring potent topical corticosteroids; Severe concurrent allergic disease associated to malignancies or immunocompromised states; skin conditions that could affect the evaluation of treatment; Active skin infections with prohibited medication, active herpes.	▪ *Primary and secondary outcome measures used:* Proportion days use of topical corticosteroids; Number of disease flares; time to flare; Improvement of condition, Quality of life Adverse effects ▪ *Method of assessing outcomes:* Clinical examination, IGA and EASI assessment DLQI and QoLIAD Patient diaries on medication use, changes in medical condition and pruritus (scale of 0-4) ▪ *Length of follow up:* 24 weeks

Results:	Pre Intervention N=96	Post Intervention	Pre Comparison N=96	Post comparison	P=value
▪ *Participant characteristics:*					
Males	36 (37.5%)		41 (42.7%)		
Mean Age (SD)	31.8 (+/-11.1)		32.5 (+/- 10.78)		
TBSA involved mean, SD (range)	17%, +/-7.6 (5.0-45.0)		16.9%, +/- 10.7 (5.0-76.0)		
EASI score mean, SD (Range)	11.2, +/-5.1 (2.0-26.6)		10.8, +/- 6.1 (2.8-35.3)		
IGA score					
moderate	62 (64.6%)		68 (70.8%)		
severe	33 (34.4%)		28 (29.2%)		
very severe	1 (1%)		0		

▪ *Amount of ointment used* % not using topical steroids Mean average use of steroids % days topical steroid used Mean, SD Median (range) For moderate disease (IGA=3) Mean, SD Median (range) For severe disease (IGA =4)* Mean, SD Median (range)		 49% (n=47) 14.2% 14.2, +/- 24.2 2.1 (0-97) 9.5 +/- 19.8 0.0 (0-97.0) 23.1 +/-29.5 7.7 (0-87.5)		 21.9% (n=21) 37.2% 37.2, +/- 34.6 27.8 (0-98.2) 37.0, +/-36.3 23.5 (0-98.2) 37.8, +/- 30.4 35.2 (0-91.7)	 P<0.001 P<0.001 P<0.001 P =0.027
▪ *Symptoms* Patients improved by at least 1 IGA score Treatment success (IGA=<2) TBSA reduction, mean Pruritus score, day 7 Reduction in EASI score EASI score (95% CI) Pt assessment “completely or “Well” controlled		 79 (82.3%) 66 (68.6%) 48.4% 1.6 48.3% 5.7 (4.1-6.9) 62 (64.6%)		 49 (51%) 35 (36.5%) 20.5% 2.5 15.9% 8.8 (7.5-10.5) 34 (35.4%)	 P<0.001 P<0.01 P<0.001 P<0.001 P<0.001
▪ *QoL* Mean Decrease in QoLIAD score Mean Decrease in DLQI		 25.6% 22%		 7.4% 6.7%	 P=0.002 P=0.01
▪ *Recurrence* Patients without flares Mean number of flares (95% CI) Median time to first flare (days)		 43 (44.8%) 1.1 (0.7-1.4) 144		 18 (18.8%) 2.4 (2.0-2.8) 26	 P<0.001

▪ *Adverse effects*					
Overall		24.0%		20.8%	
Local AEs:		38 (39.6%)		35 (36.5%)	
Site burning		10		3	
Herpes+		10		5	
Bacterial infection		4		3	
Fungal infection		2		1	
Eczema herpeticum		0		2	
Discontinuations:					
Aneurysm		1		0	
Contact dermatitis		0		3	
Application site pain		0		1	

Methodological comments

- *Prospective?* Yes
- *Consecutive patients enrolled?* Not stated
- *Blinding:* Vehicle cream same appearance and odour. All site monitoring and data management personnel were blinded.
- *Method of Randomisation: computer-generated random list with ratio of randomisation 1:1*
- *Unit of randomisation and analysis: patient*
- *Power calculation?* Calculated on the power of the study to detect a reduction in consumption of TS from 18 g/Sqm BS/week to 6/Sqm/week after 6 weeks. 172 patients were needed for significance at the 5% level - power to detect this change is not stated
- *All patients given same intervention?* Not clear due to use of moderately potent topical steroid
- *Loss to follow up?* 5 were recruited but excluded before randomisation. In the pimecrolimus group 22 discontinued (15 due to ineffective treatment, 1 lost to FU and 6 other) 74/96 completed the trial. In the control group 36 discontinued (26 due to ineffective treatment, 3 lost to FU and 7 other) 60/96 completed the trial.
- *Method of data analysis:* ITT. All randomised patients, last observation carried forward; Intervention and control group compared with Wilcoxon sum-rank test; secondary data compared with covariance analysis, sum-rank test, Fisher exact test, logistic regression. Survival analysis for time to flare (log-rank test) and Kaplan Meyer cumulative survival curves for time to first flare. Cox proportional hazard was used to analyse the effect of baseline variables (centre, EASI, IGA, age category, treatment group). Summary statistics were reported for QoL, and safety analysis was descriptive.

General comments

- *Generalisability:* High
- *Main outcome measured blind/independently:* Yes
- *Inter-centre variability:* Included in the analysis but not reported.
- *Conflicts of interest:* Study funded by Novartis Pharma AG. NW and MB are employees of Novart*is*

* one patient with severe disease was excluded from the analysis

+ Of the bacterial infections, 6 in the intervention group and 1 in the control group were herpes labialis – not at a treatment site.

A flare was defined as the disease status requiring at least 3 days topical steroid treatment.

Some items estimated from graph presentation.

Reference and Design	Intervention	Subjects	Outcome measures
▪ *Author:* Luger et al 2001 ▪ *Study design:* RCT double blind randomised parallel group ▪ *Recruitment dates:* Not stated ▪ *Setting:* 14 centres in Belgium, Denmark, Finland Germany the Netherlands Norway and the UK.	▪ *Treatment:* Pimecrolimus 0.05% 0.2% 0.6% and 1% twice daily excluding face ▪ *Comparator* Vehicle or 0.1% Betamethasone-17-valerate (BMV) (high potency TS) ▪ *"Wash out" period* Not stated ▪ *Concomitant treatment* Use of other treatment (including emollient) or corticosteroids (inhaled or oral) prohibited ▪ *Length of treatment* 3 weeks or until complete clearance ▪ *Safety levels* Physical examination, routine haematology and blood chemistry assessment at periodic intervals. No clinically significant changes reported.	▪ *Total number of patients:* 260 (42 randomised to 0.05%, 46 to 0.2%, 42 to 0.6%, 45 to 1%, 43 to vehicle, 42 to BMV) ▪ *Eczema definition:* Hanifin and Rajka ▪ *Eczema severity:* *Severity grading according to Rajka and Langeland criteria, score 4-7 moderate and 8-9 severe* ▪ *Inclusion criteria:* Aged >=18 BSA 5%-30% At least moderate severity ▪ *Exclusion criteria:* Concomitant medical condition that would interfere with treatment evaluation Pregnancy, lactation Women not using medically approved contraception if of child-bearing potential	▪ *Primary and secondary outcome measures used:* Improved clinical condition ▪ *Method of assessing outcomes:* EASI score modified to exclude the head region (score range 0 to 64.8) Pruritus assessment scores (0-3) Patient assessment of improvement 0-6 (0-100%) Assessed on days 8.15 and 22. ▪ *Length of follow up:* 3 weeks

Results:	Pre Intervention	Post Intervention	Pre Comparison	Post comparison	P=value
▪ *Participant characteristics:* Males	0.05% 18 0.2% 21 0.6% 23 1%24		BMV 19 Vehicle 22		
Mean Age (Range)	0.05% 33 (19-70) 0.2% 30 (18-51) 0.6% 28 (18-57) 1% 28 (18-62)		BMV 32 (18-71) Vehicle 33 (18-69)		
Race - Caucasian	0.05% 40 (95%) 0.2% 44 (96%) 0.6% 40 (95%) 1% 43 (96%)		BMV 42 (100%) Vehicle 41 (95%)		
EASI score mean	0.05% 12.37 0.2% 11.16 0.6% 11.49 1% 11.28		BMV 10.28 Vehicle 10.12		
Median time to first occurrence of AD (years)	0.05% 26 0.2% 23.5 0.6% 22.5 1% 22		BMV 25 Vehicle 24		
Severity of dermatitis Moderate severe	0.05% 39/3 0.2% 44/2 0.6% 39/3 1% 41/4		BMV 40/2 Vehicle 41/2		

▪ *Symptoms* Median percent reduction between last measurement of EASI score and baseline Median percent overall change in EASI score, % of baseline, by severity at baseline		0.05% 0% 0.2% -14% 0.6% -34% 1% -47% EASI <8 0.05% -5.3% n=9 0.2% -25.2% n=12 0.6% -52.7% n=12 1% -50% n=11 EASI 8-12 0.05% -1.8% n=14 0.2% -6.7% n=16 0.6% -36.7% n=14 1% -48.1% n=18 EASI >12 0.05% +14.8% n=19 0.2% -17.3% n=18 0.6% -27.6% n=16 1% -37.9% n=16		BMV 78% Vehicle 0% BMV –86.7% n=15 V. –6.9% n=14 BMV –88.2% n=13 Vehicle -0% n=17 BMV –64.1% n=14 Vehicle –2.7% n=12	
Patients with absent or mild pruritus at baseline and at endpoint	0.05% 2/42 4.8% 0.2% 4/46 8.7% 0.6% 5/42 11.9% 1% 3/45 6.7%	0.05% 10/42 23.8% 0.2% 17/46 37% 0.6% 22/42 52.4% 1% 21/45 46.7%	BMV 5/42 11.9% Vehicle 2/43 4.7%	BMV 34/42 81% Vehicle 8/43 18.6%	P values compared to vehicle 0.05% 0.604 0.2% 0.063 0.6% 0.001 1% 0.007 BMV <0.001
▪ *Adverse effects* Number developed at least one local AEs: Site burning Pruritus Worsening dermatitis		0.05% 32/42 76% 0.2% 29/46 63% 0.6% 24/42 57% 1% 32/45 61% 0.05% 14/42 33% 0.2% 11/46 24% 0.6% 18/42 43% 1% 22/45 49% 0.05% 10/42 24% 0.2% 9/46 20% 0.6% 11/42 26% 1% 14/45 31% 0.05% 9/42 21% 0.2% 9/46 20% 0.6% 3/42 7% 1% 2/45 4%		BMV 19/42 45% Vehicle 36/43 84% BMV 4/42 10% Vehicle 15/43 35% BMV 5/42 12% Vehicle 15/43 35% BMV 1/42 2% Vehicle 9/43 21%	

Methodological comments

- *Prospective?* Yes
- *Consecutive patients enrolled? Not stated*
- *Blinding:* Described as a double blind study
- *Method of Randomisation:* Not stated
- *Unit of randomisation and analysis:* Patient
- *Power calculation?* Not stated
- *All patients given same intervention?* All patients were followed according to the same protocol
- *Loss to follow up:* 61 patients in total discontinued treatment (17 in 0.05%, 8 in 0.2%, 7 in 0.6%, 7 in 1%, 19 in vehicle, 3 in BMV). 18 patients reported adverse effects (4 in 0.05%, 1 in 0.2% 2 in 0.6%, 3 in 1%, 7 in vehicle and 1 in BMV). 35 for treatment failures (11 in 0.05%, 7 in 0.2%, 4 in 0.6%, 2 1%, 0 in BMV and 11 vehicle). 6 patients were discontinued for consent withdrawal, protocol violation or loss to follow-up (2 in 0.05%, 2 in 1%, 1 each in BMV and vehicle). 2 patients withdrew because of success of therapy (1 each in 0.6% and BMV)
- Method of data analysis: ITT, including patients who received at least one application. Analysis of covariance with last EASI measurement as dependent variable and centre and baseline EASI as covariates;

General comments

- *Generalisability:* High
- *Main outcome measured blind/independently:* Not clear
- *Inter-centre variability:* accounted for in the analysis
- *Conflicts of interest:* None reported

Note: Data for an extra outcome is presented in the FDA submission as trial B202:

Subjects with Clear or "Almost Clear" IGE at week 3

Treatment group	No. (%) pts.	P-value vs Vehicle
Vehicle (n=43)	0 (0%)	-
0.05% pimecrolimus (n=42)	0 (0%)	-
0.2% pimecrolimus (n=46)	1 (2%)	1.00
0.6% pimecrolimus (n=42)	2 (5%)	0.241
1.0% pimecrolimus (n=45)	5 (11%)	0.056
BMV (n=42)	21 (50%)	<0.001

Reference and Design	Intervention	Subjects	Outcome measures
▪ *Author:* Wahn et al 2002 ▪ *Study design:* Double blind RCT ▪ *Recruitment dates:* July – December 1999 ▪ *Setting:* 53 centres in 13 countries (Europe, USA, Canada, South Africa, Australia)	▪ *Treatment:* Pimecrolimus 1% twice daily applied to area at first sign (erythema) or symptom (itch) to prevent flare ▪ *Comparator* Emollients, short term flare treatment with moderately potent topical steroids (0.02 difluprednate, 0.25% prednicarbate, 0.1% hydrocortisone butyrate, 0.05% clobetasone butyrate, 0.02% triamcinolone acetonide, 0.1% hydrocortisone valerate creams, depending on country) ▪ *"Wash out" period* Phototherapy or systemic therapy one month, topical therapy 7 days, systemic antibiotics 2 weeks. ▪ *Concomitant treatment* Emollients and moderately potent topical steroids. Anti-histamines/H1 blockers. ▪ *Length of treatment* 12 months ▪ *Safety levels* AEs, physical exams, vital signs, haematology, urinalysis, clinical chemistry assessments. Skin immune response to standard panel of allergens.	▪ *Total number of patients:* 713 (476 pimecrolimus, 237 control) 474 pimecrolimus and 237 in control received therapy. ▪ *Eczema definition:* Williams criteria ▪ *Eczema severity:* IGA ▪ *Inclusion criteria:* Ages 2-17 >=5% BSA, IGA >=2 ▪ *Exclusion criteria:* Infections that required prohibited medication or that could affect evaluation of skin	▪ *Primary and secondary outcome measures used:* Ranked flares in 6 months. Ranked flares in 12 months. First time to flare Clinical improvement ▪ *Method of assessing outcomes:* Flares measured using IGA (0-5, clear to very severe disease) assessed at 4 or 5 at a scheduled or unscheduled visit) – 2nd line TS treatment began within 3 days and was preceded by at least 7 days off TS. Method of measuring steroid use not reported EASI At baseline weeks 2, 4, 7, 15, 27, 39, 53. And unscheduled visits ▪ *Length of follow up:* Mean days (SE) Pimecrolimus 303.7(+-5.3) Control 235.2(+-9.4)

Results:	Pre Intervention N=474	Post Intervention	Pre Comparison n=237	Post comparison	P=value
▪ *Participant characteristics:*					
Males	47.3%		47.3%		
Mean Age (Range)	8.0 (1-17)		7.9 (2-17)		
Aged 2<12yrs	73.4%		73.4%		
Aged 12-18yrs	25.9%		24.9%		
EASI score mean (range)	13.3 (0.6-61.2)		13.8 (1.2-61.3)		
BSA affected % Mean (range)	24.2% (1.5-93.0)		23.8% (2.8-94.0)		
IGA (%)					
1 (almost clear)	0.2%*		0		
2 (mild)	26.2%		27.8%		
3 (moderate)	55.3%		50.6%		
4 (severe)	15.6%		17.7%		
5 Very severe	2.7%		3.8%		

*1 pt had IGA score 1, but EASI score of >10 (mild-moderate)

▪ *Symptoms*		*6mos*	*12mos*		*6mos*	*12mos*	
0 flares (completers)		61.0%	50.8%		34.2%	28.3%	P<0.001
0 flares (ITT)		76%	71%		52%	43%	
1 flare		17%	18%		30%	35%	
2 flares		3%	7%		14%	14%	
>2 flares		4%	4%		4%	7%	
0 flares by severity (n)							
Mild			74			26	
Moderate			137			37	
Severe			26			4	
Topical steroid use required (completers)		35.0%	42.6%		62.9%	68.4%	
0 days use of TS			57.4%			31.6%	
1-14 days TS			17.1%			27.5%	
>14 days TS			25.5%			41.0%	
Average % of study days on TS			4.08%			9.10%	
Use of antihistamines			57.2%			62.9%	
▪ *Adverse effects*							
AEs		24.7%			18.7%		
Serious AEs		8.3%			5.2%		
Bacterial infects.		14.2%			30.9%		P=0.286
Impetigo		8.3%			26.7%		P=0.079
Folliculitis		3.0%			4.2%		P=0.456
Bact. Infect NOS		1.7%			1.0%		P=0.662
Stye		0.6%			0		P=0.227
Abscess NOS		0.5%			0.7%		P=0.876
Staph. Infect. NOS		0.4%			0		P=0.321
Cellulitis		0.2%			0		P=0.515
Strep. infect		0.2%			0		P=0.487
Viral skin infects.		12.4%			6.3%		P=0.038
Herpes simplex		3.0%			2.8%		P=0.558
Papilloma		2.8%			0.6%		P=0.125
Molluscum contagiosum		2.7%			1.8%		P=0.698
Eczema herpeticum		2.1%			0.8%		P=0.274
Herpes zoster		1.0%			0		P=0.199
Pityriasis rosea		0.5%			0		P=0.391
Flat warts		0.3%			0		P=0.556
Herpes viral infect. NOS		0.3%			0		P=0.556
Viral rash NOS		0			0.4%		P=0.157
Skin Burning		10.5%			9.3%		P=0.484
Nasopharyngitis		28.9%			27.1%		P=0.944
Headache		23.0%			21.5%		P=0.576
Bronchitis		13.2%			13.7%		P=0.794
Influenza		14.6%			9.5%		P=0.083
Cough		19.3%			11.8%		P=0.045
Pyrexia		15.4%			11.8%		P=0.484

Methodological comments

- *Prospective?* Yes
- *Consecutive patients enrolled?* Not clear
- *Blinding:* Described as double blind. Control groups used emollient at first sign/ symptoms of flare for prevention – same indication as treatment.
- *Method of Randomisation:* 2:1 allocation, balanced within and between centres. Validated system that automates random assignment of treatment groups to randomisation numbers. Blocks of 6. Randomisation schedule reviewed and locked after approval.
- *Unit of randomisation and analysis:* Patient
- *Power calculation?* 660 patients with 2:1 ratio needed to show a doubling of the proportion of patients with 2 or fewer flares in 6 months (25%-50%) incorporating <20% drop-out using Wilcoxon rank sum test at the α = 5%, power of 80% (2 sided). Power estimated using simulations, % of rejections of null hypothesis obtained from 1000 data sets provided power estimation.
- *All patients given same intervention?* yes
- *Loss to follow up:* 20 eligible but not randomised due to protocol violation. 713 randomised, 711 received treatment (2 in pimecrolimus group did not.) In pimecrolimus group 114 (24.1%) discontinued at 6 months (42 lack of efficacy, 7 LTFU, 65 other) and a further 36 by 12 months (17 lack of efficacy, 8 lost to follow up, 9 other) – 324 completed the study, control group 114 (48.1%) discontinued at 6 months (65 lack of efficacy, 7 LTFU, 42 other) and a further 8 by 12 months (7 lack of efficacy, 1 other) 115 completed the study.
- *Method of data analysis*: Described as ITT analysis but 2 patients randomised to receive treatment did not receive study medication and were excluded from analysis. Incidence of flares ranked (discontinuers ranked as having poorer control than continuers, after Gould, 1980) Those who discontinued in first 6 months of study were ranked according to the number of flares that they experienced over unit time on the study, and patients that continued after 6 months were ranked according to the number of flares recorded. Wilcoxon rank sum test adjusted for centre and tested treatment differences. Data tested at 6 and 12 months. Cumulative Kaplan Meirer survival curves investigated time to first flare. Affect of baseline variables on time to flare – Cox proportional hazard model. EASI – analysis of covariance, with EASI at baseline as reference with treatment effect, centre and baseline EASI fitted. Safety analysis – differences in adjusted incidence assessed using log-rank test.

General comments

- *Generalisability:* High
- *Main outcome measured blind/independently:* Not clear
- *Inter-centre variability:* Tested in analysis – not reported
- *Conflicts of interest:* Study sponsored by Novartis

% flares taken from graphs

Reference and Design	***Intervention***	***Subjects***	***Outcome measures***
▪ *Author:* Meyer et al (Novartis) ▪ *Study design:* Parallel group Double blind active controlled study ▪ *Recruitment dates:* Not clear – study from March 1998 to Macrh 2000 ▪ *Setting:* 35 centres in Europe and Canada	▪ *Treatment:* 1% pimecrolimus cream twice daily ▪ *Comparator:* 0.1% triamcinolone acetonide cream (potent steroid) on trunk and limbs, 1% hydrocortisone (mild steroid) for face and intertriginous areas twice daily ▪ *"Wash out" period* Phototherapy or systemic therapy 1 months Topical therapy (excluding tar shampoo for scalp treatment) 24 hours ▪ *Concomitant treatment* Emollients Antihistamines Oral and topical antibiotics Oral and topical anti-fungul Oral and topical antivirals ▪ *Length of treatment* Until complete clearance of inflammation and itch. Repeated when symptoms recurred. ▪ *Safety levels* Physical examination, clinical chemistry, urinalysis, pregnancy tests. No pharmacology	▪ *Total number of patients:* 658 (328 pimecrolimus, 330 corticosteroid group) ▪ *Eczema definition:* Hanifin and Rajka ▪ *Eczema severity:* ▪ *Inclusion criteria:* >=5% BSA affected Age 18 and over ▪ *Exclusion criteria:* Malignancy or history of malignancy, including skin cancer within 5 years Acute or chronic bacterial, viral or fungal diseases Known HIV positive status Women of childbearing age not using approved contraception, pregnant or breast feeding. Known hypersensitivity to ingredients of study medication. Use of investigational drug within the previous 8 weeks. History of drug or alcohol abuse in previous year, those uncooperative or unlikely to follow instructions or attend visits.	▪ *Primary and secondary outcome measures used:* Efficacy QoL AEs Costs ▪ *Method of assessing outcomes:* EASI Overall evaluation of dermatitis Pruritus severity score (0-3, absent – severe) Time to remission Time to recurrence Overall evaluation – 7 point scale (treatment success - = 0-3, failure = 4-6) DLQI (transformed into a 0-100 scale from a 0-30 scale), EuroQoL AEs – patient diary and clinical exam. ▪ *Length of follow up:* 12 months Assessment visits at week 4, months 4,7, 10 and 12.

Results:	**Pre Intervention N=328**	**Post Intervention**	**Pre Comparison N=330**	**Post comparison**	**P=value**
Participant characteristics:					
Males %	44.5		46.4		
Mean Age	33.4		33.5		
Min-Max	18-79		18-72		
Race -%					
Caucasian	89.6		88.8		
Black	1.8		4.5		
Other/missing	8.5		6.6		
Body Weight (kg)	69.6		69.8		
Mean	40-115		40-106		
Min-max					
Body Height (cm)	170.2		170.2		
Mean	144-193		105-198		
Min-max					
Area of involvement					
Mean (SD)	26.5 (+-19.27)		27.0 (+-19.26)		
Min Max	3-95		1.4-96.6		
EASI score					
Mean (SD)	15.0 (+-10.95)		15.3 (+-10.9)		
Min-max	1.9-66.2		1.2-63.6		
Head/neck involvement %	89.6		89.7		

Severity *Mild* *Moderate* *Severe* *Concomitant medication* *Antibiotics* *Antifungal* *Antihistamines* *Anti viral* *Emollients* *Steroids*	 2.1 65.9 32.0 17.7 3.0 42.1 3.4 62.2 40.9			 3.0 63.6 33.3 15.5 4.5 40.9 5.2 62.7 41.2			
Effectiveness		**6mnths n=163**	**12mnths n=135**		**6mnths n=263**	**12mnths n=250**	**P value**
Investigator global rating Moderately clear or better –n(%)		125 (76.7)	110 (81.5)		226 (85.9)	222 (88.8)	P=0.008 at 6 months P=0.067 at 12 months
Investigator global rating Moderately clear or better –n(%) LOCF		177/327 (54.1)	171/327 (52.3)		269/326 (82.5)	267/326 (81.9)	P<0.001
Patient global rating moderately improved or better n(%)		120 (73.6)	109 (80.7)		223 (84.8)	226 (90.4)	P=0.003 at 6 months P=0.008 at 12 months
EASI score Mean Change		-6.9	-7.6		-10.3	-11.3	P<0.001 at 6 months P=0.006 at 12 months
Mean EASI score		6.3	5.1		5.2	4.1	
Mean EASI score – LOCF		-4.0	-3.9		-9.6	-9.6	P<0.001 at 6 & 12 months
Mean EASI score – head and neck		0.057	0.05		0.057	0.005	
Pruritus score 0-1 (mild or none) n(%)		94 (57.7)	81 (60)		180 (68.2)	173 (69.2)	P=0.025 at 6 months P=0.069 at 12 months
Median time to first remission (days)			225			212	
Median time to first recurrence (days)			2			25	
QoL Mean % change from DLQI		-27.3	-48.2		-39.1	-48.3	
DLQI score	32.4	18.4	14.6	33.0	13.3	14.9	
EuroQoL- mode (%) across all patients *Mobility* *Self care* *Usual Activities* *Pain/discomfort* *Anxiety/ depression*	 1 (92.4) 1 (96.0) 1 (72.0) 2 (61.9) 1 (59.8)	Day 22 1 (90.6) 1 (93.5) 1 (74.3) 2 (53.1) 1 (68.7)	 1 (91.4) 1 (92.8) 1 (85.6) 1 (59.0) 1 (74.8)	 1 (93.6) 1 (95.5) 1 (73.6) 2 (57.3) 1 (66.1)	Day 22 1 (93.9) 1 (93.9) 1 (83.5) 1 (60.6) 1 (75.2)	 1 (92.6) 1 (93.0) 1 (85.2) 1 (67.2) 1 (77.3)	

Frequent Adverse effects (>=2%) –n(%)			N=328		N=330		
Infections							
Total			136		168		
Nasopharyngitis			25 (7.6)		46 (13.9)		
Influenza			32 (9.8)		38 (11.5)		
Folliculitis			20 (6.1)		26 (7.9)		
Skin infection (NOS)			21 (6.4)		13 (3.9)		
Herpes Simplex			13 (4.0)		17 (5.2)		
Upper resp. tract infect. NOS			14 (4.3)		10 (3.0)		
Bronchitis NOS			8 (2.4)		13 (3.9)		
Impetigo			8 (2.4)		8 (2.4)		
GI NOS			6 (1.8)		8 (2.4)		
Sinusitis NOS			2 (0.6)		10 (3.0)		
Skin Papilloma			0		7 (2.1)		
Application site disorders:							
Burning			85 (25.9)		36 (10.9)		
Reaction NOS			48 (14.6)		24 (7.3)		
Irritation			21 (6.4)		11 (3.3)		
Pruritus			18 (5.5)		6 (1.8)		
Erythema			7 (2.1)		2 (0.6)		
General*:*							
Flu like			6 (1.8)		8 (2.4)		
Aggravated condition			8 (2.4)		2 (0.6)		
Nervous system disorders							
Headache NOS			23 (7.0)		33 (10.0)		
Insomnia NEC			2 (0.6)		9 (2.7)		
Most frequently reported skin infections >0.5%							
Bacterial:							
NOS			5 (1.5)		5 (1.5)		
Erysipelas			0		4 (1.2)		
Folliculitis			20 (6.1)		26 (7.9)		
Furuncle			4 (1.2)		0		
Impetigo			8 (2.4)		8 (2.4)		
Straph. NOS			3 (0.9)		1 (0.3)		
Fungal: total			1 (0.3)		4 (1.2)		
Tinea pedis			0		2 (0.6)		
Viral: total			14 (4.3)		26 (7.9)		
Herpes simplex			13 (4.0)		17 (5.2)		
Herpes simplex dermatitis			2 (0.6)		0		
Herpes simplex ophthalmic			2 (0.6)		1 (0.3)		
Herpes zoster			1 (0.3)		2 (0.6)		
Molluscum contagiosum			0		2 (0.6)		
Skin papilloma			0		7 (2.1)		

Methodological comments

- *Prospective?* Yes
- *Consecutive patients enrolled?* Not clear
- *Blinding:* Same number and type of tubes of cream were packed together for control and treatment. Creams, as far as possible, the same in appearance and odour. Investigator was not involved in handling study medication. All personnel involved in the conduct of the study were kept blinded until end of the study.
- *Method of Randomisation:* Randomisation list prepared by the sponsor. Centres phoned for a treatment number. Randomisation used ClinPhone, with validated automatic system. Minimisation technique was used to ensure a balance between groups of BSA <5% and 5-30%.
- *Unit of randomisation and analysis:* Patient
- *Power calculation?* Yes. Primary endpoint was demonstration that no excess skin infections occurred with pimecrolimus compared to TS. 12 months safety data for at least 100 patients was required by the TDA. Allowing for 66% drop out, 300 patients in each arm were needed. Assume that infection rates were 10% and an increase to 20% would be cause for clinical concern (80% power, 95% two sided CI) (power of test decreases as incidence in control group decreases).
- *All patients given same intervention?* Yes but concomitant medication including topical corticosteroids
- *Loss to follow up:* At 12 months, 192 (58.5%) did not complete study in the pimecrolimus group (28 AEs, 119 unsatisfactory therapeutic effect, 10 protocol violation, 11 withdrawal of consent, 19 LTFU, 5 admin problems) and 79 (23.9%) discontinued in the corticosteroid group (5 AEs, 27 unsatisfactory therapeutic effect, 9 protocol violation, 12 withdrawal of consent, 24 LTFU, 2 admin problems). Most withdrawals for unsatisfactory therapeutic effect occurred in the first 4 months.
- *Method of data analysis*: ITT was not undertaken – patients were analysed in the group of the medication they received. AEs, 95% CI calculated. Descriptive analyses of efficacy stratified on areas involved (5-30% >30%), time to remission and recurrence. Percentages of success were based on scores 0-3 (clear to moderate). Descriptive statistics for EASI scores. Between treatment differences for absent and mild pruritus scores were calculated. Time to remission using Kaplan Meier, estimating median and $25^{th}/75^{th}$ quartiles. Test for homogeneity using Fishers exact test for qualitative and Wilcoxon Rank Sum Test for quantitative data. Mantel Haenszel chi-square test used for severity of AD.

General comments

- *Generalisability:* High
- *Main outcome measured blind/independently:* Yes
- *Inter-centre variability:* Not examined
- *Conflicts of interest:* Sponsored by Novartis Pharma AG.

* LOCF = Last observation carried forward

9.6 Appendix 6: Data extraction sheet – tacrolimus for eczema

Reference and Design	Intervention	Subjects	Outcome measures
▪ *Author:* Paller et al 2001 ▪ *Study design:* Double blind, vehicle control, RCT ▪ *Recruitment dates:* 08/1997-06/1998 ▪ *Setting:* 23 centres in USA	▪ *Treatment:* Tacrolimus ointment (0.03% or 0.1%) applied twice daily ▪ *Comparator* Vehicle ▪ *"Wash out" period* 6 weeks astemizole, 4 weeks (systemic corticosteroids, light treatment, immunosuppressants, investigational drugs) 14 days (steroids, >2 mg prednisone-equivalent) 7 days (Topical steroids, antihistamines, antimicrobials) 1 day vehicle ▪ *Concomitant treatment* Sedating antihistamines allowed ▪ *Length of treatment* 12 weeks. Cleared lesions could be excluded from treatment after 3 weeks evaluation, as long as treated for a week beyond clearing. ▪ *Safety levels* Incidence of adverse effects; tacrolimus blood concentration (<0.5 ng/mL) 1 patient had q 1 sample >2ng/mL. Mean and median levels were below limit at all evaluation points.	▪ *Total number of patients: 351 (117 0.03% tacrolimus, 118 0.1% tacrolimus, 116 vehicle)* ▪ *Eczema definition:* Hanifin and Rajka criteria, Rajka and Langeland criteria ▪ *Eczema severity:* Moderate to severe atopic dermatitis ▪ *Inclusion criteria:* 2-15 years of age Diagnosis of moderate to severe dermatitis BSA 10-100% ▪ *Exclusion criteria:* Other skin disorder, pigmentation, scarring; Clinically infected dermatitis; Systemic disease with counter-inidication for tacrolimus; Non well-controlled chronic condition Pregnancy or lactation	▪ *Primary and secondary outcome measures used:* Clinical improvement of eczema symptoms; patient's assessment of symptoms improvement ▪ *Method of assessing outcomes:* Global assessment of clinical response (0-100% improved) EASI scores Global scores for clinical signs of atopic dermatitis (erythema; oedema/induration/papulation; excoriation; oozing/weeping/crusting; scaling; lichenification. Reported separately and in combination) Body area affected (%) Patients assessment of pruritus and overall response Adverse events ▪ *Length of follow up:* No mean reported

Results: Patients characteristics

Arm		**Tacrolimus 0.03% N=117**	**Tacrolimus 0.1% N=118**	**Comparison N=116**	**P=value**
Age	*2-6*	74 (63.2%)	69 (58.5 %)	72 (62.1 %)	
	7-15	43 (36.8%)	49 (41.5 %)	44 (37.9%)	
Males		55 (47%)	57 (48.3%)	53 (45.7 %)	
Race	*White*	76 (65%)	76 (65%)	78 (67.2%)	
	African American	28 (24.1%)	32 (27.4%)	28 (24.1%)	
	Asian	8 (6.9%)	7 (6%)	8 (6.9%)	
	Other	2 (1.7%)	2 (1.7%)	2 (1.7%)	
Severity	*Moderate*	45 (38.5%)	43 (36.4%)	47 (40.5 %)	
	Severe	72 (61.5%)	75 (63.6%)	69 (59.5 %)	
BSA affected	*10-25%*	41 (35%)	27 (22.9%)	33 (28.4%)	
	25-50%	27 (23.1%)	36 (30.5%)	30 (25.9%)	
	50-75%	28 (23.9%)	34 (28.8%)	25 (21.6%)	
	75-100%	21 (17.9%)	21 (17.8%)	28 (24.1%)	
BSA affected mean (range)		45.6% (10-100%)	48.3% (10-97.6%)	49.2% (10-100%)	
Dermatitis of Head and Neck		100 (85.5%)	93 (78.8%)	100 (86.2 %)	

Results: Effectiveness					
Arm		**Tacrolimus 0.03%**	**Tacrolimus 0.1%**	**Comparison**	**P=value**
Amount of ointment used	*Mean*	4.6 g/day	4.1 g/day	7.4 g/day	Not reported
Length of treatment	*Median*	85 days	85 days	46 days	
Physicians' global evaluation of improvement	*Cleared*	12.1%	11.3%	3.8%	P<0.001
	Excellent	23.8%	29.4%	3.1%	
	Marked	20.6%	15.3%	8.8%	
	Moderate	16.1%	22%	11%	
EASI score		-14	-15	–2.4	P<0.001
Total score		-5.8	-6.1	–1.6	P<0.001
Reduction in Pruritus score		–3.9	–3.9	–0.8	P<0.001
Reduction in BSA affected		-26%	-27%	-7%	P<0.001
Reduction in signs and symptoms score	*Oedema*	-0.7	-0.8	-0.2	P<0.001
	Erythema	-0.8	-0.8	-0.2	P<0.001
	Excoriation	-0.7	-0.9	-0.2	P<0.001
	Lichenification	-0.8	-0.7	-0.2	P<0.001
	Oozing	-0.5	-0.5	0	P<0.001
	Scaling	-0/9	-0.1	-0.3	P<0.001
Adverse effects Adjusted 12-weeks incidence rate, (SE)	*Skin burning*	42.7 (+/- 4.67)	33.7 (+/-4.42)	29 (+/-4.74)	0.04 (0.03%) 0.46 (0.1%)
	Pruritus	41.2 (+/-4.65)	32.2 (+/- 4.51)	26.6 (+/-4.9)	0.04 (0.03%) 0.39 (0.1%)
	Varicella	4.8 (+/-2.36)	1.1 (+/-1.06)	0	0.04 (0.03%) 0.32 (0.1%)
	Vescicobullosus rash	3.3 (+/-1.85)	1.0 (+/-0.99)	0	0.04 (0.03%) 0.32 (0.1%)
	Sinusitis	3.3 (+/-1.9)	1 (+/-1.05)	8 (+/-3.34)	0.22 (0.03%) 0.046 (0.1%)
	Erythema n(%)	1 (0.4%)		0	Not stated
	Herpes n(%)	6 (2.6%) (of which 2 had herpeticum eczema)		1 (0.9%) and 1 after the end of treatment	Not stated
	Molluscum contagiosum n(%)	6 (2.6%)		1 (0.9%)	Not stated
	Warts n(%)	1 (0.4%)		0	Not stated

Methodological comments

- *Prospective?* Not reported
- *Consecutive patients enrolled?* Not reported
- *Method of Randomisation:* randomisation with 1:1:1 allocation ratio stratified by age within each centre.
- *Unit of randomisation and analysis* Patient
- *Blinding:* Investigator, patient, parent, study co-ordinator and other site personnel reported blind to treatment allocation.
- *Power calculation?* Not reported
- *All patients given same intervention?* Yes
- *Loss to follow up:* 105 did not complete the study. Tacrolimus 0.03% 23 - 6 because of adverse effects, 4 for lack of efficacy, 13 non-compliance, patient refusal and LTFU; Tacrolimus 0.1% total 17 - 3 for adverse events, 5 lack of efficacy, 9 for non-compliance, patient refusal and LTFU ; Comparator total 65 of whom 9 for adverse events, 46 lack of efficacy 10 for non-compliance, patient refusal and LTFU
- *Method of data analysis:* Not clear if ITT – based on 351 patients who were enrolled and received at least one dose of treatment. Tests for association for discrete variables (X^2) and ANOVA for continuous variables; Cochrane Mantel Haenszel controlling for age; general linear methods for severity scores. Kaplan Meyer survival analysis for adverse effects incidence in treatment and comparison group (not reported). Adjusted 12 week incidence rates for AEs.

General comments

- *Generalisability:* High
- *Main outcome measured blind/independently?* Yes
- *Inter-centre variability?* Not stated, not accounted for in the analy*sis*
- *Conflicts of interest*: All authors have received support for the research from Fujisawa and Novartis; Two authors have been on the speakers' bureau for Fujisawa, Glaxo and Schering. The article was part of a supplement sponsored by Fujisawa.

Some data extracted from graphs and may be subject to inaccuracies

Reference and Design	Intervention	Subjects	Outcome measures
▪ *Author:* Boguniewicz et al 1998 ▪ *Study design:* Double blind, vehicle controlled RCT ▪ *Recruitment dates:* Not stated ▪ *Setting:* 18 centres in USA	▪ *Treatment:* Tacrolimus 0.03%, 0.1% 0.3% twice daily ▪ *Comparator* Vehicle ▪ *"Wash out" period* Topical and inhaled corticosteroids: 1 week Systemic corticosteroids: 6 weeks PUVA UVA or immunotherapy: 1 month Non-sedating antihistamines: discontinued ▪ *Concomitant treatment* Emollient as needed ▪ *Length of treatment* Up to 22 days ▪ *Safety levels* Blood concentration <0.05 ng/mL. Mean Tacrolimus concentration at day 4 0.03% 0.1 (+/-0.17), 0.1% 0.21 (+/- 0.32), 0.3% 0.31 (+/- 0.41)	▪ *Total number of patients: 180 (43 T 0.03%, 49 0.1%, 44 0.3%, and 44 comparator)* ▪ *Eczema definition:* Hanifin and Rajka criteria ▪ *Eczema severity:* Moderate to severe ▪ *Inclusion criteria:* Age 7 to 16 BSA 5%-30% affected Menstruating women practising reliable contraception ▪ *Exclusion criteria:* Patients requiring anti-infective drugs Pregnant women	▪ *Primary and secondary outcome measures used:* Clinical improvement of eczema symptoms; patient's assessment of symptoms improvement ▪ *Method of assessing outcomes:* Physician global evaluation of clinical response (0%-100% improvement) mEASI score Head and Neck Region Total Score, physician's rating of 3 signs in 4 body areas (0-3) Pruritus patient's evaluation (VAS 10cm) adjusted to 0-3 scale. Assessed on days 4, 8, 14, 22 and 36 ▪ *Length of follow up:* 36 days

Results: Patients characteristics

Arm		**Tacrolimus 0.03% n=43**	**Tacrolimus 0.1% n=49**	**Tacrolimus 0.3% n=44**	**Comparison N=44**	**P value**
Age	Mean	10.1	10.8	10.5	10.4	0.669
Males		18	21	23	18	0.687
Race	*White*	24	38	32	27	
	Black	12	10	11	14	
	Other	7	1	1	3	
Severity	*Moderate*	38	42	39	32	
	Severe	5	7	5	12	
Duration of AD, years (SD)	Mean	8.1 (3.5)	7.8 (3.5)	8.8 (3.4)	8.7 (3.7)	0.468
TBSA	Mean	17.7%	15.5%	19.3%	19.7%	0.049
Severity	Moderate	38	42	39	32	
	Severe	5	7	5	12	
Pruritus rating at baseline	**Mean**	**5.7**	**4.9**	**5.2**	**5.4**	

Results: Effectiveness

Arm		**Tacrolimus 0.03%**	**Tacrolimus 0.1%**	**Tacrolimus 0.3%**	**Comparison**	**P value**
Amount of ointment used	Limited to 10g per application	94 g	86 g	91 g	98 g	
Length of treatment	Median					
Physicians' global assessment % (95% CI)	Cleared to marked	69% (53-82%)	67% (52-81%)	70% (54-83%)	38% (24-54%)	=<0.007

	No improvement to worse	5 pts	2 pts (no treatment specification given)		16 pts	
EASI score	Mean improvement	72%	77%	81%	26%	<0.001
Mean % increase in Head and Neck region total score		65%	83%	81%	- 2%	p<0.001
Pruritus	Mean (mean % improvement	1.8 (64.7%)	1.7 (47.1%)	1.8 (47.8%)	3.6 (3.6%) paper has a typo here	P=0.027
	Median % improvement	88.7%	73.6	77.1	50.5	
QoL	-	-	-	-	-	
Recurrence after clearing (2-weeks follow-up)		18 (72%)	17 (81%)	21 (88%)	9 (75%)	Not stated
Pt reporting feeling "better" or "much better"		76%	91%	91%	52%	For tacrolimus vs vehicle p<=0.025
Adverse effects	Increased pruritus at site	11 (25.6%)	10 (20.4%)	13 (29.5%)	7 (15.9%)	.445
	Skin burning	9 (20.9%)	5 (10.2%)	10 (22.7%)	3 (6.8%)	.092
	Increased erythema at site	0	1 (2%)	3 (6.8%)	2 (4.5%)	.309
	Increased serum creatine	1 (2.3%)	0	0	0	0.361

Methodological comments

- *Prospective? Yes*
- *Consecutive patients enrolled ?* Not stated
- *Method of Randomisation:* Centralised computer generated schedule using permutation of blocks of 8 within centres
- *Unit of randomisation and analysis:* Patient
- *Blinding:* Tacrolimus and vehicle ointment were identical in appearance and in identical coded tubes. All investigators, study co-ordinators, patients and sponsor were bind, except for Fujisawa staff who prepared the study medication.
- *Power calculation?* Expected difference in marked or better improvement rated by physician's global evaluation: 30% (50% for control and 80% for intervention), number of patients calculated to detect difference at 80% power and alpha=0.05
- *All patients given same intervention?* Suspension of treatment is allowed if clearance is achieved within the study period
- *Discontinuation rates:* Tacrolimus 0.03% total 2 of whom 1 lack efficacy and 1 non compliance; Tacrolimus 0.1% total 5 of whom 4 non compliance 1 adverse event; Tacrolimus 0.3% total 4 of whom 4 adverse events Comparison total 7 of whom 4 lack of efficacy 1 non compliance 2 adverse events
- *Loss to follow up?* 1 in 0.03% group, 7 in 0.1% group, 1 in 0.3% group, 2 in comparison
- *Method of data analysis:* Analysis excluded patients randomised but not receiving at least 3 days treatment (2 in vehicle; 1 in 0.03%; 7 in 0.1%; 1 in 0.3%) Outcomes variables analysed with ANOVA, X^2 and Kruskal Wallis tests. Scores were analysed with general linear models and logistic regression.

General comments

- *Generalisability:* High
- *Main outcome measured blind/independently?* Yes
- *Inter-centre variability*? Not reported
- *Conflicts of interest*:? Study funded by Fujisawa. IL is an employee of Fujisawa

Reference and Design	Intervention	Subjects	Outcome measures
▪ *Author:* Granlund et al 2001 ▪ *Study design:* *RCT* ▪ *Recruitment dates:* Not stated ▪ *Setting:* Not stated (authors from Finland)	▪ *Treatment:* Tacrolimus 0.1% ▪ *Comparator* *Vehicle* ▪ *"Wash out" period* Not stated ▪ *Concomitant treatment* Emollient, bath oil ▪ *Length of treatment* 2 weeks ▪ *Safety levels* Not stated	▪ *Total number of patients:* *14 (Intervention 6 control 8)* ▪ *Eczema definition:* Rajka and Lageland ▪ *Eczema severity:* Moderate to severe ▪ *Inclusion criteria:* Age 18-60 years Presence of lichenified area on the elbow of 12 cm^2 Lichenification score of 2 or more (scale 1-3) ▪ *Exclusion criteria:* Not stated ▪ *Participant characteristics:* *Not stated*	▪ *Primary and secondary outcome measures used:* Clinical improvement of eczema symptoms; patient's assessment of symptoms improvement Skin water loss and thickness ▪ *Method of assessing outcomes:* Primary endpoint: change in combined score for symptoms and pruritus Symptoms: graded score (0-3) for severity of pruritus, erythema, oedema, crust/oozing excoriation, lichenification of involved skin, dryness of non-involved skin. Pruritus patients' rating VAS 0-10, converted to a score 0-3 Physicians rating of clinical improvement (completely resolved, markedly, moderately or slightly improved, no change or worse) Extent of affected skin measured. Transepidermal water loss – superficial blood flow measured with laser Doppler flowmeter. Skin thickness measured with high frequency ultrasound ▪ *Length of follow up:* 1 month

Results: Patients characteristics

Arm		**Tacrolimus 0.1%**	**Comparison**	**P=value**
Age				
Males				
Severity	Moderate			
	Severe			
TBSA	Average			

Results: Effectiveness

Arm		**Tacrolimus 0.1%**	**Comparison**	**P=value**
Amount of ointment used				
Length of treatment	Median			
Physicians' global assessment	Cleared	6 (100%)	0	
	Excellent	0	0	
	Marked	0	0	
	Moderate	0	4 (50%)	
	Slight	0	2 (25%)	
	No improvement	0	2 (25%)	
Symptom score	Mean improvement	-68.5%	-13.4%	0.002
Head and Neck region total score				
Pruritus		-80%	0	Not stated
Area of symptomatic skin		-45.6%	-2.9%	Not stated
Adverse effects				
Skin thickness - % decrease		-5.8%	-1.1%	P=0.478

Methodological comments

- *Prospective?* Yes
- *Consecutive patients enrolled?* No
- *Method of Randomisation:* Patients randomisation ratio 1:1 no further details.
- *Unit of randomisation and analysis:* Patient
- *Blinding:* Investigator, patient and study monitor blind to allocation.
- *Power calculation?* Not stated
- *All patients given same intervention?* Yes
- *Loss to follow up?* 2 recruited but not randomised. Other details not stated
- *Method of data analysis:* Comparisons between groups done with Wilcoxon Rank sum test

General comments

- *Generalisability:* Low
- *Main outcome measured blind/independently? Yes*
- *Inter-centre variability*? Not stated, not accounted for in the analysis
- *Conflicts of interest*:? The study was sponsored by Fujisawa Inc

Reference and Design	Intervention	Subjects	Outcome measures
▪ *Author:* Hanifin et al 2001 ▪ *Study design:* 2x double blind RCTs ▪ *Recruitment dates:* 08/1997 to 07/1998 ▪ *Setting:* 41 centres in the US	▪ *Treatment:* Tacrolimus 0.03% or 0.1% twice daily ▪ *Comparator* Vehicle ▪ *"Wash out" period* Astemizole 7 days, non-sedating antihistamines 6 weeks, systemic corticosteroids, light treatment (UVA UVB), immunosuppressants, investigational drugs 4 weeks; Intranasal or inhaled steroids, >2 mg prednisone-equivalent 14 days; Topical steroids, antihistamines, antimicrobials other medicated topical agents 7 days; Non medicated topical agents (vehicle, emollient) 1 day ▪ *Concomitant treatment* Sedating antihistamines (but increase not allowed) ▪ *Length of treatment* 12 weeks or until 1 week after clearance ▪ *Safety levels* Not stated	▪ *Total number of patients:* 632 (Intervention 211 (0.03%) 209 (0.1%) 212 control) ▪ *Eczema definition:* Hanifin and Rajka criteria ▪ *Eczema severity:* Moderate or severe AD (Rajka and Langeland) ▪ *Inclusion criteria:* Age >=16 BSA 10%- 100% ▪ *Exclusion criteria:* Pregnancy or lactation Concomitant other skin disorder, pigmentation, scarring in affected areas Clinically infected AD Systemic disease for which tacrolimus is contraindicated Chronic conditions- not well controlled .	▪ *Primary and secondary outcome measures used:* Clinical improvement of eczema symptoms; patient's assessment of symptoms improvement ▪ *Method of assessing outcomes* Physician global evaluation of clinical response; EASI score % TBSA affected Patient's assessment of pruritus (VAS 0-10) Global scores for clinical signs of atopic dermatitis (erythema; oedema/induration/papulation; excoriation; oozing/weeping/crusting; scaling; lichenification; each in 4 body regions (head and neck, trunk, upper limbs, lower limbs) Clinical score = average for each clinical parameter for all body regions. Total score: sum of clinical scores for each sign plus pruritus score (converted to a 4-point score) EASI = composite score combined with % BSA in each of 4 body zones (max 72) Weeks 1, 2, 3, 6, 9, 12, 14. ▪ *Length of follow up:* 14 weeks

Results: Patients characteristics

Arm		**Tacrolimus 0.03%**	**Tacrolimus 0.1%**	**Comparison**	**P=value**
Age range 15-79	Mean (SD)	37.9 (+/- 13.8)	39.3 (+/- 14.5)	38.5 (+/-14.0)	Non significant
Males		45%	40.7%	44.8%.	Non significant
Race	White	68.2%	66.5%	66%	Non significant
	African American	26.1%	26.3%	26.9%	Non significant
	Other	5.7%	7.2%	7.1%	Non significant
Severity	Moderate	44.4%	41.1%	46.2%	Non significant
	Severe	55.9%	58.9%	53.8%	Non significant
BSA	Mean (SD)	44.9%(+/-25.8)	44.9% (+/-27.0)	45.5% (+/-25.7)	Non significant
Dermatitis of Face and Neck	% patients	86.3%	85.6%	89.2%	Non significant

Results: Effectiveness

Arm		**Tacrolimus 0.03%**	**Tacrolimus 0.1%**	**Comparison**	**P=value**
Amount of ointment used	(Median)	4.5 g/day	4.7 g/day	6.3 g/day	
Physicians' global assessment	Cleared	9.6%	9.8%	0.6%	P<0.001 vs vehicle 0.03% vs 0.1 p=0.041
	Excellent	17.3%	28.5%	5.2%	
	Marked	19.3%	18.7%	8%	
	Moderate	15.4%	15.7%	6%	
PGA >=90% improvement	n(%)	58 (27.5%)	77 (36.8%)	14 (6.6%)	P<0.001 for 0.03% and 0.1% vs vehicle

PGA >=90% improvement	Patients with Severe AD only	23/118 (19.5%)	43/123 (35%)	N/a	0.009
PGA >=90% improvement	Patients with TBSA 75%-100%	2/39 (5.1%)	13/43 (30.2%)	N/a	0.004
Physicians' global assessment	Afro-American patients	9/55 (16.4%)	16/55 (29.1%)	7% (number not provided)	0.03% vs 0.1% 0.107 0.03% vs vehicle 0.112 TYPO IN THE TEXT 1% vs vehicle = 0.002
EASI score	Mean improvement	-11.7	-14.4	–2.3	P<0.001 for both Vehicle and 0.03% to 0.1%
Total Score		-5.2	-5.9	–1.3	P=0.001
Pruritus		-3.4	–3.8	–0.7	P<0.001
BSA		-19	-24	-5	P<0.001 for both Vehicle and 0.03% to 0.1%
Decease in signs and symptoms score	Oedema	-0.7	-0.9	-0.1	T vs vehicleP<0.001 0.3% vs 0.1% p<0.05
	Erythema	-0.8	-0.9	-0.2	T vs vehicleP<0.001
	Excoriation	-0.7	-0.8	-0.1	T vs vehicleP<0.001 0.3% vs 0.1% p<0.05
	Lichenification	-0.7	-0.8	-0.2	T vs vehicleP<0.001
	Oozing	-0.3	-0.4	0	T vs vehicleP<0.001
	Scaling	-0.8	-1.0	-0.3	T vs vehicleP<0.001 0.3% vs 0.1% p<0.05

Methodological comments

- *Prospective?* Yes
- *Consecutive patients enrolled?* Not stated
- *Method of Randomisation:* 1:1:1 within each centre
- *Unit of randomisation and analysis:* Patient
- *Blinding* Described as double blind – no details.
- *Power calculation?* Not reported
- *All patients given same intervention?* Yes
- *Rates of discontinuation and loss to follow up:* 1 lost after randomisation – excluded from analysis. Tacrolimus 0.03% 61 patients (28.9%) of whom 26 (12.3%) lack of efficacy, 13 (6.2%) for adverse events and 22 (10.4%) for loss to follow-up, patients' refusal or noncompliance; Tacrolimus 0.1% Total 52 (24.9%) of whom 18 (8.6%) lack of efficacy 11 (5.3%) adverse events 23 (11%) loss to follow-up, patients refusal, noncompliance; Comparison Total 145 (68.4%) of whom 95 (44.8%) for lack of efficacy 26 (12.3%) adverse events and 24 (11.3%) loss to follow up, patients' refusal, noncompliance
- *Method of data analysis:*1 patient excluded post randomisation as received no treatment – not known from which group. X^2 and analysis of variance for baseline variables; Fisher exact test and Cochran Mantel Henszel test stratified by study for combined results. Breslow-Day test for homogeneity between studies; General linear methods for outcomes.

General comments

- *Generalisability:* High
- *Main outcome measured blind/independently? Not reported*
- *Inter-centre variability*? Not tested Not reported
- *Conflicts of interest*:? The study was funded by Fujisawa Inc and published in a supplement sponsored by Fujisawa. All authors have received grant support and/or acted as consultants to Fujisawa Inc.

Some data extracted from graphs and may be subject to inaccuracies

Reference and Design	Intervention	Subjects	Outcome measures
▪ *Author:* Kawashima 1998 (translated by Fujisawa) ▪ *Study design:* Randomised parallel group comparison ▪ *Recruitment dates:* Unclear – project from June 1996 to Feb. 1997 ▪ *Setting:* 25 medical institutes in Japan	▪ *Treatment:* 0.1% Tacrolimus twice daily *Comparator:* 0.12% Betamethasone Valerate (BVM, a potent steroid) twice daily ▪ *"Wash out" perio*d Systemic steroid therapy, UV treatment 4 weeks Very strong TS 1 week Betamethasone preparations 4 weeks Astemizole 4 weeks ▪ *Concomitant treatment* Oral antihistamines or anti allergics (excluding tranilast and suplatast tosilate, astemizole and terfenadine) Medication for complications Length of treatment 3 weeks ▪ *Safety levels* Tests undertaken prior to trials and at 3 weeks after start, or discontinuation of application: Erythrocyte count, haemoglobin count, haematocrit count, platelet count, leukocyte count plus blood chemistry and urinanalysis. In the BVM group 2/82 (2.4%) had increased s-GOT and/or s-GPT. 3/88 (3.4%) in the tacrolimus group were judged to be "unsafe".	▪ *Total number of patients:* 181 (89 tacrolimus, 92 BVM) Eczema definition: Hanifin and Rajka Rajka and Langeland Eczema severity: Moderate or severe ▪ *Inclusion criteria:* Age >=16 Patients who could be treated with <=5g ointment per application to trunk and extremities. ▪ *Exclusion criteria*: Previous Tacrolimus use Serious drug hypersensitivity Complications of severe cardiac, renal, hepatic, pancreatic diseases Complications of malignant tumours, infections Pregnancy, breast feeding or intention to become pregnant Participation in other trials within 6 months Inability to give consent Enrolment considered inadvisable by the investigator. Only trunk and extremities were treated – head, face, neck, hands and feet were excluded sites.	▪ *Primary and secondary outcome measures used:* Severity of eczema Global Improvement AEs Safety Compliance Method of assessing outcomes: Severity 5 point scale: 0 none, 1 slight, 2 mild, 3 moderate, 4 severe If exacerbated, digit 4 was double circled. Global rating scale: 1 Cured, 2 Markedly improved, 3 moderately improved, 4 mildly improved, 5 unchanged, 6 aggravated. AEs: Irritation on a 3 point scale: 1 Mild (virtually unnoticeable) 2 Moderate (application could be continued, but quite noticeable) 3 Severe (too severe to continue application) Accompanying symptoms excl. irritation and infection 1 Mild (application could be continued without any counter measures) 2 Moderate (application could be continued with countermeasures) 3 Severe (too severe to continue application) Possibly relation to treatment rated on a 5 point scale: 1 related, 2 probably related, 3 possibly related, (1-3 considered to be related) 4 probably unrelated, 5 unrelated Compliance was measured on a 4 point scale: able to apply study medication: 1 90%+ of the time 2 70-90% of the time 3 50-70% of the time 4 <50% of the time Length of follow up: Assessed at weeks 1, 2 and 3.

Results:	Pre Intervention N=89	Post Intervention (n=78)	Pre Comparison N=92	Post comparison (n=84)	P=value
Participant characteristics:					
Males %	43.6		64.3		
Mean Age (SD)	25.9 (+-5.7)		26.3 (+-7.6)		
Min-Max	16-42		16-53		
Median	25.0		24.0		
Body Weight (kg)					
Mean (SD)	55.7 (+-9.8)		58.0 (+-8.6)		
Min-max	42.0-90.0		41.0-80.0		
Median	53.5		57.0		
Duration of disease-months					
mean (SD)	196.2 (+-95.4)		188.5 (+-112.2)		
Min max	12-444		4-552		
Median	222.0		204.0		
Inpatient/ Outpatient -%					
Inpatient	5.1		9.5		
Outpatient	88.5		83.3		
In-out	6.4		7.1		
Severity -%					
Moderate	51.3		60.7		P=0.293
Severe	48.7		39.3		
Previous medication? %					P=0.948
Yes	57.7		56.0		
Systemic	n=5		n=3		
Topical	n=6		n=9		
Systemic & topical	n=34		n=35		
Effectiveness		***N=78***		***N=84***	***P value***
Signs and symptoms scores:					
Erythema-n (%)					
None		0		0	P=0.489
Slight		1 (1.3)		2 (2.4)	
Mild		11 (14.1)		8 (9.5)	
Moderate		44 (56.4)		47 (56.0)	
Severe		22 (28.2)		27 (32.1)	
Swelling –n(%)					
None		11 (14.1)		21 (25.0)	P=0.081
Slight		15 (19.2)		14 (16.7)	
Mild		22 (28.2)		27 (32.1)	
Moderate		20 (25.6)		14 (16.7)	
Severe		10 (12.8)		8 (9.5)	
Papule –n(%)					
None		1 (1.3)		4 (4.8)	P=0.768
Slight		13 (16.7)		8 (9.5)	
Mild		24 (30.8)		28 (33.3)	
Moderate		29 (37.2)		31 (36.9)	
Severe		11 (14.1)		13 (15.5)	
Prurigo nodularis					
None		27 (34.6)		30 (35.7)	P=0.754
Slight		17 (21.8)		12 (14.3)	
Mild		14 (17.9)		19 (22.6)	
Moderate		15 (19.2)		17 (20.2)	
Severe		5 (6.4)		6 (7.1)	

Lichenification None Slight Mild Moderate Severe		 5 (6.4) 8 (10.3) 15 (19.2) 31 (39.7) 19 (24.4)		 3 (3.6) 5 (6.0) 18 (21.4) 38 (45.2) 20 (23.8)	P=0.552
Desquamation None Slight Mild Moderate Severe		 2 92.6) 8 (10.3) 29 (37.2) 26 (33.3) 13 (16.7)		 6 (7.1) 8 (9.5) 25 (29.8) 33 (39.3) 12 (14.3)	0.901
Erosion – n(%) None Slight Mild Moderate Severe		 20 (25.6) 21 (26.9) 19 (24.4) 15 (19.2) 3 (3.8)		 30(35.7) 14 (16.7) 26 (31.0) 9 (10.7) 5 (6.0)	0.394
Incrustation n(%) None Slight Mild Moderate Severe		 15 (19.2) 19 (24.4) 28 (35.9) 14 (17.9) 2 (2.6)		 19 (22.6) 19 (22.6) 34 (40.5) 9 (10.7) 3 (3.6)	0.520
Itching – n(%) None Slight Mild Moderate Severe		 0 1 (1.3) 8 (10.3) 40 (51.3) 29 (37.2)		 1 (1.2) 9 (10.7) 39 (46.4) 35 (41.7)	0.649
Overall Symptom score Mean (SD) Min max Median		 2.28 (+-0.7) 0.8 ~4.0 2.3		 2.25 (+-0.69) 0.7 ~4 2.3	P=0.624
Final global improvement rating n (cum. %) Cured Markedly improved Moderately improved Slightly improved No change		 13 (16.7) 41 (69.2) 19 (93.6) 3 2		 9 (10.7) 43 (61.9) 24 (90.5) 7 1	 Not sig.
Global improvement rating at 3 weeks – n (cum. %) Cured Markedly improved Moderately improved Slightly improved No change		N=66 10 (15.2) 38 (72.7) 15 (95.5) 2 1		N=71 8 (11.3) 40 (67.6) 17 (91.5) 6 0	 Not sig.

Adverse effects Irritations: n(%) TOTAL Flush (incl burning&heat) Mild Moderate Severe Total Tingling (incl. pricking & smarting) Mild Moderate Severe Total Itching Mild Moderate Severe Total		N=88 52 (59.1) 10 12 3 25 (28.4) 19 10 2 31 (35.2) 5 0 2 7 (7.9)		N=90 8 (8.9) 3 0 0 3 (3.3) 5 0 0 5 (5.6) 1 0 0 1 (1.1)	P<0.001
Infections TOTAL Folliculitis Furuncle/boil Impetigo Herpes simplex Kaposi's varicelliform eruption Herpes zoster Trichophytosis		5 (5.7) 1 0 1 0 1 1 1		6 (6.7) 4 1 0 1 - 0 0	Not sig.

Methodological comments
Prospective? Yes
Consecutive patients enrolled? Not clear
Blinding: Identical 5g tubes used for both ointments and packed in 14 unit packs.
Method of Randomisation: Central randomisation using permuted blocks of 6. Key code kept centrally.
Unit of randomisation and analysis: Patient. However only one site with "typical lesions" was assessed.
Power calculation? None stated
All patients given same intervention? Yes
Loss to follow up: 19 (11 tacrolimus, 8 BVM) not included in analysis. In the tacrolimus group: 7 due to poor compliance, 1 using banned concomitant drugs, 2 no observation recorded, 1 no visit to institution. In the BVM group 2 poor compliance, 2 using banned concomitant drugs, 1 no observation recorded, 1 no visit to institution, 1 no consent of guardian obtained. In 3 of these cases overall, safety, but not effectiveness ratings were recorded.
Method of data analysis: ITT was not undertaken, inclusion of incomplete cases, drop-outs etc. in the analyses was determined by the executive committee. 11 patients in the treatment group and 8 in the control group were excluded from effectiveness analyses and 1 and 2 respectively from the safety analysis. Chi-square test, Fisher's exact test or Mann Whitney U- test for differences between groups. Homogeneity of odds ratios for global score examined with Breslow-Day test, and Mantel-Haeszel or extended Mantel test. Direct standardisation method used for CIs for differences in improvement rate. Chi square test, Fisher's exact test, Mann-Whitney U-test, or t test used for intergroup comparison, paired-t test or Wilcoxon's signed rank test for intra-group comparison. 5% significance level used for 2-tailed tests and 15% level and clinically acceptable improvement of 10% used to test for differences in population and demonstration of equivalency.

General comments
Generalisability: High
Main outcome measured blind/independently: Yes
Inter-centre variability: not stated
Conflicts of interest: Funded by Fujisawa

Reference and Design	Intervention	Subjects	Outcome measures
▪ *Author:* Ruzicka et al 1997 ▪ *Study design:* Double blind RCT ▪ *Recruitment dates:* 04/1995 to 03/1996 ▪ *Setting:* 16 centres in Europe	▪ *Treatment:* Tacrolimus 0.03% 0.1% and 0.3% twice daily ▪ *Comparator* Vehicle (oil-oil emulsion – propylene carbonate, white wax, mineral oil, paraffin and petroleum) ▪ *"Wash out" period:* 1 week. AD therapy, other than emollient and antihistamines stopped within 3 weeks of washout phase. ▪ *Concomitant treatment:* emollient ▪ *Length of treatment:* 3 weeks ▪ *Safety levels* Sat 3 days, 0.03% 10 (29%) and 0.1% 5 (14%) >1ng/mL At 3 weeks 1 (3%) in the 0.1% group.	▪ *Total number of patients: 215 ((54 (0.03%) 54 (0.1%) 51 (0.3%) and 54 control)* ▪ *Eczema definition:* Rajka and Lageland ▪ *Eczema severity:* Moderate to severe ▪ *Inclusion criteria:* Age 13 to 60 years 200-1000cm^2 non contagious area of trunk, extremities, face and neck. At least 200cm^2 on neck or extremities. ▪ *Exclusion criteria:* Use of experimental treatments, traqulilizers and sleeping pills, systemic, topical or inhaled corticosteroids, antihistamines and antimicrobial drugs.	▪ *Primary and secondary outcome measures used:* Clinical improvement of eczema symptoms; patient's assessment of symptoms improvement, adverse effects ▪ *Method of assessing outcomes:* Investigator grading of severity of erythema, oedema, oozing, excoriation, lichenification of involved skin and dryness of non-involved skin in the treated area Patients grading of pruritus VAS 10cm Score 1: sum of erythema oedema and pruritus (converted to a score 0-3) Score 2: score 1 plus remaining symptoms Physician evaluation of clinical effectiveness (symptoms completely resolved, markedly, moderately or slightly improved, unchanged or worse) Absolute and percent change in score 1 and score 2 from baseline BSA assessed by rule of nines, or using 100-1000cm^2 shapes ▪ *Length of follow up:* 4 weeks

Results: Patients characteristics

Arm ***Baseline***		**Tacrolimus 0.03% n=54**	**Tacrolimus 0.1% n=54**	**Tacrolimus 0.3% n=51**	**Comparison N=54**	P=value
Age	Mean (SD)	30 (+/-12)	28 (+/-9)	27 (+/-10)	29 (+/-11)	
Females		28 (52%)	32(59%)	32 (63%)	28 (52%)	
Race	*White*	52 (96%)	51 (94%)	48 (94%)	53 (98%)	
	Other	2 (4%)	3 (6%)	3 (6%)	1 (2%)	
Mean total body involvement (cm^2) SD	*Trunk/limbs*	3848 (+/-3680)	3452 (+/-4361)	3367(+/-3654)	3453(+/-3730)	
	Face/neck	307 (+/-341)	354 (+/-331)	344 (+/-254)	404 (+/-260)	
BSA	Median	13.5	13	14	14	
Area selected for treatment	*Mean in cm^2 (SD)*	809 (+/-273)	778 (+/-271)	821 (+/-254)	821 (+/-260)	
Score 1 at baseline, area selected for treatment	Median	6	6	6	6	

Results: Effectiveness

Arm		**Tacrolimus 0.03%**	**Tacrolimus 0.1%**	**Tacrolimus 0.3%**	**Comparison**	P=value T vs vehicle
Decrease in score 1 (Median)	Trunk/limbs	66.7%	83.3%	75%	22.5%	**P<0.001**
	Face/neck	71.4%	83.3%	83.3%	25%	**P<0.001**
Decrease in score 2 (Median)	Trunk/limbs	61.5%	71.4%	70%	21.8%	**P<0.001**
	Face/neck	70.6%	75%	77.8%	27.3%	**P<0.001**

Physicians' global assessment	Cleared to marked improvement	59%	81%	71%	10%	P<0.001
	Moderate to worse	41%	19%	29%	90%	P<0.001
Exacerbation (Untreated area)		4	4	2	7	
Adverse effects N	Total AEs	32	33	32	23	
	Pruritus	7	2	7	4	
	Skin burning	20	25	25	8	P<0.001
	Erythema	3	6	6	3	
Adverse effects leading to withdrawal	Folliculitis	1	-	-	-	
	Burning	-	3	2	1	
	Pruritus	-	1	-	1	
	Viral infection	-	-	1	-	
	Exacerbation of symptoms	-	-	-	3	

Methodological comments

- *Prospective?* Yes
- *Consecutive patients enrolled?* Not stated
- *Method of Randomisation:* Ratio 1:1:1 stratified by centre
- *Unit of randomisation and analysis:* Patient
- *Blinding:* Investigators, patients and study monitors not aware of treatment assignment.
- *Power calculation?* Not reported
- *All patients given same intervention?* Yes
- *Discontinuation or loss to follow up*: 250 approached, 215 randomised. 2 excluded after randomisation (1 never treated, 1 baseline data only) Described as ITT but based on 213 pts only (12 excluded as received no treatment and one only provided baseline data). Tacrolimus 0.03% total 7, of whom 2 for use of prohibited therapy, 1 adverse event; 4 other; Tacrolimus 0.1% total 7. of whom 4 adverse events, 3 other reasons; Tacrolimus 0.3% total 7 of whom 3 use of prohibited therapy, 3 adverse events, 1 other reasons; Control total 21 of whom 13 use of prohibited therapy, 5 adverse events, 3 other reasons
- *Method of data analysis:* Jonckheere test for differences in the distribution of total scores for the 4 study groups; analysis of variance, area under the curve for score 1 then separate analysis carried out for face/neck and trunk/extremities.

General comments

- *Generalisability:* Medium
- *Main outcome measured blind/independently? Yes*
- *Inter-centre variability*? Included in the analysis
- *Conflicts of interest*:? The study was supported by a grant of Fujisawa Germany

Some data taken from graphs and may be subject to inaccuracies.

Reference and Design	Intervention	Subjects	Outcome measures
▪ *Author:* Soter et al 2001 ▪ *Study design:* 2x double blind RCTs ▪ *Recruitment dates:* 08/1997 to 07/1998 ▪ *Setting:* 41 centres in the US (Companion paper to Hanifin et al 2001)	▪ *Treatment:* Tacrolimus 0.03% or 0.1% twice daily ▪ *Comparator* Vehicle ▪ *"Wash out" period* Astemizole 6 weeks Systemic corticosteroids, light treatment (UVA UVB), immunosuppressants, investigational drugs 4 weeks; Intranasal or inhaled steroids, >2 mg prednisone-equivalent 14 days; Topical steroids, antihistamines, antimicrobials other medicated topical agents 7 days; Non medicated topical agents (vehicle, emollient) 1 day ▪ *Concomitant treatment* Not stated ▪ *Length of treatment* 12 weeks ▪ *Safety levels* Blood concentration <0.05 ng/mL in 80% of samples. Found > 0.5ng/ML in 3/1014 of samples. Highest 8.13 ng/mL	▪ *Total number of patients:* 632 (210 (0.03%) 209 (0.1%) 212 control) ▪ *Eczema definition:* Hanifin and Rajka, Rajka and Lageland ▪ *Eczema severity:* Moderate to severe ▪ *Inclusion criteria:* Adults aged 16+ BSA 10%-100% ▪ *Exclusion criteria:* Pregnancy or lactation Concomitant other skin disorder, pigmentation, scarring in affected areas Clinically infected AD Systemic disease for which tacrolimus is contraindicated Chronic conditions, not well controlled	▪ *Primary and secondary outcome measures used:* Treatment adverse events ▪ *Method of assessing outcomes:* Incidence of treatment adverse events ▪ *Length of follow up:* 14 weeks

Results: Patients characteristics

Arm		**Tacrolimus 0.03% N=210**	**Tacrolimus 0.1% n=209**	**Comparison N=212**	P=value
Age range 16-76	Mean (SD)	38.0 (+/-13.7)	39.3(+/-14.5)	38.5(+/-14.0)	Non significant
Males		94 (44.8%)	85 (40.7%)	95 (44.8%)	Non significant
Race	*White*	143 (68.1%)	139 (66.5%)	140 (66%)	Non significant
	African American	55 (26.2%)	55 (26.3%)	57 (26.9%)	Non significant
	Other	12 (5.7%)	15 (7.2%)	15 (7.1%)	Non significant
Severity	*Moderate*	92 (43.8%)	86 (41.1%)	98 (46.2%)	Non significant
	Severe	118 (56.2%)	123 (58.9%	114 (53.8%)	Non significant
BSA range 10-100	Mean (SD)	45% (+/-26.7)	44.9%(+/-27.0)	45.5% (+/-25.7)	Non significant
Dermatitis of Head and Neck		182 (89.1%)	179 (85.6%)	187 (89.2%)	Non significant

Results: Effectiveness

Arm		**Tacrolimus 0.03% N=210**	**Tacrolimus 0.1% n=204**	**Comparison n=212**	**P=value**	
Amount of ointment used	(Median)	4.5 g/day	4.7 g/day	6.3 g/day		
Length of treatment	Days (mean)	69.4	68.1	40	**Vs 0.03%**	**Vs 0.1%**
Adverse effects %(SD)	Skin burning	45.6% (+/-3.4)	57.7% (+/-3.52)	25.8% (+/-3.43)	<0.001	<0.001
	Pruritus	46.1% (+/-3.57)	46.1%(+/-3.59)	36.5% (+/-3.70)	0.059	0.062
	Flu-like symptoms	23.2% (+/-3.28)	30.8% (+/-3.61)	19.3% (+/-4.06)	0.451	0.034
	Erythema	24.8% (+/-3.07)	27.9% (+/-3.19)	19.8% (+/-3.04)	0.250	0.066
	Headache	20% (+/-2.99)	19.2% (+/-2.99)	10.7% (+/-2.76)	0.022	0.036
	Skin infection	12.4% (+/-2.5)	4.7% (+/-1.65)	10.6% (+/-2.67)	0.617	0.63

	Alcohol intolerance	3.4% (+/-1.36)	6.9%(+/-1.92)	0	0.013	<0.01
	Folliculitis	6.2% (+/-1.74)	4.3%(+/-1.5)	0.5% (+/-0.51)	0.002	0.016
	Rash	4.9% (+/-1.77)	2.1% (+/-1.27)	0.5%(+/-0.5)	0.017	0.23
	Sinusitis	3.9% (+/-1.45)	2.2% (+/-1.09	0.7% (+/-0.68)	0.048	0.241
	Myalgia	2.8% (+/-1.28)	1.6%	0 (0)	0.026	0.081
	Back pain	2.3% (+/-1.26)	1.6% (+/-0.92)	0 (0)	0.046	0.081
	Skin tingling	3.4% (+/-1.27)	7.6% (+/-1.91)	2.4% (+/-1.04)	0.0522	0.015
	Hyperestesia	3% (+/-1.19)	6.5%(+/-1.74)	0.5% (+/-0.47)	0.052	0.001
	Acne	4.3% (+/-1.48)	7.1% (+/-2.02)	1.8% (+/-1.3)	0.213	0.028
	Cyst	1.1% (+/-0.81)	3.1% (+/-1.55)	0 (0)	0.159	0.46
Other diseases	Herpes simplex	9 (4.3%)	7 (3.3%)	4 (1.9%)		
	Eczema herpeticum	2 (1%)	1	0		
	Leukopenia	0	1	1		
	Molluscum contagiosum	1 (0.5%)	1 (0.5%)	0		
	Herpes zoster	0	1 (0.5%)	0		
	Warts	1 (0.5%)	1 (0.5%)	0		
Discontinuation across all groups due to AEs	Pruritus	30 (4.8%)				
	Skin Burning	19 (3.0%)				
	Erythema	12 (1.9%)				
	Infection	3 (0.5%)				
Abnormal lab reports		5 (2.4%)	4 (1.9%)	5 (2.4%)		

Methodological comments

- *Prospective?* Yes
- *Consecutive patients enrolled?* Not stated
- *Method of Randomisation:* Not stated
- *Blinding:* Described as double blind – further details not stated
- *Unit of randomisation and analysis:* Patient
- *Power calculation?* Not reported
- *All patients given same intervention?* Yes
- *Rates of discontinuation and loss to follow up:* One 15 year old, and one patient who did not receive treatment excluded from analysis. Not known form which group. Tacrolimus 0.03% 61 patients (28.9%) of whom 26 (12.3%) lack of efficacy, 13 (6.2%) for adverse events and 22 (10.4%) for loss to follow-up, patients' refusal or noncompliance; Tacrolimus 0.1% Total 52 (24.9%) of whom 18 (8.6%) lack of efficacy 11 (5.3%) adverse events 23 (11%) loss to follow-up, patients refusal, noncompliance; Comparison Total 145 (68.4%) of whom 95 (44.8%) for lack of efficacy 26 (12.3%) adverse events and 24 (11.3%) loss to follow up, patients' refusal, noncompliance
- *Method of data analysis:* Adverse events analysed with Kaplan-Meier estimates adjusted for number of days treatment. No other details provided

General comments

- *Generalisability:* Low
- *Main outcome measured blind/independently?* Not clear
- *Inter-centre variability*? Not reported and not accounted for in the analysis
- *Conflicts of interest*:? All authors received grants from Fujisawa Inc. except IL who is an employee of Fujisawa Inc. AF and GW received research support from Fujisawa Inc. and GW has been on the speakers bureau of Fujisawa Inc. The article was published in a supplement sponsored by Fujisawa Inc.

Reference and Design	Intervention	Subjects	Outcome measures
▪ *Author:* Reitamo et al 2002 II ▪ *Study design:* Double blind parallel group RCT ▪ *Recruitment dates:* *Not stated* ▪ *Setting:* 27 centres in 8 European countries	▪ *Treatment:* Tacrolimus 0.03% and 0.1% ointment twice daily ▪ *Comparator* Hydrocortisone-17-butyrate 0.1% ointment twice daily (mid-potent/potent) ▪ *"Wash out" period* 5 days to 6 weeks for prohibited therapies (topical and systemic corticosteroids; antihistamines and antimicrobials; coat tar; topical nonsteroidal anti-inflammatory drugs, immunosuppressants Light treatment (UVA UVB) hypnotics and sedatives, other interventional drugs ▪ *Concomitant treatment* Inhaled or intranasal corticosteroids (<1 mg/day); Emollients, bath oils ▪ *Length of treatment* 3 weeks – regardless of clearing ▪ *Safety levels* Haematology, clinical chemistry, renal and hepatic function	▪ *Total number of patients:* 570 (193 (0.03%) 191 (0.1%) 186 (Hydrocortisone) ▪ *Eczema definition:* Hanifin and Rajka; Rajka and Langeland ▪ *Eczema severity:* Moderate to severe ▪ *Inclusion criteria:* Age 16 to 70 BSA > 5% ▪ *Exclusion criteria:* Adherence to washout rules	▪ *Primary and secondary outcome measures used:* Clinical improvement of eczema symptoms; patient's assessment of symptoms improvement AEs ▪ *Method of assessing outcomes:* Modified eczema area and severity index (mEASI) mean area under the curve as a percentage of baseline mEASI score Patients rating of itching (VAS 0-10) IGA (Cleared (100%), excellent (90-99%) marked (75-89%) moderate (50-74%) slight (30-49%) no appreciable improvement (0-29%) worse (less than 0%)) Adverse effects monitored, related and unrelated to the study. Days 3,7,14,21,60 ▪ *Length of follow up:* 5 weeks

Results: Patients characteristics

Arm		**Tacrolimus 0.03% N=193**	**Tacrolimus 0.1% N=191**	**Comparison Hydrocortisone N=186**	P=value
Age	Mean (SD)	31.1 (+/-11.5)	32.4 (+/-11.4)	30.8 (10.3)	
Males		43.5%	42.9%	46.8%	
Race	*White*	*183 (94.8%)*	*184 (96.3%)*	*182 (97.8%)*	
	Other	*10 (5.2%)*	*7 (3.7%)*	*4 (5.2%)*	
Severity	*Moderate*	*46.1%*	*50.8%*	*44.6%*	
	Severe	*53.9%*	*49.2%*	*55.4%*	
Duration of AD (years)	Median	23	25	24	
Duration current episode (months)	Median	7.8	13.3	9.5	
Affected body region	Head/neck	*180 (93.3%)*	*183 (95.8%)*	*178 (95.7%)*	
	Upper limbs	190 (98.4%)	190 (99.5%)	186 (100%)	
	Trunk	174 (90.2%)	172 (90.1%)	170 (91.4%)	
	Lower limbs	170 (88.1%)	163 (85.3%)	164 (88.2%)	
BSA	Median	*35%*	*30%*	*36.3%*	

Results: Effectiveness

Arm		**Tacrolimus 0.03%**	**Tacrolimus 0.1%**	**Comparison**	P=value
Physicians' global assessment at end of treatment	Cleared	5.6%	10.7%	12.4%	Significant difference 0.1% ad 0.03% tacrolimus (p<0.05) Hydrocortisone and tacrolimus 0.03% (p<0.05)
	Excellent	31.8%	38.5%	39.6%	
	Marked	20.5%	27.7%	18.9%	
	Moderate	22%	8.1%	8.3%	
Physicians' global	Cleared	1.6%	2.5%	2.4%	

assessment at end follow-up	Excellent	9.9%	13.3%	16.4%	
	Marked	15.7%	16.5%	18%	
	Moderate	15%	22.5%	10.6%	
mEASI score	Average Median improvement over 3 wks	53.0%	63.5%	63.9%	Tacrolimus 0.03% and 0.1% P<0.001 hydrocortisone and Tacrolimus 0.03% p<0.002
MEASI score	% decrease in Median MAUC	47%	36.5%	36.1%	
mEASI score	Median improvement at 21 days	71%	82%	83%	P<0.05
TBSA	Median decrease at 21 days	60%	76%	77%	Not stated
Adverse effects	Skin burning	87 (45.1%)	113 (59.2%)	24 (12.9%)	<0.05
	Increased pruritus at site	39 (20.2%)	29 (15.2%)	18 (9.7%)	<0.05
	Folliculitis	15 (7.8%)	15 (7.9%)	13 (7%)	
	Erythema	4 (2.1%)	7 (3.7%)	1 (0.5%)	
	Maculopapular rash	1 (0.5%)	5 (2.6%)	2 (1.1%)	
	Flu-like symptoms	8 (4.1%)	12 (6.3%)	12 (6.5%)	
	Allergic reaction (rhinitis, conjunctivitis)	6 (3.1%)	5 (2.6%)	12 (6.5%)	
	Headache	10 (5.2%)	9 (4.7%)	14 (7.5%)	
	Herpes simplex	5 (2.6%)	5 (2.6%)	1 (0.5%)	

Methodological comments

- *Prospective?* Yes
- *Consecutive patients enrolled?* Unsure
- *Method of Randomisation:* Block randomisation supplied to each centre by sponsor
- *Blinding:* ointment in identical tubes. Patients and investigators blind to allocation.
- *Unit of randomisation and analysis:* Patient
- *Power calculation?* 180 patients per group were required for an ANOVA with an alpha value of 0.05 and 90% power to detect 15% difference among the groups
- *All patients given same intervention?* Yes
- *Discontinuation or Loss to follow up?* 1 patient not treated after randomisation, excluded from ITT. Discontinuation Tacrolimus 0.03% total 22 of whom 7 for adverse events, 6 withdrawal consent, 3 non compliance or loss to follow up, 2 prohibited therapy, 2 lack of efficacy; Tacrolimus 0.1% total 22 of which 8 adverse events, 6 withdrawal of consent, 4 non compliance or loss to follow up, 3 prohibited therapy, 1 lack of efficacy; Hydrocortisone total 17, of whom 3 adverse events, 4 withdrawal of consent, 6 non compliance or loss to follow up, 2 prohibited therapy, 2 lack of efficacy.
- *Method of data analysis:* Non parametric methods (Wilcoxon rank-sum test) and X^2 for IGA. Fisher exact test for incidence of adverse events.

General comments

- *Generalisability:* High
- *Main outcome measured blind/independently? Yes*
- *Inter-centre variability*? Not reported
- *Conflicts of interest*:? Study sponsored by Fujisawa

MAUC = mean area under the curve.

Some data taken from graphs and may be subject inaccuracies.

Reference and Design	Intervention	Subjects	Outcome measures
▪ *Author:* Drake et al 2001 ▪ *Study design:* 3 RCTs ▪ *Recruitment dates:* Not stated ▪ *Setting:* Multicentre study, US	▪ *Treatment:* Tacrolimus 0.03% and 0.1% ▪ *Comparator* Vehicle ▪ *"Wash out" period* Not stated ▪ *Concomitant treatment* Not stated ▪ *Length of treatment* 12 weeks or 1 week after clearance ▪ *Safety levels* Not stated	▪ *Total number of patients: 985 (No distribution of patients at baseline is provided, results of 902 patients only reported, 579 adults, 178 children and 145 toddlers)* ▪ *Eczema definition:* Rajka and Langland ▪ *Eczema severity:* Moderate or severe ▪ *Inclusion criteria:* Age: adults (>15) children (5-15) toddlers (2-4) ▪ *Exclusion criteria:* Not stated	▪ *Primary and secondary outcome measures used:* Changes in quality of Life of eczema patients treated with tacrolimus ▪ *Method of assessing outcomes:* DLQI (Dermatology Life quality Index, 10 items, 6 categories) for adults, CDLQI (Children's Dermatology Life Quality Index, 10 items, 6 categories) for children and Toddler's version for CDLQI, 8 items, 4 categories Physician's global evaluation of clinical response ▪ *Length of follow up:* 12 weeks

Results: Patients characteristics

Arm		**Tacrolimus 0.03%**	**Tacrolimus 0.1%**	**Comparison**	P=value
Age	Mean	for adults 39 years, children 9 years, toddlers 3 years			
Males		Approx. half of the patients were male in each group			
		Approx. two-thirds were white.			
Severity	Moderate	Half of the children and adults and 1/3 of toddlers			
	Severe	Approx. half of children and adults and 3/2 of toddlers			
		Adults	**Children**	**Toddlers**	
% affected at baseline (combined categories	Itchiness/pain	100	100	100	
	Self – consciousness	95	90	N/A	
	Shopping/ housekeeping	60	N/A	N/A	
	Dressing/clothes	90	70	70	
	Social activities	80	N/A	N/A	
	Sports	70	50	N/A	
	Working/studying	80	N/A	N/A	
	Relationships	60	N/A	N/A	
	Sexual Difficulties	40	N/A	N/A	
	Problems with treatment	70	70	70	
	Friendships	N/A	70	N/A	
	Playing	N/A	60	70	
	School	N/A	50	N/A	
	Teasing	N/A	60	N/A	
	Sleeping	N/A	90	90	
	Upset/sad	N/A	N/A	90	
	Going out	N/A	N/A	70	
	Activities	N/A	N/A	70	

Results: Quality of Life

Arm		**Tacrolimus 0.03%**	**Tacrolimus 0.1%**	**Comparison Vehicle**	P=value
QoL scores change from baseline to end of treatment, adults (Mean improvement) *N=579*	Symptoms and feelings	**-33.7**	**-41.1**	**-10.4**	All differences between Tacrolimus and vehicle are significant (p<= 0.000) All differences between tacrolimus 0.03% and 0.1% are significant (p<=0.025) except for treatment (p=0.58)
	Daily activities	-20.9	-28.4	-6	
	Leisure	-21.9	-28.6	-7.3	
	Work/School	-22	-31.8	-5.7	
	Personal relationships	-10.2	-15.1	-0.6	
	Treatment	-13.3	-14.8	-3.1	

	Total Score	-21.1	-27.1	-5.6	
QoL scores change from baseline to end of treatment, children (Mean improvement) *N=178*	Symptoms and feelings	-36.4	-35.9	-12.5	All differences between Tacrolimus and vehicle are significant (p<= 0.024) except for personal relationships (p=0.09) All differences between tacrolimus 0.03% and 0.1% are non-significant
	Leisure	-18.2	-17.8	-8.4	
	School/Holidays	-17.5	-21.9	-5.2	
	Personal relationships	-11.3	-15.8	-5.6	
	sleep	-37.6	-32.5	-5.7	
	Treatment	-35	-34.7	-7	
	Total Score	-24.4	-24.1	-8.1	
QoL scores change from baseline to end of treatment, toddlers (Mean improvement) N=145	Symptoms and feelings	-41.2	-42.8	-8.5	All differences between Tacrolimus and vehicle are significant (p<= 0.001) All differences between tacrolimus 0.03% and 0.1% are non-significant
	Activities	-20.1	-26.5	-4.3	
	Sleep	-43.4	-45.7	-10.2	
	Treatment	-38.3	-44.6	-20.2	
	Total Score	-30.8	-35.6	-7.9	
Patients' preferences Adults	100% sure/very likely to continue	121 (68.8%)	141 (79.7%)	46 (28.8%)	Tacrolimus 0.03% vs vehicle p=0.001 Tacrolimus 0.01% vs vehicle p=0.001 Tacrolimus 0.03% vs Tacrolimus 0.1% p=0.048
	Probably would/would not continue	26 (14.8%)	20 (11.3%)	43 (26.9%)	
	Very unlikely/ 100% sure not to continue	29 (16.5%)	16 (9%)	71 (44.4%)	
Patients' preferences Children	100% sure/very likely to continue	46 (82.1%)	51 (83.6%)	26 (50%)	Tacrolimus 0.03% vs vehicle p=0.001 Tacrolimus 0.01% vs vehicle p=0.001 Tacrolimus 0.03% vs Tacrolimus 0.1% p=0.363
	Probably would/would not continue	5 (8.9%)	8 (13.1%)	8 (15.4%)	
	Very unlikely/ 100% sure not to continue	5 (8.9%)	2 (3.3%)	18 (34.6%)	
Patients' preferences Toddlers	100% sure/very likely to continue	42 (84%)	41 (91.1%)	17 (39.5%)	Tacrolimus 0.03% vs vehicle p=0.001 Tacrolimus 0.01% vs vehicle p=0.001 Tacrolimus 0.03% vs Tacrolimus 0.1% p=0.535
	Probably would/would not continue	5 (10%)	3 (6.7%)	6 (14%)	
	Very unlikely/ 100% sure not to continue	3 (6%)	1 (2.2%)	20 (46.5%)	
QoL	Associated with clinical severity at baseline except for Treatment scale in children				P<0.01
QoL	Associated to clinical improvement Total score for adults improved 28.7 (patients who 'cleared') 14 (patients with slight improvement) 4.4 (patients with no appreciable improvement)				Not stated

Methodological comments

- *Prospective?* Yes?
- *Consecutive patients enrolled?* Not stated
- *Method of Randomisation:* Not stated
- *Blinding:* Not stated
- *Unit of randomisation and analysis:* Not stated
- *Power calculation?* Not stated
- *All patients given same intervention?* Unsure
- *Loss to follow up?* 6-10% (no detail provided)
- *Method of data analysis:* ITT methods were not used; One-way ANOVA and X^2; general linear methods. Categories of "very much / a lot / a little affected" were combined to produce a binary at baseline.

General comments

- *Generalisability:* Low
- *Main outcome measured blind/independently?* Not stated
- *Inter-centre variability*? Not reported, not accounted for in the analysis

Conflicts of interest:? LD and DB received grants from Fujisawa Inc; MP RM NK YS are employees of Fujisawa Inc. The paper was published in a supplement sponsored by Fujisawa Inc.

Reference and Design	Intervention	Subjects	Outcome measures
▪ *Author:* Reitamo et al 2002 ▪ *Study design:* Double blind parallel group RCT ▪ *Recruitment dates:* ▪ *Setting:* 27 centres in 6 European countries and Canada	▪ *Treatment:* Tacrolimus 0.03% and 0.1% ointment twice daily ▪ *Comparator* 1% Hydrocortisone acetate ointment twice daily ▪ *"Wash out" period* 5 days to 6 weeks for prohibited therapies (topical and systemic corticosteroids; antihistamines and antimicrobials; coal tar; topical nonsteroidal anti-inflammatory drugs, immunosuppressants; Light treatment (UVA UVB) hypnotics and sedatives, other interventional drugs ▪ *Concomitant treatment* Inhaled or intranasal corticosteroids (<1 mg/day); Emollients, bath oils ▪ *Length of treatment* 3 weeks – or seven days beyond clearance. ▪ *Safety levels* Haematology, clinical chemistry, renal and hepatic function at week 3 and 5. 3/188 0.03% and 21/186 0.1% tacrolimus patients had >1ng/mL concentrations at some point in the study. Highest value was 2.8ng/mL in 1 patients on day 3.	▪ *Total number of patients:* 560 (189 (0.03%) 186 (0.1%) 185 (Hydrocortisone) ▪ *Eczema definition:* Hanifin and Rajka; Rajka and Langeland ▪ *Eczema severity:* Moderate to severe ▪ *Inclusion criteria:* Age 2 to 15 BSA > 5% <60% ▪ *Exclusion criteria:* Serious skin disorder other than AD History of eczema herpeticum	▪ *Primary and secondary outcome measures used:* Clinical improvement of eczema symptoms; patient's assessment of symptoms improvement AEs ▪ *Method of assessing outcomes:* Modified eczema area and severity index (mEASI) mean area under the curve as a percentage of baseline mEASI score Patients rating of itching (VAS 0-10) IGA (Cleared (100%), excellent (90-99%) marked (75-89%) moderate (50-74%) slight (30-49%) no appreciable improvement (0-29%) worse (less than 0%)) Adverse effects monitored, related and unrelated to the study. Days 3,7,14,21,35 ▪ *Length of follow up:* 5 weeks

Results: Patients characteristics

Arm		**Tacrolimus 0.03% N=189**	**Tacrolimus 0.1% N=186**	**Comparison Hydrocortisone N=185**	P=value
Age	Mean (SD)	7.6 +/-4.4	7.2 +/-3.9	7.2 +/-4.0	
Males		40.2	51.6	51.4	
Race	*White*	74.1	77.4	81.1	
Severity	*Moderate*	60.8	54.3	51.4	
	Severe	39.2	45.7	48.6	
Duration current episode (months)	Median	6.4	6.2	10.9	
Affected body region N(%)	Head/neck	164 (86.8%)	164 (88.2%)	160 (86.5%)	
	Upper limbs	187 (98.9%	184 (98.9%)	183 (98.9%)	
	Trunk	143 (75.7%)	154 (82.8%)	155 (83.8%)	
	Lower limbs	181 (95.8%)	181 (97.3%)	176 (95.1%)	
BSA	Median	26.0	23.3	25.0	

Results: Effectiveness

Arm		**Tacrolimus 0.03%**	**Tacrolimus 0.1%**	**Comparison**	P=value
Physicians' global assessment at end of treatment	Cleared	6.7%	11.4%	2.9%	
	Excellent	31.8%	37.7%	12.8%	
	Marked	24.6%	24.7%	17.2%	
	Moderate	17.1%	11.5%	18.5%	
Physicians' global assessment at end follow-up (for those	Cleared	1.3%	2.4%	2.5%	
	Excellent	16.2%	9%	5.5%	
	Marked	20%	19%	8.8%	

with at least moderate improvement at end of treatment)	Moderate	16.2%	17.5%	23.0%	
mEASI score	Average Median improvement over 3 wks	55.2%	60.2%	36.0%	P<0.001 Tac. vs TS P=0.006 0.03% vs 0.1% tac.
mEASI score	Median MAUC	44.8%	39.8%	64.0%	
mEASI score for head and neck only	Median mAUC improvement	62.5%	75.2%	43.3%	
mEASI SCORE	Median % decrease at 21 days	75%	82%	37%	P<0.001%
BSA	Median % decrease at 21 days	60%	75%	30%	
Adverse effects	N=	189	186	185	
	Skin burning	35 (18.5%)	38 (20.4%)	13 (7%)	
	Increased pruritus at site	25 (13.2%)	21 (11.3%)	14 (7.6%)	
	Folliculitis	11 (5.8%)	8 (4.3%)	5 (2.7%)	
	Erythema	4 (2.1%)	1 (0.5%)	3 (1.6%)	
	Flu syndrome	15 (7.9%)	14 (7.5%)	16 (8.6%)	
	Fever	9 (4.8%)	1 (0.5%)	8 (4.3%)	
	Rhinitis	0	6 (3.2%)	4 (2.2%)	
	Pharyngitis	2 (1.1%)	1 (0.5%)	6 (3.2%)	
	Diarrhoea	0	5 (2.7%)	2 (1.1%)	
	Skin infection	6 (3.2%)	4 (2.2%)	4 (2.2%)	

Methodological comments

- *Prospective?* Yes
- *Consecutive patients enrolled?* Not clear
- *Method of Randomisation:* Parallel groups assigned 1:1:1. Stratified by age (2-6 years, 7-15years) and centre. Sponsor supplied each centre with a unique block of sequentially ordered patient numbers form a randomisation list. Assignment of a number occurred in the order the patients passed selection criteria.
- *Blinding:* Ointment in identical tubes. Described as double blind.
- *Unit of randomisation and analysis:* Patient
- *Power calculation?* 180 patients in each arm needed for an ANOVA with α value of 0.05 and a power of 90% to detect a difference of 15% among the three treatment groups.
- *All patients given same intervention?* Yes
- *Discontinuation or Loss to follow up?* Tacrolimus 0.03% 3 (1.6%) Lack of efficacy, 3 (1.6%) adverse event (1 skin infection, 1 pruritus, 1 skin burning and pain), 7 (3.7%) prohibited therapy, 2 (1.1%) withdrawal of consent, 6 (3.2%) administration (LTFU, violation of selection criteria, non-compliance etc.); Tacrolimus 0.1% 1 (0.5%) Lack of efficacy, 3 (1.6%) adverse event (2 chicken pox, 1 allergic reaction to food), 2 (1.1%) prohibited therapy, 7 (3.8%) admin.; hydrocortisone 7 (3.8%) Lack of efficacy, 4 (2.2%) adverse event (1 folliculitis and urticaria, 1 skin infection, 1 reaction at sits, 1 maculopapular rash and pruritus) , 3 (1.6%) prohibited therapy, 1 (0.5%) withdrawal of consent, 5 (2.7%) admin
- *Method of data analysis:* Described as ITT analysis but 1 patient from TS group did not receive treatment and was excluded after randomisation. Non-parametric tests (Wilcoxon rank sum test) for all continuous variables (mEASI, mAUC, pruritus, BSA). Chi^2 to compare treatment groups for GPA. AEs summarised and groups compared using Fisher's exact test.

General comments

- *Generalisability:* High
- *Main outcome measured blind/independently?* Yes
- *Inter-centre variability*? Not stated
- *Conflicts of interest*:? Study sponsored by Fujisawa

Some data taken from graphs and may be subject to inaccuracies.

Reference and Design	Intervention	Subjects	Outcome measures
▪ *Author:* Petan et al 2003 ▪ *Study design:* RCT ▪ *Recruitment dates:* Not clear from 10/11/2000 ▪ *Setting:* 57 centres in 12 European countries (Austria, Belgium, Denmark, Finland, Germany, Italy, Netherlands, Spain, Sweden, Norway, UK.	▪ *Treatment:* Tacrolimus 0.1% twice daily to head, neck, trunk and extremities (1cm for 100cm^2) ▪ *Comparator* 1% hydrocortisone acetate ointment to head and neck 0.1% hydrocortisone butyrate to trunk and extremities twice daily. (1cm for 100cm^2) ▪ *"Wash out" period* 3 days – corticosteroids, H1 and H2 histamines, NSAIDs, doxepin, medicated topical agents, 5 days – coal tar, antimicrobials, systemic anti histamines. 1 weeks intranasal/ inhaled corticosteroids. 2 weeks – systemic non-steroidal immunosuppressants. 4 weeks – systemic corticosteroids, other investigational drugs, 6 weeks UV light treatments. ▪ *Concomitant treatment* Emollients and protectives. Used were anti-histamines (TS 20.4%, Tac. 20.1%), analgesics (14.8%; 19.1%), systemic anti-bacterial agents (13.4%; 14.6%), cortico-steroids (10.1%; 7.8%), anti-inflammatory / antirheumatic products (9.7%; 9.0%) ▪ *Length of treatment* 6 months. Lesions treated until they cleared and then for a further 7 days. ▪ *Safety levels* Haematology, enzymes, electrolytes, substrates measured at baseline, months 3 and 6.	▪ *Total number of patients:* 975 randomised (488 tacrolimus, 487 TS), 972 ITT (487 tac. 485 TS), 715 per protocol (359 Tac. 356 TS). ▪ *Eczema definition:* Hanifin and Rajka ▪ *Eczema severity:* Moderate to severe by Rajka and Langeland ▪ *Inclusion criteria:* Aged 18 and over Patient capable of understanding purposes and risks of the trials and gives written consent Patient agrees to and is able to comply with study requirements and attend clinic for scheduled visits Women of child bearing potential agree to practice effective birth control during study and 28 days after. On day 1 blood screening parameters normal Comply with washouts. ▪ *Exclusion criteria:* Infections requiring treatment, HIV infection, systemic disease (cancer, AIDS etc) that would contraindicate use of tacrolimus. Impairment of renal or hepatic function. Pregnancy of breast feeding Skin disorder other than AD on area to be treated. Infected AD. Scaring of pigmented lesion in area that would affect rating of efficacy. Any lesion (other than scalp and mucosa) that the investigator considers cannot be treated by the study ointment. Known allergic response to macrolides or any expedient of the ointments. Previous treatment with tacrolimus or participation in a Fujisawa sponsored trial. Participation in another drug trial within 28 days. Substance abuse, psychiatric disorder or condition that is considered could invalidate communication with investigator. Non compliance with wash	▪ *Primary and secondary outcome measures used:* Response rate at 3 months Response rate Affected body area Drug usage Days of treatment Adverse effects Quality of Life ▪ *Method of assessing outcomes:* Modified EASI (individual signs as assessed by physician, BSA affected, patient's assessment of itch) – at least 60% improvement in this score between 0 and 3 months was primary outcome. EASI (similar to mEASI but without itch assessment) Physician's global evaluation Patient's assessment of global response Physician's assessment of individual signs and affected BSA, Patient's assessment of itch (10 cm VAS – 0 = no itch, 10= worst itch imaginable) and quality of sleep (10cm VAS =- 0 = slept badly, 10= slept well), % of days with treatment in study period Patient and physician assessment of global response for head and neck Patient diaries for days of treatment Monitoring of AEs and clinical laboratory tests SF-36 DLQI ▪ *Length of follow up:* 6 months

		out criteria.		
Results: Patients characteristics				
		Tacrolimus 0.1% n=488	**Comparison N=487**	P=value
Age (mean, SD)		32.1 +-11.6	32.9 +-12.0	
Males %		46.2%	46.2%	
Ethnic group (n)	Caucasian	465	473	
	Black	6	3	
	Oriental	7	4	
	Other	9	5	
Duration of AD	Mean yrs +-SD	24.9 +-13.7	26.1 +-13.1	
	Median yrs (range)	24 (0-84)	25 (0-72)	
Duration of current episode	Mean mths +-SD	64.8 +-118.6	59.7 +-112.2	
	Median mths (range)	9.6 (0.2-726.8)	10.9 (0.1-786.7)	
Severity on day 1 (n)	Moderate	273	285	
	Severe	214	200	
Total BSA on day 1	Mean +-SD	36.4 +-23.9	37.5+-24.4	
	Median (range)	30.0 (0.7-100.0)	32.5 (1.4-100.0)	
Total BSA on day 1 (n)	0 <=25%	193	187	
	>25%<=50%	166	159	
	>50% <=75%	86	90	
	>75% <=100%	42	49	
Affected body region on day one (n)	Head and Neck	455	451	
	Upper limbs	480	479	
	Trunk	423	445	
	Lower limbs	415	439	
% Affected BSA on day one median (range)	Head and Neck	50 (0-100)	45 (0-100)	
	Upper limbs	40 (0-100)	40 (0-100)	
	Trunk	30 (0-100)	30 (0-100)	
	Lower limbs	20 (0-100)	25 (0-100)	
Patient assessment of itch	Median (25%/75%)	6.4 (4.4/8.0)	6.4 (4.4/8.1)	
Patient assessment of sleep	Median (25%/75%)	5.7 (3.2/ 8.6)	5.8 (3.0/8.2)	
Results: Effectiveness				
Ointment used		**Tacrolimus 0.1% n=488**	**Comparison n=487**	P=value
Total amount of ointment used (g)	Mean +-SD	416.8 +-519.9 (n=366)	389.5 +-435.3 (n=365)	
	Median (25%/75%)	264 (94/520)	264 (111/540)	
Amount of ointment used –head and neck (g)	Mean +-SD	77.5 =-114.1 (n=400)	76.9 +-102.9 (n=399)	
	Median (25%/75%)	42 (11 / 96)	42 (15/109)	
Amount of ointment used – trunk and extremities (g)	Mean +-SD	337.1 +-431.0 (n=377)	317.5 +-348 (N=376)	
	Median (25%/75%)	215 (68 / 430)	227 (90/417)	
Efficacy				
Response rate at 3 months (ITT population)	>=60% Improvement in mEASI	304/487	220/485	P<0.001 (95% CI 2-sided 0.139, 0.267)
Response rate at 3 months (per protocol population)	>=60% Improvement in mEASI	267/359	199/356	P<0.001 (95% CI 2-sided 0.116, 0.253)
Response rate at 6 months (ITT)	>=60% Improvement in mEASI	274/380	181/377	P<0.001
% change from baseline to 3 months (ITT)	Median mEASI (25%/75%)	-83.3 (-94.2 /-63.1) (n=387)	-76.9 (-90.6 /-47.5) (n=337)	P<0.001
% change from baseline to 4 months (ITT)	Median mEASI (25%/75%)	-85.4 (-94.4/ -67.9) (n=371)	-81.7 (-93.6 / -51.4) (n=300)	P=0.024
% change from baseline to 6 months (ITT)	Median mEASI (25%/75%)	-87.7 (-95.7/ -72.3) (n=328)	-82.5 (-95.3 / -55.3) (n=253)	P=0.008
% changes from baseline at 3 months (ITT)	Median EASI (25%/75%)	-82.1 (-92.9) / -63.3) (n=389)	-75.0 (-88.7 / -43.6) (n=343)	P<0.001

% changes from baseline at 4 months (ITT)	Median EASI (25%/75%)	-83.3 (-93.4 / -65.9) (n=372)	-78.7 (-92.3 / -52.6) (n=305)	P=0.028
% changes from baseline at 6 months (ITT)	Median EASI (25%/75%)	-85.0 (-94.4 / -69.5) (n=331)	-81.5 (-94.3 / -48.9) (n=259)	P<0.001
Affected total BSA change from baseline at 3 months (ITT)	Median EASI (25%/75%)	-81.9 (-93.6 / -63.6) (n=390)	-71.4 (-90.6/ -45.9) (n=343)	<0.001
Affected total BSA change from baseline at 6 months (ITT)	Median EASI (25%/75%)	-88.2 (-95.8 / -65.0) (n=331)	-80.3 (-94.8 / -40.3) (n=259)	P<0.001
Physician's assessment of individual signs (ITT) month 3 Mean (SD)	Oedema / induration Papulation	2.3 (+-2.2) (n=390)	2.9 (+-2.6) (n=343)	
	Erythema	3.0 (+-2.2) (n=390)	3.7 (+-2.6) (n=343)	
	Excoriations	1.8 (+-2.1) (n=390)	2.2 (+-2.5) (n=343)	
	Lichenification	2.1 (+-2.3) (n=390)	2.5 (+-2.5) (n=343)	
	Oozing /weeping/crusting	0.8 (+-1.4) (n=390)	1.1 (+- 1.9) (n=343)	
	Scaling	1.4 (+-1.7) (n=390)	1.9 (+-2.2 (n=343	
Physician's assessment of individual signs (ITT) month 6 Mean (SD)	Oedema / induration Papulation	2.2 (+-2.2) (n=331)	2.6 (+-2.5) (n=259)	
	Erythema	2.8 (+-2.2) (n=331)	3.4 (+-2.6) (n=259)	
	Excoriations	1.5 (+-1.9) (n=331)	1.9 (+-2.3) (n=259)	
	Lichenification	1.7 (+-2.0) (n=331)	2.2 (+-2.7) (n=259)	
	Oozing /weeping/crusting	0.7 (+-1.3) (n=331)	0.8 (+-1.6) (n=259)	
	Scaling	1.3 (+-1.7) (n=31)	1.7 (+-1.9) (n=259)	
Physicians Global Evaluation at month 3	Cleared or excellent	207/390	126/342	Cleared versus all other categories tac. vs TS p<0.001
	Marked	100/390	72/342	
	Moderate	44/390	62/342	
	Slight improvement	26/390	44/342	
	No appreciable improvement	8/390	16/342	
	Worse	5/390	22/342	
Physicians Global Evaluation at month 6	Cleared or excellent	203/331	120/259	Cleared versus all other categories tac. vs TS p<0.001
	Marked	68/331	50/259	
	Moderate	40/331	29/259	
	Slight improvement	11/331	32/259	
	No appreciable improvement	6/331	13/259	
	Worse	3/331	15/259	
Patient's assessment of global response at month 3	Much better or better	312/387	220/340	Cleared versus all other categories tac. vs TS p<0.001
	Slightly better	35/387	58/340	
	Same	20/387	33/340	
	Slightly worse	12/387	15/340	
	Worse	5/387	11/340	
	Much worse	3/387	3/340	
Patient's assessment of global response at month 6	Much better or better	285/329	183/255	Cleared versus all other categories tac. vs TS p<0.001
	Slightly better	26/329	35/255	
	Same	11/329	25/255	
	Slightly worse	2/329	5/255	
	Worse	4/329	6/255	
	Much worse	1/329	1/255	
Patients assessment of itch at month 3	Median (25%/75%))	1.6 (0.4 / 3.2)	2.3 (0.8/5.0)	
Patients assessment of itch at month 6	Median (25%/75%))	1.4 (0.4/3.0)	1.9(0.6/3.6)	

Patients assessment of sleep quality at month 3	Median (25%/75%))	9.1 (7.7 /9.7)	8.4 (6.1 / 9.5)	
Patients assessment of sleep quality at month 6	Median (25%/75%))	9.2 (7.9 /9.7)	8.8 (6.8 /9.7)	
Number of days in study (n=? missing data excluded)	Mean (SD)	161.1 +-58.4	138.5 (+-68.4)	
	Median (25%/75%)	183 (169/190)	176 (77/187)	
Days in treatment - % of study days	Mean (SD)	78.6 (+-21.2)	85.1 (+-20)	
	Median (25%/75%)	84 (62 / 98)	95 (77 / 100)	
Physician's assessment of global response head and neck area at 3 months	Cleared or excellent	230/364	110/314	
	Marked	64/364	56/314	
	Moderate	29/364	54/314	
	Slight improvement	25/364	35/314	
	No appreciable improvement	8/364	24/314	
	Worse	8/364	35/314	
Physician's assessment of global response head and neck area at 6 months	Cleared or excellent	219/312	107/238	
	Marked	49/312	33/238	
	Moderate	24/312	30/238	
	Slight improvement	11/312	26/238	
	No appreciable improvement	3/12	17/238	
	Worse	6/312	25/238	
Patient's assessment of global response for head and neck area at 3 months	Much better or better	301/369	179/319	
	Slightly better	35/369	60/319	
	Same	18/369	46/319	
	Slightly worse	7/369	18/319	
	Worse	6/369	11/319	
	Much worse	2/369	5/319	
Patient's assessment of global response head and neck area at 6 months	Much better or better	281/317	149/241	
	Slightly better	19/317	38/241	
	Same	12/317	37/241	
	Slightly worse	3/317	7/241	
	Worse	1/317	8/241	
	Much worse	1/317	2/241	
Adverse effects - n *(most common effects – i.e. those affecting >=2% in either group)*	No. of patients	396/487	330/485	P<0.001
	Skin burning	259	67	P<0.001
	Pruritus	96	79	
	Flu syndrome	89	81	
	Lack of drug effect	51	78	P=0.011
	Folliculitis	62	51	
	Headache	38	42	
	Allergic reaction	32	29	
	Herpes simplex	33	18	P=0.043
	Skin erythema	26	18	
	Skin infection	18	21	
	Alcohol intolerance	36	1	
	Pustular rash	17	16	
	Exacerbation of treated area	18	12	
	Pharyngitis	13	16	
	Asthma	16	9	
	Pain	14	9	
	Gastroenteritis	10	12	

	Rhinitis	14	6	
	Accidental injury	11	7	
	Eczema	11	7	
	Infection	12	6	
	Cough increased	11	6	
	Skin tingling	13	3	P=0.020
	Face oedema	10	4	
	Fever	10	4	
	Hyperesthesia	10	2	P=0.037
Most common infections (>1<2%)	Bronchitis	5	8	
	Sinusitis	7	6	
	Conjunctivitis	7	5	
	Herpes zoster	6	1	
	Fungal dermatitis	6	0	
Incidence of benign neoplasms and malignancies	Lymphadenopathy	3	5	
	Viral warts	2	2	
	Neoplasm benign	2	0	
	Lymphoma like reaction	0	1	
	Skin carcinoma	0	1	
Quality of life at month 3	% change from baseline	-66.7 (-87.5 / -41.7) (n=386)	-58.5 (-80.0/ -27.8) (n=338)	
Quality of life and month 6	% change for baseline	-74.3 (-90.1 / -45.8) (n=328)	-69.2 (-84.2 / -40.0) (n=257)	

Methodological comments

- *Prospective?* Yes
- *Consecutive patients enrolled?* Unclear
- *Method of Randomisation:* 1:1 stratified by centre. Randomisation list generated centrally by Fujisawa and randomisation took place strictly in the order that patients passed selection criteria form Day 1. Each patient received a unique randomisation number from centres assigned block of sequentially ordered patient numbers. This patient number was printed on a sealed box containing ointment tubes for that patient.
- *Unit of randomisation and analysis:* Patient
- *Blinding:* Colour coded monthly supply box containing 7 tubes identical in size and appearance. Either all Tacrolimus, or 5 0.1% hydrocortisone butyrate and 2 1% hydrocortisone acetate. Those for head and neck labelled blue and those for extremities labelled white.
- *Power calculation?* Aim to prove non-inferiority and possible superiority of tacrolimus. Assuming 75% of patients would exhibit 60% improvement in mEASI in hydrocortisone group. Non-inferiority limit of 10%, α=5%, 322 patients required per treatment group to conclude non-inferiority if both treatments were identically effective with a power of 90%. To account for possible withdrawals, approx. 30% more patients had to be randomised. Planned to randomise 840 patients.
- *All patients given same intervention?* Yes
- *Loss to follow up?* 975 were randomised, 972 received at least one application and analysed as ITT population, 715 per-protocol population (129/485 excluded in hydrocortisone group; 128/487 in tacrolimus group). 204/485 in hydrocortisone group discontinued (124 lack of efficacy, 16 AE, 13 required prohibited therapy, 16 withdrew consent, 12 LTFU, 2 incl/excl criteria not met, 6 non compliant, 3 pregnant, 2 sponsor withdrew patient, 10 other) 124/487 in tacrolimus group withdrew (52 lack of efficacy, 10 AE, 13 required prohibited therapy, 15 withdrew consent, 15 LTFU, 1 incl/excl criteria not met, 6 non compliant, 7 pregnant, 0 sponsor withdrew patient, 5 other)
- *Method of data analysis:* ITT included all patients randomised and receiving at least one ointment application. Missing values for efficacy and vital signs at months 3 and 6 were replaced with the last value after baseline carried forward. Patients withdrawing due to lack of efficacy in the first 3 months were counted as non-responders regardless of mEASI assessment. For primary end point, one-sided 95% CI for difference in response rates on per protocol population firstly calculated, as lower limit was above zero, study aim changed to proving superiority – analysis repeated on ITT population, also with missing values replaced with last observation, and two-sided 95% CI. Other efficacy endpoints summarised by visit with frequencies or descriptive statistics as appropriate – tests and CI performed on an exploratory basis (for PGE and PAGR 1- and 2-sided 95% CIs for differences between groups, and chi-sq. tests; for mEASI, EASI and affected area – non parametric 2-sided 95% CIs for the median in each group, Wilcoxon rank-sum tests) Separate analyses for head and neck were performed. Exact Fisher's test for the proportions of individuals reporting adverse effects. Exploratory sub group analyses for centre, severity at baseline and BSA affected.

General comments

- *Generalisability:* High
- *Main outcome measured blind/independently?* Yes
- *Inter-centre variability*? Each centre required to recruit between 16 and 48 patients with exception of Helsinki which was allowed 80 patients due to local amendments (treatment for 12 months). Examined in subgroup analysis.
- *Conflicts of interest*:? Fujisawa sponsored study and company representatives performed study monitoring and statistical analysis.

Reference and Design	Intervention	Subjects	Outcome measures
▪ *Author:* Reitamo et al 2003 ▪ *Study design:* RCT Double blind ▪ *Recruitment dates:* Not stated ▪ *Setting:* 42 centres in 11 European countries	▪ *Treatment:* Tacrolimus 0.03% ointment once or twice daily ▪ *Comparator* 1% Hydrocortisone acetate ointment twice daily ▪ *"Wash out" period* 5 days medicated topical agents, systemic antihistamines and sedatives. 6 weeks astemizole and UVB treatments. 4 weeks systemic corticosteroids and non-steroidal immuno-suppressants. ▪ *Concomitant treatment* Inhaled or intranasal corticosteroids up to 1mg/day. Bath oils and non-medicated emollients. ▪ *Length of treatment* Minimum 2 weeks, with cleared area treated for an additional 7 days. ▪ *Safety levels* 1 pt in once daily tacrolimus group had a low white blood count on Day 16. 1 pt in twice daily tacrolimus had leukopenia on day 21	▪ *Total number of patients:* 624 (0.03% tac. twice daily 210, once daily 207) TS 207) ▪ *Eczema definition:* Hanifin and Rajka Rajka and Langeland ▪ *Eczema severity:* Moderate to severe ▪ *Inclusion criteria:* Aged 2-15 Moderate to severe eczema 5-100% BSA affected Written consent of parent / guardian Adherence to wash outs ▪ *Exclusion criteria:* None stated	▪ *Primary and secondary outcome measures used:* Clinical improvement of eczema symptoms Response rate Adverse effects ▪ *Method of assessing outcomes:* MEASI (including measurement of itch using 10cm VAS converted to an ordinal 0-3 scale) Response rate defined as % with at least 60% improvement in mEASI PGA Patient's assessment of global response (much better, better, slightly better, same slightly worse, worse, much worse) BSA Patient's assessment of sleep quality (10cm VAS 0=slept badly, 10=sleep well) AEs – any undesirable experience - ,monitoring and clinical lab. assessment. Assessments on days 1, 4 and 8 weeks 2 and 3 ▪ *Length of follow up:* 5 weeks.

Results: Patients characteristics

Arm		**Tacrolimus 0.03% once daily**	**Tacrolimus 0.03% Twice daily**	**Comparison Hydrocortisone**	
Age	Mean (SD)	6.7 (+-3.9)	6.9 (+-4.2)	7.2 (+-4.1)	
Males	%	48.3	45.2	51.7	
Race	*White*	83.1	81.9	86.5	
Severity	*Moderate*	52.2	52.9	44.9	(1 pt in TS group mild disease)
	Severe	47.8	46.7	55.1	
Overall duration of AD (months)	Mean (SD)	5.7 (+-3.8)	6.1 (+-4.0)	6.3 (+-4.0)	
	Median (min-max)	5.0 (<1-15)	5.0 (<1-15)	5.0 (<1-15)	
Duration current episode (months)	Mean (SD)	26.5 (+-35.8)	28.1 (+-40.0)	27.5 (+-37.4)	
	Median (min-max)	9.2 (0.2-168.9)	7.9 (0.1-171.8)	9.9 (0.2-176.4)	
Affected BSA	Mean (SD)	37.2 (+-26.0)	37.1 (+-23.7)	38.9 (+-24.2)	
	Median (min-max)	31.5 (5.0-100.0)	32.0 (4.7-100.0)	36.0 (5.0-99.0)	
Affected BSA (%)	0 to <=25%	43.0	41.4	36.2	
	>25% to <=50%	25.6	30.0	30.4	
	>50% to <=75%	20.8	20.5	24.6	
	>75%to<=100%	10.6	8.1	8.7	
Itch	Mean (SD)	6.3 (+-2.7)(n=206)	6.1(+-2.6)(n=209)	6.2(+-2.6)(n=207)	
Quality of Sleep	Mean (SD)	5.9(=-3.2)(n=206)	5.6(+-3.1) (n=209)	5.6(+-3.1)(n=207)	

Results: Effectiveness at week 3					
Arm		**Tacrolimus 0.03% once a day**	**Tacrolimus 0.03% twice a day**	**Comparison**	P=value
Physicians' global assessment at end of treatment	Cleared or Excellent	57/205 27.8%	77/210 36.7%	28/206 13.6%	Tac vs TS p<0.001 Twice vs once daily p=0.016
	>moderate	152/205 74.1%	170/210 81.0%	109/206 52.9%	
mEASI Median (25^{th}/75^{th}) % decrease over 3 wks	Moderate at baseline	79.3 (57.1 / 91.3) (n=107)	81.6 (60.7 / 91.8) (n=110)	59.7 (21.5 / 83.9) (n=92)	Tac vs TS p<0.0001
	Severe at baseline	54.1 (18.0 / 80.0) (n=97)	75.5 (52.3 / 86.8) (n=96)	41.6 (10.7 / 65.6) (n=112)	Tac vs TS p<0.001 Once vs twice daily p=0.001
	Overall	70.0%	78.7%	47.2%	P<0.001 (tacvsTS) P=0.007 (once vs twice daily)
Median % decrease in EASI		66.7%	76.7%	47.6%	Tac vs TS p<0.001 Once vs twice daily p=0.015
Patients global assessment	Much better	87/206 42.2%	99/210 47.1%	43/205 21.0%	
	Better or much better	138/206 67.0%	174/210 82.9%	104/205 50.7%	
Itch	Mean (SD)	3.3 (+-3.0) (n=206)	2.6(+-2.6)(n=208)	4.2(+-3.1)(n=204)	
Quality of sleep	Mean (SD)	7.5(+-3.0)(n=206)	8.1(+-2.4)(n=208)	7.0(+-3.2)(n=204)	
Ointment use over three weeks	Mean	112.0g (tac. plus placebo)	122.5g	175.2g	
Adverse effects Reported by at least 2% of pts in any treatment group	N=	207	207	210	
	Skin burning	48 (23.2%)	50 (23.8%)	30 (14.5%)	
	Pruritus	38 (18.4%)	45 (21.4%)	33 (15.9%)	
	Folliculitis	8 (3.9%)	11 (5.2%)	8 (3.9%)	
	Erythema	6 (2.9%)	6 (2.9%)	2 (1.0%)	
	Flu syndrome	6 (2.9%)	12 (5.7%)	11 (5.3%)	
	Fever	5 (2.4%)	6 (2.9%)	4 (1.9%)	
	Headache	2 (1.0%)	8 (3.8%)	6 (2.9%)	
	Rash	3 (1.4%)	6 (2.9%)	2 (1.0%)	
	Skin infection	3 (1.4%)	6 (2.9%)	6 (2.9%)	
	Pustular rash	3 (1.4%)	3 (1.4%)	5 (2.4%)	
Adverse effects causing discontinuation	Skin burning	1	1	0	
	Exacerbation	1	0	1	
	Pustular rash	1	0	1	
	Folliculitis	0	1	0	
	Herpes simplex	0	2	0	
	Lack of effect	0	2	1	
	Skin infection	0	2	3	

Methodological comments

- *Prospective?* Yes
- *Consecutive patients enrolled?* Not stated
- *Method of Randomisation:* 1:1:1 stratified by centre and age (2-6 years and 7-15 years)
- *Blinding:* Separate identical tubes supplied for morning and evening application – in the case of once daily group the p.m. tube contained vehicle.
- *Unit of randomisation and analysis:* Patient
- *Power calculation?* None stated
- *All patients given same intervention?* Yes
- *Discontinuation or Loss to follow up?* 26/207 once daily 0.03% tac. (lack of efficacy 8/207, adverse event 3/207, prohibited therapy 5/207, withdrawal of consent 6/207, other 4/207), 21/210 twice daily 0.03% tac. (lack of efficacy 4/210, adverse event 8/210, prohibited therapy 1/210, withdrawal of consent 4/210, other 4/210), 41/207 withdrawn TS (lack of efficacy 17/207, adverse event 6/207, prohibited therapy 1/207, withdrawal of consent 11/207, other 6/207)
- *Method of data analysis:* Says it is ITT, based on all those receiving at least one application – no exclusions after randomisation are stated but results appear to be based on different numbers of evaluable patients (for example 204/207 once daily 0.03% tac. 206/210 twice daily 0.03% tac, 204/207 TS for median mEASI reduction). Efficacy analysed using Wilcoxon rank-sum tests. Descriptive p-values for pair wise comparisons of treatment groups also used Wilcoxon rank sum est. Fisher's exact test compares incidence of adverse effects.

General comments

- *Generalisability:* High
- *Main outcome measured blind/independently?* Not clear
- *Inter-centre variability*? Not examined
- *Conflicts of interest*:? Study sponsored by Fujisawa

9.7 Appendix 7 – Pooled analyses

Data were pooled for an IGA score of "cleared" or "almost cleared" after three weeks and six weeks of treatment. Adult and child data are presented separately as well as in pooled estimates. Although different severities of eczema are studied in the different trials, there is overlap between the mild to moderate and moderate to severe categories, and consdierable uncertainty around the methods to identify levels of severity. It was therefore considered reasonable to pool the results of individual trials.

Data reported by Eichenfield and colleagues[64] combined data from two separate trials. These data are available from an FDA submission and were used separately in the meta-analysis. Pimecrolimus use results in significantly better IGA score compared to vehicle at both three and six weeks of follow up. See Figure 41.

Pooled data for number of flares at 6 months (Figure 43) shows that a pimecrolimus based regimen has significantly less flares than a vehicle based regimen (RR 1.78, 95% CI 1.10 to 2.86).

Meta-analysis of data on avoiding corticosteroids use showed those using pimecrolimus were significantly more likely to avoid using corticosteroids than those using vehicle alone (RR 1.82, 95% CI 1.51 to 2.21). See Figure 44.

Pooled estimates of pruritus score after three weeks and six weeks treatment with pimecrolimus or vehicle are shown in Figure 45 and Figure 46. Pruritus was more likely to be absent or mild for those using pimecrolimus compared to those using vehicle, RR = 1.99 (95% CI 1.53 to 2.58) at three weeks and RR 1.67 (95% CI 1.29 to 2.16) at six weeks.

Figure 41: Forest plot showing IGA score of 0-1 (cleared or almost cleared) in children with mild to moderate eczema and adults with moderate to severe eczema after three weeks treatment with pimecrolimus or vehicle

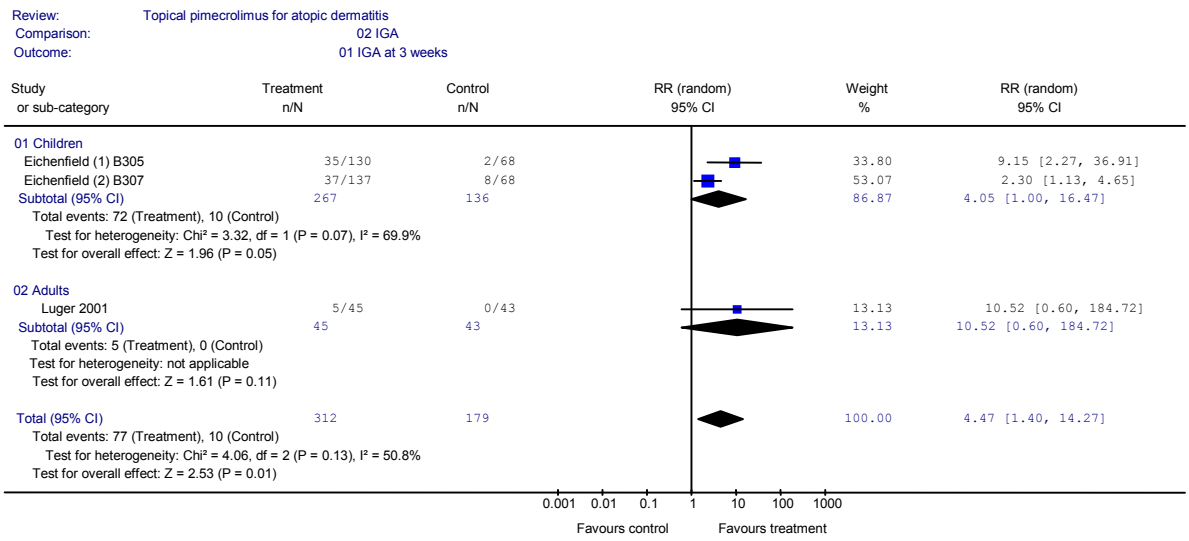


Figure 42: Forest plot showing IGA score of 0-1 (cleared or almost cleared) in children with mild to moderate atopic eczema after six weeks treatment with pimecrolimus or vehicle

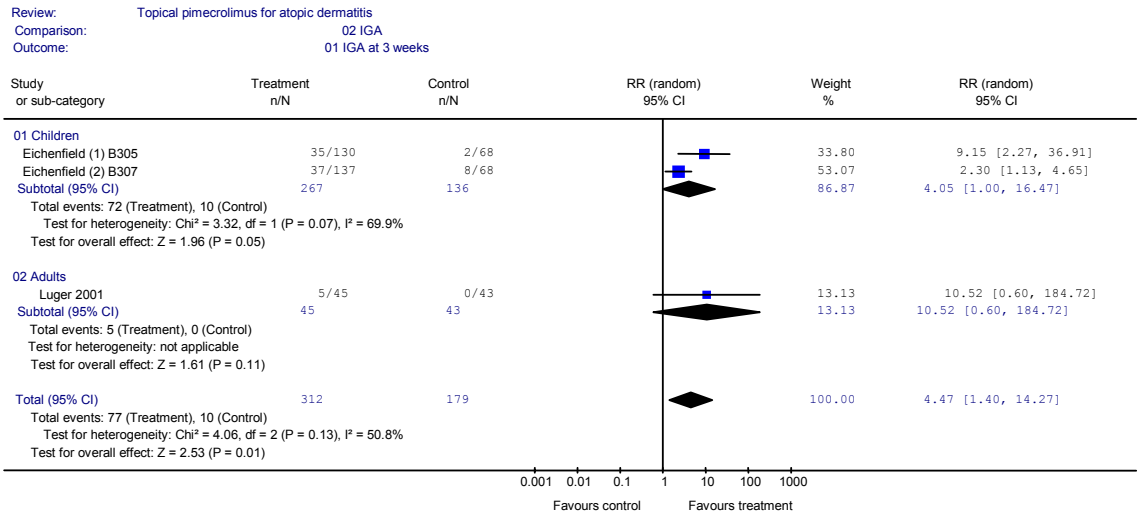


Figure 43: Forest plot showing experience or absence of flares in children with mild atopic eczema and adults with moderate to severe atopic eczema at 6 months with pimecrolimus compared to vehicle

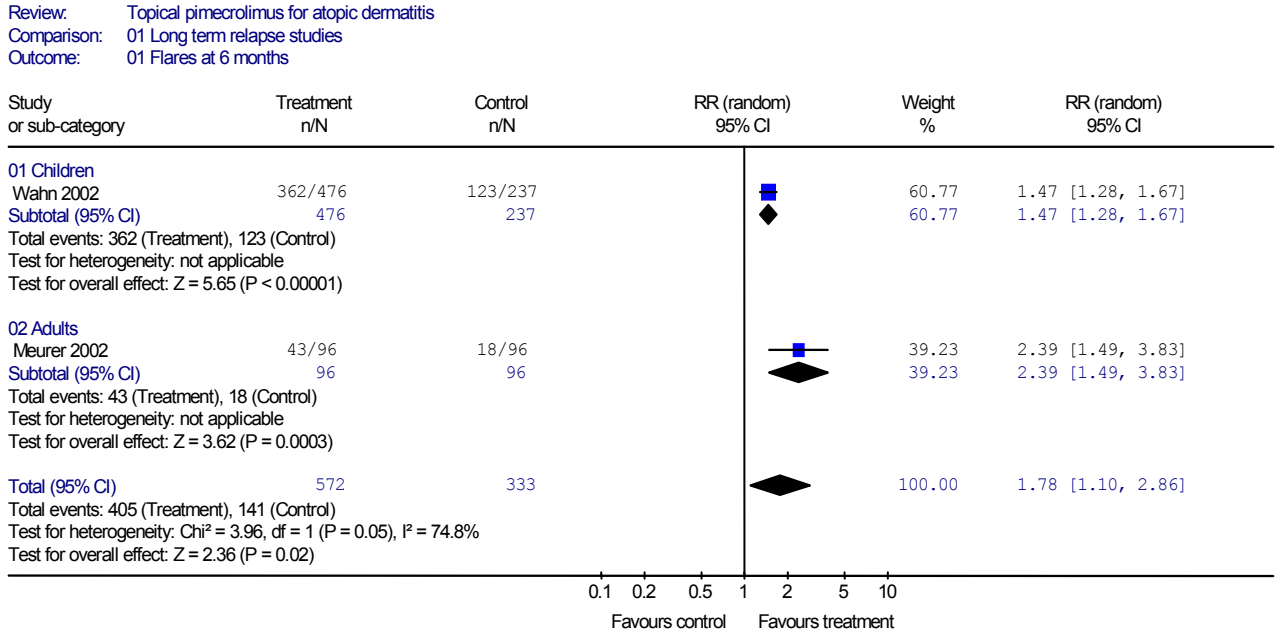


Figure 44: Forest plot showing topical corticosteroid avoidance in children with mild atopic eczema and adults with moderate to severe atopic eczema through treatment with pimecrolimus compared to vehicle.

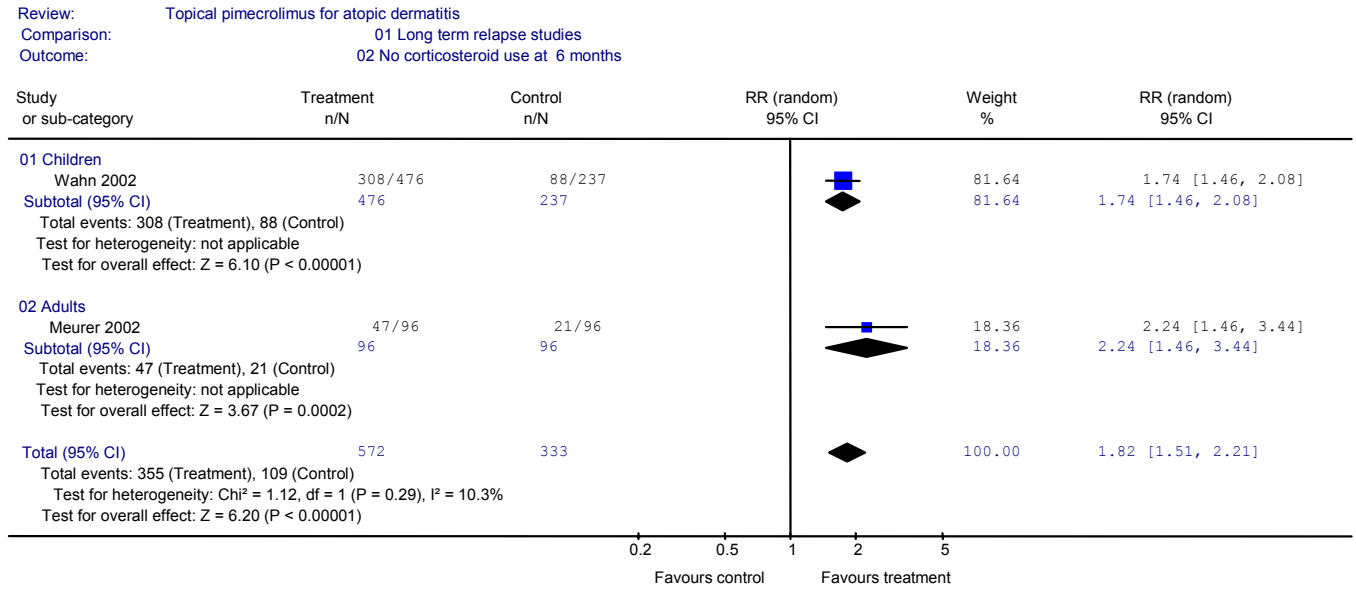


Figure 45: Forest plot of pruritus score in children with mild to moderate eczema and adults with moderate to severe eczema after three weeks of treatment with pimecrolimus or vehicle

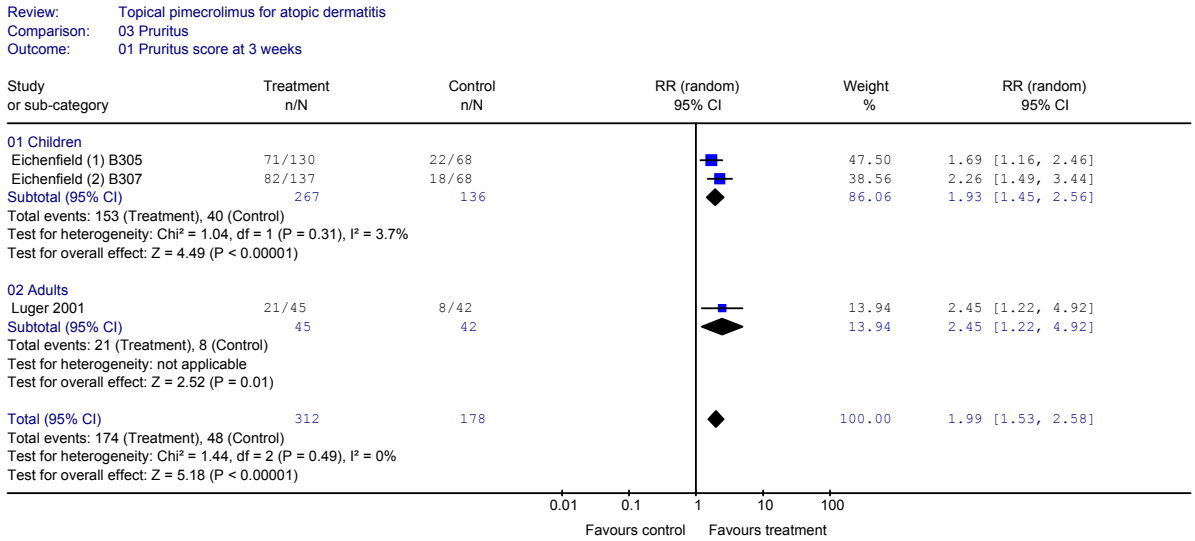
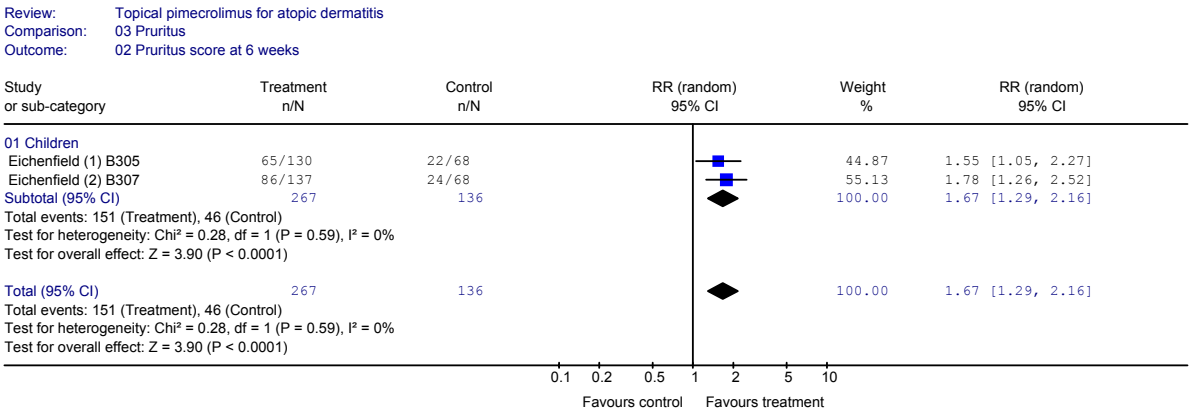


Figure 46: Forest plot of pruritus score in children with mild to moderate atopic eczema after six weeks of treatment with pimecrolimus or vehicle



Data for 0.03% tacrolimus vs vehicle 75%+ PGE demonstrates heterogeneity – results are not reliable.

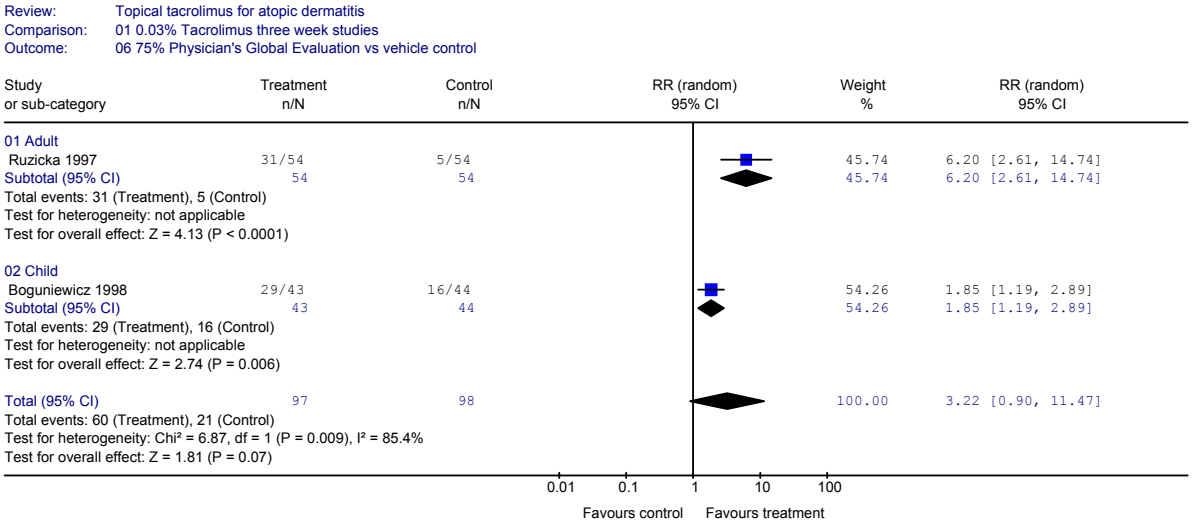


Figure 47: Forest plot showing rate of viral infection during treatment with pimecrolimus or vehicle

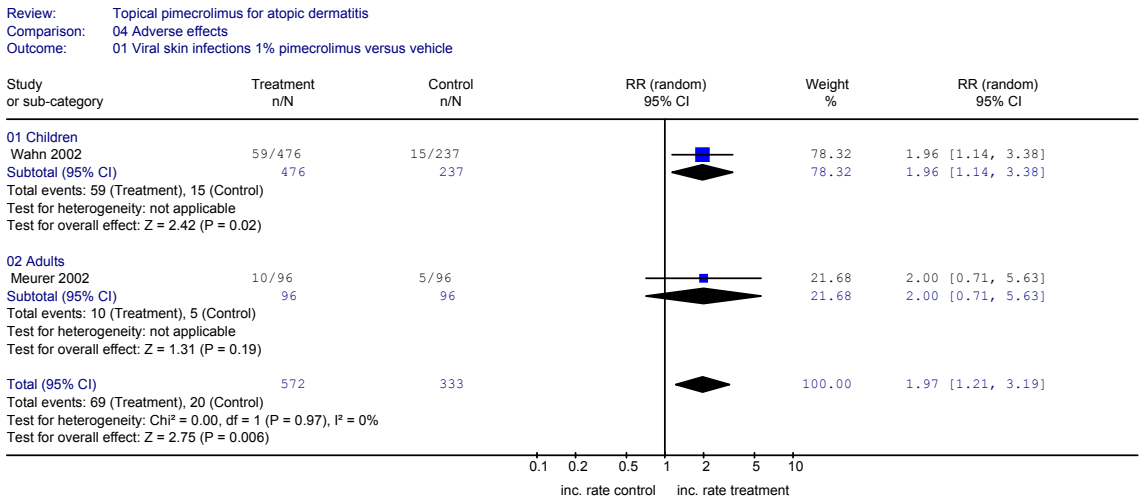


Figure 48: Forest plot of bacterial skin infection during treatment with pimecrolimus or vehicle

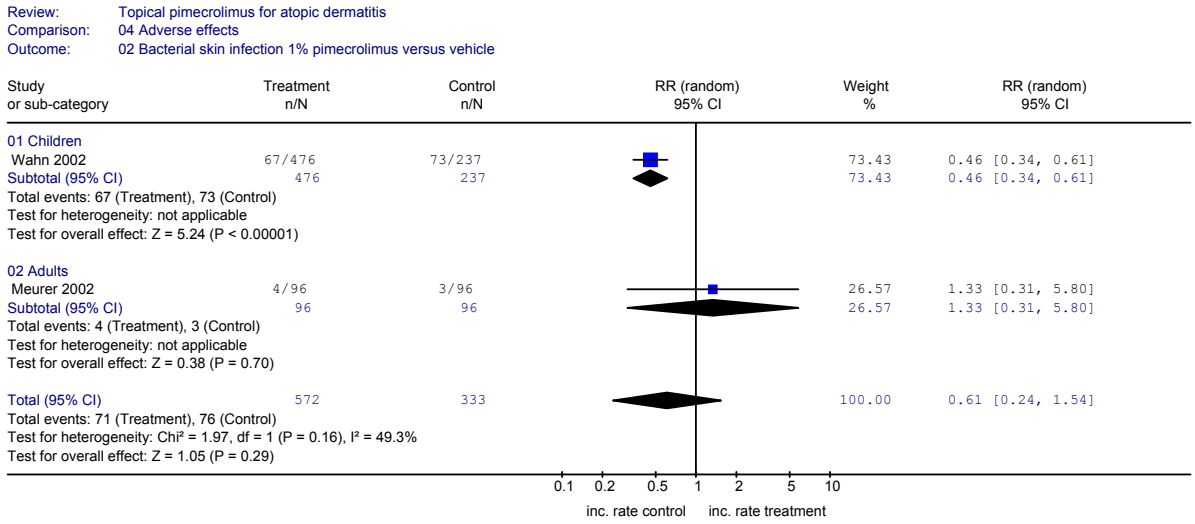
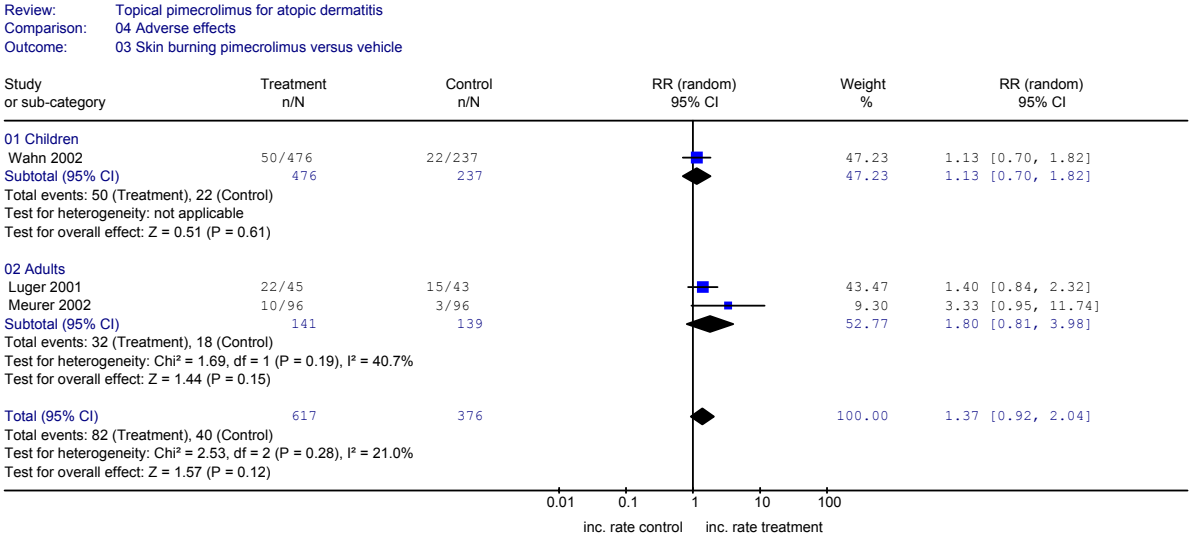


Figure 49: Forest plot showing rates of skin burning with pimecrolimus and vehicle



9.8 Appendix 8: Economic analyses assessed using the Sculpher framework

Items: from Sculpher framework		Study		
		Novartis	**Fujisawa**	**Ellis**
Structure of the Model	Is there a clear statement on the decision problem, context and perspective?	Decision problem: yes. Context not stated Perspective not stated	Context: secondary hospital outpatient setting Perspective: yes	Decision problem: yes Context: Not stated Perspective: third party payer
	Theory of underlying disease?	Yes	Yes	Yes
	Assumptions in the model clearly specified? Justified? Relaxed?	Main assumptions are not provided in full. Transition probabilities applied from 2nd week in children and adults model. First week modelled with direct input of numbers of patients in each state obtained from patients' numbers in the trial. Progression across states not discussed. Assumptions are made on extrapolations of transitions beyond follow-up but not discussed. Model assumes that all patients experiencing a flare are assigned to sate IGA 4/5. No sensitivity analysis conducted on probabilities.	Long list of assumptions on transitions specified. In both scenarios, disease-free days can only accrue during first line treatment, whilst costs can accrue during first and second line treatment. Scenario 1: patients who enter second line treatment cannot revert to first line treatment. Patients experiencing a flare can stay in first line or move to second line. Patients who discontinued assumed to have shifted to second line therapy Scenario 2, patients with moderate improvement during first line cannot switch to second line treatment. Patients with flares are assumed to remain in first line and cannot move to second line therapy. Sensitivity analysis provided on main transition probabilities and costs	Tacrolimus treatment assumed to be used in the long term; HPTC restricted to 2 or 4 weeks treatment. Secondary treatment is assumed non-effective at week 4 (relaxed in sensitivity analysis) Disease free days accumulated in disease-controlled state only; in sensitivity analysis, disease-controlled days accrued in second-line therapy too. Relapse rates assumed equal for HPTC and tacrolimus (relaxed in sensitivity)
Disease states	Model type appropriate for the time dimension of the disease?	Yes	Yes	Yes

Items: from Sculpher framework		Study		
		Novartis	**Fujisawa**	**Ellis**
	Justification of the choice of states provided	The model adequately represents fluctuation across disease severity Transition across 4 states of eczema severity. The model compares a scenario where patients with mild and moderate eczema (IGA 2 and 3) are started on pimecrolimus whilst patients in state IGA 4-5 are treated with topical corticosteroids. Patients in IGA 4-5, treated with topical steroids are assigned to pimecrolimus (IGA 2 and 3) or maintenance therapy (IGA 0-1) with emollient only, upon improvement. In the alternative scenario, patients in IGA 4-5 are treated with corticosteroids, patients with IGA 2 and 3 are treated with vehicle and emollients and patients in IGA 0-1 are treated with maintenance therapy of emollient only. Subanalysis by body area involved: patients definition with EASI scores	Each treatment and patients group is modelled within a sub-branch including a first-line treatment, three additional branches modelling possible outcomes from first line, a second line branch and, similarly, possible outcomes from second line treatment. Patients enter first line treatment (Tac or CS), with 3 possible outcomes, virtually cleared, moderately improved and with no appreciable improvement. In the following cycle, they progress to subsequent states where they may remain in the same severity stage, progress to clearance or regress to uncontrolled disease. Cleared patients may have a relapse (flare) and undergo second treatment cycle. Scenario 1 incorporates time spent in flare as an outcome on the 'virtually cleared branch' whilst scenario 2 incorporates a self-standing branch accounting for flares and time spent in flare, thus accounting for a larger proportion of time in the flare state. Uncontrolled patients at all stages may continue therapy or switch to second line therapy. Once patients have entered second line therapy they may achieve clearance, achieve moderate control or uncontrolled.	The states are defined based on treatment rather than on disease stages. First stage, 1st line treatment with tacrolimus or HPTC for 2 or 4 weeks, followed by second line treatment or disease controlled (not actively treated) for 4 weeks. Patients lacking improvement greater than 75% after 4 weeks either followed to second line therapy (HPTC arm) or continue tacrolimus. Secondary treatment: association of mid-potency topical steroids and oral antibiotics.
	Empirical evidence of the suitability of the states?	The model assumes that state IGA 4/5 is equivalent to a 'flare'	Patients graded moderate or severe according to the Hanifin and Rajka criteria. Patients defined uncontrolled, moderate and cleared or virtually cleared (Physician Global Evaluation criteria). Definition of flare: 'a patient going from the virtually cleared or cleared state to the not controlled or moderately controlled (scenario 1) or recurrence of AD in the same or other site and requiring an unscheduled visit to the dermatologist (scenario 2)'	Patients are graded 'disease controlled' if achieve greater than 75% improvement (Physician Global Assessment of disease) Relapse is assumed equal for the three arms (sensitivity shows no impact on results)

Items: from Sculpher framework		Study		
		Novartis	**Fujisawa**	**Ellis**
	Any important states omitted?	No	No	No
Options and strategies	Is there a clear statement of the options being evaluated?	Yes	Yes	Yes
	Cover full range of logical and feasible options	The model excludes standard practice (corticosteroids in mild and moderate disease), despite it being a viable option for the majority of patients. For severe patients, existing alternatives have not been included (i.e. second line treatment, light therapy, cyclosporine etc.) No consideration was made of complications related to treatment (i.e. skin infections or viral infections) with a potential for an increase in costs.	Main second-line options included. A third comparator is included in scenario 2, cyclosporine, in the adult model only (not licensed for use in children) Adverse effects are incorporated in the cost of treatment in proportion to their occurrence from trial data (scenario 1) but they have not been included in scenario 2.	Second-line therapy does not consider light therapy, systemic immunosuppressants or systemic steroids.
Time horizon	Exhaustive in time and coverage of option through time	Yes	Yes	Yes
	Justification based on disease and effect of interventions	Yes	Yes	Yes
Cycle length	Used if relevant? Justified? Related to disease?	Yes (but shorter than treatment cycle)	Yes	Not stated. Model divided in introductory period (2-4 weeks) and subsequent 4-weeks periods

Items: from Sculpher framework		Study		
		Novartis	**Fujisawa**	**Ellis**
Data Identification	Sources of parameter values	Effectiveness: study DE-01 (adults) and study B313 (children) The model includes direct medical care costs (intervention and other drugs, outpatient and primary care consultations, hospital admissions). Consumption of drugs and concomitant treatment measured in trial. Consumption of GP and specialists visits and hospital admissions obtained from a published study (Su and colleagues) set in Australia, adjusted to the UK context reducing resource consumption by half. In the original paper, costs are derived for mild, moderate and severe patients according to the Rajka criteria. The model assumes that these three states are equivalent to respectively, IGA 2, IGA 3, IGA 4/5. Alternative profile of resource consumption assumed (IGA 0/1, 1 visit; IGA 2, 2 visits; IGA 3, 3 visits; IGA 4/5, 4 visits). Obtained from an expert pane. Two other scenarios tested (doubling resources used) in base case and sensitivity. Costs and resource consumption other than the cost of drugs (intervention and other drugs), visits and hospital admissions assumed constant with respect to severity of disease. No information provided on the cost of adverse events. Unit costs were derived from appropriate UK sources	Scenario 1 described the disease based on trial data, with transition probabilities for adults obtained from trial FG-506-06-26 and FG-506-97-0-037. Scenario 2: experts interviews. Type and effectiveness of steroid medications are assumed equal for children and adults. Another assumption is that treatment with tacrolimus is composed of a first burst of 0.1% and a maintenance with 0.03% tacrolimus. Quality of life outcomes have been adjusted to obtain Quality of Life rewards. DLQI scores range from 0 (best quality of life) to 30 (worst quality of life). Rewards were computed with the formula 1-(DLQI score/30). However, the DLQI rewards were not mapped as utility scores. The model includes direct medical care costs and workday lost for adults. Methods of cost calculation reported in detail. Resource consumption profiled elicited from experts.	Effectiveness: for HPTC, derived from meta-analysis of literature (Class I/II HPTC) conducted on Medline (10 studies, with 597 patients). Studies excluded if did not report Physician Global Assessment measures, follow-up of less than 2 weeks, paediatric patients. tacrolimus: derived from Hanifin (adults) and Paller (paediatric), and an internal report (Fujisawa, REF IN XXX). Resource use: assumed 1 physician consultation per change of state, 0 when entering disease-controlled state. Cost of HPTC: published average wholesale price; cost of tacrolimus: average cost of marketed concentrations (0.1% and 0.03%). Physician costs: median value of published charges

Items: from Sculpher framework		Study		
		Novartis	**Fujisawa**	**Ellis**
	Is reasonable empirical justification from early iterations of the model given that these data are obtained from all low-cost data sources (i.e. secondary data)	Transition probabilities from the model have been tested iteratively and compared with actual trial data with a X^2 test. No comparison with other independent data or models is reported. Authors report good fit of model data to the trial data for the adult population, whilst in the children model there was a significant difference from week 39 due to the drop out of patients in the trial. Total time spent in each disease state can be calculated from data provided (number of patients in each state at some time points). A systematic review of all published evidence was not carried out and primary data of one trial for adults and one for children only have been used.	No	No
	Are ranges specified for parameters?	Yes	Yes	Sensitivity: ranges only provided for effectiveness and cost of second line
	Evidence to suggest selective use of data?	Yes	Yes	Yes
	If parameters are valued based on elicitation of expert opinion methods, have methods been adequately described (inclusion criteria, sample size, elicitation methods?	Yes for utility, no for costs.	All data for second-line therapy and resource utilisation are collected from the Delphi panel (8 experts) chosen from list of UK dermatologists approved by Fujisawa, a list of contact details is provided. Elicitation methods not detailed.	An expert panel composed of the physicians authors of the paper derived time-dependent decrease in response to HPTC reported in meta-analysis (75% effectiveness, reduced to 50% (-33%) over 52 weeks (averaged -15% over week 2 and 4)

Items: from Sculpher framework		Study		
		Novartis	**Fujisawa**	**Ellis**
	Are the claims made by model 'tempered' by limitations in the data?	Yes	Yes	Yes
Data incorporation	For each parameter, is there a clear justification on how data have been incorporated into the model?	Probabilities: some specification is provided (for number of individuals that enter the model at week 0, and for extrapolation of transition probabilities).	Transition probabilities are time-dependent in both models, despite with an unclear pattern since data are taken directly from trial data; The model states assumptions on the relationship between costs and disease severity The cost of moderately controlled patients is constant, the cost of maintenance therapy for cleared patients decrease in week 6 to 9, for patients with no appreciable improvement increase from the 6th week.	Broadly for some parameters (however it is the only paper examined from publication rather than report)
	Has a stochastic analysis been undertaken? If so, do the distributions in parameters reflect second order uncertainty? Have appropriate distributions been selected for each parameter?	Probabilistic distributions were used to model costs (gamma distribution) and utilities (beta distribution). A probabilistic sensitivity analysis was carried out only for the children model	No	No
	Have interval rates been translated into transition probability using the appropriate formula?	Transition probabilities were computed counting the number of changes from one state to another at each visit. No other details provided	Transition probabilities were computed from trial data based on health states at the end of three weeks cycles. LOCF probabilities.	Not stated
	Has a half-time related estimate been applied?	No (based on the length of the cycle (1week)	Not stated	Not stated
Internal consistency	Does it work? Is there a statement about internal consistency?	The children model seems to contain a programming error in the probabilistic sensitivity analysis. The cost of corticosteroids is overwritten in each		

Items: from Sculpher framework		Study		
		Novartis	**Fujisawa**	**Ellis**
		simulation with the central estimate, the final result yields the same value repeated over the 10000 runs.		

Internal Consistency

Novartis

Generally the model works in terms of internal consistency although there seems to be a small programming error in generating confidence intervals for probabilistic analysis when choosing the Su et al settings.

Fujisawa

The *TreeAge* model has not been submitted so consistency checking of the model is not possible. Excel spreadsheets of data parameters and outputs are well presented and seem to be consistent.

9.9 Appendix 9: Basecase and Results of the Sensitivity Analyses in the Novartis Model

Study	Total cost, Elidel	Total effectiveness, Elidel	Total cost, vehicle	Total effectiveness, vehicle	ICER
Base case (1 year) adults	£968	0.808 (QALY)	£83	0.776 (QALY)	£27,350
Sensitivity, 6 months, adults	£501	0.402 (QALY)	£42	0.386 (QALY)	£28,148
Base case (1 year) children	£1,062	0.766 (QALY)	£756	0.754 (QALY)	£24,489
Sensitivity, 6 months, children	£536	0.383 (QALY)	£351	0.378 (QALY)	£32,230

Sensitivity: point estimates, adults		By scenario: utility estimate				
		MERG	Brazier	Duke (Wolfson):	Duke (Torrance):	Duke (Feeney):
By Cost	Base case Assumed visits per year: (IGA0/1=1; IGA2=2; IGA3=3; IGA4/5=4	£27,350	£49,323	£36,426	£39,411	£42,661
	Su x 0.5	£22.050	£39,765	£29,367	£31,774	£34,394
By Body area (cost=base case)	Head/Neck	£21,766	£40,861	£28,398	£30,612	£33,016
	Trunk	£28,219	£51,057	£45,698	£49,948	£54,614
	Upper limbs	£28,066	£49,670	£35,777	£38,678	£41,837
	Lower limbs	£36,149	£62,265	£47,944	£52,032	£56,499
Sensitivity: point estimates, children			Brazier	Duke (Wolfson):	Duke (Torrance):	Duke (Feeney):
By Cost	Base case (Su x 0.5)		£24,489	£16,524	£17,818	£19,226
	Su x 1		£ 7341	£4,953	£5,341	£5,763
	Assumed visits per year: (IGA0/1=1; IGA2=2; IGA3=3; IGA4/5=4		£40.927	£27,136	£29,261	£31,573
By Body area (cost=base case)	Head/Neck		£ 4,668	£7,456	£8540	£9809
	Trunk		Dominates	Dominates	Dominates	Dominates
	Upper limbs		£27,928	£23639	£25748	£28056
	Lower limbs		£22,787	£14266	£15325	£16474

9.10 Appendix 10: Basecase and Results of the Sensitivity Analyses in the Fujisawa model

Fujisawa results including workdays lost Scenario 1

Scenario 1	Tacrolimus	Topical corticosteroids	Sensitivity (Item [range of variation]): result
Moderate eczema	Tacrolimus dominates §		Workdays lost [0, 7]: break-even undetermined, tacrolimus superior for all values in range % virtually cleared patients experiencing no flares [0, -20%]: tacrolimus superior for values lower than break-even -17.6% % continuing treatment after moderate improvement after 1st cycle [0, 100%]: tacrolimus is superior for values lower than break-even 46% % lesions cleared after cycle 1 [25%, 100%]: tacrolimus superior for values higher than: 26% for cleared patients, 23% moderately cleared, 50% for patients with no improvement.
Mean % time in first line treatment (per year)	176.87/189 days	154/189 days	
Total cost	£975.49	£988	
Total effectiveness	89.53 (DCD)	57.51 (DCD)	
Average cost-effectiveness ratio	£10.90 /DCD	£17.19 /DCD	
Severe eczema	Tacrolimus dominates §		Workdays lost [0, 21]: break-even undetermined, tacrolimus superior for all values in range % continuing treatment after moderate improvement after 1st cycle [0, 100%]: tacrolimus is superior for values lower than break-even 12%
Mean % time in first line treatment (per year)	164.02/189 days	136.71/189 days	
Total cost	£2,856.	£2,930.84	
Total effectiveness	57.33 (DCD)	27.47 (DCD)	
Average cost-effectiveness ratio	£49.83/DCD	£106.69/DCD	

§ Incremental cost-effectiveness ratios were recalculated within this TAR based on total costs and effectiveness provided in the model report

Sensitivity analyses - Scenario 2

Scenario 2	Tacrolimus	Topical steroids	Cyclosporine	Sensitivity (Item [range of variation]): result
Moderate eczema	ICER £6.18/DCD §			Workdays lost [0, 7]: tacrolimus inferior for values higher than break-even 2.4 days % virtually cleared patients experiencing no flares [10%, 70%]: tacrolimus superior for values higher than break-even 28% % lesions cleared after cycle 1 [25%, 100%]: tacrolimus superior for values higher than 51% for cleared patients, 32% for patients with no improvement, and lower than 17% moderately cleared
Mean % time in first line treatment (per year)	229.48/357 days	214.29/357 days		
Total cost	£1,905.43	£1,787.65		
Total effectiveness	175.06 (DCD)	156.00 (DCD)		
Average cost-effectiveness ratio	£10.88/DCD	£11.46/DCD		
Severe eczema	Tacrolimus	Topical steroids	Cyclosporine	Sensitivity (Item [range of variation]): result
	Tacrolimus vs. corticosteroids: ICER £26.76/DCD § Cyclosporin vs. tacrolimus: ICER £4.84/DCD §			Workdays lost [0, 21]: tacrolimus inferior for values higher than break-even, 11.5 days. Days of hospitalisation [0, 3]: tacrolimus inferior for values higher than break-even 1.8 days. % virtually cleared patients experiencing no flares [5%, 30%]: tacrolimus superior for values lower than break-even 13% % lesions cleared after cycle 1 [10%, 80%]: tacrolimus superior for values lower than 35% and % of moderately controlled patients lower than 31% % moderately controlled patients having lesions cleared [10%, 70%]: tacrolimus superior for values lower than break-even 34% Cyclosporine superior to tacrolimus/corticosteroids for all analyses and for all values in range
Mean % time in first line treatment (per year)	145.38/357 days	140.35/357 days	250.64/357 days	
Total cost	£5,017.41	£4,794.67	£5,527.36	
Total effectiveness	84.98 (DCD)	76.66 (DCD)	177.61 (DCD)	
Average cost-effectiveness ratio	£59.04/DCD	£62.54/DCD	£31.12/DCD	

§ Incremental cost-effectiveness ratios were recalculated within this TAR based on total costs and effectiveness provided in the model report

Fujisawa Results, Adults, excluding workdays lost Scenario1

Scenario 1 (27 weeks): tacrolimus vs topical corticosteroids						
Patients subgroup	Intervention and comparator	Mean % time in first line treatment (per year)	Total cost	Total effectiveness	Average cost-effectiveness ratio	Sensitivity
Moderate eczema	Tacrolimus	176.87/189 days	£806.97	89.53 (DCD)	£9.01 /DCD	N/A
	Topical corticosteroids	154/189 days	£755.65	57.51 (DCD)	£13.14 /DCD	
	Tacrolimus dominates§					
Severe eczema	Tacrolimus	164.02/189 days	£1,536.63	57.33 (DCD)	£26.80/DCD	
	Topical corticosteroids	136.71/189 days	£1,536.44	27.47 (DCD)	£55.93/DCD	
	Tacrolimus dominates§					

Fujisawa results including workdays lost Scenario 2

Scenario 2 (51 weeks): tacrolimus vs topical corticosteroids vs cyclosporine						
Patients subgroup	Intervention and comparator	Mean % time in first line treatment (per year)	Total cost	Total effectiveness	Average cost-effectiveness ratio	Sensitivity
Moderate eczema	Tacrolimus	229.48/357 days	£1477.68	175.06 (DCD)	£8.44/DCD	N/A
	Corticosteroids	214.29/357 days	£1340.46	156.00 (DCD)	£8.59/DCD	
	ICER £7.2/DCD §					
Severe eczema	Tacrolimus	145.38/357 days	£3025.33	84.98 (DCD)	£35.60/DCD	
	Corticosteroids	140.35/357 days	£2893.77	76.66 (DCD)	£37.75/DCD	
	Cyclosporine	250.64/357 days	£3713.71	177.61 (DCD)	£20.91/DCD	
	Tacrolimus vs. corticosteroids: ICER £15.8/DCD§ Cyclosporine vs. tacrolimus: ICER £7.4/DCD§					

Fujisawa Results in children

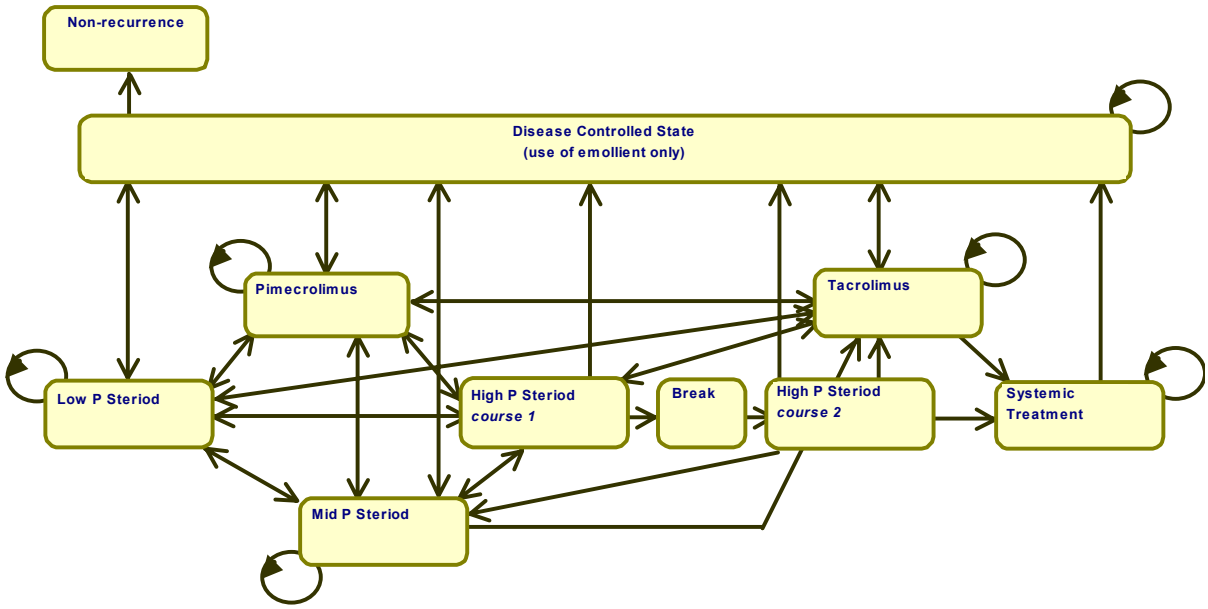
Scenario 1 (15 weeks): tacrolimus vs. topical corticosteroids						
Patients subgroup	Intervention, comparator	Mean % time in first line treatment (per year)	Total cost	Total effectiveness	Average cost-effectiveness ratio	Sensitivity (Item [range of variation]): result
Moderate eczema	Tacrolimus 0.03%	94.77/105	£631.65	24.23 (DCD)	£26.07	Nr. consultation per cycle in moderately controlled and cleared eczema [0.7, 1]: tacrolimus 0.1% superior for values higher than breakeven 0.9 tacrolimus 0.3% inferior for all values in range % patients having clearance after 1st cycle [10%, 40%]: tacrolimus 0.03% superior for values higher than breakeven 23% and T0.1% superior for values higher than breakeven 28% % moderately controlled patients having clearance after 2nd cycle [5%, 40%]: T0.03% superior for values higher than breakeven 30% or T0.1% inferior for values lower than breakeven point 12% % moderately controlled patients continuing treatment [80%, 100%]: tacrolimus 0.1% inferior for values lower than breakeven 92% tacrolimus 0.03% inferior for all values in range
	Tacrolimus 0.1%	99.32/105	£624.27	31.16 (DCD)	£20.04	
	Topical corticosteroids	92.76/105	£545.30	26.34 (DCD)	£20.70	
	Tacrolimus 0.03% vs. corticosteroids: corticosteroids dominates Tacrolimus 0.1% vs. corticosteroids: ICER £16.41 Tacrolimus 0.1% vs. tacrolimus 0.03%: tacrolimus 0.1% dominates					
Severe eczema	Tacrolimus 0.03%	95.85/105	£1,130.81	16.61 (DCD)	£68.09	Days hospitalisation [0, 3]: tacrolimus 0.1% superior for all values in range, T0.3% superior for values higher than break-even 1.74 % patients having clearance after 1st cycle [5%, 30%]: tacrolimus 0.03% superior for values higher than breakeven 8% tacrolimus 0.1% superior for values higher than 10% % moderately controlled patients having clearance after 1st cycle [0%, 30%]: tacrolimus 0.03% superior for all values in range, tacrolimus 0.1% superior for values higher than breakeven point 8.9% % % moderately controlled patients continuing treatment [60%, 100%]: tacrolimus 0.1% inferior for all values, tacrolimus 0.03% superior for values higher than breakeven point 69%
	Tacrolimus 0.1%	97.24/105	£1,156.69	11.46 (DCD)	£100.92	
	Topical corticosteroids	87.08/105	£1,051.00	12.20 (DCD)	£86.17	
	Tacrolimus 0.03% vs. TC: ICER £18.10 Tacrolimus 0.1% vs. CS: CS dominates Tacrolimus 0.1% vs. Tacrolimus 0.03%: Tacrolimus 0.03% dominates					

Results in children – scenario 2

Scenario 2 (51 weeks): tacrolimus vs topical corticosteroids

Patients subgroup	Intervention and comparator	Mean % time in first line treatment (per year)	Total cost	Total effectiveness	Average cost-effectiveness ratio	Sensitivity (Item [range of variation]): result
Moderate eczema	tacrolimus	229.48	£1,778.25	175.06 (DCD)	£10.16	Cost of medication during maintenance [£10, £45]: tacrolimus inferior for values higher than break-even point £35.6 % patients having clearance after 1st cycle [25%, 85%]: tacrolimus superior for values higher than breakeven point 53% % cleared patients having no flare [10%, 70%] tacrolimus superior for values higher than breakeven point 26%
	Topical corticosteroids	214.29	£1,715.23	156.00 (DCD)	£11.00	
	Tacrolimus vs. corticosteroids: ICER £3.31					
Severe eczema	Tacrolimus	145.38	£3,332.50	84.98 (DCD)	£39.21	N. days hospitalisation [0, 3]: tacrolimus inferior for values higher than break-even 1.36 % patients having clearance at 1st cycle [10%, 80%] tacrolimus superior for values higher than breakeven point 36% % moderately controlled patients having clearance after 1st week [10%, 70%]: tacrolimus superior for values higher than breakeven 36% % patients having no flares [5%, 30%] tacrolimus superior for values higher than breakeven 16%
	Topical corticosteroids	140.35	£3,198.45	76.66 (DCD)	£41.72	
	Tacrolimus vs. CS: £16.11					

9.11 Appendix 11: Generic Markov model used in cost-utility analysis



9.12 Appenix 12: Scenarios used by PenTAG to obtain utility values from the Utility Panel

SEVERE ECZEMA SCENARIO
This scenario is derived from an outcome measure in which the following statements were used to indicate the severity of various aspects of the condition

- Not at all
- A little
- A lot
- Very much

- Your skin is red, sometimes scaly, has small lumps within it and may feel a little thickened. Sometimes the areas affected crack, ooze or weep.
- Your skin almost always itches or hurts, stings a lot and sometimes very much. Your sleep is often disturbed by the itch.
- You feel embarassment or self consciousness because of your skin - usually a lot and sometimes very much
- Over a third of your skin area is affected. Your face, neck and upper limbs are more likely to be affected than your trunk or legs, although all areas may be included.
- Your skin condition limits your ability to go shopping, or look after your home or garden - usually a lot but sometimes only a little.
- The condition of your skin influences the clothes you choose to wear - usually a lot but sometimes a little.
- Your skin limits your ability to carrry out social or leisure activities and sport - usually a lot but sometimes a little
- Your ability to study or work is usually affected a lot but sometimes only a little
- Your personal relationships and sex life are affected a little by your skin condition
- The treatments you have to take affect your life a lot - they can be messy and applying them takes up time

MODERATE ECZEMA
This scenario is derived from an outcome measure in which the following statements were used to indicate the severity of various aspects of the condition

- Not at all
- A little
- A lot
- Very much

- may feel Your skin is red and sometimes has small lumps within it. It may be scaly and a little thickened.
- Your skin almost always itches, hurts, or stings a little and sometimes a lot. Your sleep is sometimes affected.
- You feel embarassment or self-counsciousness because of your skin - usually a little but sometimes a lot

- More than 10% of your skin area is affected by the condition, but less than a third. Your face, neck and upper limbs are more likely to be affected than your trunk or legs, although all areas may be included.
- Your ability to go shopping, or look after your home or garden is often limited a little by your skin but sometimes a lot. The condition of your skin influences the clothes you choose to wear usually only a little but sometimes a lot.
- Your skin limits your ability to carrry out social or leisure activities and sport - often a little but sometimes a lot
- Your ability to study or work is often affected a little and sometimes there is a lot of impact
- Your personal relationships and sex life are usually not affected at all by your skin condition but sometimes there is a little impact
- The treatments you have to take affect your life a little - they can be messy and applying them takes up some time

MILD ECZEMA

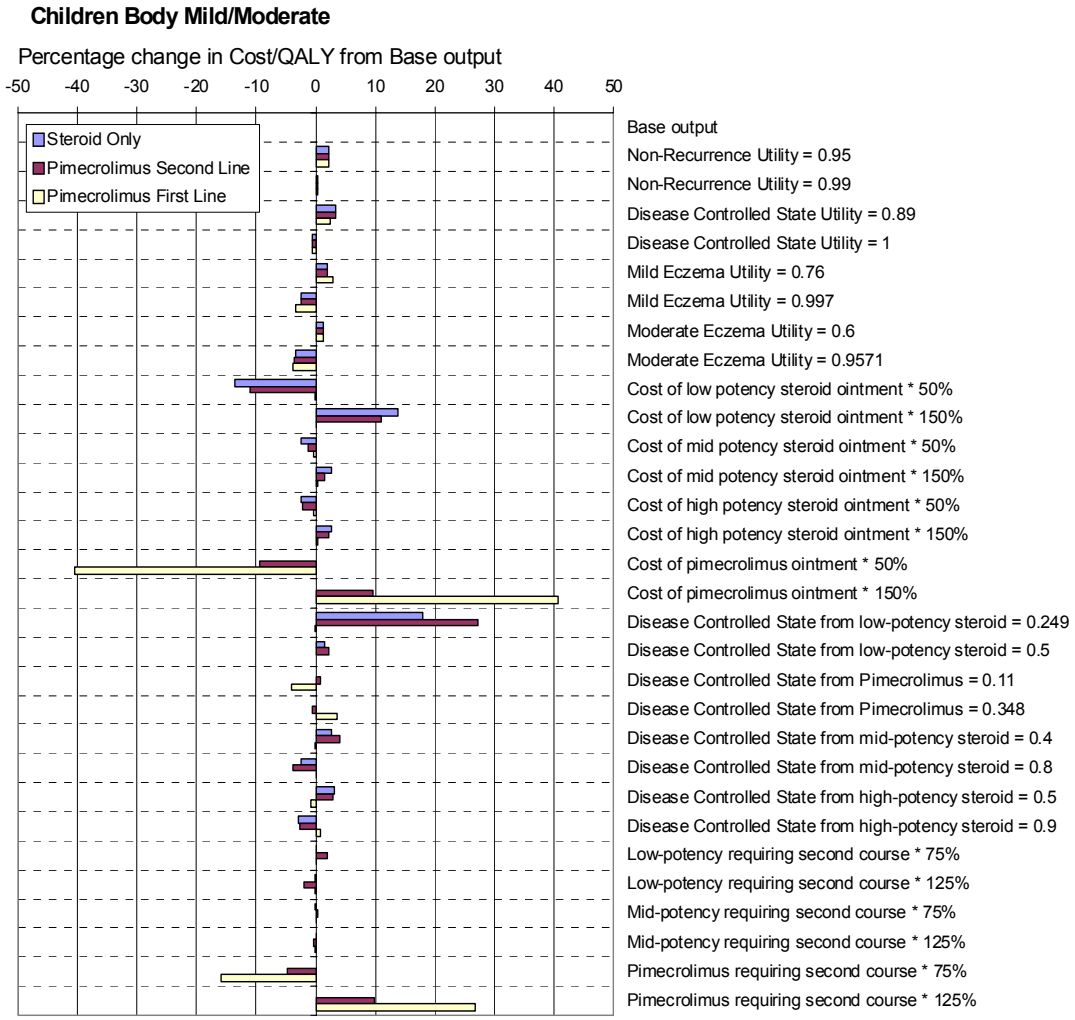
This scenario is derived from an outcome measure in which the following statements were used to indicate the severity of various aspects of the condition

- Not at all
- A little
- A lot
- Very much

- Your skin is red and sometimes has small lumps within it. It may feel scaly but is not likely to be thickened.
- Your skin may itch, hurt, or sting a little but sometimes not at all. It is exceptional for your sleep to be affected.
- You sometimes feel embarassed or self conscious because of your skin, but not often.
- Less than 10% of your body area is affected. Your arms and hands are more likely to be affected than your face, trunk or legs.
- Your ability to go shopping, or look after your home or garden may be reduced by your skin - usually a little, but sometimes a lot.
- Your skin usually has no influence on the clothes you choose to wear but sometimes might have a little impact
- Your skin usually does not limit your ability carrry out social or leisure activities and sport but sometimes there is a little impact
- Your ability to study or work is usually not at all affected by your skin but sometimes it has a little impact
- Your personal relationships and sex life not affected at all by your skin condition
- The treatments you have to take sometimes affect your life a little but usually not at all- they can be messy and applying them takes up some time

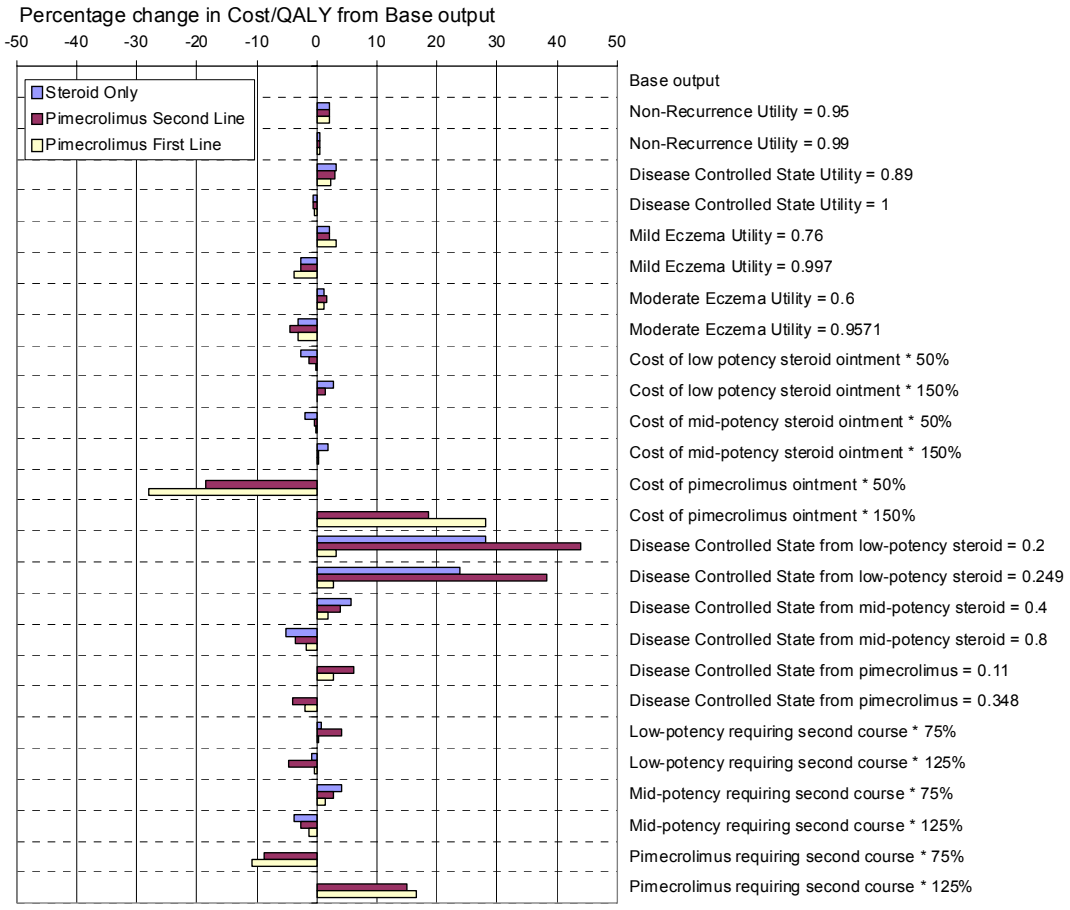
9.13 Appendix 13: PenTAG Cost Utility Model: One way sensitivity analyses

Model 1a



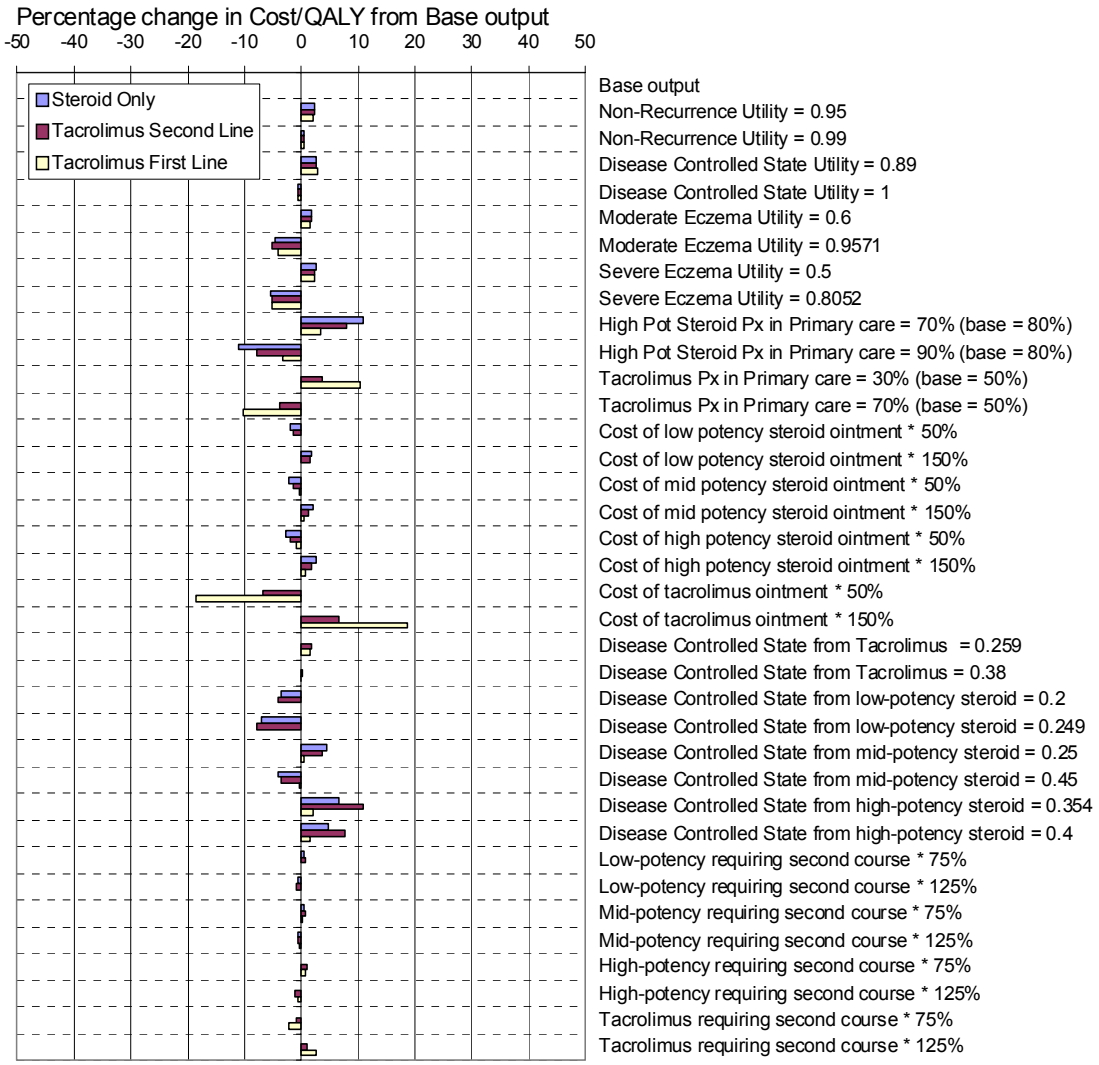
Model 1b

Children Facial Mild/Moderate



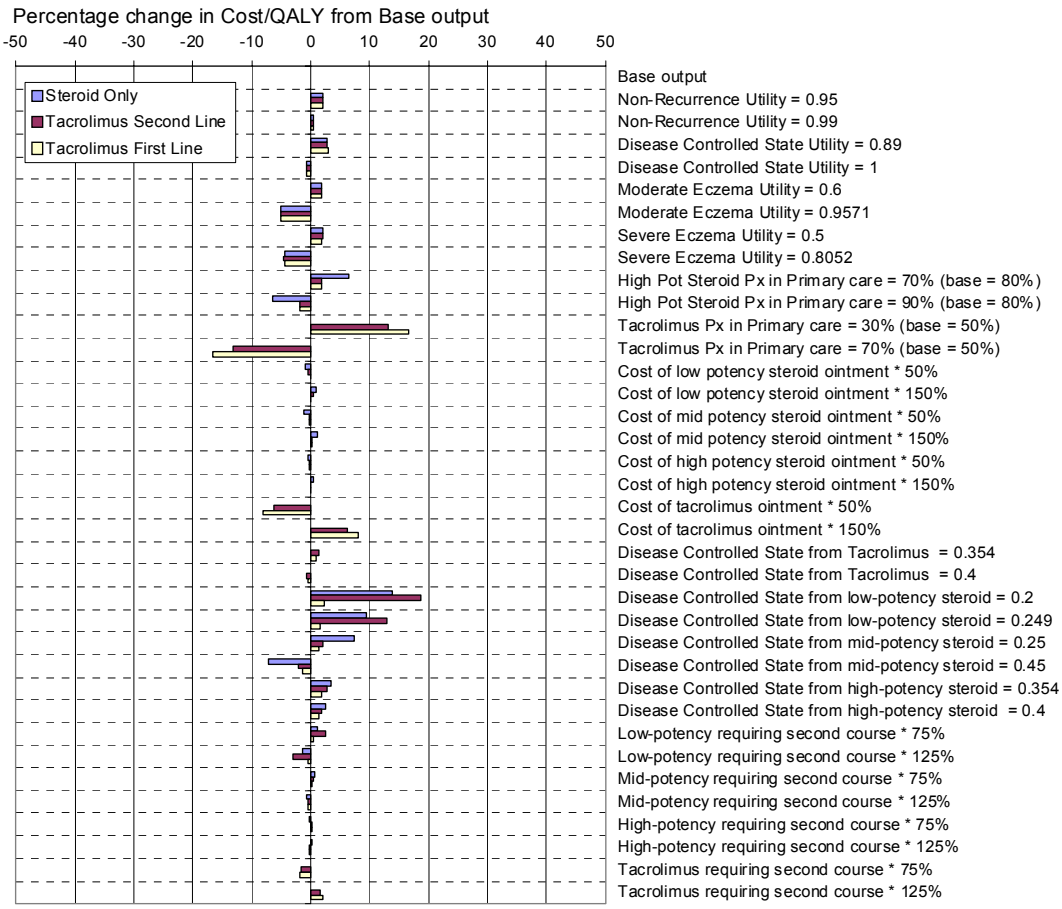
Model 2a

Children Body Moderate/Severe



Model 2b

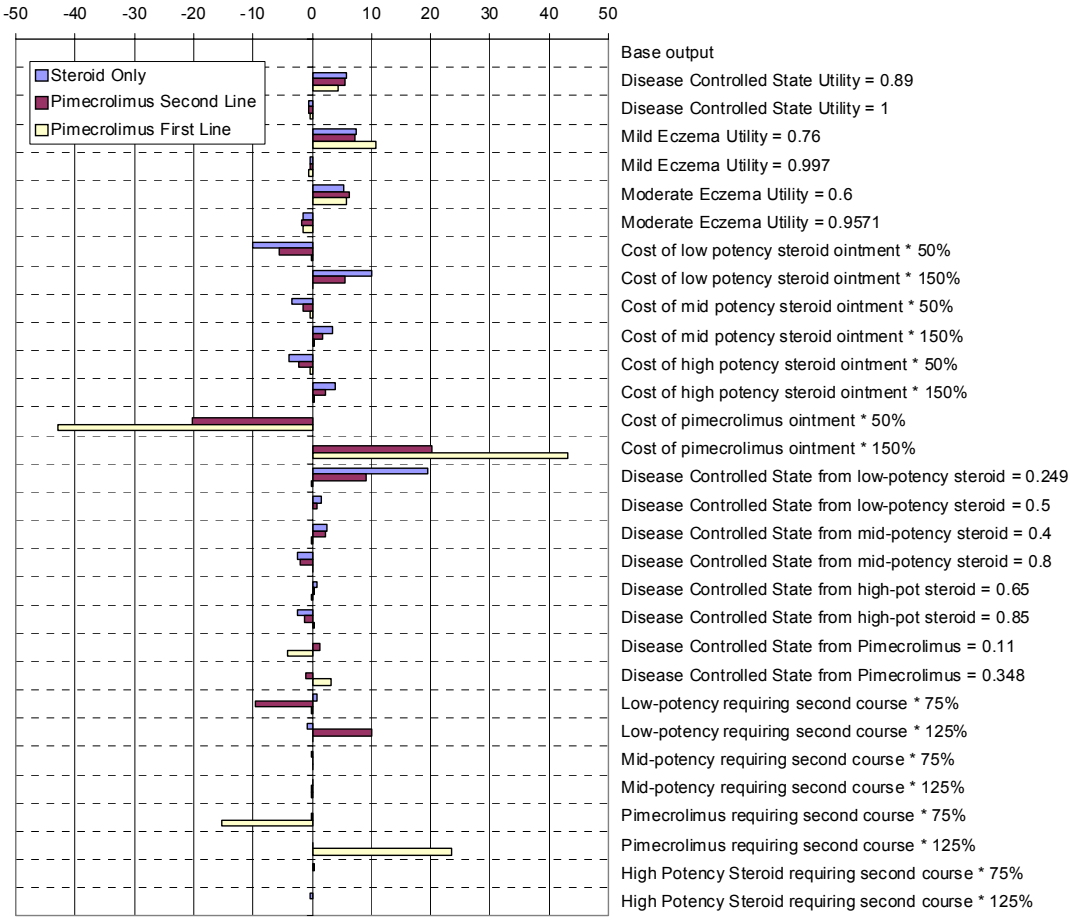
Children Facial Moderate/Severe



Model 3a

Adult Body Mild/Moderate

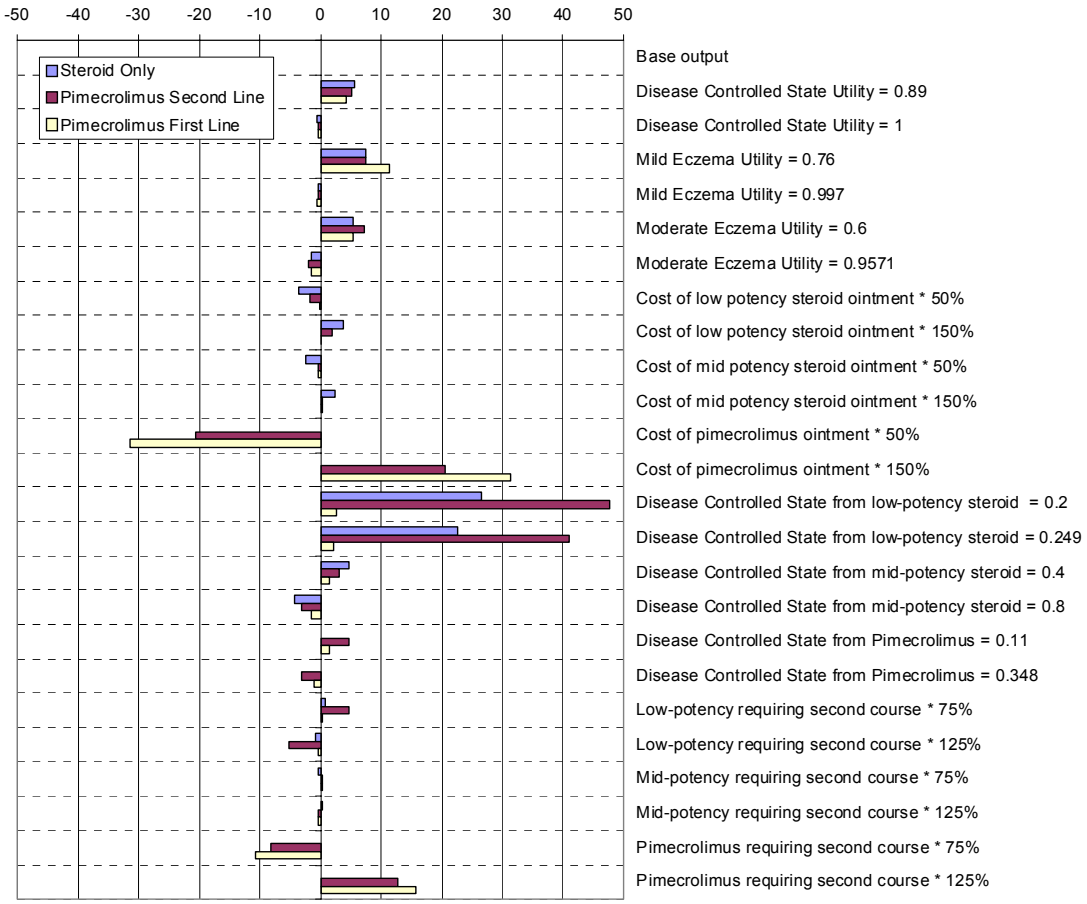
Percentage change in Cost/QALY from Base output



Model 3b

Adult Facial Mild/Moderate

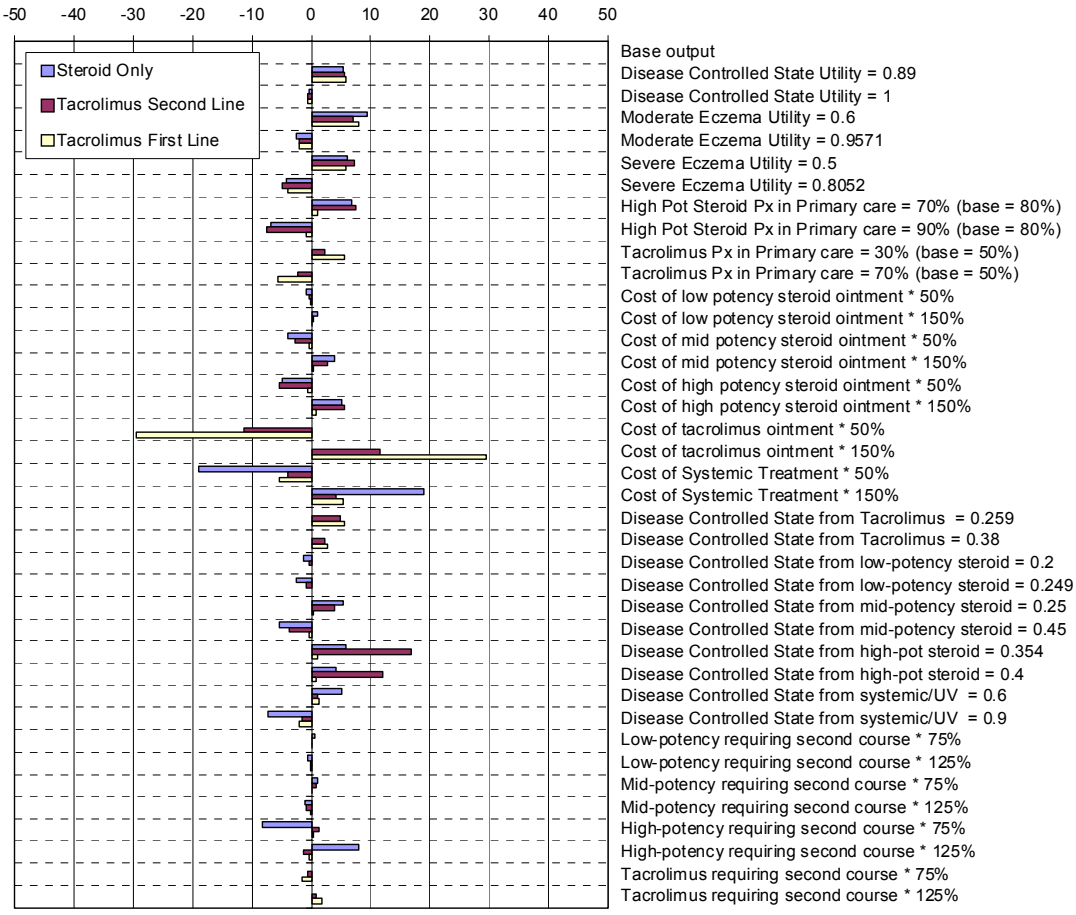
Percentage change in Cost/QALY from Base output



Model 4a

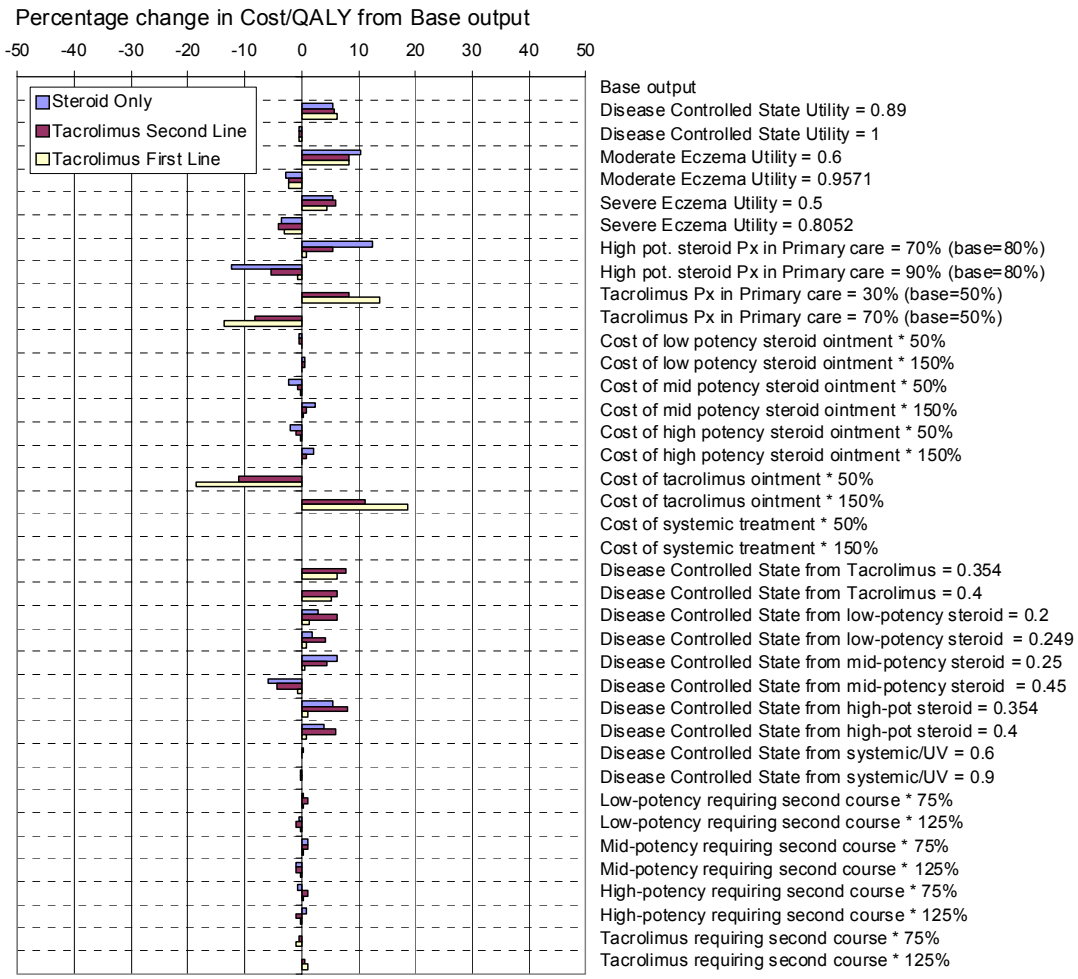
Adult Body Moderate/Severe

Percentage change in Cost/QALY from Base output

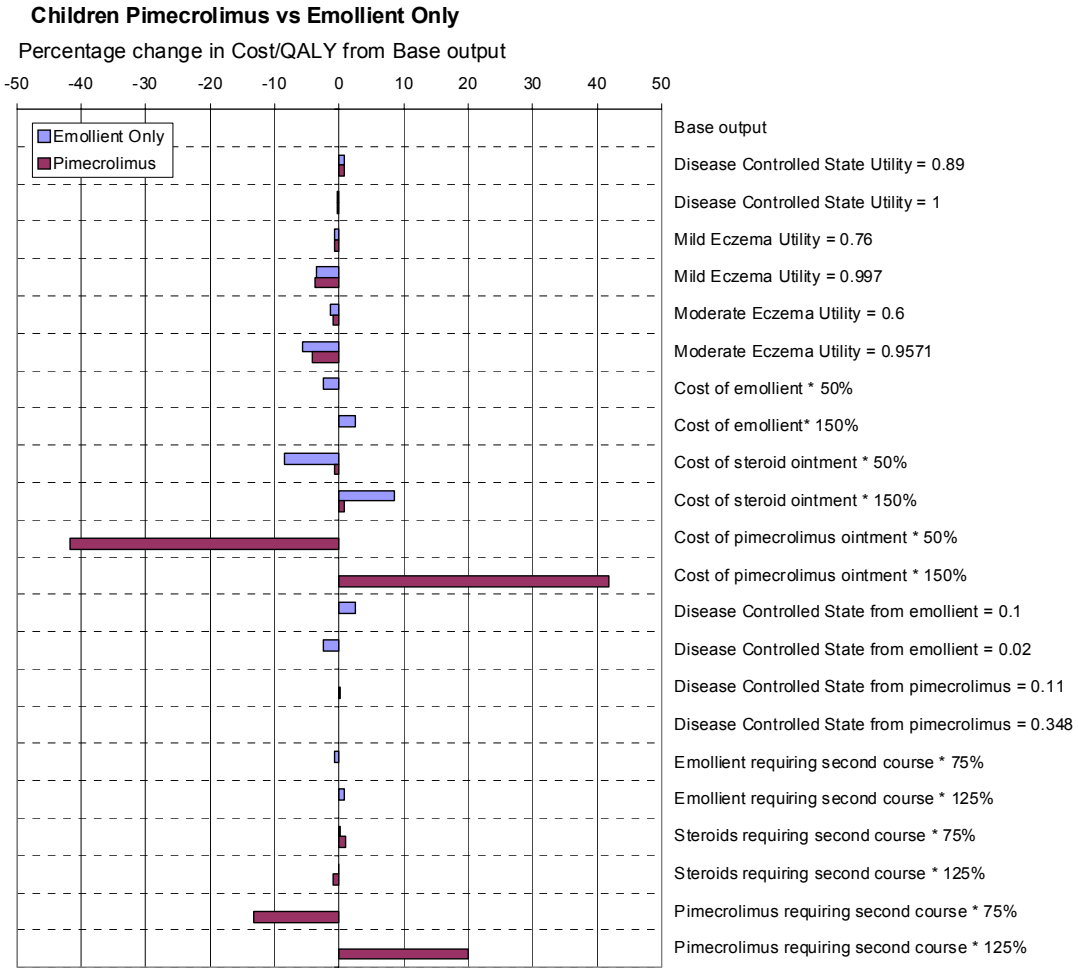


Model 4b

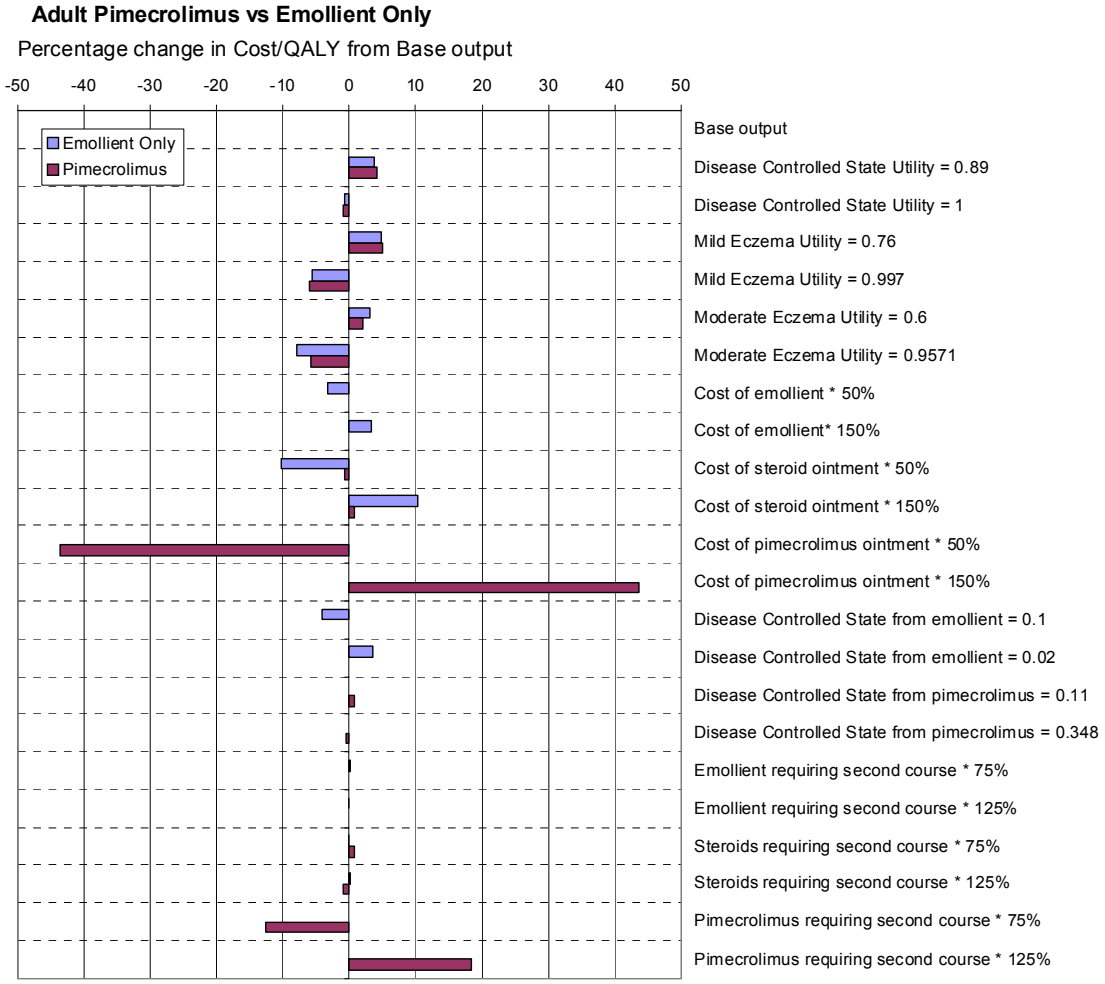
Adult Facial Moderate/Severe



Model 5


Children Pimecrolimus vs Emollient Only
Percentage change in Cost/QALY from Base output
-50
-40
-30
-20
-10
0
10
20
30
40
50
Emollient Only
Pimecrolimus
Base output
Disease Controlled State Utility = 0.89
Disease Controlled State Utility = 1
Mild Eczema Utility = 0.76
Mild Eczema Utility = 0.997
Moderate Eczema Utility = 0.6
Moderate Eczema Utility = 0.9571
Cost of emollient * 50%
Cost of emollient* 150%
Cost of steroid ointment * 50%
Cost of steroid ointment * 150%
Cost of pimecrolimus ointment * 50%
Cost of pimecrolimus ointment * 150%
Disease Controlled State from emollient = 0.1
Disease Controlled State from emollient = 0.02
Disease Controlled State from pimecrolimus = 0.11
Disease Controlled State from pimecrolimus = 0.348
Emollient requiring second course * 75%
Emollient requiring second course * 125%
Steroids requiring second course * 75%
Steroids requiring second course * 125%
Pimecrolimus requiring second course * 75%
Pimecrolimus requiring second course * 125%

Model 6


Adult Pimecrolimus vs Emollient Only
Percentage change in Cost/QALY from Base output
-50
-40
-30
-20
-10
0
10
20
30
40
50
Emollient Only
Pimecrolimus
Base output
Disease Controlled State Utility = 0.89
Disease Controlled State Utility = 1
Mild Eczema Utility = 0.76
Mild Eczema Utility = 0.997
Moderate Eczema Utility = 0.6
Moderate Eczema Utility = 0.9571
Cost of emollient * 50%
Cost of emollient* 150%
Cost of steroid ointment * 50%
Cost of steroid ointment * 150%
Cost of pimecrolimus ointment * 50%
Cost of pimecrolimus ointment * 150%
Disease Controlled State from emollient = 0.1
Disease Controlled State from emollient = 0.02
Disease Controlled State from pimecrolimus = 0.11
Disease Controlled State from pimecrolimus = 0.348
Emollient requiring second course * 75%
Emollient requiring second course * 125%
Steroids requiring second course * 75%
Steroids requiring second course * 125%
Pimecrolimus requiring second course * 75%
Pimecrolimus requiring second course * 125%

9.14 Appendix 14: References

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