NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL (STA)

SPECIFICATION FOR MANUFACTURER/SPONSOR SUBMISSION OF EVIDENCE

Update to reflect the new

Guide to the Methods of Technology Appraisals

Contents

Section A

1 Description of technology under assessment

1.1 Give the brand name, approved name and, where appropriate, therapeutic class.

Toctino®, oral alitretinoin (9-cis retinoic acid)

1.2 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission?

Oral alitretinoin was granted a Marketing Authorisation for the UK on 5th September 2008 following recommendation for approval under the EMEA decentralised procedure and became commercially available on the 22nd September 2008.

1.3 What are the (anticipated) indication(s) in the UK?

Oral alitretinoin (9-cis retinoic acid) is indicated for use in adults who have severe chronic hand eczema that is unresponsive to treatment with potent topical corticosteroids.

1.4 To what extent is the technology currently being used in the NHS for the proposed indication?

Toctino (oral alitretinoin) was launched on 8th September 2008 and became commercially available on the 22nd September 2008.

1.5 Does the technology have regulatory approval outside the UK?

Oral alitretinoin has regulatory approval in Germany, France, Denmark, and Finland.

1.6 Is the technology subject to any other form of health technology assessment in the UK?

A new product assessment form for alitretinoin was submitted to the Scottish Medicines Consortium (SMC) on Monday 22nd September 2008. It is anticipated that the review will follow the timescale outlined below.

Deadline for Company Submission to Secretariat	NDC Meeting Date	NDC Draft Advice to Company	Deadline for Patient Submission to SMC	Deadline for Company Response to SMC	SMC Meeting Date	Advice issued to NHS Scotland	Advice issued to Comparator Company for Comment	Deadline for Comparator Comments	Advice posted on SMC Website
3 Nov 2008	16 Dec	19 Dec	12 Jan	16 Jan	3 Feb	06 Feb	09 Feb	18 Feb	09 Mar 2009

1.7 For pharmaceuticals, what formulation(s) (for example, ampoule, vial, sustained-release tablet, strength(s) and pack size(s) will be available?

Oral alitretinoin is available in 10mg and 30mg soft capsules.

1.8 What is the proposed course of treatment?

The recommended dose range for alitretinoin is 10mg-30mg once daily, with a meal.
The recommended start dose for alitretinoin is 30mg once daily. A dose reduction to 10mg once daily may be considered in patients with unacceptable adverse reactions to the higher dose.

A treatment course of alitretinoin may be given for 12 to 24 weeks depending on response. In the phase III trial, the average time to response was 12.9 weeks in responders (patients achieving clear/almost clear hands) and 15.4 weeks overall. Discontinuation of therapy should be considered for patients who still have severe disease after the initial 12 weeks of treatment. In the event of relapse, patients may benefit from further treatment courses of alitretinoin.

Prescriptions of alitretinoin for women of childbearing potential should be limited to 30 days of treatment per prescription. Continuation of treatment requires a new prescription and pregnancy testing; issuing a prescription and dispensing of alitretinoin should ideally occur on the same day. Dispensing of alitretinoin should occur within a maximum of 7 days of the prescription.

1.9 What is the acquisition cost of the technology (excluding VAT)?

Oral alitretinoin has the same price for both 10mg and 30mg soft capsules with the NHS list price of both being £411.43 per 30 capsule pack (one capsule to be taken daily).

1.10 What is the setting for the use of the technology?

Oral alitretinoin should be used only under the supervision of dermatologists or physicians experienced in the use of systemic retinoid therapy, for adult patients with severe CHE who are unresponsive to potent topical corticosteroids, as an alternative to phototherapy or systemic immunosuppressants.

Although phototherapy and immunosuppressants are used commonly at present, oral alitretinoin will be the first drug treatment licensed for treatment of severe CHE which is unresponsive to topical corticosteroids.

1.11 For patients being treated with this technology, are there any other aspects that need to be taken into account?

Alitretinoin should not be prescribed if the patient's eczema can be adequately controlled by standard measures, including skin protection, avoidance of allergens and irritants, and treatment with potent topical corticosteroids.

Alitretinoin is TERATOGENIC. Alitretinoin is contraindicated in women of childbearing potential unless all of the following conditions of the **Pregnancy Prevention Programme** are met:

- She understands the teratogenic risk
- She understands the need for rigorous follow-up, on a monthly basis
- She understands and accepts the need for effective contraception, without interruption, 1 month before starting treatment, throughout the duration of treatment and 1 month after the end of treatment. At least one and preferably two complementary forms of contraception including a barrier method should be used
- Even if she has amenorrhoea she must follow all of the advice on effective contraception
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy
- She understands the need and accepts to undergo pregnancy testing before, during and 5 weeks after the end of treatment
- She has acknowledged that she has understood the hazards and necessary precautions associated with the use of alitretinoin

These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.
The prescriber must ensure that:

- The patient complies with the conditions for pregnancy prevention as listed above, including confirmation that she has an adequate level of understanding
- The patient has acknowledged the aforementioned conditions
- The patient has used at least one and preferably two methods of effective contraception including a barrier method for at least 1 month prior to starting treatment and is continuing to use effective contraception throughout the treatment period and for at least 1 month after cessation of treatment
- Negative pregnancy test results have been obtained before, during and 5 weeks after the end of treatment. The dates and results of pregnancy tests should be documented

Contraception

Female patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. As a minimum requirement, female patients at potential risk of pregnancy must use at least one effective method of contraception. Preferably the patient should use two complementary forms of contraception including a barrier method. Contraception should be continued for at least 1 month after stopping treatment with alitretinoin, even in patients with amenorrhea.

Pregnancy testing

According to local practice, medically supervised pregnancy tests with a minimum sensitivity of 25mIU/mL are recommended to be performed in the first 3 days of the menstrual cycle, as follows:
One month prior to starting therapy - In order to exclude the possibility of pregnancy prior to starting contraception, it is recommended that an initial medically supervised pregnancy test should be performed and its date and result recorded. In patients without regular menses, the timing of this pregnancy test should reflect the sexual activity of the patient and should be undertaken approximately 3 weeks after the patient last had unprotected sexual intercourse. The prescriber should educate the patient about contraception.
At the start of therapy - A medically supervised pregnancy test should also be performed during the consultation when alitretinoin is prescribed or in the 3 days prior to the visit to the prescriber, and should have been delayed until the patient had been using effective contraception for at least 1 month. This test should ensure the patient is not pregnant when she starts treatment with alitretinoin.
Follow-up visits - Follow-up visits should be arranged at 28 day intervals. The need for repeated medically supervised pregnancy tests every month should be determined in consideration amongst other of the patient's sexual activity and recent menstrual history (abnormal menses, missed periods or amenorrhea). Where indicated, follow-up pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.
End of treatment - Five weeks after stopping treatment, women should undergo a final pregnancy test to exclude pregnancy.

Prescribing and dispensing restrictions

Prescriptions of alitretinoin for women of childbearing potential should be limited to 30 days of treatment and continuation of treatment requires a new prescription. Ideally, pregnancy testing, issuing a prescription and dispensing of alitretinoin should occur on the same day. Dispensing of alitretinoin should be completed within a maximum of 7 days of the prescription.

Lipid Metabolism

Alitretinoin has been associated with an increase in plasma cholesterol and triglyceride levels. Serum cholesterol and triglycerides (fasting values) should be monitored and clinically relevant changes may be managed by changes in diet or standard lipid lowering therapies.

Alitretinoin should be discontinued if hypertriglyceridaemia cannot be controlled at an acceptable level or if symptoms of pancreatitis occur. Triglyceride levels in excess of 800mg/dL (9mmol/L) are sometimes associated with acute pancreatitis, which may be fatal.

2 Statement of the decision problem

	Final scope issued by NICE	**Decision problem addressed in the submission**
Population	Adults with severe chronic hand eczema refractory to potent topical corticosteroids	Adults with severe chronic eczema of the hand that is unresponsive to topical corticosteroids
Intervention	Alitretinoin	Toctino® (alitretinoin) in its licensed indication
Comparator(s)	▪ immunosuppressive therapies ciclosporin and azathioprine ▪ oral and topical PUVA	▪ ciclosporin ▪ oral and topical PUVA ▪ azathioprine
Outcomes	The outcome measures to be considered include: ▪ measures of disease severity ▪ measures of symptom control ▪ disease free period/maintenance of remission ▪ time to relapse/prevention of relapse ▪ adverse effects of treatment ▪ health-related quality of life	A range of outcomes to assess the impact of treatment with alitretinoin on CHE will be considered, including the following: ▪ the primary efficacy measure for therapeutic response – Physicians Global Assessment (PGA) of overall CHE severity ▪ modified total lesion symptom score (mTLSS) ▪ patient's global assessment of improvement (PaGA) ▪ time to response ▪ time to relapse ▪ disease specific quality of life measure (DLQI) ▪ safety and tolerability via analysis of adverse events
Economic Analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	The cost effectiveness of treatment is assessed in terms of incremental cost per quality-adjusted life year with quality adjustments made using a mapping function relating changes in the DLQI disease specific quality of life instrument and the EQ5D. The model considers the use of standard therapies over time of 3 years with sensitivity analysis run over 1, 6,10 and 20 years. Costs are considered from an NHS perspective in the base case economic model analysis.
Subgroups to be considered		▪ Patients with different forms of chronic hand eczema, e.g. hyperkeratotic hand eczema

		▪ Women of child-bearing potential
Special considerations, including issues related to equity or equality		The economic modelling will consider the cost effectiveness of alitretinoin in line with the proposed licensed indication

Section B

3 Executive summary

It is estimated that between 0.5 and 0.7% of the general population suffer from severe chronic hand eczema (CHE), and that approximately 50% of affected patients will be refractory to treatment with topical corticosteroids.[1] These patients suffer from painful cracks and blisters susceptible to secondary infections, itching and bleeding, which can limit manual dexterity and prevent employment. The visibility of disease, need for frequent visits to the doctor and regular application of greasy topical agents, all add to the burden of the disease. Severe CHE carries a debilitating social stigma which is associated with a impaired quality of life, comparable to that seen in patients with generalised eczema and psoriasis.[2] In addition hand eczema has been shown to be a major cause of prolonged sick leave and has been reported to lead to job loss.[3] Patients with CHE have a poor prognosis; it is a self-perpetuating condition with a long-lasting and chronically relapsing course.[4] No licensed treatment options are available for these patients. The unlicensed options used in clinical practice include immunosuppressants, such as ciclosporin and azathioprine, and phototherapy, although there are either limited or no data to support their use in the treatment of severe CHE.

Oral alitretinoin (9-cis-retinoic acid, Toctino®), an endogenous retinoid, is indicated for use in adults who have severe chronic hand eczema that is unresponsive to treatment with potent topical corticosteroids. Retinoids are derivatives of vitamin A that display key regulatory functions in epidermal growth and differentiation. The exact mechanism of action of alitretinoin in the treatment of CHE is unknown. Alitretinoin has been described as a panagonist of retinoid receptors because it binds to retinoic acid receptors and the retinoid X receptor. Binding to and activation of the various retinoid receptors might be responsible for certain biological effects of alitretinoin. However, no definite link has been demonstrated between patterns of receptor binding and therapeutic activity in CHE. Alitretinoin was launched on 8th September 2008 in the UK and became commercially available on the 22nd September 2008. Oral alitretinoin is available in 10mg and 30mg soft capsules with the NHS list price of both being £411.43 per 30 capsule pack.

The recommended dose range for alitretinoin is 10mg-30mg once daily. A treatment course of alitretinoin should be started at the higher dose of 30mg and may be given for 12 to 24 weeks depending on response.In the phase III trial the average time to response was 12.9 weeks. Discontinuation of therapy should be considered for patients who still have severe disease after the initial 12 weeks of treatment.

In contrast to the mostly anecdotal evidence for current unlicensed treatments, the clinical trial programme for alitretinoin provides robust evidence which demonstrates both efficacy in the treatment of severe CHE unresponsive to topical steroids and suitability as a long-term intermittent treatment. Evidence for the efficacy of alitretinoin comes primarily from a phase III randomised placebo-controlled double-blinded trial BAP00089 and an extension study BAP00091.[5, 6]

- Following daily treatment with 30mg alitretinoin in BAP00089, 47.7% of patients with severe CHE achieved the primary endpoint of clear or almost clear hands by week 24

compared to 16.6% in the placebo arm, as assessed by the physician's global assessment (PGA).

- Patients who responded to alitretinoin treatment demonstrated a low relapse rate; during the 24 week follow up period during which no active treatment was permitted, 65% of responders did not relapse.
- Patients who did relapse demonstrated a high response rate when retreated with alitretinoin: 79.6% of severe CHE patients achieved clear or almost clear hands by week 24 compared to 8.3% in the placebo arm, as assessed by the PGA.
- Alitretinoin significantly reduced the signs and symptoms of the disease, as measured by the modified Total Lesion Symptom Score (mTLSS), as well as the extent of the disease
- Alitretinoin also significantly reduced the severity of disease as assessed by patients using the patient global assessment (PaGA).

From the phase III studies alitretinoin was found to be well tolerated with a predictable side effect profile consistent with other retinoids including headache, mucocutaneous effects such as dry lips and dry mouth. Headache was the most common adverse event and clearly showed a dose dependent effect. Alitretinoin is teratogenic and is contraindicated in women of childbearing potential unless all of the conditions of a pregnancy prevention programme are met. These conditions include monthly pregnancy testing and the use of two methods of contraception throughout and for one month following treatment.

There are no head to head clinical trials of alitretinoin versus the comparators stated in the decision problem; azathioprine, ciclosporin and PUVA. The efficacy of alitretinoin was investigated in placebo-controlled trials due to the absence of any clear rationale for inclusion of potential alternative interventions as comparators. No other treatments are licensed for severe CHE and there is no reliable evidence from trials to demonstrate efficacy in the treatment of patients with severe CHE.

An indirect comparison with the comparators was not possible because no trials were identified in which azathioprine was used in the treatment of CHE and in the controlled studies identified for PUVA and ciclosporin there was no placebo control to link trials of alitretinoin, PUVA and ciclosporin.

[redacted] It is therefore expected that the use of alitretinoin in patients would improve patient quality of life by lessening the severity of their disease. In addition to amelioration of the distressing symptoms and signs of CHE, from the wider perspective, clearing of CHE may entail return of hand function sufficient to allow return to work (in itself associated with improved quality of life)[8] and bring wider economic benefits to society.

Cost effectiveness

Due to the absence of alternative drugs licensed for severe CHE all comparative trials of alitretinoin were placebo controlled, therefore no active comparator data are available. An indirect comparison could not be carried out since there are no comparator studies available that include a placebo arm.

A discrete event simulation (DES) cost-utility model was constructed to assess the clinical and economic outcomes relevant to patients treated with alitretinoin or the comparators. The decision criteria used to assess cost-effectiveness is societal willingness to pay for quality-adjusted life years (QALY).

The model was designed so that all patients enter the model in the severe state of CHE, in line with the licensed indication for alitretinoin and are are assumed to continue treatment (whilst having breaks in treatment between treatment cycles) until one of the following conditions are met; they reach the remission state, are unresponsive to treatment (i.e. have entered refractory group), have withdrawn from treatment following an adverse event or the

time horizon of the model has expired. Only those patients that enter remission are re-treated in subsequent treatment cycles.

The base-case analysis was run over 3 years as this is the time period over which the health outcomes and costs of patients are likely to differ between the treatment and comparator arms. Since the treatments are not curative and are used to manage the symptoms of CHE, a lifetime model was considered. A lifetime model would however imply that currently available treatments could be used repeatedly over an indefinite period and this is not the case. In the case of the comparators, ciclosporin in particular, there are recommendations on the number of treatment cycles that patients can receive on the grounds of safety.[9] The effect of adhering to these recommendations would be that after the maximum number of treatment cycles has been reached, only the effects of the supportive treatments (such as emollients) could be modelled. Comparable recommended limits do not exist for azathioprine and topical PUVA, however lifetime use of either approach is not generally considered safe by dermatologists because of potential to increase the rate of malignancy, particularly of the skin. Furthermore, indefinite treatment with courses of azathioprine or PUVA is unlikley to be acceptable to patients because of its requirement for frequent monitoring and hospital attendance.

In the base case analysis it was found that alitretinoin was cost-effective compared to all the comparators with ICERS for PUVA, ciclosporin and azathioprine of -£468.98, £8,614.43 and £10,611.80 respectively. Sensitivity analysis showed that cost-effectiveness of alitretinoin was maintained out to 20 years.

A key uncertainty around the calculation of the cost-effectiveness of alitretinoin is the quality of the data available for the comparators. Because of the lack of robust trial data in the population specified in the decision problem. the model is based on clinician opinion of efficacy of comparator treatments. It was decided therefore to run a threshold analysis for all three comparators against alitretinoin. It was found that alitretinoin remained cost effective even when its efficacy was reduced by 30%. It also remained cost effective if the efficacy of the comparators was increased by 50%.

Oral alitretinoin should be used only under the supervision of dermatologists or physicians experienced in the use of systemic retinoid therapy, for adult patients with severe CHE who are unresponsive to potent topical corticosteroids, as an alternative to phototherapy or systemic immunosuppressants (see treatment pathway, page 12). It is anticipated that there will be in the region of 127,321 patients in England and Wales who will have severe CHE unresponsive to topical steroids. Clinical opinion suggests that only 25% of these patients will go on to be treated with second line agents, which means that around 31,830 patients may be eligible for treatment with alitretinoin. Gradual replacement of comparator therapies with alitretinoin over a period of 5 years could result in savings to the NHS of £24 million.

Alitretinoin should be recommended for use in England and Wales as a treatment option for severe CHE unresponsive to topical steroids, due to its proven efficacy in both short-term and long-term intermittent treatment, convenient dosing regimen and likely long term safety. It is the only treatment currently licensed for this indication with robust data to support its use. Alitretinoin is the only currently available treatment option with the potential to alleviate the long term suffering of patients with severe CHE and is shown be cost-effective when compared to currently available treatments.

4 Context

4.1 Please provide a brief overview of the disease/condition for which the technology is being used.

The most common dermatosis affecting the hands is eczema which is a major cause of morbidity and lost earnings.[1, 3] Mild forms of hand eczema can be managed by both preventative measures, including emollients, and application of topical corticosteroids, however a small proportion of patients with hand eczema develop a severe chronic form which does not respond to topical steroids and is difficult to treat.

The exact prevalence of hand eczema in the general population is unknown but is estimated to be around 10%.[1, 10] Consequently it is difficult to determine a precise figure for the prevalence of severe CHE. Estimates suggest that approximately 5-7% of all hand eczema patients suffer from severe CHE, of which 50% will be unresponsive to topical treatments.[1] The prevalence of hand eczema is associated with occupation, jobs involving 'wet work' such as nursing, catering, building and hairdressing having the highest prevalence.[11] Incidence is also poorly observed but has been documented as 5.5 cases per 1000 people per year.[12]

Severe chronic hand eczema (CHE) is diagnosed where hands show marked signs of dermatitis, oedema, fissures, or functional impairment. It is a distressing and debilitating disease which has limited treatment options. Patients with severe CHE suffer from painful cracks, blisters, itching and bleeding, which can limit manual dexterity and prevent employment.[1] Severe CHE typically has a long-lasting and chronically relapsing course, with an estimated mean duration of 11.6 years.[4, 13]

The causes of CHE are often multi-factorial, with irritant, allergic and endogenous factors acting in concert.[1] Evidence suggests that this is often the reason for the chronic nature of the condition and the poor response to treatment.[1] The original aetiology of the disease may no longer contribute either to the clinical features or the activity of long standing CHE and therefore it is often extremely difficult to identify and remove potential causative factors.

Severe CHE carries a debilitating social stigma which may result in major psychosocial problems and this condition has been shown to impact on quality of life (QoL). Severity of hand eczema has been shown to be associated with impaired QoL as measured by the Dermatology Life Quality Index (DLQI).[2, 14] Patients with severe hand eczema had scores comparable to those seen in patients with atopic eczema or psoriasis.[2, 14] Additionally, in a Swedish study of 1238 patients by Meding et al (1990), 80% of patients with hand eczema experienced disturbance to their social or emotional lives, considered to be caused by their hand eczema.[15] The visibility of disease, location on the hands, need for frequent visits to the doctor and regular application of greasy topical agents, all add to the burden of the disease.

The interconnected physical, emotional and economic consequences of severe CHE should be considered when planning healthcare resources. Hand eczema has been shown to be a major cause of prolonged sick-leave and job loss: 20% of patients reported taking sick-leave and 23% reported they had lost their job at least once in a 12 month period due to their hand eczema.[3, 15] Severity of hand eczema was associated with prolonged sick leave.[3] Fowler et al. (2006) demonstrated that quality of life, along with work productivity and activity impairment, were significantly worse for patients with chronic hand eczema compared to those without hand eczema.[16]

Management of any degree of hand eczema includes avoidance of allergens and irritants, skin protection measures and use of topical corticosteroids where necessary. Patients with chronic disease may require treatment with the most potent steroid preparations available because drug penetration is impaired by significant hyperkeratosis of the hands. Once severe CHE becomes unresponsive to corticosteroids, treatment options are limited.

The following agents are known to be used in the management of severe CHE. These treatments are not licensed for this indication and data to support their use are limited or non-existent:

- Topical immunomodulators (TIMS), including pimecrolimus and tacrolimus, are sometimes used in the treatment of CHE, but their efficacy is limited.[17, 18]

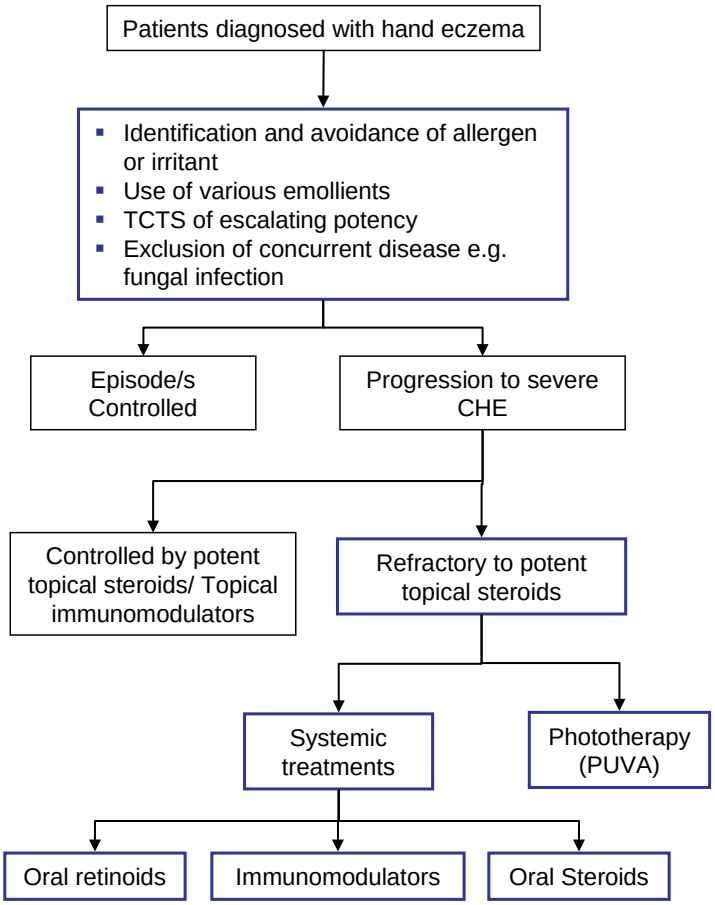
- Phototherapy, mainly topical psoralens in combination with UVA (PUVA), is used to treat many skin conditions including CHE.[1] Significant hyperkeratosis in the hands reduces the penetration of UV treatment and renders it less effective in CHE than in other dermatoses. In some areas of the UK PUVA is a limited resource and therefore not available to all patients with CHE.

- Oral immunosuppressants used most commonly to control severe CHE are ciclosporin and azathioprine. Both of these treatments require intensive monitoring due to their potential for toxicity and ciclosporin is not appropriate for long-term use. In addition, oral prednisolone may be used for short periods.[18]

- The oral retinoid acitretin is occasionally used to reduce the hyperkeratosis of CHE prior to PUVA or in combination with PUVA. Clinical use is limited by lack of efficacy in reducing the inflammatory features of CHE,[19] mucocutaneous side effects and the requirement in women of childbearing potential for a minimum of 2 years pregnancy prevention after therapy due to an extremely long elimination half life.[20]

Alitretinoin is currently the only treatment licensed for use in severe steroid unresponsive CHE. Figure 4.2 demonstrates the current treatment pathway for patients with CHE.

Figure 4.2: Treatment pathway for CHE



Immunomodulators: Ciclosporin, Azathioprine, Methotrexate, Mycophenolate
Oral Retinoids: Acitretin
Oral Steroids: Prednisolone

4.2 What was the rationale for the development of the new technology?

Despite the medical and social burden of severe CHE, management options are limited. Unlicensed systemic therapies and phototherapy are used in the treatment of severe CHE unresponsive to topical corticosteroids although there is a lack of well-controlled trials with validated outcomes to support their use.[21] The lack of consensus amongst dermatologists as to the standard or preferred treatment option for refractory CHE suggests that no treatment has demonstrated any particular benefit in clinical practice relative to its associated risks.

Retinoids have been used in severe dermatological conditions since the early 1980s and have potent immunomodulatory and anti-inflammatory effects. Unlike other oral retinoids, alitretinoin has been shown to have a minimal effect on sebum secretion, which correlates with a reported lack of efficacy in acne treatment[22, 23] and is the probable basis for a low incidence of mucocutaneous side effects during alitretinoin treatment. These observations supported its evaluation in eczematous disease, which might be expected to be worsened by the drying effects of conventional retinoids. Following positive results in an exploratory study,[24] alitretinoin was developed for the treatment of severe CHE that is unresponsive to topical corticosteroids.

4.3 What is the principal mechanism of action of the technology?

Alitretinoin (9-cis-retinoic acid) is a physiological, endogenous retinoid. Retinoids are derivatives of vitamin A that display key regulatory functions in epidermal growth and

differentiation. The exact mechanism of action of alitretinoin in the treatment of severe CHE is unknown. Alitretinoin has been described as a panagonist of retinoid receptors because it binds to both retinoic acid receptors and the retinoid X receptor. Binding to and activation of the various retinoid receptors may be responsible for certain biological effects of alitretinoin, but no definite link has been demonstrated between patterns of receptor binding and therapeutic activity in severe CHE.

Recent small animal studies suggest that immunomodulatory and anti-inflammatory effects of alitretinoin may be achieved by down regulation of cytokines chemotactic for leucocytes, suppression of co-stimulatory molecule expression on antigen presenting cells and suppression of the very early activation antigen CD69 on activated T, B and dendritic cells leading to reduced leukocyte activation.[25]

4.4 What is the suggested place for this technology with respect to treatments currently available for managing the disease/condition?

Oral alitretinoin is the first drug licensed for treatment of severe CHE which is unresponsive to topical corticosteroids and should be used as an alternative to phototherapy or systemic immunosuppression. Alitretinoin should only be used under the supervision of dermatologists or physicians experienced in the use of systemic retinoid therapy.

4.5 Describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

Most patients with severe CHE are treated with highly potent topical corticosteroids. It is well documented however that overuse and long-term use can result in cutaneous atrophy and potential systemic absorption.[26]

There are no licensed treatment options currently available for severe CHE that becomes unresponsive to topical corticosteroids. The evidence base for alternative treatment options is insufficient to guide clinical practice, with a lack of well designed, well controlled randomised trials.[21] As a consequence considerable variation in prescribing preferences among physicians and patients is noted.[21]

Topical immunomodulators (TIMS) may provide benefit in some patients and there is some evidence to suggest efficacy in mild-moderate CHE.[27] However clinician experience suggests that efficacy in severe CHE is very low.[18] As TIMS are associated with a risk of cancer, it has been proposed that they should be used with caution and only when other treatment options have failed.[26] Beyond potent topical corticosteroids and TIMS, the choice of treatment approach is influenced by many factors, including the morphology of CHE present (inflammatory versus hyperkeratotic appearance), the perceived risks of organ toxicity or malignancy resulting from treatment and practical aspects such as the availability of facilities (e.g. for PUVA), clinician familiarity and training and the ability of patients to comply with treatment that may require frequent visits to hospital for monitoring and treatment.

Topical PUVA is commonly used to treat patients with CHE refractory to topical corticosteroids. Although generalised PUVA is acknowledged to be unsuitable as a long term treatment option due to the risk of skin cancer[28] the risks of localised PUVA are poorly studied and consensus regarding cumulative dose limits does not exist. Currently topical PUVA is considered a relatively benign option compared to systemic immunosuppression and is therefore more likely to be used intermittently in the long term management of severe CHE patients that have proven refractory to other therapies.[18] PUVA treatment may also be somewhat inconvenient for patients, requiring frequent travel to one of the centres that performs PUVA treatment. A typical course of PUVA treatment for severe CHE requires 30 outpatient visits, with on average of two sessions per week.[17, 18]

Data to support the use of systemic immunosuppressants are very limited. Despite this ciclosporin and azathioprine are both used in practice for the treatment of severe CHE. The main concern associated with these treatments is their pronounced toxicity. Ciclosporin is both carcinogenic and nephrotoxic; its use requires careful monitoring of renal function, liver

function, and blood pressure. This limits its use in skin conditions and on any long-term basis.[29]

Azathioprine may cause a number of side-effects including myelosuppression, hepatotoxicity, greater occurrence and severity of infection and possible development of skin cancer.[29] Although there is evidence for the use of azathioprine in certain dermatological conditions, particularly autoimmune dermatoses, and evidence of modest benefit over placebo in atopic dermatitis[30, 31] there is no evidence for use in CHE. This makes it difficult to counsel patients on the potential benefits so that they might make an informed decision on their treatment.[32]

4.6 Provide details of any relevant guidelines or protocols.

There are currently no specific national guidelines for the treatment of hand eczema. Guidelines relating to the treatment of eczema or dermatitis are listed below but no clear guidance is available for the treatment of patients unresponsive to topical steroids. Although not licensed for the treatment of severe CHE, guidelines for PUVA, topical immunomodulators and azathioprine have been included.

- Guidelines for the management of atopic eczema, 2005. Primary Care Dermatology Society and British Association of Dermatologists[33]

  This broad guideline on the management of atopic eczema includes criteria for diagnosis, recommendations for referral to secondary care and principles of primary care management. It outlines the use of emollients, topical steroids and topical immunomodulators.

  The guideline states that "Third line/secondary care treatments include phototherapy and various immunosuppressive agents". However there is no further information to guide their use in atopic eczema.
- Dermatology - Hand and Foot Eczema Patient Pathway. April 2005[34]
- Guidelines for care of contact dermatitis, 2001 (on behalf of the British Association of Dermatologists). British Journal of Dermatology[35]

  These guidelines support the use of PUVA, azathioprine and ciclosporin in treatment of steroid resistant chronic hand dermatitis.
- Guidelines for topical PUVA: a report of a workshop of the British Photodermatology Group, 2000. British Journal of Dermatology[28]

  These guidelines state that topical PUVA appears to be of value in the treatment of chronic hand and foot dermatoses, although randomised comparative studies demonstrating efficacy of PUVA are scarce.
- Frequency of application of topical corticosteroids for atopic eczema, 2004. NICE Technology Appraisal Number 81[36]
- Tacrolimus and pimecrolimus for atopic eczema, 2004. NICE Technology appraisal Number 82[37]
- Pimecrolimus cream (Elidel) SMC summary of recommendations Number 35/03. November 2003/August 2004[38]
- Tacrolimus ointment (Protopic). SMC summary of recommendations Number 12/12. October 2002[39]
- Guidelines for prescribing azathioprine in dermatology (British Journal of Dermatology 2004, on behalf of the British Association of Dermatologists)[32]

5 Equity and equality

5.1 Identification of equity and equalities issues

There are no equity or equality issues related to this submission.

6 Clinical evidence

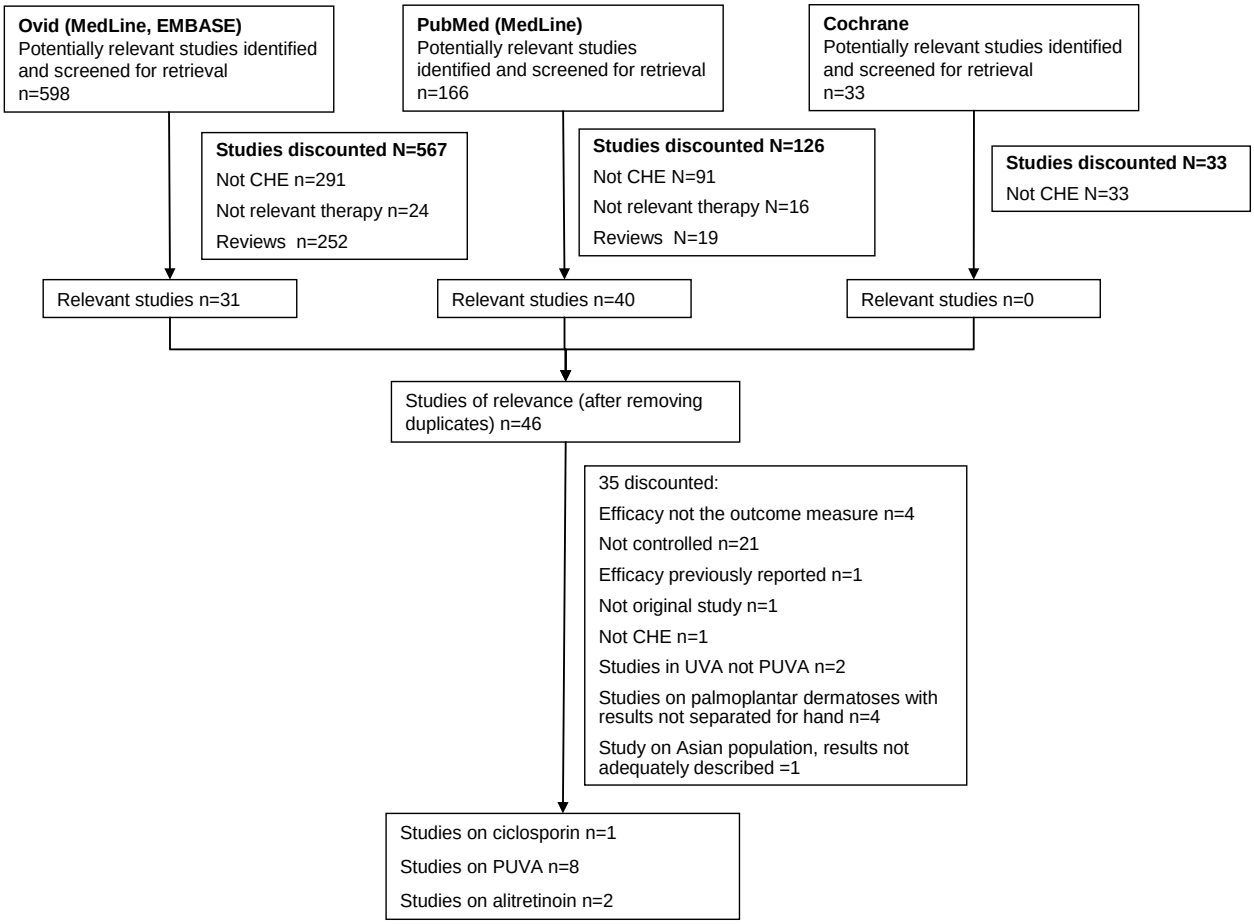
6.1 Identification of studies

Systematic literature searches were conducted to identify trials of alitretinoin for the treatment of CHE. Once the trials had been identified, randomised controlled trials of alitretinoin for the treatment of CHE were retrieved manually.

A number of databases were searched, with relevant search terms combined to form search strings. The search methodology was adapted from the Cochrane Collaboration: Interventions for hand eczema (protocol).[40] The titles and abstracts (if available) of all papers revealed at this stage were then reviewed and eliminated manually if they were not relevant to the decision problem. Appendix 2, Section 10.2, details the search strategies and subsequent results from the database sites searched.

The most recent search was carried out on 22nd of October 2008.

Figure 6.1.1 Overview of the literature search for studies using alitretinoin, ciclosporin, PUVA or azathioprine to treat CHE.



6.2 Study selection

6.2.1 Complete list of RCTs

Placebo Controlled Randomised Studies for Alitretinoin:

BAP00003[41]
Phase II placebo-controlled trial which investigated alitretinoin for the treatment of patients with moderate to severe CHE unresponsive to topical steroids. The phase II study was a dose finding trial in moderate or severe CHE over a 12 week treatment period, and provided the rationale for the subsequent 12-24 week dosing regimen and the dose of 30mg selected for phase III trials.

BAP00089[6] (BACH, Benefit of Alitretinoin in Chronic Hand dermatitis)
Phase III placebo-controlled clinical trial which investigated alitretinoin for the treatment of patients with severe CHE unresponsive to topical steroids.

BAP00091[5, 42]
Phase III extension study which investigated alitretinoin treatment of two cohorts of patients from the BAP00089 study:

- Cohort A: Patients who had responded to alitretinoin (that is achieved clear or almost clear hands) but had relapsed within the 24 week follow-up period
- Cohort B: Patients who were not classed as responders in the BAP00089 study. The severity of CHE at entry to this cohort was mild or moderate in the majority of cases.

A summary of RCTs that compare alitretinoin to placebo are shown in Table 6.2.1 below. There are no head-head trials that compare alitretinoin with other therapies.

Table 6.2.1 Summary of RCTs for alitretinoin

Study ID Number of Centres, Locations, Duration, Total Enrolment	**Design, control, type**	**Study & control drugs, dose, route & regimen**	**Study objec-tive**	**Number of subjects by treatment arm entered**	**Diagnosis, inclusion criteria**	**Primary endpoints**
BAP00003[41, 42] (phase II) 43 centres in 10 European countries 12 weeks N=319	Prospective, randomised, double-blind, placebo controlled trial	10mg, 20mg or 40mg oral alitretinoin or placebo once daily for 12 weeks	Efficacy , safety, time to relapse	Placebo N=78, 10mg alitretinoin N=80 20mg alitretinoin N=80 40mg alitretinoin N=81	CHE, moderate to severe, refractory to topical therapy	PGA* of clear or almost clear at week 12
BAP00089[6] (BACH, Phase III) 111 centres in Europe and Canada 48 weeks N=1032	Double-blind, randomised, placebo controlled, parallel-group, multicentre trial	Placebo, 10 mg or 30 mg oral alitretinoin once daily for 12 or 24 weeks	Efficacy , safety, time to relapse	Placebo N=205, 10mg alitretinoin N= 418 and 30mg alitretinoin N=409	Severe CHE refractory to topical therapy. Duration of disease from diagnosis at least 6 months.	PGA* of clear or almost clear at week 12 or 24
BAP00091[5, 42] (Re-treatment study, Phase III extension) 81 centres in Europe and Canada 24 weeks N=360	The study included two patient cohorts: Patients in Cohort A were included in a double-blind, randomised, placebo-controlled, multicentre study design. Patients in Cohort B were included in an open-label,	Cohort A: Placebo, 10 mg or 30 mg oral alitretinoin once daily for 12 or 24 weeks Cohort B: 30 mg oral alitreti-noin once daily for 12 or 24 weeks	Efficacy , safety	Cohort A: Placebo N=47, 10mg alitretinoin N= 21 and 30mg alitretinoin N=49 Cohort B: 30mg alitretinoin N=243	Patients with CHE who participated in study BAP00089 and were either: Responders relapsing within 24 weeks after the end of treatment, (**Cohort A**) or Non-responders, rated mild,	PGA* of clear or almost clear at week 12 or 24

	multicentre study design				moderate or severe after 24 weeks of treatment (**Cohort B**).	
*PGA – Physicians Global Assessment (explained in detail in section 6.3.4)						

6.2.2 Inclusion and exclusion criteria

The inclusion and exclusion criteria to identify the list of relevant RCTs did not differ from the criteria applied to the search strategy used to identify the complete list of RCTs in Section 6.2.1. There are limited published data on alitretinoin for the treatment of CHE and therefore the relevant RCTs were extracted with relative ease. Appendix 2, Section 10.2 details the search strategies and subsequent hits from the databases searched.

Inclusion criteria:

All randomised controlled trials (RCTs) comparing alitretinoin to an alternative treatment (including placebo) when used for the treatment of CHE.

Exclusion criteria:

Reviews, uncontrolled studies.

6.2.3 List of relevant RCTs

There are no RCTs which directly compare alitretinoin with PUVA, ciclosporin or azathioprine in the treatment of severe CHE.

6.2.4 List of relevant non-randomised controlled trials

BAP00626

An open label study to assess the safety and efficacy of alitretinoin in patients with severe CHE unresponsive to topical steroids. This study provides additional information on the efficacy and safety of alitretinoin. In addition, this study supports the role of reduction from initial dose of 30mg to 10mg for the management of toxicity which was not permitted in the RCTs.

BAP00200[43, 44]

A randomised, double-blinded, multi-dose single-centre study to investigate the pharmacokinetics, efficacy and safety of alitretinoin in patients with severe CHE unresponsive to topical steroids. Although this study was randomised, it was not placebo controlled and therefore was not included in section 6.2.1.

6.2.5 Ongoing studies

BAP00731[45]

This open-label multi-centre study is to investigate the safety and efficacy of alitretinoin in the treatment of relapsed CHE, unresponsive to topical steroids.

The primary objective of this study is to assess the safety of alitretinoin.

The secondary objective is to:

- Determine the efficacy of alitretinoin in patients with relapsed refractory CHE who responded to previous treatment in clinical trials involving alitretinoin, based on:

- Proportion of patients with response (PGA rating of clear or almost clear);
- Proportion of patients with at least partial response (PGA rating of clear, almost clear or mild);
- Patient's Global Assessment (PaGA)

A total of 150 patients will be enrolled at approximately 28 centres in Europe and Canada.

Table 6.2.2: Inclusion and Exclusion criteria for BAP00731

Inclusion criteria
▪ Male patients, or female patients if post-menopausal or hysterectomised, or if premenopausal and willing to use two methods of contraception under supervision of the investigator or a gynaecologist. ▪ Aged 18 to 80 years ▪ Previous participation in the therapeutic trials BAP00089 or BAP00200, involving oral alitretinoin for CHE. ▪ Relapse with development of CHE, defined as 75% of the mTLSS of baseline of the initial study, despite ongoing treatment with topical therapy including topical steroids, or insufficient treatment response. ▪ Written informed consent provided.
Exclusion criteria
▪ Patients unable to comply with the requirements of the study ▪ Female patients who are pregnant or who plan to become pregnant or who are breast feeding ▪ Female patients of childbearing potential who cannot use or will not commit to using two effective forms of contraception simultaneously under supervision of the investigator or a gynaecologist ▪ Patients whose disease is adequately controlled by standard non-medicated therapy (skin moisturisation and protection, avoidance of irritants and allergens) and standard topical corticosteroid therapy ▪ Patients who have participated in study BAP00091 ▪ Patients with known hypersensitivity to other retinoids or vitamin A derivatives, or to any study medication component, especially soybean oil and partly hydrogenated soybean oils ▪ Patients with known clinically relevant allergic contact dermatitis of the hands, as demonstrated by a prior positive patch test, who have not made a reasonable effort to avoid relevant contact allergens ▪ Patients presenting with a) psoriasis lesions (including palmo-plantar psoriasis, b) atopic dermatitis lesions requiring medicated treatment, c) acute (non-chronic) episodes of pompholyx/ dyshydrosis or of contact dermatitis d) active bacterial, fungal or viral infections of the hands ▪ Patients with any serious medical condition which, in the opinion of the investigator, may interfere with the safety or the evaluation of the study, including chronic heart failure, recent myocardial infarction (chest pain within the last 3 months with changes in ECG and/or increased cardiac enzymes), chronic renal failure, chronic liver failure, unstable hypothyroidism, chronic biliary disease, uncontrolled diabetes mellitus ▪ Patients with Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >2.5x upper limit of normal (ULN)

- Patients with fasting triglyceridemia > 1.5x ULN
- Patients with cholesterol >1.5 x ULN and/or LDL/cholesterol > 1.5 x ULN
- Patients with haemoglobin <0.9 lower limit of normal (LLN)
- Patients receiving drugs with a potential for drug-drug interaction such as systemic retinoids >2000IU vitamin A, tetracyclines, ketoconazole, erythromycin or clarithromycin, simvastatin, or St. John's Wort within 1 week, or receiving systemic itraconazole within 2 weeks, before start of trial treatment
- Patients included in the study of an investigational drug other than alitretinoin within 2 months before start of trial treatment or during the study
- Patients with an active major psychiatric disorder (e.g. Major Depressive Disorder, Generalized Anxiety Disorder, Bipolar Disorder (I or II) , or schizophrenia).

6.3 Summary of methodology of relevant RCTs

6.3.1 Methods

Table 6.3.1 Summary of study design for alitretinoin RCTs

Study	Recruitment/ Trial	Intervention/Duration	Study Type/ Design	Randomisation Method	Blinding Method
BAP00003	First patient enrolled December 2001, Last patient to complete trial May 2002	Intervention: Eligible patients were randomised to treatment with placebo or with alitretinoin at 10mg, 20mg or 40mg. Treatment was given orally for 12 weeks and no dose reduction was allowed. The patients that completed treatment up to week 12 were then assessed according to the PGA. Those given "clear" or "almost clear" response were regarded as responders. These responding patients were eligible for a follow-up assessment at week 24. Two capsules of study drug were administered orally after breakfast, in the morning on a daily basis. No study drug was administered in the follow-up period. Eligible patients were randomised to receive either placebo, 10mg, 20mg or 40mg alitretinoin once daily for 12 weeks. Patients who responded to treatment with complete or almost complete clearing of disease were followed for an additional 12 weeks to assess relapse. Patients who withdrew from the trial were evaluated for efficacy parameters at the time of their scheduled 12 week assessment (in addition to evaluation at the time of withdrawal), in order to determine if alternative treatments given after withdrawal were effective. Patients who completed treatment (week 12 assessment) and who responded (given "clear" or "almost clear" according to the PGA) were asked to attend a follow-up clinic at week 24. From week 12-24 patients received no study treatment but were permitted to use anti-eczema therapy as indicated. Duration: Eligible patients were randomised to trial treatment which started within 14 days of the screening visit. Trial treatment was given once daily for 12 weeks and all patients attended a follow-up at week 12. Safety laboratory tests (haematology, blood chemistry and urinalysis) and assessments of AE's were performed at weeks 2, 4, 8 and 12. Laboratory tests for thyroid function were performed before and at the end of therapy. The secondary efficacy parameter Total Lesion Signs and Symptoms (TLSS) was performed at weeks 2, 4, 8 and 12. The primary efficacy parameter Physician Global Assessment (PGA) was evaluated before and at the end of therapy.	Phase II, randomised, double blind, parallel group, placebo controlled, multiple fixed dose, multicentre study that took place in 43 centres in 10 European countries. Primary objectives: to assess the overall safety of alitretinoin at a daily dose of 10mg QD, 20mg QD or 40mg QD in patients with chronic hand eczema. To demonstrate that at least one daily dose of 10mg QD, 20mg QD or 40mg QD of alitretinoin is more efficacious than placebo in the treatment of chronic hand dermatitis. Secondary objectives included: selection of appropriate methodology for evaluation of chronic hand eczema and its potential impact on quality of life and to assess the relapse rate within 12 weeks of completing treatment in patients showing "clear" or "almost clear" results according to the physician global assessment.	Patients were randomised by centre, in blocs of 4 without stratification. The randomisation code was prepared for each centre by AAI (Reinach, Switzerland) and incorporated into double blind coded drug packaging. After completion of screening eligible patients were assigned coded patient numbers, sequentially in the order in which they were enrolled, and the patient number was recorded in the CRF. Coded drug packages corresponding to the assigned patient numbers were then provided to patients at the start of treatment.	Placebo and active drug tablets were identical in size, colour, shape, texture and taste. Capsules and packaging did not reveal the identity of the test drug, and no open randomisation list was available at the study centre, to trial moderators or other study personnel. Coded sealed envelopes were available to the investigator, for use in cases of emergency where knowledge of the test drug was important for patient management. Each envelope contained the identity of test treatment for one patient. The investigator was required to give the reasons why an envelope was opened. At the end of the study, all envelopes were returned to Basilea unopened.

Study	Recruitment/ Trial	Intervention/Duration	Study Type/ Design	Randomisation Method	Blinding Method
BAP00089	First patient enrolled October 27th 2004. Last patient to complete treatment, October 13th 2006. Last patient to complete final visit 30th March 2007.	Intervention: Eligible patients were randomised to treatment with placebo or with alitretinoin at 10mg or 30mg doses once daily. Efficacy and safety were evaluated every 4 weeks and treatment duration was 12 or 24 weeks, depending on response after 12 weeks. Patients completing the 12 week study were allowed to enter a follow-up study (BAP00091) for continued treatment. Responding patients at the 12 week assessment (i.e. those with a PGA rating of "clear" or "almost clear") stopped the therapy and entered the 24 week treatment-free follow up, while non responders continued to receive study treatment up to 24 weeks. During follow-up, patients were evaluated for safety and efficacy 4 weeks after the end of treatment, unless they had enrolled directly in the follow-up study (BAP00091). Responding patients (CHE rating as "clear" or "almost clear" according to PGA at the end of treatment (week 12 or week 24) were monitored for relapse up to 24 weeks after the end of treatment, with relapse defined as an mTLSS score of ≥75% that of the baseline score. Duration: Study treatment started no later than 4 weeks after screening. In women of childbearing potential, pregnancy tests were repeated every 4 weeks, a negative test was required for the supply of further drug study treatment. Patients underwent PGA and mTLSS assessment every 4 weeks during treatment. PaGA (Patient Global Assessment) and extent of disease were recorded at the end of therapy (week 12 or week 24). AE's were recorded at each visit until 4 weeks after the end of therapy. Laboratory safety tests were done at screening and every 4 weeks until 4 weeks after the end of therapy. The General Health Questionnaire was completed at baseline and at the end of therapy (week 12 or 24). The Centre of Epidemiological Studies Depression Scale was applied at screening, baseline and every 4 weeks until the end of therapy. All patients who withdrew from the study underwent final efficacy evaluation at the time of withdrawal. Patients were also followed-up 4 weeks after stopping treatment to evaluate safety unless enrolled directly in the follow-up study for further treatment.	Phase III, randomised, double blind, placebo-controlled, parallel group, multicentre study that took place at 112 centres in Europe and Canada. Primary objective: To demonstrate that the response rate based on PGA in one or both alitretinoin groups is superior to that in placebo groups at the end of treatment (week 12 to week 24) or at the latest assessment for patients withdrawing prematurely. Secondary objectives: ▪ To compare time to response between alitretinoin groups ▪ To determine time to relapse of severe CHE for alitretinoin and placebo groups ▪ To determine the proportion of patients with at least partial response (PGA rating of clear, almost clear, or mild) at the end of treatment ▪ To compare the efficacy of the two alitretinoin doses in patients with severe refractory CHE, based on modified Total Lesion Symptom Score (mTLSS), Patient Global Assessment (PaGA), and extent of disease ▪ To assess the safety of alitretinoin in patients with severe refractory CHE.	Randomisation was stratified by centre. Eligible patients were allocated at a 1:2:2 randomisation ratio to placebo, alitretinoin 10mg or alitretinoin 30mg. Patients at each centre were given a randomisation number in ascending sequential order of their enrolment. The randomisation code was prepared by Basilea.	Alitretinoin and placebo capsules were indistinguishable in terms of physical characteristics including size, weight, colour, texture, odour and taste, and were provided in packaging which did not disclose drug identity. The Master Randomisation List was kept at the central repository by the Biometrics Department and Drug Safety Department. No open Key to the Code was made available to the study centres, monitors or members of the project team. The investigator had access to coded, sealed envelopes for each patient to be used in an emergency whose management would have required knowledge of this study medication. The investigator had to state reasons for opening the envelope in such a case.

Study	Recruitment/ Trial	Intervention/Duration	Study Type/ Design	Randomisation Method	Blinding Method
BAP00091	First patient enrolled January 24th 2005. Last patient to complete final visit January 26th 2007.	Intervention: Patients who responded in study BAP00089 and relapsed in the post treatment observation period were assigned to Cohort A. Eligible patients in Cohort A were allocated to trial treatment using an unbalanced randomisation scheme. Patients were assigned to the same treatment they had been receiving in BAP00089 or to placebo in a 2:1 ratio. Patients who had received placebo during BAP00089 were also assigned placebo during this study. This part of the study had a double blind design. Non responding patients to BAP00089 were assigned to Cohort B and received alitretinoin 30mg. This part of the study was open label. Duration: Enrolled patients in Cohort A received placebo, 10mg alitretinoin or 30mg alitretinoin once daily for 12 to 24 weeks. Treatment duration depended upon treatment response at 12 weeks. Patients who responded after 12 weeks of therapy (PGA rating of "clear" or "almost clear") stopped treatment at that time whilst non-responding patient received treatment for up to 24 weeks. Safety and primary efficacy assessments were carried out every 4 weeks during treatment. Secondary assessments were carried out at week 12 and 24 for patients continuing treatment.	The phase III study was conducted in patients with CHE who had previously received treatment in BAP00089. The study took place at 81 centres in Europe and Canada. Cohort A : Double blind, randomised, placebo-controlled multicentre trial Patients were randomised to one of the following dosage groups based on previously received treatment in study BAP00089 and response to treatment. ▪ Previous treatment alitretinoin 10mg: Alitretinoin 10mg or placebo taken orally once daily for 12 or 24 weeks. ▪ Previous treatment alitretinoin 30mg: Alitretinoin 30mg or placebo once daily for 12 or 24 weeks. ▪ Previous treatment placebo: Placebo capsules taken orally once daily for 12 or 24 weeks. Cohort B: Open label, multicentre study Patients who did not respond to treatment in BAP00089 were treated with 30mg alitretinoin Objective To assess the safety and efficacy of a 12 to 24-week course of alitretinoin in patients with chronic hand eczema refractory to topical therapy, who were previously treated with alitretinoin or placebo in study BAP00089	Cohort A: Patients who responded in study BAP00089 and relapsed during the post treatment observation period were assigned to the same dose that they had received or to placebo in a 2:1 ratio. Responding patients who had received placebo during BAP00089 took placebo during this trial. Cohort B: Not applicable. Non-responding patients were assigned to alitretinoin 30mg.	Cohort A: This study had a double blind design. Alitretinoin and matched placebo capsules were provided. Active and placebo capsules had indistinguishable physical characteristics including size, weight, colour, odour, texture and taste and were provided in packaging that did not reveal drug identity. A list of treatment assignments was sealed and kept in a central repository by the Biometrics Department and Drug Safety Department. No open Key to the Code was made available to the study centres, monitors or members of the project team. The investigator had access to coded, sealed envelopes for each patient to be used in emergency whose management would have required knowledge of this study medication. If the investigator wished to know the identity of the treatment given to any subjects for any other reason, this request was first to be discussed with Basilea. Cohort B: All patients received 30mg of alitretinoin.

6.3.2 Participants

Unlike the BAP00089 study, which only enrolled patients with severe CHE, the phase II trial BAP00003 enrolled patients with both moderate and severe disease. In addition, the phase II study excluded women of childbearing potential. The dosing used in the phase II study was 10mg, 20mg and 40mg of alitretinoin per day, compared to 10mg and 30mg used in the phase III study.

Table 6.3.2 Inclusion and exclusion criteria used in the RCTs for alitretinoin

Study	Inclusion Criteria	Exclusion Criteria
BAP00003	Patients were required to meet the following inclusion criteria: ▪ Male patients or female patients if post-menopausal or surgically sterile ▪ Aged 18 - 70 years ▪ Chronic hand dermatitis refractory to topical therapy, including all types and forms of chronic hand dermatitis/eczema such as pompholyx, hyperkeratotic palmar dermatitis/eczema, fingertip eczema. ▪ Chronic hand dermatitis rated moderate or severe according to investigators global assessment of severity (PGA) ▪ With duration of disease greater than 3 months since diagnosis and written consent by the patient.	Patients were excluded if they met any of the following criteria: ▪ Women in reproductive age with child bearing potential, patients with known hypersensitivity to other retinoids (vitamin A derivatives). ▪ Patients treated with potent topical therapy for dermatitis/eczema (moderately potent, potent and very potent corticosteroids, tar) within one week of start of trial treatment. ▪ Patients treated with systemic therapy e.g. corticosteroids, retinoids, immunosuppressants, within 4 weeks of start of trial treatment. ▪ Patients with clinically relevant allergic contact dermatitis of the hands as demonstrated by a positive patch test, and unable to avoid exposure to the allergen. ▪ Patients treated with phototherapy UVA, PUVA, or X-rays within 4 weeks of the start of trial treatment. ▪ Patients with skin lesions of psoriasis not limited to the hands, and requiring specific therapy of the hands. ▪ Patients with skin lesions of atopic dermatitis not limited to the hands and requiring specific therapy. ▪ Patients with active bacterial, fungal or viral infection of the hands. ▪ Patients presenting with any other skin disease that may have interfered with the conduct of the study and/or the evaluation of the results. ▪ Patients with any serious medical condition which may interfere with the safety or evaluation of the study such as chronic heart failure, chronic infection, chronic renal failure, chronic liver failure, chronic biliary disease etc. ▪ Patients known to be immunosuppressed. ▪ Patients with ALT and/or AST > 150% of upper limit of normal. ▪ Patients with triglyceridemia > 250% of upper limit of normal. ▪ Patients with cholesterolaemia of > 150% of upper limit of normal. ▪ Patients receiving tetracyclines or systemic ketoconazole, itraconazole, erythromycin or clarithromycin within two weeks of start of trial treatment. ▪ Patients receiving other retinoids oral or topical or taking vitamin supplements containing vitamin A. ▪ Patients with a known hypersensitivity to any component of the study medication. ▪ Patients included in the study of an investigational drug within the last 2 months. ▪ Patients with a history of psychiatric disorders. ▪ Patients unable to comply with the requirements of the study.

BAP00089	Patients were required to meet the following inclusion criteria: ▪ Male patients or female patients if post-menopausal or hysterectomised or if premenopausal and willing to use two methods of contraception under the supervision of the investigator or a gynaecologist ▪ Aged 18 to 75 years ▪ All types of CHE including hyperkeratotic, vesicular and fingertip dermatitis, fulfilling the following criteria: persisting for at least 6 months since initial diagnosis, rated severe according to the PGA, refractory to standard non-medicated therapy, including skin moisturisation and protection and avoidance of relevant irritants and allergens ▪ Refractory to topical corticosteroid therapy, with unsatisfactory outcome (no response, transient response to ongoing therapy or lack of tolerability) after at least 8 weeks of treatment within the previous 6 months including topical class 1 steroids applied for at least 4 weeks or as recommended by the manufacturer, unless contraindicated or not tolerated ▪ Written informed consent provided.	Patients were excluded if they met any of the following criteria: ▪ Women of reproductive age with child bearing potential if they could not or would not choose to use two effective forms of contraception simultaneously under the supervision of the investigator or a gynaecologist. ▪ Female patients who were pregnant or planned to become pregnant or were breast feeding. ▪ Unable to comply with the requirements of the study. ▪ Patients whose disease was adequately controlled by standard non-medicated therapy (skin moisturising and protection, avoidance of irritants and allergens) and standard topical corticosteroid therapy, but whose disease had relapsed after discontinuing these treatments. ▪ Known hypersensitivity to other retinoids or vitamin A derivatives, or to any study medication component, especially soyabean oil and partly hydrogenated soyabean oil. ▪ Patients who had received systemic corticosteroids, retinoids or immunosuppressants 4 weeks before the start of study treatment (inhaled steroids were permitted). ▪ Patients who had been treated with UVB, PUVA, Grenz Rays or X-Rays within 4 weeks before the start of study treatment. ▪ Patients with known clinically relevant allergic contact dermatitis of the hands as demonstrated by a prior skin patch test, who were unable to avoid exposure to the allergen or patients presenting with psoriasis lesions, atopic dermatitis lesions requiring medicated treatment, acute (non-chronic) episodes of pompholyx/dyshydrosis or of contact dermatitis or active bacterial, fungal or viral infection of the hands. ▪ Patients presenting with any other skin disease which may interfere with the conduct of the study and/or evaluation of results. ▪ Patients known to be immunocompromised. ▪ Patients with any serious medical condition which, in the opinion of the investigator, may have interfered with the conduct and/or evaluation of results within the study. ▪ Patients with ALT/AST > 2.5x upper limit of normal. ▪ Patients with fasting triglyceridaemia > 2x upper limit of normal. ▪ Patients with cholesterol >2x upper limit of normal. ▪ Patients with haemoglobin below the lower limit of normal. ▪ Patients who had received drugs with potential of drug-drug interactions, such as systemic triglycerides, ketoconazole, erythromycin, clarithromycin, simvastatin or St Johns Wort within 1 week of the start of trial drug treatment or had received systemic itraconazole within 2 weeks before the start of study treatment. ▪ Patients who had received topical retinoids, macrolides, tacrolimus or pimecrolimus on affected areas or had taken vitamin supplements containing >2000 IU of vitamin A within 1 week of commencing the study treatment. ▪ Patients who had participated in another investigational study 2 months before the start of study treatment. ▪ Patients with a score of 20 or more on the Centre of Epidemiological Studies Depression Scale or with a history of a psychiatric disorder.

BAP00091	Patients were required to meet the inclusion criteria of BAP00089 and the following: ▪ Written informed consent provided ▪ Male patients and female patients either without childbearing potential or of childbearing potential and using appropriate contraception who participated in study BAP00089 and were either: responders (rated clear or almost clear according to the PGA at the end of treatment) and relapsing within 24 weeks after the end of treatment (mTLSS score ≥75% that of baseline in BAP00089) or non-responders, rated mild or moderate according to PGA after 24 weeks of treatment.	Patients were excluded if they met any of the following criteria: ▪ Women of reproductive age with child bearing potential if they could not or would not choose to use two effective forms of contraception simultaneously under the supervision of the investigator or a gynaecologist. ▪ Female patients who were pregnant or planned to become pregnant or were breast feeding. ▪ Patients whose disease was adequately controlled by standard non-medicated therapy (skin moisturising and protection, avoidance of irritants and allergens) and standard topical corticosteroid therapy, but whose disease had relapsed after discontinuing these treatments. ▪ Patients who had received systemic corticosteroids, retinoids or immunosuppressants 4 weeks before the start of study treatment (inhaled steroids were permitted). ▪ Patients who had been treated with UVB, PUVA, Grenz Rays or X-Rays within 4 weeks before the start of study treatment. ▪ Patients with any serious medical condition which, in the opinion of the investigator, may have interfered with the conduct and/or evaluation of results within the study. ▪ Patients with ALT/AST > 2.5x upper limit of normal. ▪ Patients with fasting triglyceridaemia > 2x upper limit of normal. ▪ Patients with cholesterol >2x upper limit of normal. ▪ Patients with haemoglobin below the lower limit of normal. ▪ Patients who had received drugs with potential of drug-drug interactions, such as systemic triglycerides, ketoconazole, erythromycin, clarithromycin, simvastatin or St Johns Wort within 1 week of the start of trial drug treatment or had received systemic itraconazole within 2 weeks before the start of study treatment. ▪ Patients who had received topical retinoids, macrolides, tacrolimus or pimecrolimus on affected areas or had taken vitamin supplements containing >2000 IU of vitamin A within 1 week of commencing the study treatment. ▪ Patients who had participated in another investigational study 2 months before the start of study treatment. ▪ Patients with a score of 20 or more on the Centre of Epidemiological Studies Depression Scale or with a history of a psychiatric disorder.

Baseline demographics

BAP00003[41, 46]

The population studied was different to that in which alitretinoin was subsequently licenced although there are areas of overlap. BAP00003 included patients with both moderate and severe CHE and alitretinoin is indicated only for those patients with severe CHE. In addition this study excluded women of child-bearing potential. Alitretinoin may be used in this population in clinical practice but only if the strict conditions of the pregnancy prevention programme are met.

Table 6.3.3: Summary of baseline patients characteristics in study BAP00003 (ITT population)

	Placebo Group n=78	Alitretinoin 10 mg/d Group (n = 80)	Alitretinoin 20 mg/d Group (n = 80)	Alitretinoin 40 mg/d Group (n = 81)
Age, mean, y ± SD	48.7± 12.44	48.7± 11.91	46.7±13.59	48.7±11.90
Sex, M/F	56/22	56/24	59/21	64/17
Body weight ± SD	79.25±15.574	80.90±14.095	77.97±13.223	80.85±14.311
Race, Caucasian N(%)	75 (97%)	76 (95%)	79 (99%)	79(98%)
Disease severity				
Moderate	51 (65%)	52 (65%)	56 (70%)	52 (64%)
Severe	27 (35%)	28 (35%)	24 (30%)	29 (36%)
Type of disease, n (%)*				
Hyperkeratotic eczema	64 (82%)	66 (83%)	72 (90%)	67 (83%)
Fingertip eczema	22 (28%)	27 (34%)	31 (39%)	29 (36%)
Pompholyx	18 (23%)	13 (16%)	20 (23%)	19 (23%)
Other	4 (5%)	5 (6%)	1 (1%)	4 (5%)
Duration of disease, median (range), y	3.85 (0.3-43.7)	2.8 (0.4-36.8)	2.7 (0.3-55.5)	3.2 (0.3-37.1)
Duration of episode, median (range), mo	5.4 (0.5-226.5)	5.25 (0.3-122.4)	5.7 (0.2-274.2)	4 (0.2-260.0)
Response to prior treatment, n (%)*				
Transient response	66 (85)	61 (76)	65 (81)	62 (77)
No response	13 (17)	19 (24)	16 (20)	19 (23)
Not tolerated	2 (3)	3 (4)	0	2 (2)
Etiological factors n (%)*				
Contact allergies	15 (19)	17 (21)	10 (13)	17 (21)
Chemical irritants	20 (26)	25 (31)	23 (29)	22 (27)
Physical irritants	13 (17)	15 (19)	13 (16)	14 (17)
Atopic diathesis	13 (17)	8 (10)	10 (13)	13 (16)
None identified	39 (50)	34 (43)	40 (50)	32 (40)

*Some patients were assigned to more than 1 category

BAP00089[6]

The average age of patients enrolled in the trial was 48 years and disease was long standing, with a median duration of 4.5-5 years and a mean duration of 9 years. Although there were only slightly more males overall, women aged <45 years were a minority at around 15% of study participants. Patients in each group had similar demographic and disease characteristics. CHE was described as hyperkeratotic in over 80% of patients, with 45% described as fingertip and 27% described as pompholyx, illustrating inclusion of the main clinical subtypes of CHE and considerable overlap in features.[6] For most patients, erythema, desquamation, fissures and pruritus/pain were moderate or severe at baseline, while vesicles and oedema were less likely to be severe. The patient demographics were similar to those stated in the decision problem and reflect those of patients expected to be treated with alitretinoin in clinical practice.

Table 6.3.4: Summary of baseline patients characteristics in study BAP00089 (ITT population)[6]

Characteristic	Alitretinoin		
	Placebo	10mg	30 mg
N	205	418	409
Sex – Male, n (%)	121 (59%)	238 (57%)	223 (55%)
Age (years), Mean ± SD	48 ± 12	47 ± 15	48 ± 13
Females < 45 years, n (%)	30 (15%)	63 (15%)	62 (15%)
Body weight (kg), mean ± SD	81 ± 16	81 ± 16	81 ± 16
Race: Caucasian, n (%)	203 (99%)	402 (96%)	398 (97%)
PGA severity rating, n (%)			
Severe	205 (100%)	418 (100%)	408 (99%)
Moderate	0	0	1 (0.2%)
mTLSS score, mean ± SD	15.0 ± 2.4	15 ± 2.6	14.9 ± 2.6
Extent of disease, mean ± SD	51 ± 22	47 ± 20	48 ± 20
Type of CHE, n (%)			
Hyperkeratotic	179 (83%)	362 (87%)	349 (85%)
Pompholyx	55 (27%)	111 (27%)	111 (27%)
Fingertip	101 (43%)	180 (43%)	196 (49%)
Other	29 (14%)	61 (15%)	55 (13%)
Duration of disease (years)			
Median (Q1;Q3)	4.9 (2.3;12)	5.2 (1.9; 11)	4.4 (2.1;12)
Response to previous therapy with topical corticosteroids, n (%)			
No response	81 (40%)	181 (43%)	197 (48%)
Transient response	121 (59%)	222 (53%)	199 (49%)
Not tolerated	2 (1%)	5 (1%)	12 (3%)

BAP00091

The demography of treatment groups in this study was well matched and did not differ significantly from the demography at entry to the BAP00089 study. The proportion of patients with different clinical subtypes of CHE and disease severity as measured by the PGA and mTLSS were similar to those in the BAP00089 study, reflecting similar disease characteristics. Patient demographics were thus similar to those stated in the decision problem and reflected the population expected to be treated with alitretinoin in clinical practice.

Table 6.3.5: Summary of baseline patients characteristics in study BAP00091 (ITT population)

Characteristic	Alitretinoin			
	Cohort A Placebo	Cohort A 10mg	Cohort A 30 mg	Cohort B 30mg
N	47	21	49	243
Sex – Male, n (%)	24 (51.1%)	15 (71.4%)	25 (51.0%)	143 (58.8%)
Age (years), Mean ± SD	50±13	49±15	52±11	46±13
Females < 45 years, n (%)	1 (2.1%)	0	6 (12.2%)	34 (14.0%)
Body weight (kg), mean ± SD	80±14	86±21	82±18	81±16
Race: Caucasian, n (%)	47 (100%)	20 (95.2%)	48 (98.0%)	239 (98.4%)
PGA severity rating, n (%)				
Severe	29 (61.7%)	10 (47.6%)	34 (69.4%)	53 (21.8%)
Moderate	18 (38.3%)	9 (42.9%)	15 (30.6%)	136 (56%)
mTLSS score, mean ± SD	13.4±2.35	12.6±3.19	13.3±2.36	10.1±4.06
Type of CHE, n (%)				
Hyperkeratotic	34 (72.3%)	18 (85.7%)	45 (91.8%)	198 (81.5%)
Pompholyx	9 (19.1%)	4 (19.0%)	9 (18.4%)	64 (26.3%)
Fingertip	15 (31.9%)	5 (23.8%)	15 (30.6%)	90 (37.0%)
Other	16 (34.0%)	3 (14.3)	5 (10.2)	38 (15.6%)
Time since present episode (Months)				
Months, mean± SD	2.5±4.5	6.4±16.0	6.1±14.5	34.3±67.2

6.3.3 Patient numbers

Figure 6.3.1: BAP00003 phase II trial for alitretinoin, flow of study participants[42, 46]

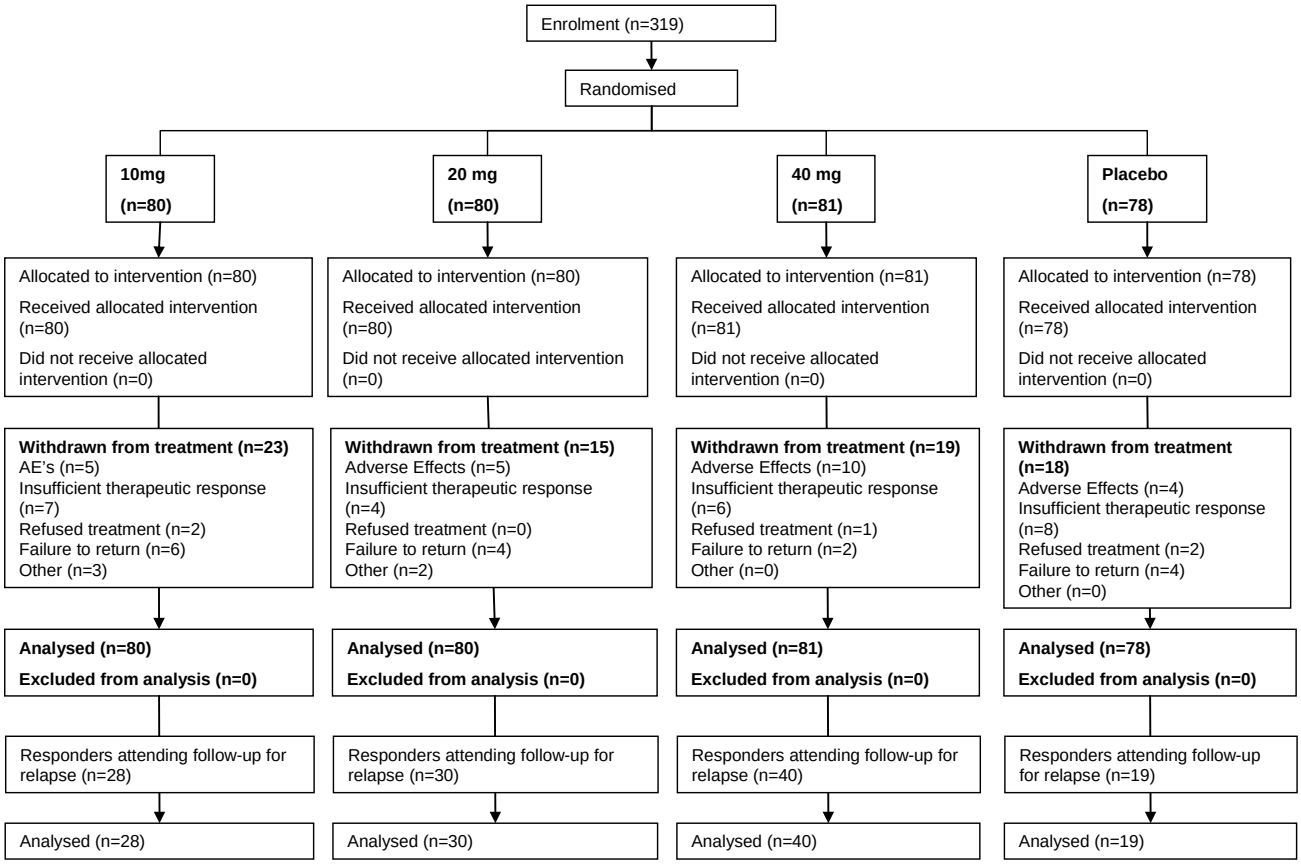


Figure 6.3.2: BAP00089 Phase III trial for alitretinoin, flow of study participants[47]

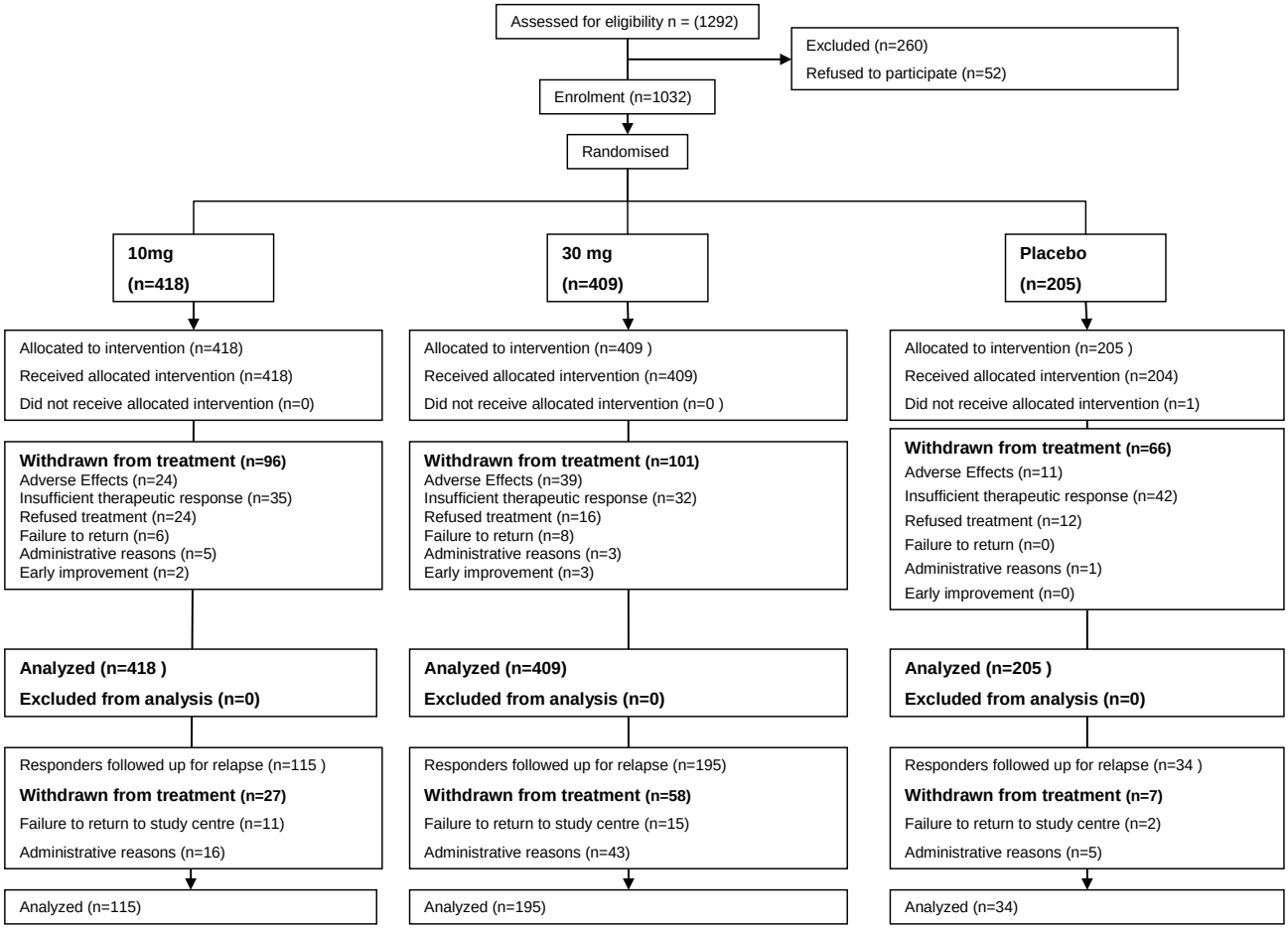
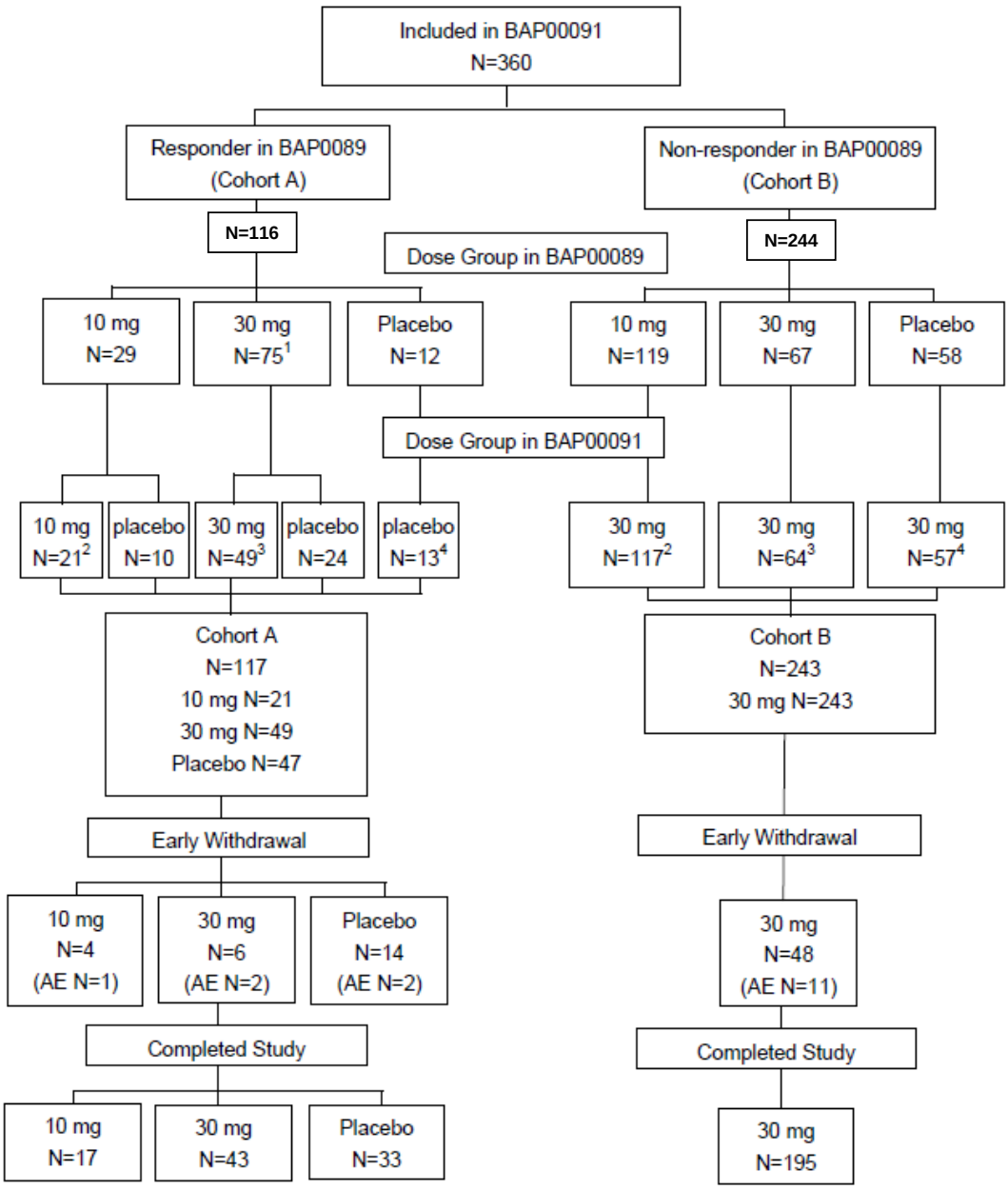
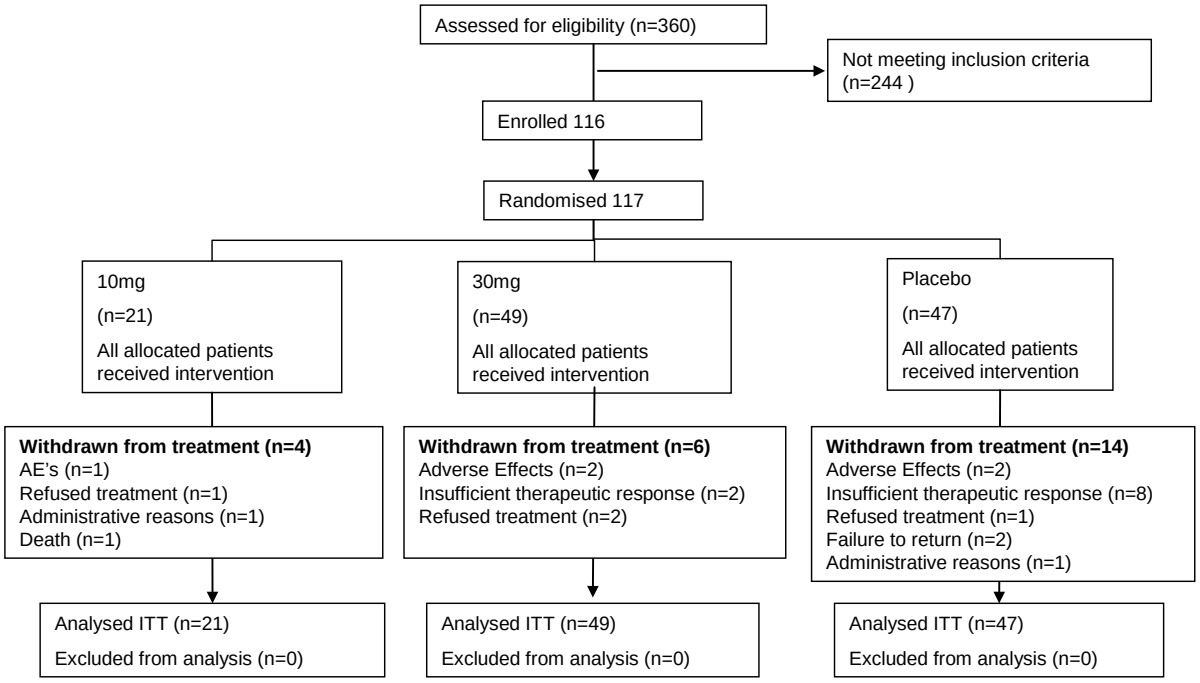


Figure 6.3.3: BAP00091 Phase III trial for alitretinoin, flow of study participants



[1] 5 patients although classified as relapse in BAP00089 were included in the non-responder (Cohort B) part of study BAP00091
[2] 2 patients who were non-responders in BAP00091 were included in the Cohort A 10 mg group
[3] 3 patients who were non-responders in BAP00089 were included in Cohort A 30 mg group
[4] One patient who was a non-responder in BAP00089 was included in Cohort A placebo group

Figure 6.3.4: BAP00091 Phase III trial for alitretinoin: Cohort A, flow of study participants[42, 42]



6.3.4 Outcomes

Table 6.3.6: Efficacy outcomes reported in the RCTs for alitretinoin

Study	Decision Problem-Final Scope	Primary Outcome(s)	Secondary Outcome(s)
BAP00003	Measures of disease severity Measures of symptom control	PGA of overall CHE severity – measured at week 12. For patients withdrawing from treatment before week 12 PGA was measured at time of treatment withdrawal and at week 12	PaGA – Measured at week 12 Total Lesion Score (TLSS) – Measured at baseline, weeks 2, 4, 8 and 12 Extent of disease – Measured at baseline, weeks 2,4 8 and 12
	Disease-free period/ maintenance of remission		Time to next use of eczema medication
	Health related quality of life		DLQI – measured at baseline and week 12
BAP00089	Measures of disease severity Measures of symptom control	PGA of overall CHE severity, response defined as clear/almost clear hands -measured at baseline and 4 weekly intervals during the treatment period (either to week 12 or 24) and 4 weeks after the end of treatment. For responding patients only (clear/almost clear hands) further measurement of PGA was also carried out at 8, 16 and 24 weeks after the end of treatment.	Partial Response mTLSS - measured at baseline and 4 weekly during the treatment period (12 or 24 weeks) and 4 weeks after the end of treatment. For responding patients only (clear/almost clear hands) further measurement of mTLSS was also carried out at 8, 16 and 24 weeks after the end of treatment. Time to Response PaGA – Measured at end of treatment (either week 12 or 24) Extent of Disease – Measured at baseline and at end of treatment (either week 12 or 24)
	Disease-free period		Not assessed
	Maintenance of remission		Time to Relapse
	Health related quality of life		Not assessed
BAP00091	Measures of disease severity Measures of symptom control	PGA of overall CHE severity, response defined as clear/almost clear hands - measured at baseline and 4 weekly intervals during the treatment period (either to week 12 or 24) and 4 weeks after the end of treatment.	Partial Response mTLSS – measured at baseline and at week 12 and 24 for patients remaining on treatment and 4 weeks after the end of treatment Time to Response PaGA – Measured at end of treatment (either week 12 or 24) Extent of Disease – Measured at baseline and at end of treatment (either week 12 or 24)
	Disease-free period/ maintenance of remission		Not assessed
	Health related quality of life		Not assessed

Validity and description of outcome measures

Physicians Global Assessment (PGA)

The primary efficacy measure for therapeutic response was the *Physicians Global Assessment (PGA)* of overall CHE severity. Investigators embarking on clinical trials in other areas of dermatology will usually have at their disposal recognised and validated measure of disease activity, eg.PASI for the assessment of psoriasis, however the EMEA recommends that categorical global measures of outcome such as PGA are also included in trials conducted for the purpose of registration.[48]

Prior to the alitretinoin clinical trial programme, CHE had received scant research attention and consequently no satisfactory measures of disease activity or global status had been published that would be acceptable for the purposes of drug registration in CHE; consequently tools were developed for this purpose. The basis for the PGA categories used in the phase II and III studies is a photographic guide, devised and validated in collaboration with dermatologists.[49] The experts reached a consensus for development of a photographic guide composed of five severity levels and four photographs per severity level. Results showed a high level of inter-rater reliability and test-re-test reproducibility. The PGA includes symptoms (pruritus/pain) and consideration of functional impairment that cannot be linked to photographic appearances alone. The relief of these distressing symptoms and their consequences such as loss of sleep are clearly important from the patient perspective as is functional impairment (eg inability to grip due to severe hyperkeratosis) that may preclude work or leisure activities.

The PGA criteria were as follows:

- Clear: no residual visible eczema
- Almost clear: minimal erythema and/or scaling
- Mild: clearly visible signs of eczema, with no hyperkeratosis, oedema, fissures or functional impact
- Moderate: moderately severe signs of eczema, with no oedema, fissures, or functional impairment
- Severe: marked signs of eczema, or oedema, fissures, or functional impairment.

Modified Total Lesion Symptom Score (mTLSS)

The mTLSS was developed for the alitretinoin trials to measure change in the severity of hand eczema using a continous scale (at this time the potential alternative HECSI score had not been published).[50] The verbal mTLSS criteria are based on the validated photographic guide appearances as above.[49] A 4-point scale (0=none, 1=mild, 2=moderate, 3= severe) was used to grade 7 signs or symptoms of CHE (Table 6.3.7). The modified total lesion/symptom score (mTLSS) was calculated as the sum of assigned scores. Scores were assigned for the most affected side (palmar or dorsal) of the hand most severely affected.

Table 6.3.7 Severity rating of Modified Total Lesion Symptom Score

Symptom	Description of Severity
Erythema	0 = absent 1 = faint erythema 2 = prominent redness 3 = deep intense red color
Scaling	0 = absent 1 = slight flaking over limited areas, mostly fine scales 2 = flaking over widespread area(s), coarser scales 3 = desquamation covering over 30% of the hand, with coarse thick scales
Lichenification/ Hyperkeratosis	0 = absent 1 = mild thickening with exaggerated skin lines over limited areas 2 = palpable thickening over widespread area(s) 3 = prominent thickening over widespread area(s) with exaggeration of normal skin markings
Vesiculation	0 = absent 1 = scattered vesicles affecting up to 10% of hand, without erosion 2 = scattered or clustered vesicles affecting up to 30% of hand, without visible erosion or excoriation 3 = high density of vesicles extending over large area(s), or with erosion or excoriation
Edema	0 = absent 1 = dermal swelling over less than 10% of hands 2 = definite dermal swelling over more than 10% of hand 3 = dermal swelling with skin induration over widespread area(s)

Patient Global Assessment

Impact of the disease was measured from a patient's perspective, as assessed by patient's global assessment of improvement (PaGA).

At the end of therapy (week 12 or 24), patients were asked by the investigator to grade their overall change from baseline by selecting one of the following descriptions, which best matched their perception of treatment effect:

- Cleared or almost clear (at least 90% clearing)
- Marked improvement (at least 75% clearing)
- Moderate improvement (at least 50% clearing)
- Mild improvement (at least 25% clearing)
- No change
- Worsening.

Despite the importance of participants' assessments, patient reported outcomes are rarely presented in clinical trials of dermatology.[51] Participants' assessments of efficacy of treatments are particularly important in dermatology as symptoms such as pruritus and sleep disturbance are difficult for physicians to assess objectively and the significance of any apparent morphological improvement cannot be reliably assumed without this being validated by the patient.

Extent of disease

At baseline and at the end of therapy (week 12 or 24), the extent of disease was estimated as the percentage of hand area (with 100% defined as the palmar and dorsal aspects) affected by dermatitis. Extent of disease was estimated separately for the left and right hands and the overall extent of disease for both hands was calculated as (left + right) divided by two.

Relapse

Relapse was defined as mTLSS score 75% that of the baseline value. This figure represents an estimate by dermatologists involved in study design of the point at which relapse would be defined in clinical practice.

Dermatology Quality of Life Index (DLQI)

The Dermatology Quality of Life Index (DLQI) is a validated scale to assess health related quality of life in patients with dermatitis. The instrument contains ten items dealing with the subject's skin. The score on the DLQI has a possible range of 0 to 30, with 30 corresponding to the worst health related quality of life (HRQL). The DLQI was developed to contain six subscale scores: symptoms and feelings; daily activities; leisure; work/school; personal relationships; and treatment. There is now 14 years experience with DLQI with over 274 peer reviewed research articles and 291 published abstracts.[52]

6.3.5 Statistical analysis and definition of study groups

Table 6.3.8 Statistical analyses used in the RCTs for alitretinoin

Study	Hypotheses	Statistical Analysis	Sample Size Calculation
BAP00003	The study was designed to provide 80% power to reject the null hypothesis of no difference between the active treatment and placebo at an alpha level of 5%.	The primary efficacy evaluation compared the proportion of patients rated as "clear" or "almost clear" according to PGA using a closed test procedure based on Cochran-Armitage trend tests and always including the placebo group. All individual tests were performed at a significance alpha level of 5%, and the multiple significance alpha level of 5% was kept. Secondary analyses were regarded as exploratory, therefore no adjustment for multiple testing was done. All individual tests were two sided at 5% alpha level.	The percentage of patients rated as "clear" or "almost clear" according to the PGA at week 12 was expected to be 30% in the active group and 10% in the placebo group. Based on these assumptions, a calculated sample of 62 evaluable patients was calculated to provide 80% power to reject the null hypothesis of no difference between the active treatment and placebo at an alpha level of 5%. Assuming a drop-out rate of 10%, 70 patients per group and a total of 280 patients for the 4 treatment groups were planned to be randomised. The sample size calculations were performed using nQuery Advisor 4.0 Software. The statistical analyses used during this trial: ▪ Cochran-Armitage closed trend test ▪ Overall Kruskall-Wallis test ▪ Jonckheere-Terpstra trend test ▪ Chi-Square test.
BAP00089	The study was designed to provide 90% power to reject the null hypothesis of no difference between alitretinoin and placebo at an adjusted alpha level of 2.5%, using a two-sided continuity corrected Chi-square test.	**Primary Efficacy Analysis (ITT Population):** Response rates based on PGA at the end of treatment (week 12 or week 24): two sided continuity corrected Chi-Squared tests at a Bonferroni adjusted alpha level of 2.5%. **Secondary Efficacy Analysis (ITT and PP Populations):** • Time to respond based on PGA: log-rank test (Kaplan-Meier Method) • Time to relapse of CHE (duration of response): life table method including medians and 95% confidence intervals • Proportion of patients with at least partial response based on	The percentage of patients whose CHE was assessed as "clear" or "almost clear" according to PGA at the end of treatment (12 weeks or 24 weeks) was assumed to be 40% in the alitretinoin 30mg treatment group, 30% in the 10mg alitretinoin treatment group and 15% in the placebo group. Based on these assumptions, a sample size of 775 evaluable patients randomised in a 1:2:2 ratio (155 in the placebo group and 310 in each alitretinoin treatment group) would provide 90% power to reject the null hypothesis of no difference between the alitretinoin and placebo at an adjusted alpha level of 2.5%, using a two-sided continuity corrected Chi-Squared

		PGA: two sided continuity corrected Chi-Squared tests (Bonferroni adjusted alpha level of 2.5%) • PaGA: two sided continuity corrected Chi-Squared tests (Bonferroni adjusted alpha level of 2.5%) • Change from baseline in mTLSS: Kruskal-Wallis test or F-Test (depending on distribution of data) at 5% alpha level • Change from baseline in extent of disease- Kruskal Wallis test or F-Test at 5% alpha level.	test. Assuming a drop out rate of 25%, a total of 1035 patients were planned to be included in the study (207 in the placebo group and 414 in each active dose group). The sample size calculations were performed using nQuery Advisor 4.0 Software.
BAP00091	No hypothesis testing was planned. PGA and PaGA were presented in listings and summary tables. TLSS was analyzed by means of descriptive statistics at each evaluation and at the end of therapy (last observation carried forward [LOCF]).	The variables for this study were: ▪ Proportion of patients rated "clear" or "almost clear" according to PGA criteria at the end of therapy (week 12 or week 24 or at time of discontinuation) ▪ Percentage change from baseline in total lesion/ symptom score TLSS at the end of therapy (week 12 or week 24 or at time of discontinuation) ▪ PaGA at the end of therapy (week 12 or week 24 or at time of discontinuation). No hypothesis testing was planned. PGA and PaGA were presented in listings and summary table. TLSS was analysed by means of descriptive statistics at each evaluation and at the end of therapy.	There was no formal sample size calculation.

6.3.6 Critical appraisal of relevant RCTs

Table 6.3.9 Critical appraisal of the RCTs for alitretinoin			
Critical Appraisal	**Study: BAP00003**	**Study: BAP00089**	**Study: BAP00091**
How was the allocation concealed?	Alitretinoin and placebo capsules were identical in size, colour, shape, texture and taste. Capsules and packaging did not reveal the identity of the test drug, and no open randomisation list was available at the study centre, to trial moderators or other study personnel. Coded sealed envelopes were available to the investigator, for use in cases of emergency where knowledge of the test drug was important for patient management. Each envelope contained the identity of test treatment for one patient. The investigator was required to give the reasons why an envelope was opened. At the end of the study, all envelopes were returned to Basilea unopened.	Alitretinoin and placebo capsules were indistinguishable in terms of physical characteristics including size, weight, colour, texture, odour and taste, and were provided in packaging which did not disclose drug identity. The Master Randomisation List was kept at the central repository by the Biometrics Department and Drug Safety Department. No open Key to the Code was made available to the study centres, monitors or members of the project team. The investigator had access to coded, sealed envelopes for each patient to be used in emergency whose management would have required knowledge of this study medication. The investigator had to state reasons for opening the envelope in such a case.	**Cohort A:** This study had a double blind design. Alitretinoin and matched placebo capsules were provided. Active and placebo capsules had indistinguishable physical characteristics including size, weight, colour, odour, texture and taste and were provided in packaging that did not reveal drug identity. **Cohort B:** All patients received 30mg of alitretinoin. **Cohort A:** A list of treatment assignments was sealed and kept in a central repository by the Biometrics Department and Drug Safety Department. No open Key to the Code was made available to the study centres, monitors or members of the project team. The investigator had access to coded, sealed envelopes for each patient to be used in emergency whose management would have required knowledge of this study medication. If the investigator wished to know the identity of the treatment given to any subjects for any other reason, this request was first to be discussed with Basilea.
Which randomisation technique was used?	Patients were randomised by centre, in blocks of 4 without stratification. The randomisation code was prepared for each centre by AAI (Reinach, Switzerland) and	Randomisation was stratified by centre. Eligible patients were allocated at a 1:2:2 randomisation ratio to placebo, alitretinoin 10mg or alitretinoin 30mg.	**Cohort A:** Patients who responded in study BAP00089 and relapsed during the post treatment observation period were assigned to the same dose that they had received or to placebo in a 2:1 ratio.

	incorporated into double blind coded drug packaging. After completion of screening eligible patients were assigned coded patient numbers, sequentially in the order in which they were enrolled, and the patient number was recorded in the CRF. Coded drug packages corresponding to the assigned patient numbers were then provided to patients at the start of treatment.	Patients at each centre were given a randomisation number in ascending sequential order of their enrolment. The randomisation code was prepared by Basilea.	Responding patients who had received placebo during BAP00089 continued to take placebo during this trial. Each patient was assigned a coded allocation of study drug containing either placebo or a dosage of active drug. **Cohort B:** Non-responding patients were assigned to alitretinoin 30mg.
Was follow-up adequate?	The follow-up included time to first use of an anti-eczema medication and do not correspond to relapse as defined in BAP00089. In addition these findings may not be relevant since the population included those with moderate disease	Responding patients were followed up for 24 weeks off all active treatment.	A follow-up of a follow up was not deemed necessary.
Were individuals undertaking the outcomes assessments aware of allocation?	Protocol design ensured that those making measurements of outcome were kept fully blinded to treatment assignment and measurement techniques were not subject to observer bias.	Protocol design ensured that those making measurements of outcome were kept fully blinded to treatment assignment and measurement techniques were not subject to observer bias.	Protocol design for **cohort A** ensured that those making measurements of outcome were kept fully blinded to treatment assignment and measurement techniques were not subject to observer bias.
Was a justification of sample size provided?	Justification of sample size was provided.	Justification of sample size was provided.	No justification of sample size was provided, patients were continuing from BAP00089.
Was the design parallel or cross over? Is there a risk for cross-over designs of carry over effect?	Parallel design.	Parallel design.	Parallel design for **cohort A**.
Was the RCT conducted in the UK?	The trial was conducted in 43 centres across Europe, including 4 centres in the UK.	The trial was conducted in 111 centres across Europe and Canada, including 6 centres in the UK.	The trial was conducted in 81 centres across Europe and Canada, including 6 in the UK.

Do patients included in the RCT compare with patients likely to receive the intervention in the UK?	Subjects in the RCT were broadly similar in terms of baseline disease severity and demographics to patients in the UK, however approximately 2/3 were of moderate severity which is not included in the licensed indication for alitretinoin	Subjects in the RCT were broadly similar in terms of baseline disease severity and demographics to patients in the UK.	Subjects in the RCT were broadly similar in terms of baseline disease severity and demographics to patients in the UK.
Are dosage regimes within those cited in the summary of product characteristics?	The 10mg and 20mg doses used in this trial are within those cited in the SPC however the 40 mg dose is not.	Yes	Yes
Were study groups comparable?	The study groups had similar demographic and clinical profiles.	The study groups had similar demographic and clinical profiles.	The study groups had similar demographic and clinical profiles.
Were statistical analyses performed appropriate?	Statistical analyses of the trial were appropriate and intention to treat analyses were undertaken.	Statistical analyses of the trial were appropriate and intention to treat analyses were undertaken.	Statistical analyses of the trial were appropriate and intention to treat analyses were undertaken.

6.4 Results of the relevant comparative RCTs

BAP00003 (Phase II)[41, 46]

A total of 319 patients with moderate or severe CHE were randomised to receive placebo, 40mg, 20mg or 10mg alitretinoin in the ratio of 1:1:1:1. Treatment was for 12 weeks, during which time 75 patients withdrew. Of 127 responders, 117 patients were followed up for 12 weeks after the end of treatment.

Demographics

Patients in each group had similar demographic and disease characteristics, with approximately two thirds of patients having moderate and one third severe CHE. A higher proportion of men were enrolled in this trial due to the exclusion of women with childbearing potential. Most patients were diagnosed with hyperkeratotic eczema and their initial diagnosis of CHE had been made several years earlier. This differs to the demographics considered within the decision problem which is only severe CHE but which does include women with childbearing potential.

Primary endpoint results

Treatment with 40mg alitretinoin led to a significant improvement in the severity of disease ($p<0.001$) with 53% of patients treated achieving the response of "clear"/"almost clear" hands as assessed by the PGA (Table 6.4.1). No statistically significant difference was seen between alitretinoin 20mg and 10mg vs. placebo.

Table 6.4.1: Primary efficacy measure in the BAP00003 phase II trial

	Placebo	**Alitretinoin**		
		10mg	**20mg**	**40mg**
PGA assessment, N	78	80	80	81
Clear or almost clear, N(%)	21 (27)	31 (39)	32 (41)	43 (53)
P value versus placebo	-	NS	NS	P<0.001

NS: Result not significant

Secondary endpoint results (Table 6.4.2)

- Patient assessment of disease severity, as measured by PaGA, significantly improved across all doses of alitretinoin compared to placebo with up to 43% patients achieving a response of clear/almost clear hands
- Alitretinoin significantly improved the signs and symptoms of CHE across all doses compared to placebo as measured by mTLSS
- Dose-dependent increases in response rates were seen for all types of CHE, regardless of previous response to topical therapy or severity of disease (moderate/severe) at baseline
- In those patients responding to alitretinoin defined as achieving clear/almost clear hands, 74% did not relapse in the follow up period of 12 weeks after the end of treatment (defined as requiring prescription therapy for CHE)
- Health related quality of life was measured by DLQI in centres in which a validated I local language DLQI questionnaire was available; approximately 60% of patients in each group completed the DLQI at baseline. DLQI showed improvement during treatment in all groups but the trial lacked power to demonstrate statistically significant differences.

Table 6.4.2: Secondary efficacy measures in the BAP00003 phase II trial

	Placebo	Alitretinoin		
		10mg	20mg	40mg
PaGA assessment, N	73	69	74	74
Clear or almost clear, N (%)	9 (12)	20 (29)	25 (34)	32 (43)
P value versus placebo	-	0.014	0.002	<0.001
mTLSS, N	78	76	78	80
Median % change in score from baseline (95% CI)	-25	-59	-52	-70.5
P value versus placebo	-	0.032	0.002	< 0.001
95% CI	(-42 to -14)	(-73 to -42)	(-73 to -42)	(-80 to -44)
Extent of disease, N	78	76	78	80
Median reduction in extent of disease	-39%	-43%	-48.5%	-61.5%
P value versus placebo	-	NS	NS	0.024
Evaluation of Relapse, no. of responders at week 12	19	28	31	41
No. of patients followed from Weeks 12 to 24	19	28	30	40
No. of patients relapsed between Weeks 12 and 24(%)	3 (26%)	7 (25%)	8 (26%)	13 (32.5%)
DLQI				
No. of patients evaluated at baseline	48	48	48	50
No. of patients evaluated at 12 weeks	41	36	43	42
Median within-patient change from baseline to week 12	-2	-2	-3	-3

NS: Not significant

Conclusions

In this phase II double-blind randomised clinical trial alitretinoin reduced both the severity and signs and symptoms of CHE in patients with moderate or severe CHE refractory to standard topical therapy.

BAP00089 (Phase III)[6, 47]

A total of 1032 patients with severe CHE refractory to topical steroids were randomised in a 2:2:1 ratio to receive alitretinoin 30mg, alitretinoin 10mg or placebo. All 1032 patients enrolled were included in the intent to treat analysis. All patients except for one (randomised to placebo) received at least one dose of either alitretinoin or placebo and were included in the analysis of safety. Patients who responded with a PGA assessment of 'clear' or 'almost clear' after 12 weeks stopped treatment at this time, while all others continued therapy until week 24. All responding patients were followed up for a further 24 weeks to assess relapse and no medication likely to be active against CHE was allowed during this time. Relapse was defined as an mTLSS score more than or equal to 75% of the baseline score. The population included in the phase III study is representative of the study population included in the decision problem.

All results presented are from the intent-to-treat (ITT) analysis.

Primary endpoint results

The primary efficacy endpoint was PGA of overall CHE severity, response defined as clear/almost clear hands.

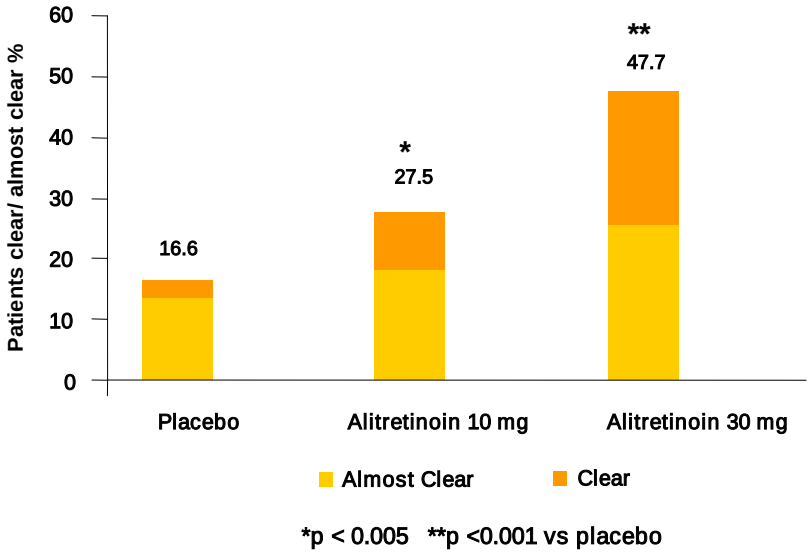
Alitretinoin was found to be highly effective in patients with severe CHE who were unresponsive to potent topical steroids in reducing disease severity as measured by the PGA:

- Response rates as assessed by PGA were significantly higher in patients treated with alitretinoin. Clear/almost clear skin was achieved in 47.7% and 27.5% of patients treated with 30mg or 10mg alitretinoin respectively, compared to 16.6% of patients in the placebo group (p<0,001 and <0.005 respectively) (Table 6.4.3, Figure 6.4.1).

Table 6.4.3 Primary efficacy endpoint in the BAP00089 trial (ITT population)

	Placebo	**Alitretinoin**	
		10mg	**30mg**
PGA assessment, N	205	418	409
Clear or almost clear, N (%)	34 (16.6%)	115 (27.5%)	195 (47.7%)
P value (versus placebo)	-	<0.005	<0.001
95% CI	(11.8,22.4)	(23.3,32.1)	(42.7,52.6)

Figure 6.4.1: PGA response rate at end of therapy



Secondary endpoint results

A summary of the secondary end-point results is shown in Table 6.4.4

In addition to the physician's assessment, patients were also asked to rate improvement in their condition over the course of treatment. The patient's global assessment of improvement (PaGA) correlated highly with the primary efficacy endpoint (physician's global assessment of improvement; correlation coefficient 0.82, Kendall's tau) confirming that the improvements were meaningful to the patient.

Both alitretinoin doses were superior to placebo (alitretinoin 10mg: $p = 0.013$; alitretinoin 30mg: $p < 0.001$; Chi-Square test) with respect to the PaGA rating. There was a statistically significant improvement in symptom control as measured by mTLSS in patients treated with both doses of alitretinoin compared to placebo ($p<0.0001$ for both doses) with a 75% and 56% improvement for the 30mg and 10mg doses respectively.

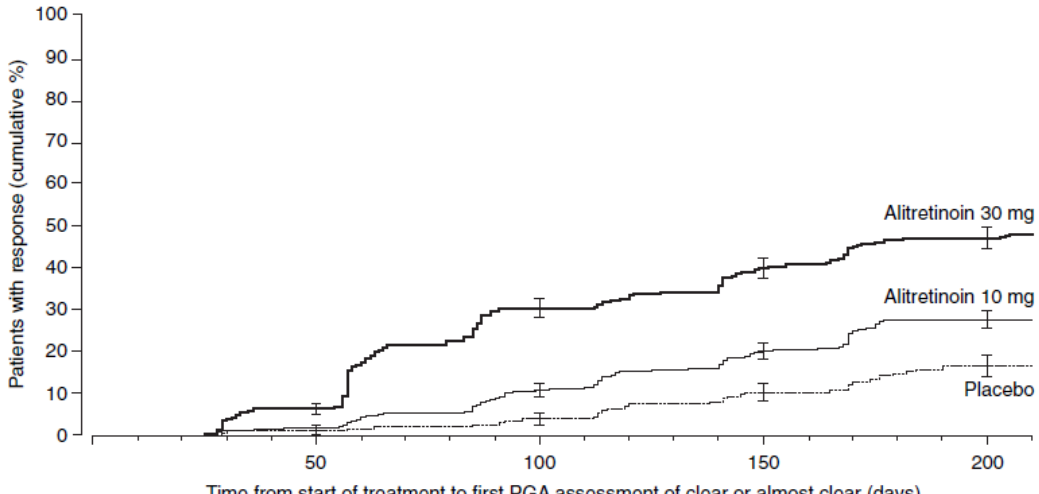
Table 6.4.4: Secondary efficacy parameters in BAP00089 (ITT population)

	Placebo	Alitretinoin	
		10mg	30mg
N	205	418	409
PaGA, N (%) (clear or almost clear)	31 (15%)	101 (24%)	163 (40%)
P value (versus placebo)	-	p<0.02	p<0.001
Median % reduction in modified TLSS (mTLSS)	39%	56%	75%
P value (versus placebo)	-	p<0.001	p<0.001
95% CI	(46.7, 27.3)	(62.5, 50.0)	(78.6, 68.8)
Median % reduction in extent of disease	33%	50%	75%
P value (versus placebo)	-	p<0.02	p<0.001
Partial response, N (%)	74 (36.1%)	207 (49.5%)	254 (62.1%)
P value (versus placebo)	-	p<0.01	p<0.001
95% CI	(29.5,43.1)	(44.6,54.4)	(57.2,66.8)
Median time to relapse (days)	168	190	168
95% CI	(109, -)	(139, 190)	(183, -)

Time to response:

Time to response was significantly shorter in the alitretinoin 30mg group compared to 10mg (p <0.001) (Figure 6.4.2)

Figure 6.4.2: Time to response (PGA of clear/almost clear hands)



No. of patients at risk	Day 0	Day 50	Day 100	Day 150	Day 200
30 mg	409	383	285	246	217
10 mg	418	411	373	334	303
Placebo	205	203	197	184	171

Efficacy in patients with sub-types of CHE

The efficacy of alitretinoin in reducing disease severity as measured by PGA was assessed across different subtypes of CHE. Baseline morphological classification of CHE in the BAP00089 trial was not mutually exclusive; 85% of patients were classified as predominantly hyperkeratotic, however inflammatory features such as erythema and vesicles were present in over 90% of such patients. Similarly, although 27% of patients were classified as pompholyx at baseline, only 5% had a classification of pompholyx alone (22% had a dual classification of pompholyx and hyperkeratotic). In 4/5 of patients classified as pompholyx alone, significant hyperkeratosis was also present according to their baseline symptom score, leaving only 1% of study patients having a highly vesicular presentation without significant hyperkeratosis. This illustrates the relative rarity of CHE of exclusively vesicular type in patients with long standing, steroid refractory CHE recruited.

The SPC emphasises that patients in whom the eczema has predominantly hyperkeratotic features are more likely to respond to alitretinoin treatment than those in whom the eczema predominantly presents as pompholyx. The response to alitretinoin was shown to be dose dependent in hyperkeratotic but not pompholyx patients as per table 6.4.5.

Table 6.4.5: Response rate by CHE subtype[53]

CHE subtype (% of ITT population)	Hyperkeratotic (64%)	Hyperkeratotic/ Pompholyx (22%)	Pompholyx (5%)
Response rate (PGA)	30mg: 54% 10 mg: 30% Placebo: 12%	30mg: 33% 10 mg: 23% Placebo: 12%	30mg: 33% 10 mg: 22% Placebo: 30%

Efficacy in the long-term management of CHE

In a 6 month follow up of responders in BAP00089, during which no other active medication was permitted, 62.6% of patients who had received 30mg alitretinoin and 70.4% who had received 10mg alitretinoin did not meet the criteria for relapse. Relapse was defined as recurrence of disease corresponding to at least 75% of the pretreatment mTLSS score.

Conclusions

In this phase III multi-centre, randomised, placebo-controlled, 48-week trial in patients with severe CHE refractory to topical steroids, treatment with alitretinoin demonstrated both statistically and clinically significant clinical improvements in severe CHE, as assessed by various measures of disease severity and symptom control including the PGA, mTLSS and PaGA. Efficacy was dose-dependent, with both 30mg and 10mg doses of alitretinoin demonstrating statistically significant improvements compared with placebo. The time to response with alitretinoin 30mg was significantly shorter than with placebo. In addition a high proportion of patients (65%) treated with alitretinoin did not meet the criteria for relapse within the 24 week follow up period.[53]

BAP00091 (Phase III extension study)[5, 42]

This phase III extension study investigated alitretinoin in two cohorts of patients from the BAP00089 study:

Cohort A: total of 117 patients who responded during BAP00089 but relapsed within the 24 week follow up period were allocated to trial treatment in a double-blind fashion using an unbalanced randomisation scheme. Patients were assigned to the same treatment they received in BAP00089 or to placebo in a 2:1 ratio. Consequently, patients who had received placebo in study BAP00089 were assigned to receive placebo again.

Cohort B: A total of 243 non-responding patients from study BAP00089 were assigned to receive alitretinoin 30 mg as open label treatment.

Enrolled patients received placebo, 10 mg or 30 mg alitretinoin once daily for 12 to 24 weeks. Patients who responded after 12 weeks of therapy (PGA rating of "clear" or "almost clear") stopped treatment at that time, while non-responding patients continued to receive therapy up to 24 weeks. Safety and the primary efficacy assessments were carried out every 4 weeks during treatment and secondary efficacy assessments at week 12 and 24 (for patients continuing on treatment).

All results presented are from the intent-to-treat (ITT) analysis.

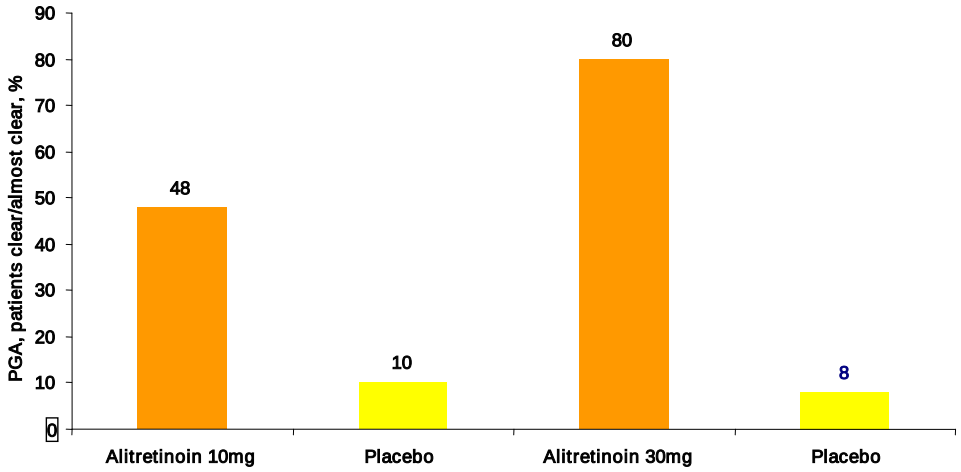
Primary endpoint results

Cohort A: 79.6% of patients who met the primary end point in BAP00089 of clear/almost clear hands with 30mg alitretinoin but subsequently relapsed, were successfully re-treated with 30mg alitretinoin (Figure 6.4.3).[5] This was a statistically significant improvement compared to the placebo arm (79.6% versus 8.3%; p<0.001, two-sided continuity corrected chi-square test).[42] In patients treated with 10mg alitretinoin in BAP00089 there was no statistically significant different in re-treatment between the 10mg dose and placebo.

Table 6.4.6: Primary efficacy parameter in BAP00091 (Cohort A, ITT population)

Treatment in BAP00089	**Placebo**	**10mg alitretinoin**		**30mg alitretinoin**	
Treatment in BAP00091	**Placebo**	**Placebo**	**10mg**	**Placebo**	**30mg**
PGA assessment, N	13	10	21	24	49
Clear or almost clear, N (%)	9 (69.2%)	1 (10%)	10 (47.6%)	2 (8.3%)	39 (79.6%)
P value (versus placebo)	-	-	P=0.10	-	p<0.001
95% CI	(0.9, 53.8)	(0.3, 44.5)	(25.7, 70.2)	(1.0, 27.0)	(65.7, 89.8)

Figure 6.4.3: PGA response to retreatment in patients who had relapsed after initially responding to alitretinoin treatment (BAP0091, Cohort A, ITT population)



Cohort B: On treatment extension of up to 24 weeks with 30mg alitretinoin, 50.9%, 50.4% and 39.1% of patients who did not respond fully to initial treatment with placebo, 10 mg alitretinoin or 30 mg alitretinoin respectively achieved clear/almost clear hands. These results suggest that further improvements may be expected in patents who have not responded with clear/ almost clear hands after an initial treatment course of alitretinoin.

Secondary endpoint results

A summary of results is shown in Table 6.4.7.

- In addition to the physician's assessment, patients were also asked to rate improvement in their CHE over the course of treatment. The patient's global assessment of improvement (PaGA) correlated highly with the primary efficacy endpoint (physicians global assessment of improvement; correlation coefficient 0.82, Kendall's tau) confirming that the improvements were meaningful to the patient.
    - Both alitretinoin doses were superior to placebo (alitretinoin 10mg: $p = 0.013$; alitretinoin 30mg: $p < 0.001$; Chi-Square test) with respect to the PaGA rating
- There was a statistically significant reduction in disease severity as measured by mTLSS in patients treated with both doses of alitretinoin compared to placebo ($p<0.0001$ for both doses) with a 67.4% and 78.3% improvement for the 30mg and 10mg dose respectively.

Table 6.4.7: Secondary efficacy parameters in the BAP00091 trial (ITT population)

	Cohort B Non Responder in BAP00089	**Cohort A Relapse in BAP00089**		
	30 mg Alitretinoin	**Placebo**	**10 mg Alitretinoin**	**30 mg Alitretinoin**
N	244	47	21	49
PaGA, N (%) (clearing or almost clearing)	103 (42.4%)	10 (23.1%)	37 (75.5%)	8 (38.1%)
Exact 95% CI	(36.1,48.9)	(10.7,35.7)	(61.1,86.7)	(18.1,61.6)
Median % reduction in modified TLSS (mTLSS)	49.7%	40.3%	78.3%	67.4%
P value versus placebo	-	-	0.022	<0.001
Median % reduction in extent of disease	60.8%	42.9%	90.0%	46.7%
P value versus placebo	-	-	0.553	<0.001
Partial response, N (%)	176 (72.4%)	19 (40.4%)	43 (87.8%)	16 (76.2%)
P value versus placebo	-	-	0.014	<0.001
Exact 95% CI	(66.4,77.9)	(26.4,55.7)	(52.8,91.8)	(75.2,95.4)
Time to response	*	*	*	85 days
95% confidence interval	(176, -)	(-, -)	(168, -)	(57,112)
*Median times to response could not be reliably calculated for the other treatment groups.				

Conclusions

Cohort A: In this multi-centre, randomised, placebo-controlled, 24-week trial, a high proportion of patients who had previously responded to treatment with alitretinoin demonstrated a

statistically and clinically significant response to retreatment with alitretinoin compared to placebo. This study demonstrates that alitretinoin is suitable for intermittent repeated use.

Cohort B: In this open-label extension study, nearly 50% of patients who had not initially responded to treatment after 24 weeks were responsive to further treatment with 30 mg alitretinoin. Therefore extended treatment courses beyond 24 weeks may prove beneficial for some patients.

Overall Conclusions for Relevant Comparative RCTs

- Alitretinoin is an effective, convenient, once-daily oral therapy for the treatment of severe CHE unresponsive to topical corticosteroids
  - Alitretinoin improved disease severity in most patients with 47.7% of patients in the phase III study BAP00089 achieving clear/almost clear skin within 12-24 weeks of treatment with 30mg alitretinoin
  - A 75% median reduction in signs and symptoms of CHE was observed after 24 weeks in the 30mg alitretinoin treatment group ($p<0.001$ compared to placebo).
- Trial data demonstrate that alitretinoin is suitable for chronic, intermittent management of severe CHE
  - After 6 months follow up of responders in the BAP00089 study, during which no other active medication was permitted, 65% and 72% of patients who had received 30mg and 10mg alitretinoin respectively remained in remission
  - Almost 80% of patients who met the end point of clear/almost clear hands with 30mg alitretinoin but subsequently relapsed were successfully re-treated with 30mg alitretinoin.
- The activity of alitretinoin is not limited to patients with any distinct combination of CHE signs and symptoms.

Additional Clinical Trial Data

BAP00200

A total of 32 patients with severe CHE refractory to topical steroids were enrolled in this randomised, double-blinded, single-centre study. Patients were treated with 10mg or 30 mg alitretinoin for 12 or 24 weeks, with a 4 week post-treatment safety follow-up period. The primary objective of this study verify the pharmacokinetics of alitretinoin under normal (repeated dose) treatment conditions in patients with CHE. (Table 6.4.8). As observed in BAP00089 time to response was shorter in the group treated with 30mg alitretinoin than with 10mg. Secondary efficacy parameters, PaGA, extent of disease and change from baseline, showed similar trends.

Table 6.4.8: Primary efficacy parameter in BAP00200

Treatment in BAP00089	10mg alitretinoin	30mg alitretinoin
PGA assessment, N	16	16
Clear or almost clear, N (%)	2 (12.5%)	10 (62.5%)
Exact 95% confidence interval	(1.6, 38.3)	(35.4, 84.8)

6.5 Meta-analysis

Only two trials (BAP00089 and BAP00091) treated patients with placebo and 30mg altretinoin. Since BAP00091 is an extension study of BAP00089 it is not appropriate to carry out a meta-analysis on these studies. Although not the recommended starting dose for alitretinoin, a meta-analysis was carried out on the results of patients treated with 10mg alitretinoin in BAP00003 and BAP00089. The patient populations in these studies differed in respect to CHE severity, however the meta-analysis demonstrates that 10mg of alitretinoin is significantly more effective in treatment of CHE compared to placebo.

Methods
The effects of treatment within trials were calculated using exact methods. The pooled alitretinoin analysis was conducted using an exact fixed effects method. All exact analyses were conducted using StatsDirect software (Camcode, Cambridge 2008).

Results
A comparison of the odds ratios for treatment with 10mg or 30mg alitretinoin versus placebo in the BAP00089 study is shown in Table 6.5.1. The likelihood of achieving clear hands is significantly greater with both doses of alitretinoin when compared with placebo, whilst the likelihood of disease remaining severe is significantly greater in patients on placebo.

Table 6.5.2 shows the results of a direct comparison between the efficacy of treatment with 10mg alitretinoin versus placebo in the phase III BAP00089 study and the phase II BAP00003 study. The probability of achieving clear or almost clear hands is higher in the 10mg group than placebo and combination of efficacy results from the two trials showed that this difference is highly significant. The trials were not heterogenous.

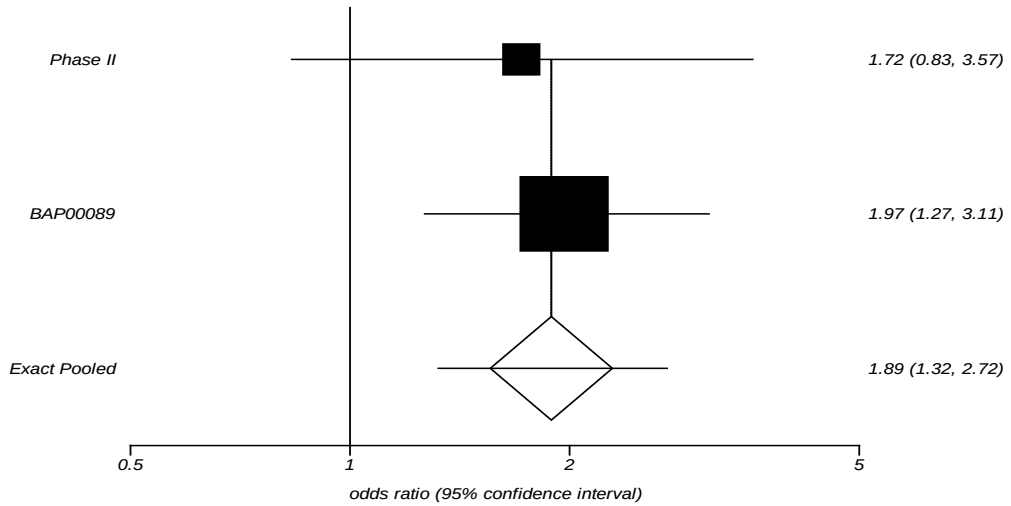
Table 6.5.1: Analysis of alitretinoin versus placebo – Protocol BAP00089 – Odds Ratio and 95% CI

Comparison	Outcome	Odds Ratio	Lower 95% CI	Upper 95% CI	P value
Alitretinoin 30mg versus placebo	Clear	9.33	4.24	23.97	< 0.0001
	Almost clear	2.18	1.39	3.49	0.0005
	Mild	0.70	0.45	1.09	0.1109
	Moderate	0.63	0.43	0.93	0.0192
	Severe	0.39	0.26	0.58	< 0.0001
Alitretinoin 10mg versus placebo	Clear	3.49	1.52	9.22	0.0019
	Almost clear	1.44	0.91	2.34	0.1244
	Mild	1.20	0.79	1.83	0.4000
	Moderate	1.02	0.71	1.47	0.939
	Severe	0.48	0.33	0.71	0.0002

Table 6.5.2: Analysis of Alitretinoin 10 mg versus Placebo – Phase II Protocol - Odds Ratio and 95% CI and Meta Analysis of Phase II and BAP00089

Comparison	Outcome	Odds Ratio	Lower 95% CI	Upper 95% CI	P Value
BAP00003 Alitretinoin 10mg versus placebo	Clear/almost clear	1.71	0.87	3.39	0.1184
Meta Analysis (BAP0089 and BAP00003) Alitretinoin 10mg versus placebo	Clear/almost clear	1.89	1.32	2.72	0.0004

Figure 6.5.1: Meta Analysis of Alitretinoin Phase II and BAP00089 – 10 mg versus placebo, outcome "clear / almost clear", Exact Odds Ratio and 95% CI



Test for Heterogeneity: Breslow-Day = 0.112047 (df = 1) P = 0.7378

6.6 Indirect/mixed treatment comparisons

Identification and selection of RCTs

No studies comparing alitretinoin to the comparators were identified from the literature search. Therefore a search was carried out to identify comparative studies for the use of the comparators PUVA, ciclosporin and azathioprine in order to carry out an indirect treatment comparison.

The strategy used to identify RCTs using PUVA, ciclosporin or azathioprine for the treatment of CHE was the same as that described in Section 6.1 and Appendix 2, Section 10.2. From the studies identified initially with potential relevance to the decision problem, the majority were subsequently discounted since they were not controlled trials. Studies were also discounted for the following reasons:

- Efficacy was not the outcome measure

- Studies were not carried out in patients with hand eczema: several studies on PUVA were carried out on palmoplantar dermatoses and treated patients with a mixture of dermatological conditions including psoriasis and atopic eczema. These studies were not used in the indirect/mixed treatment comparison since they either did not separate results by disease or did not distinguish between hand or foot disease.
- In one study results were not described adequately in English.

Little evidence was found to support the use of PUVA and ciclosporin in the treatment of severe CHE. Thirteen trials investigating the efficacy of PUVA in the treatment of hand eczema were identified. Five trials were excluded due to incomplete reporting of data, inadequate controls, or inclusion of patients with mixtures of hand and foot dermatoses. A summary of the trials considered for the indirect treatment comparison is shown in Table 6.6.1. No studies were identified in which the efficacy of azathioprine in the treatment of hand eczema (of any severity) was investigated were identified.

Table 6.6.1 Summary of RCTs for PUVA and ciclosporin

Study ID Total Enrolment	**Design, Control Type**	**Study & Control Drugs Dose, Route & Regimen**	**Number of Subjects by Treatment Arm Entered**	**Diagnosis Inclusion criteria**	**Primary endpoints**
PUVA					
Petering et al. 2003[54] N=27	Within patient trial of UVA-1 or topical PUVA	PUVA: (8-MOP cream, frequency not stated) UVA-1: 5 times weekly for 3 weeks	Not applicable (within patient trial)	Chronic vesicular dishydrotic eczema	Dishydrotic area severity index
Sezer et al. 2007[55] N= 15	Open label randomised, within-patient trial of UVB vs topical PUVA	PUVA (topical 0.1% 8-methoxypsoralen) or UVB 3 times a week for 9 weeks	Not applicable (within patient trial)	A diagnosis of biopsy proven chronic hand eczema of dry and dishydrotic types of more than 4-month duration Conventional therapies, including topical and oral corticosteroids, topical anthralin, tar, pimecrolimus and emollients ineffective	Change in total severity scores from baseline: erythema, squamation, induration, fissures and itching, assessed on a 4 point scale: none 0 to severe 3 Complete clearance defined as total clinical score of 0, marked clinical improvement as reduction of 70% or more from baseline at week 9.
Rosen et al. 1987[56] N=35	Open label, randomised controlled trial of UVB and oral PUVA with untreated hand controls.	Patients treated 3 times weekly for maximum of 3 months. Mean of 16 PUVA and 35 UVB sessions. *Concomitant treatment with topical keratolytic in all patients.*	N= 18 PUVA and N=17 UVB	Bilateral hand dermatitis, symmetrical distribution. Duration of at least 6 months. (Predominantly females (31/35) with vesicular CHE (26/31) enrolled) No benefit from previous topical steroids, potency not specified.	Desquamation, erythema, vesiculation, infiltration and fissures assessed on a four point scale: 0; none to 3; severe. Patient rating of pain or itch registered as 1 point. Global evaluation of cleared, much improved or somewhat improved
Simons et al.	Open-label	UVB 3 times weekly,	Not applicable	Bilateral chronic hand	Clinical assessment score of 7 features rated

1997[57] N=13	randomised within-patient study of UVB and topical bath PUVA	PUVA 2 times weekly (0.1% trioxsalen) for up to 6 weeks	(with-in patient trial)	dermatitis with vesicles or hyperkeratotic plaques of the hands present for > 6 months.	0-3 (none to severe), corrected for size of the affected skin Independent 0-3 rating of pain and itch
Sheehan-Dare et al. 1989[58] N= 25	Double-blind randomised within-patient study of PUVA and superficial radiotherapy	Topical PUVA 3 times a week for 6 weeks (1% 8-methoxypsoralen) or radiotherapy 3 times with 21 day intervals	Not applicable (with-in patient trial)	Chronic bilateral constitutional hand eczema with continuous or intermittent vesiculation for at least 6 months. Resistant to conventional therapy	Clinical severity grading from 0 (normal skin) to 4 (active pompholyx) and patient linear analogue scale
Van Coevorden et al. 2004[59] N=158	Open-label, randomised, controlled study comparing oral and bath PUVA	30 home sessions following oral methoxypsoralen 0.6mg/kg or 20 hospital sessions following trioxpsoralen 0.2mg/ml soak	Oral PUVA at home N=78, Hospital bath PUVA N=80	Chronic bilateral or unilateral hand eczema (no subtype exclusions) of at least 1 year duration Moderate to severe hand eczema Responsiveness to topical steroids not stated.	Change in observer rated hand eczema score at 10 weeks. (Desquamation, erythema, vesiculation, infiltration, fissures, itch and pain were rated on a 4 point scale)
Adams et al. 2007[60] N= 15	Prospective randomised study comparing PUVA and UVA-1. Right versus left hand	Before starting the treatment, patients' palms were randomized Period for treatment/therapy: 5 weeks, irradiation 3 times per week 15 treatments administered with weekly checkups	N= 11, one hand received PUVA and the other UVA-1	At least 18 years old Dishydrotic eczema (chronic recurrent) for at least 1 month	DASI (dishydrotic eczema area and severity index)

Grattan et al. 1991[61] N=15	Double-blind randomised within - patient trial comparing topical PUVA with UVA Right versus left hand	Treatment for 8 weeks (3 times a week) with 24 PUVA sessions, topical 0.1% 8-methoxypsoralen, mean cumulative UVA dose 105.5 J/ cm^2 Treatment for 8 weeks, follow-up 8 weeks and 18 months	N=12, one hand received PUVA and the other UVA	At least 16 years old Bilateral symmetrical vesicular hand eczema (recurrent disabling) for at least 6 months	Global rating scale: (clear 0; minimal 1; mild 2; moderate 3; severe 4) Visual analogue scale and area of involvement
Ciclosporin					
Granlund et al. 1996[62] N=41	Randomised double-blind study comparing efficacy of ciclosporin and a topical corticosteroid	Ciclosporin 3mg/kg/day and placebo cream or topical corticosteroids (betamethasone-17,21-dipropionate (BDP)) and placebo capsules were taken for 6 weeks. Non-responders were switched to the alternative treatment for a further 6 weeks	N=20 initial treatment with ciclosporin, N=21 initial treatment with topical steroids	Hand eczema causing significant disability for at least 6 months Inadequate response to conventional treatment. Relevant cohort considered to be those patients not responding to BDP in first phase of study who were then treated with ciclosporin	Decrease in severity scores (Signs of erythema, scaling, infiltration, excoriation, crusting and vesicles were graded on a scale of 0-3: 0, none; 1, mild; 2, moderate; 3, severe). Investigator and patient assessment of overall efficacy on a scale of 1-5: 1, very good; 2, good; 3, moderate; 4, slight; 5, none.
Abbreviations used: PUVA: psoralens UVA, 8-MOP: Methoxypsoralen, DASI:dishydrotic eczema area and severity index					

PUVA

An analysis of the eight trials considered for inclusion in the indirect comparison is shown in Table 6.6.2 below. The majority of these trials were carried out in patients with certain subtypes of hand eczema, in some cases in a more acute form of disease, such as vesicular hand eczema. The study populations are therefore not strictly comparable to the population in the alitretinoin studies. In addition it is difficult to compare the results since the outcome measures are varied, have not been validated for CHE and in most cases are not internally validated by concurrent patient rating of outcome.

The largest trial, carried out by Coevorden et al.[59] used a seven item measure of severity scored 0-3 that was similar to the mTLSS used in the BAP00089 study. As this trial did not exclude any subtypes of hand eczema the population would have been expected to be comparable to that of the BAP00089 trial. However, the mean severity score at baseline in this trial was approximately 8 out of a theoretical maximum of 21 for the measure used whereas in the BAP00089 study the mean baseline severity score was 15.6 out of 21 for mTLSS. In addition, as it was not stated whether patients included in the study were unresponsive to topical steroids, patients participating were both less severe and less refractory at baseline than in the BAP00089 study. This study reported a 41% and a 31% reduction in hand eczema severity after treatment with oral and bath PUVA respectively.

In four of the PUVA trials patient level data are not reported. Mean reduction in disease severity or extent of disease were reported. Since the number of patients responding to treatment was not stated, these data could not be analysed. Due to the paucity of quality data available the four remaining trials (Rosen et al. 1987,[56] Simons et al. 1997,[57] Sezer et al. 2007[55], Petering et al. 2004,[54]) have been included in the indirect comparison analysis to gain as complete a picture as possible.

A summary of the results of the studies used in the indirect comparison is shown in Table 6.6.3.

Table 6.6.2 Critical analysis of studies investigating PUVA for the treatment of hand eczema		
Author, Year	**Adams et al. 2007**	**Grattan et al. 1991**
Comparison	Prospective randomised study comparing PUVA and UVA-1. 5 weeks treatment Right versus left hand	Double-blind randomised within -patient trial comparing topical PUVA with UVA Right versus left hand Treatment for 8 weeks (3 times a week) with 24 PUVA sessions, topical 0.1% 8-methoxypsoralen, mean cumulative UVA dose 105.5 J/ cm^2
Number of patients entered into trial	N=15	N=15
Inclusion criteria	At least 18 years old Dishydrotic eczema (chronic recurrent) for at least 1 month	At least 16 years old Bilateral symmetrical vesicular hand eczema (recurrent disabling) for at least 6 months
Exclusion criteria	Patients with pustular psoriasis, hyperkeratotic rhagadiform or lichenificated hand eczema Pregnant or breast-feeding, patients with previous PUVA or other light therapies within the last 4 weeks or a glucocorticosteroid therapy in the weeks before study begin, patients with more than 200 PUVA treatments	Patients with pustular psoriasis, chronic hyperkeratotic dermatitis and chronic fungal infection Pregnancy Need for phototoxic or immunosuppressive drugs Patients with positive patch test of current relevance or irritant dermatitis
Adequacy of randomisation	Unclear	Psoralen and placebo treatment randomised and coded by an independent investigator
Blinding	Unclear	Double-blinded
Loss to Follow-up	4	3
Length of Follow-up	Treatment for 5 weeks	Treatment for 8 weeks, follow-up 8 weeks and 18 months
Outcome measures	DASI (dishydrotic eczema area and severity index)	Global rating scale: (clear 0; minimal 1; mild 2; moderate 3; severe 4) Visual analogue scale and area of involvement
Baseline measures		
Disease severity	DASI 14	Mean severity score at week 0 =<2.5 (mild to moderate) PUVA approx 2.35, UVA approx 2.25 on global rating scale
Patch testing		Yes-positive in 75% patients but not considered the primary cause of chronicity
Disease duration	> 1 month	2 to 40 years (mean 13.2)
Unresponsive to topical steroids	Yes	Prior use of moderate to high potency topical steroids with little or no benefit

Author, Year	Petering et al. 2003	Sezer et al. 2007
Trial design	With-in patient trial of UVA-1 or topical PUVA UVA-1: 5 times weekly for 3 weeks, cumulative dose of 1720 J/cm^2 PUVA: cumulative dose of 130 J/cm^2	Open label randomised, within-patient trial of UVB vs topical PUVA (Left vs right hand) 27 sessions (3 times a week), topical 0.1% 8-methoxypsoralen + mean cumulative UVA dose of 111.5J/ cm ^{2} and UVB dose of 34.9 cm^2
Patients entered into trial	N=27	N= 15
Inclusion criteria	At least 18 years old Chronic vesicular dishydrotic eczema	A diagnosis of biopsy proven chronic hand eczema of dry and dishydrotic types of more than 4-month duration Conventional therapies, including topical and oral corticosteroids, topical anthralin, tar, pimecrolimus and emollients ineffective
Exclusion criteria	Patients with pustular psoriasis and fungal infections Need for immunosuppressant, antihistaminic or phototoxic drugs Use of topical corticosteroids within last 2 weeks	Hyperkeratotic hand eczema Topical treatment with corticosteroids within 2 weeks or systemic treatment with corticosteroids or other immunosuppressive agents within the last 4 weeks, unilateral disease, pregnancy, and the inability to meet for follow-up consultations
Adequacy of randomisation	Unclear	Adequate
Blinding	Unclear	Unclear
Loss to Follow-up	Unknown	3
Length of Follow-up	Treatment for 3 weeks, follow-up 3 weeks	Treatment for 9 weeks. Follow up for 10 weeks
Disease severity scoring system	DASI	Change in total severity scores from baseline: erythema, squamation, induration, fissures and itching, assessed on a 4 point scale: none 0 to severe 3 Complete clearance defined as total clinical score of 0, marked clinical improvement as reduction of 70% or more from baseline at week 9
Baseline demographics		
Disease severity	***DASI score 10-12 (out of maximum 60)*** Approx 10.5 PUVA, 12.5 UVA	Mean total clinical scores: UVB – 10.5, PUVA – 9.83 of a maximum possible 15
Patch testing	Yes	No
Disease duration	6 months – 5 years	0.5 to 14 years
Unresponsive to topical steroids	***Not stated***	Topical and oral steroids, topical anthralin, tar and pimecrolimus had been ineffective

Author, Year	Rosen et al. 1987	JR Simons et al. 1997
Trial design	Open label, randomised controlled trial of UVB vs. oral PUVA with untreated hand controls	Open label randomised study of UVB vs. topical bath PUVA (after 0.1% trioxsalen for 15 mins) in right versus left hands
	Patients treated 3 times weekly for maximum of 3 months. Mean of 16 PUVA and 35 UVB sessions	UVB 3 times weekly (mean 17 sessions), PUVA 2 x weekly (mean 11 sessions) for up to 6 weeks
	Concomitant treatment with topical keratolytic in all patients	
Patients entered into trial	N= 18 PUVA and N=17 UVB	N=13
Inclusion criteria	Bilateral hand dermatitis, symmetrical distribution. Duration of at least 6 months	Bilateral chronic hand dermatitis with vesicles or hyperkeratotic plaques of the hands present for > 6 months
	No benefit from previous topical steroids, potency not specified	
Exclusion criteria	Previous or present psoriasis, ongoing fungal infections of the feet, pregnancy, impaired liver/renal function, alcohol abuse	Severe vesiculation /evidence of psoriasis
		Photodermatoses, light-aggravated dermatoses, history of melanoma, immunosuppressive therapy, impaired liver/ renal function.
Randomisation	Adequate	Alternate patients administered UVA or UVB on right or left hand
Blinding	Not stated	Not stated
Loss to Follow-up	N= 4 PUVA and N=1 UVB did not complete treatment	N=3 did not complete treatment
Length of Follow-up	Treatment for 3 months maximum. Follow-up up to 16 months – unclear how many patients	6 weeks treatment, unclear follow-up
Disease severity scoring system	Desquamation, erythema, vesiculation, infiltration and fissures assessed on a four point scale: 0; none to 3; severe. Patient rating of pain or itch registered as 1 point	Clinical assessment score of 7 features rated 0-3 (none to severe), corrected for size of the affected skin
		Independent 0-3 rating of pain and itch
	Global evaluation of cleared, much improved or somewhat improved	
Baseline demographics		
Disease severity	***Mean severity scores 10.3 (PUVA) and 10.5 (UVB) out of maximum 21*** possible range (5-18)	Mean severity score 8.98 (UVB) and 10.17 (PUVA)
Patch testing	Yes, 22/35 positive at study entry (duration of contact allergy avoidance prior to study entry not stated)	Yes-5/13 positive-none considered relevant to the eczema
Disease duration	Mean of 10 yrs (PUVA) and 7 yrs (UVB) stated however very wide range included (0.5 to 48 yrs)	Mean 5 .75 yrs
Unresponsive to topical		Yes-potency of steroid therapy not specified

steroids

Author, Year	Sheehan-Dare et al. 1989	Van Coevorden et al. 2004
Trial design	Double-blind randomised study of PUVA vs. superficial radiotherapy in R vs. L hand Topical PUVA 3 times a week for 6 weeks; 1% 8-methoxypsoralen	Open-label, randomised, controlled study of oral PUVA at home vs. hospital bath PUVA 30 home sessions following oral methoxypsoralen 0.6mg/kg or 20 hospital sessions following trioxpsoralen 0.2mg/ml soak
Number of patients entered into trial	N= 25	Oral PUVA at home N=78, Hospital bath PUVA N=80
Inclusion criteria	Chronic bilateral constitutional hand eczema with continuous or intermittent vesiculation for at least 6 months Resistant to conventional therapy	Chronic bilateral or unilateral hand eczema (no subtype exclusions) of at least 1 year duration Moderate to severe hand eczema with a hand eczema severity score at the start of the study of at least 6
Exclusion criteria	Irritant and contact allergic dermatitis excluded	Active eczematous lesions on other parts of the body Unallowed concurrent medication, such as medication causing photosensitivity and anticoagulants Unallowed past medication, such as treatment with cytostatics or ionizing radiation or PUVA of the hands less than 6 months previously Alcohol abuse, liver dysfunction, renal dysfunction, congestive heart failure, hypertension, or epilepsy Malignant or premalignant skin tumours Pregnancy or planning to become pregnant
Randomisation	Adequate	Computer-generated randomisation
Blinding	Double-blinded	Open-label
Loss to Follow-up	N=4	N=15 (oral), N=18 (bath) did not complete treatment N=4 (oral), N=4 (bath) discontinued follow-up
Length of Follow-up	Treatment 6 weeks, Follow-up at 9 and 18 weeks	10 weeks treatment, 8 weeks follow-up
Disease severity scoring system	Clinical severity grading from 0 (normal skin) to 4 (active pompholyx) and patient linear analogue scale	Primary: Change in observer rated hand eczema score at 10 weeks. (Desquamation, erythema, vesiculation, infiltration, fissures, itch and pain were rated on a 4 point scale) Secondary: Observer rated hand eczema score at 8 weeks follow up
Baseline demographics		
Disease severity	Mean severity score 3-4. Approx 3.6 PUVA, 3.6 radiotherapy treated	Described as moderate to severe *(however mean score 8.1/ maximum 21 possible)*

Patch testing	Yes (allergic contact dermatitis excluded)	*Not reported*
Unresponsive to topical steroids	Yes-potency not specified	*Not reported*

Abbreviations used: PUVA: psoralens UVA, DASI:dishydrotic eczema area and severity index

Table 6.6.3 Summary results of trials investigating PUVA for treatment of CHE used in the mixed treatment comparison

Study ID Total Enrol-ment	Baseline disease demographics	Response	Relapse
Petering et al. 2003 N=27	Chronic vesicular dishydrotic eczema for, DASI score 10-12 (out of maximum 60)	DASI scores decreased significantly and were reduced to nearly half of the pre-treatment values in both cases	After 3 weeks no relapse was observed in 23 of 27 patients
Sezer et al. 2007 N= 15	Subtype only CHE of dry and dishydrotic types, (hyperkeratotic CHE excluded). Mean total clinical scores: UVB – 10.5, PUVA – 9.83 of a maximum possible 15	Significant reductions in total clinical scores for both treatments. 17% cleared and 75% had marked clinical improvement with UVB; 8% cleared and 75% marked clinical improvement with PUVA	At 10 weeks follow up, 8 of 12 patients relapse free with UVB and 6 of 12 relapse free with PUVA
Rosen et al. 1987 N=35	Bilateral hand eczema, symmetrical distribution. Predominantly females (31/35) with vesicular CHE (26/31) enrolled. Mean severity scores 10.3 (PUVA) and 10.5 (UVB) out of maximum 21 possible range (5-18)	PUVA: 14 patients cleared (4 patients at 3 weeks, 5 patients at 6 weeks and 5 patients at 9 weeks, $p<0.001$) UVB: Improvement in both treated and untreated hands, no clearance in either.	In 9/14 PUVA patients dermatitis recurred within 3 months of end of treatment
Simons et al. 1997 N=13	Patients with vesicles or hyperkeratotic plaques of the hands present for > 6 months. Mean severity score 8.98 (UVB) and 10.17 (PUVA)	Mean severity scores reduced to 5.51 (UVB) and 7.66 (PUVA) 6 patients free of itch and pain by 6 weeks One patient cleared at 3 weeks (both hands)	Not assessed

Ciclosporin

One RCT was identified in which ciclosporin was used to treat CHE. This study included a population comparable to the BAP00089 population but treatment success was defined as a decrease in disease severity of 50% or more, which clearly differs from the end-point in BAP00089 (clear or almost clear hands). A critical analysis of this study is shown in Table 6.6.4 below. A summary of the results are shown in Table 6.6.5.

Table 6.6.4 Summary and critical analysis of study investigating ciclosporin for the treatment of hand eczema

Author, Year	**Granlund et al. 1996**
Trial design	Randomised double-blind study of 41 patients treated with either ciclosporin or topical corticosteroids. Patients not responding to initial treatment were switched to the other therapy
Number of patients entered into trial	N=20 initial treatment with ciclosporin, N=21 initial treatment with topical steroids
Inclusion criteria	Patients aged 18-70, with hand eczema causing significant disability for at least 6 months Inadequate response to conventional treatment
Exclusion criteria	Standard exclusion criteria for ciclosporin treatment
Randomisation	Adequate
Blinding	Double-blinded
Loss to Follow-up	N=4 (ciclosporin), N= 3 (topical steroid) did not complete Part I Only patients responding in part I were evaluated for relapse
Length of Follow-up	Treatment 12 weeks, follow-up for further 24 weeks
Outcome measure	Decrease in severity scores (signs of erythema, scaling, infiltration, excoriation, crusting and vesicles were graded on a scale of 0-3: 0, none; 1, mild; 2, moderate; 3, severe). Investigator and patient assessment of overall efficacy on a scale of 1-5: 1, very good; 2, good; 3, moderate; 4, slight; 5, none
Baseline demographics	
CHE diagnosis	Hyperkeratotic and vesicular CHE
Disease severity	Mean severity scores: 12.9 (ciclosporin), 13.7 (topical corticosteroids) (Max score 36)
Patch testing	Yes
Disease duration	Mean 5 years (ciclosporin) and 8 years (topical steroids)
Unresponsive to topical steroids	Yes

Table 6.6.5 Summary results of the Granlund study investigating ciclosporin for treatment of CHE

Study ID **Total Enrolment**	**Baseline disease demographics**	**Response**	**Relapse**
Granlund et al. 1996 N=41	Hyperkeratotic and vesicular CHE. Mean severity scores: 12.9 (ciclosporin), 13.7 (topical corticosteroids) (Max score 36 for both hands) Baseline severity score approx 75% of theoretical maximum per hand	Mean severity scores: ciclosporin, 7.3 (57% of baseline); betamethasone-17, 21-dipropionate, 7.9 (58% of baseline).	50% of patients relapsed within 2 weeks (increase in disease severity score/ extent of disease to >75% of baseline score)

Indirect Treatment Comparison

Since none of the controlled trials using PUVA or ciclosporin had a placebo control arm, no link can be established between the trials of alitretinoin, PUVA and ciclosporin upon which to base an indirect comparison. The data presented are a comparison between PUVA and UVB treatment.

Methods

The comparison of PUVA with UVB was conducted in SAS version 9.1(SAS Institute, Cary NC, 2008).

PUVA trials

The available trials comparing PUVA with alternative therapies randomise inadequate numbers of subjects and have a number of design features which limit their ability to estimate treatment effect.

In the trials comparing PUVA with alternative treatments, three small trials contrast PUVA with UVB and provide data on the outcome 'patient response' (Sezer et al. 2007,[55] Rosen et al. 1987,[56] JR Simons et al. 1997[57]). Two trials randomised 'hands' rather than individual patients (Sezer et al. 2007,[55] JR Simons et al. 1997[57]). A random effects meta-analysis of the PUVA versus UVB trials was undertaken, accounting for randomisation of patients' hands to alternative therapy in those trials in which this was conducted.

There was significant trial heterogeneity (P<0.0001), and no evidence of any difference in treatment effect between the two experimental conditions (odds ratio 0.72, 95% CI 0.000005 to 110990.51; P = 0.79).

One small within-subject trial compared PUVA with UVA and provided data on response (Petering 2003[54]). Response rates were the same in hands receiving either treatment.

Table 6.6.6: Results of studies used in the analysis

Author (Year)	Comparator	Patients/ hands randomised (N)	Patients responding (N)
Rosen et al. 1987	Oral PUVA	18	14
	UVB	17	0
	No treatment	35	1
Simons et al 1997	Topical PUVA	13	1
	UVB	13	1
Sezer et al. 2007	Topical PUVA	15	1
	UVB	15	2
Petering et al. 2003	Topical PUVA	27	24
	UVA	27	24

Ciclosporin trials

One small trial (Granlund et al. 1996[62]) was identified in which ciclosporin and topical steroid therapy was compared. There was no difference in the rate of response between the groups (odds ratio 1.65; 95% CI 0.44 to 6.43; P = 0.465).

Table 6.6.7: Results of the study used in the analysis for ciclosporin

Author (Year)	Comparator	Patients/ hands randomised in part 1 (N)	Patients responding in part 1 (N)	Patients entering Part 2	Patients responding in part 2 (N)
Granlund et al. 1996	Ciclosporin Topical steroids	20 21	8 6	12 8	8 5

6.7 Safety

Safety was determined through an evaluation of the adverse events and serious adverse events reported in clinical studies of alitretinoin in patients with CHE

The main focus of the safety analysis is on the results of the phase III clinical study, BAP00089. Additional safety analysis is provided from the other randomised controlled studies BAP00003 and BAP00091 described in section 6.2 of this submission as well as from BAP00200 described in section 6.4.

BAP00089[6, 47]

BAP00089 provides the most complete and reliable information on the safety of alitretinoin in the population defined in the decision problem, with BAP00091 providing efficacy and safety data from extended treatment in the same study population.

The BAP00089 study is the most relevant for the following reasons:

1. The study population was large (n = 1031, safety population) and represents fully the target population outlined in the decision problem for alitretinoin.
2. The dose regimens investigated (10 mg or 30 mg given for 12 or 24 weeks) represent the range intended for therapeutic use of alitretinoin.
3. Dose groups were sufficiently large to allow characterisation of the safety of alitretinoin at the two dose levels (alitretinoin 30 mg safety population: n = 410; alitretinoin 10 mg safety population: n = 418).
4. The use of a placebo group (n = 203; safety population) allowed objective assessment of the safety profile of alitretinoin for the two dose regimens.

In BAP00089, approximately 50% of the patient population experienced at least one adverse event (AE). Treatment-emergent AEs were more frequent in the 30 mg group rather than the 10 mg group. Fewer patients receiving alitretinoin 30 mg experienced a serious adverse event (SAE) than those receiving alitretinoin 10 mg. Treatment related SAEs showed no difference in incidence across the active or placebo arms.

Table 6.7.1 Summary of adverse events in BAP00089

	Alitretinoin 30mg	Alitretinoin 10mg	Placebo
	N=410	N=418	N=203
Any adverse event N (%)	244 (59.5%)	216 (51.7%)	101 (49.8%)
Serious adverse events N (%)	11 (2.7%)	17 (4.1%)	3 (1.5%)
Serious adverse events related to study treatment N	4 (1%)	4 (15)	2 (1%)

(%)			
Discontinuation due to adverse events N (%)	38 (9.3%)	22 (5.3%)	11 (5.4%)

The most frequent adverse events observed in BAP00089 are shown in Table 6.7.2.

The types of AEs seen in alitretinoin treated patients were not unexpected and included events associated with oral retinoid use such as headache, mucocutanous effects (dry lips, dry mouth) and elevated blood lipids which were more common in the 30mg group. Headache was the most common AE reported and clearly showed a dose dependent effect, with erythema and flushing also relatively common in the alitretinoin 30mg group. Notably, AEs reported as eczema and dermatitis were slightly more common in placebo treated patients. All other treatment-emergent AEs were of similar frequency in the two alitretinoin groups.

Table 6.7.2: Frequent adverse events observed in BAP00089[6]

	Alitretinoin		**Placebo**
	30mg n/%	**10mg n/%**	**n/%**
Infections and infestations			
Nasopharyngitis	24 (6%)	22 (5%)	14 (7%)
Influenza	6 (2%)	10 (2%)	4 (2%)
Upper respiratory tract infection	9 (2%)	5 (1%)	4 (2%)
Rhinitis	2 (1%)	2 (1%)	4 (2%)
Skin and subcutaneous tissue disorders			
Erythema	30 (7%)	7 (2%)	3 (2%)
Eczema	13 (3%)	16 (4%)	10 (5%)
Dermatitis	7 (2%)	7 (2%)	5 (3%)
Dry skin	10 (2%)	7 (2%)	2 (1%)
Nervous system disorders			
Headache	81 (20%)	45 (11%)	13 (6%)
Gastrointestinal disorders			
Dry lips	15 (4%)	9 (2%)	4 (2%)
Nausea	14 (3%)	10 (2%)	3 (2%)
Dry mouth	10 (2%)	10 (2%)	2 (1%)
Vascular disorders			
Flushing	18 (4%)	5 (1%)	2 (1%)
Investigations			
Elevated blood creatine phosphokinase	13 (3%)	8 (2%)	4 (2%)
Elevated blood triglycerides	12 (3%)	3 (1%)	0 (0%)

Laboratory Parameters

In BAP00089, clinical laboratory evaluations showed the anticipated effects of oral retinoids comprising dose-dependent increases in serum lipids as well as effects of retinoid X receptor (RXR) agonists comprising dose-dependent decreases in thyroid stimulating hormone (TSH) in some cases associated with decreased serum thyroxine.

The most frequent and relevant changes in individual laboratory values included elevated levels of fasted cholesterol and triglycerides, and lowered levels of TSH, predominantly in the 30 mg dose group. Table 6.7.3 summarises the laboratory changes seen with BAP00089.

Table 6.7.3: Laboratory changes observed in BAP00089[6]

	Alitretinoin		Placebo
	30mg n/%	10mg n/%	n/%
TSH (High) >7.4 mU/L (age ≤20 yrs) >6.3 mU/L (age > 20yrs)	4 (1%)	3 (1%)	4 (2%)
TSH (Low) <0.6 mU/L (age ≤20 yrs) <0.3 mU/L (age > 20yrs)	28 (7%)	21 (5%)	3 (2%)
Thyroxine (High) >26.7 pmol/l (age ≤65 yrs) >17.4 pmol/l (age >65yrs)	1 (0%)	1 (0%)	1 (1%)
Thyroxine (Low) <8.3pmol/l (age ≤65 yrs) < 8.0pmol/l (age >65 yrs	5 (1%)	2 (1%)	0 (0%)
Cholesterol (High) >7.77mmol/l	37 (14%)	8 (3%)	4 (3%)
Triglycerides (High) >5.66 mmol/l	20 (8%)	9 (4%)	3 (2%)
ALT (High) >96 U/L	5 (1%)	2 (1%)	4 (2%)
Bilirubin (High) > 37 µmol/l	1 (0%)	2 (1%)	2 (1%)

Additional safety data from randomised clinical trials

The adverse event rates from all randomised-controlled patient studies are stated in table 6.7.4. Adverse event rates were similar across the trials except for BAP00200 in which no severe adverse events or withdrawals were seen. In all studies the pattern of adverse events reported was similar to that seen in BAP00089 and were those expected from oral retinoid use.[63]

Table 6.7.4: Any adverse event from randomised-controlled patient studies BAP00089, BAP00091 BAP00003 and BAP00200

Study No.	Alitretinoin 30mg	Alitretinoin 10mg	Placebo

BAP00089	244/410 (59.5%)	216/418 (51.7%)	101/203 (49.8%)
BAP00091	22/50(44.0%)	9/21(42.9%)	12/46(26.1%)
BAP00003	N/A	28/80 (35%)	27/78 (35%)
BAP00200	15/16 (93.8%)	15/16 (93.8%)	N/A

Table 6.7.5: Serious adverse events from randomized-controlled patient studies BAP00089 BAP00091,BAP00003 and BAP00200

Study No.	Alitretinoin 30mg	Alitretinoin 10mg	Placebo
BAP00089	11/410 (2.7%)	17/418 (4.1%)	3/203 (1.5%)
BAP00091	2/50 (4.0%)	1/21 (4.8%)	0
BAP00003	N/A	1/80 (1.25%)	0
BAP00200	0	0	N/A

Table 6.7.6: Discontinuation due to adverse events from randomised-controlled patient studies BAP00089 BAP00091, BAP00003 and BAP00200

Study No.	Alitretinoin 30mg	Alitretinoin 10mg	Placebo
BAP00089	38/410 (9.3%)	22/418 (5.3%)	11/203 (5.4%)
BAP00091	2/50 (4.0%)	2/21 (9.5%)	2/46 (4.3%)
BAP00003	N/A	5/80 (6.25%)	4/78 (5.1%)
BAP00200	0	0	N/A

Special Safety Assessments

In addition to standard evaluation of routine safety endpoints such as adverse events, laboratory assessments, vital signs, physical examination and ECGs collected in all clinical trials, specific potential effects that have been associated with use of oral retinoids or RXR agonists without evidence of causality, were actively investigated. These comprised psychiatric effects including depression, suicidal ideation or suicide effects on bone including appearance of spurs and decrease in mineral density and ophthalmological effects including night-blindness. These effects were investigated in specific safety sub-studies, defined prospectively within the therapeutic trials.[63]

As with all oral retinoids, teratogenicity is the major potential adverse effect of alitretinoin. Alitretinoin must therefore not be given to women of childbearing potential unless stringent contraceptive measures have been taken and are adhered to. One pregnancy occurred during clinical trials with alitretinoin in a patient who failed to comply with the defined contraceptive measures. The pregnancy was terminated and failure of the pregnancy prevention program was reported as an SAE.

Psychiatric, bone and ophthalmological adverse effects were investigated in safety sub-studies as follows:

- Psychiatric status was investigated in all patients in studies BAP00089/91, BAP00200, and BAP00626, by use of the CES-D (Centre for Epidemiologic Studies Depression Scale) and the GHQ (General Health Questionnaire). Analysis of data revealed similar fluctuations in scores in patients given active drug and placebo, and no drug-related effects. Existing data cannot rule out the possibility of rare effects and therefore patients

treated with oral alitretinoin should be observed for signs of depression and referred for appropriate treatment if necessary.

- Ophthalmologic examinations were carried out on 99 patients included in studies BAP00089/91 and BAP00200. Analysis of data revealed few changes in any visual function, and no drug-related effects except for dry eyes, which were frequently reported as an AE. Dry eyes can be managed by use of moisturising eye drops. Some patients may be unable to use contact lenses during therapy with oral alitretinoin.
- Skeletal abnormalities and bone mineral density were investigated in 86 patients (skeletal radiographs) and 70 patients (Dual-Energy X-ray Absorptiometry, DXA) in studies BAP00089/91/626. Analysis of data revealed extensive skeletal abnormalities at baseline, consistent with the age of the target population and DXA scores generally within the expected range, with no evidence of drug-related progression or deterioration in any parameter or at any site.

Additional safety data

Additional data from a phase III open label study are available (BAP00626).

Demographics

Patients participating in this open-label study had demographic and disease characteristics generally consistent with results of previous clinical trials of oral alitretinoin in severe refractory CHE and were refractory to previous treatment, including topical corticosteroids.

Primary endpoint results

A total of 248 (99.6%) patients were evaluable for safety. Overall, the safety findings in this trial were consistent with the results of previous studies[6, 41, 44] and indicate that alitretinoin was well tolerated when given at 30mg, once daily for up to 24 weeks. A summary of frequently reported adverse events is shown in Table 6.7.7.

Table 6.7.7: Summary of frequently reported treatment-emergent adverse events

	Alitretinoin 30mg (n=248)	
Headache	46	(18.5%)
Migraine	5	(2.0%)
Nasopharyngitis	23	(9.3%)
Influenza	6	(2.4%)
Pruritus	8	(3.2%)
Erythema	5	(2.0%)
Nausea	6	(2.4%)
Vomiting	5	(2.0%)
Flushing	17	(6.9%)
Fatigue	6	(2.4%)
Blood – raised creatinine phosphokinase	6	(2.4%)

Safety Conclusions

In clinical studies in CHE, alitretinoin was found to be well tolerated with adverse effects consistent with the expected profile of a retinoid. The most frequent adverse event was headache which was dose dependent. With regard to laboratory parameters the most frequent adverse events were increases in both total cholesterol and triglycerides. These occurred more frequently with the 30mg dose than the 10mg dose.

6.8 Non-RCT evidence

6.8.1 Details of how the relevant non-RCTs have been identified and selected

Additional efficacy data for alitretinoin comes from an open-label study, BAP00626, conducted to provide further safety data for the 30mg alitretinoin dose and available in the Basilea database of clinical trials.

6.8.2 Summary of methodology of relevant non-RCTs

BAP00626[44]

A total of 249 patients with severe CHE refractory to topical steroids were enrolled in this open-label, multi-centre study. Patients were treated with 30 mg alitretinoin for up to 24 weeks, with a 4 week post-treatment safety follow-up period. The primary objective of this study was to assess the safety of alitretinoin (discussed in section 6.7). Secondary efficacy analysis data were also collected:

- PGA of overall CHE severity
- mTLSS
- PaGA
- Median time to response
- Questionnaire on Treatment Objectives in Hand Dermatitis (QTO-HE)

The following inclusion and exclusion criteria were applied to patients within this study:

Inclusion Criteria	Exclusion criteria
▪ Male patients, or female patients if post-menopausal, or hysterectomised, or if premenopausal and were willing to use two methods of contraception under supervision ▪ of the investigator or a gynaecologist ▪ Aged 18 to 75 years ▪ Chronic hand eczema; all types of chronic hand eczema including hyperkeratotic, ▪ vesicular (e.g. pompholyx), and fingertip dermatitis, and fulfilling the following criteria: ▪ Lasting for at least 6 months since initial diagnosis ▪ Rated severe according to the Physician Global Assessment (PGA) ▪ Refractory to standard non-medicated therapy, including skin moisturisation and	▪ Patients unable to comply with the requirements of the study ▪ Female patients who were pregnant or who were planning to become pregnant or who were breast feeding ▪ Female patients of childbearing potential who could not use or would not commit to using two effective forms of contraception simultaneously under supervision of the investigator or a gynaecologist ▪ Patients whose disease was adequately controlled by standard non-medicated therapy (skin moisturisation and protection, avoidance of irritants and allergens) and standard topical corticosteroid therapy ▪ Patients with known hypersensitivity to other retinoids or vitamin A derivatives, or to any study medication component, especially soybean oil and partly hydrogenated soybean oil ▪ Patients treated with systemic corticosteroids, retinoids, or immunosuppressants, within four weeks before start of trial treatment 1 (use of inhaled steroids was permitted) ▪ Patients treated with phototherapy UVB, PUVA, Grenz rays, or X-rays within four weeks before start of trial treatment 1 ▪ Patients with known clinically relevant allergic contact dermatitis of the hands, as demonstrated by a prior positive patch test, and who had not made a reasonable

protection, and avoidance of relevant irritants and allergens ▪ Refractory to topical corticosteroid therapy, with unsatisfactory outcome (no response, transient response to ongoing therapy, or lack of tolerability) after at least 8 weeks of treatment within the previous 12 months unless contraindicated or not tolerated ▪ Written informed consent provided	effort to avoid relevant contact allergens, ▪ Patients who presented with (a) psoriasis lesions (including palmo-plantar psoriasis), (b) atopic dermatitis lesions requiring medicated treatment, (c) acute (non-chronic) episodes of pompholyx/dyshydrosis or of contact dermatitis, or (d) active bacterial fungal or viral infection of the hands ▪ Patients who presented with any other skin disease likely to interfere with the conduct of the study and/or the evaluation of the results ▪ Patients with any serious medical condition which, in the opinion of the investigator might interfere with the safety or the evaluation of the study, including chronic heart failure, recent myocardial infarction (chest pain within the 3 months prior to starting trial treatment with changes in ECG and/or increased cardiac enzymes), chronic renal failure, chronic liver failure, unstable hypothyroidism, chronic biliary disease, uncontrolled diabetes mellitus ▪ Patients known to be immunocompromised ▪ Patients with ALT and/or AST > 2.5 x ULN (upper limit of normal range) ▪ Patients with fasting triglyceridemia > 1.5x ULN ▪ Patients with cholesterol > 1.5 x ULN and/or LDL/cholesterol > 1.5 x ULN ▪ Patients with haemoglobin <0.9 x LLN (lower limit of normal range) ▪ Patients receiving drugs with a potential for drug-drug interactions such as systemic tetracyclines, ketoconazole, erythromycin or clarithromycin, simvastatin, or St. John's Wort within one week, or receiving systemic itraconazole within 2 weeks, prior to start of trial treatment 1 18. Patients receiving topical retinoids, macrolides, tacrolimus, or pimecrolimus on affected areas, or taking vitamin supplements containing >2000 IU vitamin A within one week before start of trial treatment ▪ Patients who had been included in the study of an investigational drug within 2 months before start of trial treatment ▪ Patients who had an active major psychiatric disorder (e.g. Major Depressive Disorder, Generalized Anxiety Disorder, Bipolar Disorder (I or II), or schizophrenia)

6.8.3 Critical appraisal of relevant non-RCTs

BAP00026[44, 44]

This is an open label non randomised study in which assessment of response may be influenced by the lack of blinding with regards to treatment identity and the lack of control group permits limited objective assessment of treatment effects.

6.8.4 Results of the relevant non- RCTs

BAP00026 [44]

Table 6.8.1: Secondary efficacy parameters in the BAP00626 trial (ITT population)

	30 mg Alitretinoin N=249
PGA assessment: Clear or almost clear, N (%)	116 (46.6%)
PaGA, N (%) (clearing or almost clearing)	115 (46.2%)
Median % reduction in modified TLSS (mTLSS)	67.6%
Median % reduction in extent of disease	57.1%
PGA assessment: Partial response (Clear, almost clear or mild), N (%)	159 (63.9%)
Median time to response (responders)	86.5 days

Questionnaire on Treatment Objectives in Hand Dermatitis (QTO-HE)

Prior to initiation of treatment in open label study BAP00626, a subgroup of patients was asked to define their expectations of treatment according to their importance on a scale of 1 (least important) to 5 (most important) prior to the treatment course. The same questionnaire was applied at the end of the treatment to evaluate to what degree their expectations were met.

Baseline Evaluations:	End of Treatment Evaluation:
How important is it to you for the treatment to achieve the following objective:	How successful has the treatment been so far with regard to the following objective:
-- = does not apply to me	1 = Not at all
2 = Somewhat	3 = Moderately
4 = Quite	5 = Very
-- = does not apply to me	1 = Not at all
2 = Somewhat	3 = Moderately
4 = Quite	5 = Very

After treatment, patients completed a questionnaire in which they rated the extent to which treatment with alitretinoin had met the pre-defined expectations

Results at baseline:

- 78% (18/23) of the treatment objectives selected were rated as either quite important or very important by patients (scores ≥ 4).
- 30% (7/23) of the treatment objectives received weighted scores > 4 (maximum possible score 5)
- The highest weighting was given to the achievement of control over the disease and a return to normal life.

Results after treatment:

- The objectives ranked highest in importance (4.7 or 4.8) also received the highest success scores, and these were:
  - Have confidence in the therapy
  - No longer have a burning sensation on the skin
  - Get an improvement of the skin lesions
  - Be free of itching
  - Find a clear diagnosis and therapy

This data suggests that treatment with alitretinoin generally met patient's expectations of treatment and that those objectives identified as particularly important to patients at baseline were particularly well met by alitretinoin therapy.

Conclusion

Efficacy results were consistent with the results of previous trials, indicating marked improvement in disease signs and symptoms and in disease severity with 46.6% patients achieving clear or almost clear hands by PGA assessment with treatment with alitretinoin found to generally meet patients expectations.

6.9 Interpretation of clinical evidence

6.9.1 Provide a brief statement of the relevance of the evidence base to the decision problem.

The phase II and III clinical trials for alitretinoin were placebo controlled and therefore no active comparator data are available from randomised controlled clinical trials.

Placebo-controlled were carried out due to the the absence of any clear rationale for inclusion of potential alternative interventions as comparators. No drugs have been licensed for severe CHE and there is no trial evidence or clinical consensus that any of the alternative approaches are either more effective than placebo treatment or effective in the broad population of steroid unresponsive CHE which is the target for alitretinoin treatment

Patients in the phase III trial were specifically screened and selected as being refractory to potent topical corticosteroids. Consequently, no comparison between oral alitretinoin and topical corticosteroids was justified in these patients,

The decision problem specifies that alitretinoin should be compared to PUVA and the immunosuppressants, ciclosporin and azathioprine.

Efficacy data for these interventions have as far as possible been taken from trials conducted in a similar, steroid refractory CHE population in which exclusion of clinical subtypes of CHE was not reported. Few data from randomised clinical studies for ciclosporin and PUVA are available and no such studies have been placebo controlled. For azathioprine no data were identified. The use of data from studies in different disease states such as atopic dermatitis, was not considered appropriate. Therefore no indirect treatment comparisons can be made with the comparators identified in the decision problem.

Improvement in disease severity
The primary efficacy endpoint of the phase II and III trials was the achievement of “clear” or “almost clear” hands as defined by the Physicians Global Assessment (PGA).

- In the phase III clinical study, 48% of patients achieved a PGA of clear/almost clear hands representing improvement from severe disease including inflammatory features, pain and fissures, to having undetectable or minimal residual disease
- Both the 10mg and 30mg dosing regimens were effective, with the 30mg dose leading to a higher response rate and more rapid responses.[6]
- The activity of alitretinoin was not limited to patients with any distinct combination of CHE signs and symptoms.[6]

The efficacy demonstrated in the phase III study was seen in patients with severe disease refractory to topical steroids which is the population targeted to receive alitretinoin in clinical practice.

The categorical outcome of PGA clear/almost clear is highly relevant to clinical practice because it represents the desired outcome of treatment. This endpoint is not a surrogate of desired outcome such as % change in an individual or composite severity score and has been employed in the majority of trials to date in CHE.

PGA response in the trial was assessed essentially in the same global way that an individual dermatologist would assess treatment success in routine clinical practice; on the basis of visual appearance and questioning about symptoms, with additional trial measures employed to ensure standardised severity assessment across the wide range of participating centres.

PGA response requires the complete absence of the more troublesome inflammatory or acutely distressing features such as vesiculation and fissuring, pruritus and pain. As in the trial, attainment of clear/almost clear hands would justify discontinuation of systemic therapy . In current clinical practice however, such a definite endpoint is infrequently achieved with systemic immunosuppressive therapy,leading to prolonged, sometimes indefinite use to maintain a degree of disease control until safety, tolerability or patient acceptability preclude further use.

In addition to physician assessment of disease by PGA, patient global assessment (PaGA) was measured as a secondary endpoint. In clinical practice, it is important to verify that patients perceive similar benefit from treatment to their physicians in order to ensure concordance with therapy that is invariably less closely supervised than in clinical trials. Close agreement of PaGA with PGA in the phase III trial provides internal validation that the PGA measures outcomes of treatment that are meaningful for physicians and patients alike.

- The basis for the PGA criteria used in the phase III studies is a photographic guide, devised and validated in collaboration with dermatologists.[49] The experts reached a consensus for development of a photographic guide composed of five severity levels and four photographs per severity level. Results showed a high level of inter-rater reliability and test-re-test reproducibility.
- The PGA includes one symptom (pruritus/pain) that cannot be linked to the photographic guide but is clearly relevant to disease severity and is a major driver for patients to seek medical help.

Signs and Symptoms of Disease

The alitretinoin trials measured change in mTLSS as a secondary endpoint. mTLSS provides a continuous measure of the severity of signs and symptoms of CHE and is similar in concept to the severity scoring systems used in the available trials of comparator agents such as ciclosporin.

The mTLSS grades 7 signs and symptoms of CHE: erythema, scaling, hyperkeratosis, vesiculation and edema. In BAP00089 the mean mTLSS score at baseline was 15 out of a maximum score of 21. After treatment with alitretinoin, this was reduced by 75% and 50% for the 30mg and 10mg doses respectively

In the alitretinoin trials, change in mTLSS is included to supplement the stringently defined primary endpoint with information regarding the qualitative aspects of treatment response and their timing. In contrast, most trials of comparators have applied arbitrary cut off values to disease severity scores (eg 50%) and defined these as the primary efficacy endpoint which is considerably easier to achieve. .

Time to response

Time to response is a highly relevant outcome from the physician and patient perspective because rapid alleviation of distressing acute symptoms such as painful fissures and vesiculation is a key goal of treatment and time to response will determine how quickly patients with functional impairment due to chronic skin changes can return to work. Some comparator treatments (eg Azathioprine, PUVA) are reported to be associated with a relatively slow improvement in CHE and treatment with oral steroids may be neccesary to bring CHE under control whilst these interventions begin to take effect. Time to response was significantly shorter in the alitretinoin 30 mg group compared with 10 mg although it should be noted that the BAP00089 analysis represents time to complete/almost complete response as defined in the protocol rather than time to meaningful improvement as it would be recognised by patients.

Time to relapse/disease free period

Time to relapse is a highly relevant clinical outcome in the management of chronic disease and is one of the most important determinants of the cost effectiveness of treatment for such conditions.

For patients, CHE is associated with distressing symptoms, functional impairment and chronically impaired quality of life, all of which are revisited during relapses in disease. In addition relapse may entail a return to treatment regimens which are associated with unpleasant side effects and cumulative toxicity risks (such as systemic immunosuppression) or which are are inconvenient and expensive for patients to attend (such as outpatient PUVA).

For physicians and the NHS, relapse after treatment necessitates additional outpatient consultation, re-treatment with the same or different agents (that may require additional baseline investigations) and overall consumes healthcare resources that are not consumed by the patient in prolonged remission. Clinical feedback suggests that the possibility of relapse often leads to the continuation of immunosuppressive treatments for a number of weeks after response has been achieved in order to prolong the disease-free (if not the treatment-free) period.[18]

Although no direct comparisons are available, the time to relapse following alitretinoin treatment would appear to be longer than that reported for other treatments for CHE; 65% of responders (as defined previously) did not relapse during the 6 month period post-treatment with a median time to relapse of 168 days in patients responding to 30mg alitretinoin.[64] In one study (Granlund et al.) comparing treatment of severe CHE with ciclosporin and potent topical corticosteroids, it was reported that 50% of patients in both groups relapsed after 2 weeks.[62] Clinical opinion estimated that in patients responding to ciclosporin, time to relapse is on average around 9 weeks. Experience of PUVA suggests that after cessation of therapy relapse is observed frequently with this treatment[56,65] with clinical opinion estimating an average relapse time of around 18 weeks. There are no published data on relapse rates for CHE patients treated with azathioprine although clinical opinion estimates that patients relapse within 2-3 months of stopping treatment.[18]

Safety

Rigorous evaluation of the safety of new therapies is clearly important. Assessment of the safety of alitretinoin was based on both the reported frequency of AEs in double blind placebo controlled trials and on the proactive investigation of safety issues previously associated with the retinoid class without proof of causality (see section 6.7). In contrast, no rigorous assessment of spontaneous adverse events or targeted safety investigation is available for comparators used in CHE. In this submission, as in clinical practice; reliance is placed on reported safety in different indications (eg atopic eczema) or on anecdotal experience in CHE.

Since alitretinoin is intended for chronic intermittent treatment of CHE, and other retinoids have been associated with the potential for cumulative toxicity[20] the safety of a second treatment course was investigated in a retreatment study. A second course of treatment with alitretinoin was well tolerated, with an adverse event profile similar to that observed with the first exposure to alitretinoin, with no new or apparent late toxicity.

Although no direct comparison of safety is available for alitretinoin vs the comparators stated in the decision problem, the comparator agents are recognised to be associated with significant safety issues. Although the safety data is available for ciclosporin in other dermatological indications, its safety profile in CHE would be expected to be similar. The BAD guidelines for ciclosporin use in psoriasis emphasise the risk of nephrotoxicity, hypertension, headache, paraesthesiae and tremor. Ciclosporin can also raise serum cholesterol and triglyceride levels.[9, 42]

As with ciclosporin, there is no safety data available for the use of azathioprine in CHE but studies in patients with atopic dermatitis have highlighted the risk of nausea, abdominal pain, infection, lymphopenia, neutropenia and raised ALT and significant differences in its safety profile when used in CHE are unlikely.

The use of systemic immunosuppressants is known to significantly increase the risk of diverse malignancies, including cutaneous tumours and lymphomas, however data relating to use in transplant is not necessarily applicable to use in dermatological patients due to the considerably lower doses used. Cutaneous malignancy may however remain a significant

hazard in dermatology patients who have in addition received PUVA. The risk of non-melanoma skin cancer (NMSC) is recognized following multiple treatments with oral PUVA, with an 11-13-fold relative risk of squamous cell carcinoma (SCC) and 3-7-fold relative risk of basal cell carcinoma (BCC) after more than 260 treatments. No equivalent data exist for topical PUVA and there is currently insufficient evidence upon which to base guidelines regarding cumulative limits.

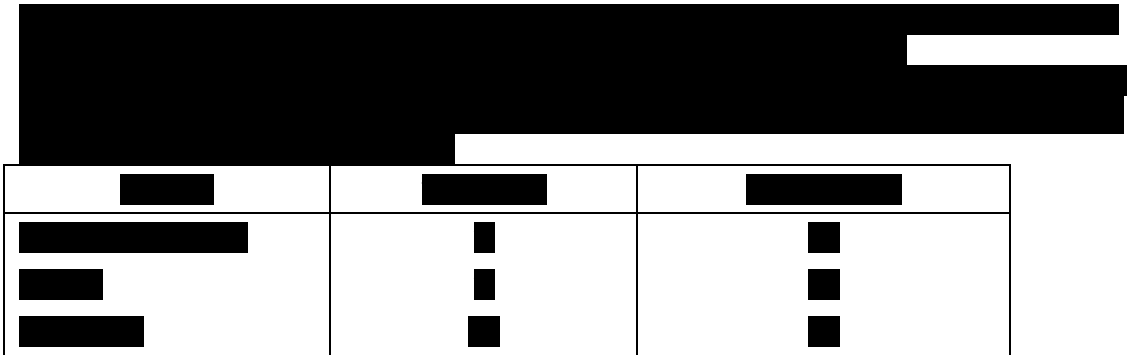
Health Related Quality of Life

Indirect evidence is presented that CHE patients moving from the severe to the clear/almost clear state, as per the primary endpoint of the BAP00089 and BAP00091 studies experience a significant improvement in quality of life (QoL) as measured by DLQI.

QoL data were not collected during either the BAP00089 or the BAP00091 study. QoL data collected during the phase II trial BAP00003 was reanalysed for the purpose of this submission to examine the relationship between change in PGA state and DLQI, independent of treatment effect.[66]

This value suggests that the impact of severe CHE on QoL is comparable to that associated with severe psoriasis in which a DLQI of >10 has been recommended by NICE as a threshold for treatment with anti TNF therapy.

Due to a lack of previous research, no published estimate of the minimally important difference (MID) in DLQI exists for patients with CHE. The minimally important difference (MID) is the smallest difference in score that is considered to be worthwhile or important and has also been defined as "the smallest difference in a score which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management.[67]



[redacted]	[redacted]	[redacted]

[redacted] This is comparable to the estimated MID values for DLQI in other dermatological conditions which range from 2 to 5 (See Table 6.9.3). [redacted]

Table 6.9.3: Minimal important difference in DLQI for dermatology conditions

Condition	MID threshold
Chronic idiopathic urticaria	2.24 to 3.10[68]
Moderate to severe psoriasis	2.4 to 3.4[68]
Axillary and palmar hyperhidrosis	2.2 and 3.0 respectively[69]
General dermatologic population	5.0[70]
[redacted]	[redacted]

[redacted] From the results of DLQI analysis by disease state presented, it would be anticipated that patients making the transition to milder disease states under the effect of alitretinoin, or any other treatment, would experience a similar decrease in DLQI unless negative aspects of therapy, eg toxicity specific to alitretinoin or other treatments, acted to mitigate these improvements in QoL.

Additional data presented from the BAP00626 study is relevant because it provides evidence that alitretinoin meets patients expectations of treatment both in terms of disease improvement and also in terms of their ability to function and enjoy life, suggesting that treatment is likely to be associated with improved utility, although.it does not directly address the impact of alitretinoin treatment on a recognised measure of utility. The results indicate that alitretinoin treatment had no obvious negative effect on a number of indicators of patient well being that were defined by patients prior to treatment, namely:

- confidence in the therapy
- being able to lead a normal daily life
- being able to lead a normal working life
- require fewer clinic appointments
- participate in normal leisure activities
- experience greater enjoyment of life

Thus the results of the BAP00626 study provide further supportive evidence that the improvement in QoL associated with improved PGA disease states as demonstrated in the observational studies presented in this submission would be experienced in patients whose CHE improved as a result of treatment with alitretinoin.

Efficacy in subtypes of severe CHE

Because of the lack of morphological exclusion criteria in the phase III trial and the large population recruited, this trial demonstrates for the first time both the highly polymorphic nature of steroid refractory CHE and the ability to effectively treat a broad range of CHE morphologies with simple once a day oral agent monotherapy. This finding has the potential to considerably simplify the management of severe CHE in clinical practice; currently characterised by treatment that is often individualised according to the perceived responsiveness of different CHE morphologies and is influenced by numerous other factors

such as clinician experience, patient risk/ability to comply with complex regimens and the availability of appropriate facilities for PUVA delivery or immunosuppressant monitoring.

6.9.2 Identify any factors that may influence the applicability of study results to patients in routine clinical practice.

Relapse
In the alitretinoin trials, relapse was defined as a return to 75% of baseline mTLSS and the use of any other active drug treatment during the observation period for relapse was not permitted. In clinical practice, return to 75% baseline severity would be viewed as a suitable threshold for re-treatment. Patients may well receive concomitant treatment such as topical corticosteroids before reaching this stage of severity or may receive them routinely as soon as clear/almost clear hands are attained. Such actions would tend to prolong the time to relapse observed in clinical practice.

Dosing
The BAP00089 and BAP00091 phase III trials patients were treated once daily with 10 mg and 30 mg doses of alitretinoin, the doses specified in the summary of product characteristic. The doses were chosen to provide the highest possible efficacy whilst maintaining an acceptable safety profile. In the phase II study 10 mg, 20 mg, and 40 mg doses of alitretinoin were used. The highest response rates were achieved with the 40 mg dose. The higher dose was associated with increased dose-related toxicity typical of oral retinoids or RXR agonists, and therefore the upper dose selected in the phase III studies was limited to 30 mg once daily. This is the recommended starting dose for alitretinoin in clinical practice.

Dose adjustment was not permitted during the BAP0089 or BAP00091 phase III studies in the event of toxicity on the 30mg dose. The incidence of withdrawals and adverse events is likely to be lower in clinical practice where dose adjustments will be made and are recommended in the SPC to manage toxicity.

Placebo response

The placebo response rates observed in the alitretinoin clinical trials are comparable to those encountered in other dermatology trials.[71] Diseases of the skin such as atopic dermatitis and CHE are recognised as susceptible to psychologically and seasonally related improvements as well as fluctuation in disease severity over time.[72, 73]

The placebo rates observed in the BAP0089 study may also have been augmented by a direct “trial participation effect”. The trial is likely to have involved more scrupulous attention to ongoing skin protection and avoidance of allergic or irritant factors than normal clinical care and almost certainly involved more regular medical contact and supervision of treatment and emollient therapy than normal clinical practice. The recognition that placebo or trial participation effects may be appreciable in dermatology trials was an important factor in inclusion of a placebo group and in the setting of the stringent primary efficacy endpoint of clear/almost clear hands.

Attainment of the trial secondary endpoint of partial improvement in CHE (PGA clear/almost clear or mild severity) would generally be accepted as representing a meaningful improvement in clinical practice and this was achieved in 61% of patients in the 30mg group. It is notable that the placebo response rate for this softer endpoint is seen to increase to 36.6% resulting in a reduced treatment difference, albeit still statistically significant.

Since the majority of trials to date in CHE effectively measure only the endpoint of partial response (usually as % improvement in continuous symptom score) and have not included a placebo group, it is by no means certain (on the basis of the placebo group response in

BAP00089) that the efficacy claimed for comparators is greater than would have been achieved by supportive care and optimised emollient use alone.

7 Cost effectiveness

7.1 Published cost-effectiveness evaluations

7.1.1 Identification of studies

A systematic search of the economic literature was conducted. The objective of the literature review was to identify current evidence for the cost effectiveness of alitretinoin, PUVA, ciclosporin or azathioprine in the treatment of patients with CHE. We sought relevant published literature, in humans in, any language (see Section 10.3, Appendix 3 for search methodology).

7.1.2 Description of identified studies

On the basis of the searches, no relevant prior studies on the cost-effectiveness of the treatment of chronic hand eczema exist. Of the 2 studies highlighted for further review, one analysed only travel costs and time off work the other reported medical attention utilisation (direct and indirect costs), change of occupation and sick leave.[59, 74]

7.2 De novo economic evaluation(s)

In the absence of a relevant published economic evaluation, manufacturers or sponsors should submit their own economic evaluation. When estimating cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal'). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Element of health technology assessment	Reference case	Section in 'Guide to the methods of technology appraisal'
Defining the decision problem	The scope developed by the institute	5.2.5 & 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 & 5.2.6
Perspective costs	NHS and Personal Social Services	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 to 5.2.12
Synthesis of	Bases in a systematic review	5.3

evidence on outcomes		
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12

HRQL, health related quality of life; NHS, National Health Service; QALYs, quality-adjusted life years

7.2.1 Technology

7.2.1.1 How is the technology (assumed to be) used within the economic evaluation? For example, give indications, and list concomitant treatments, doses, frequency and duration of use.

Alitretinoin (Toctino) is indicated for use in the treatment of adults with severe chronic hand eczema (CHE) that is refractory to potent topical steroids. The recommended dose range for alitretinoin is 10mg-30mg once daily, with a meal. The recommended start dose for alitretinoin is 30mg once daily. A dose reduction to 10mg once daily may be considered in patients with unacceptable adverse reactions to the higher dose.

A treatment course of alitretinoin may be given for 12 to 24 weeks depending on response. Discontinuation of therapy should be considered for patients who still have severe disease after the initial 12 weeks of treatment. In the event of relapse, patients may benefit from further treatment courses of alitretinoin. It is priced at 411.43 per pack of 30 soft capsules (one capsule to be taken per day) for both doses. Patients are treated concomitantly with emollients.

7.2.1.2 Has a treatment continuation rule been assumed? Where the rule is not stated in the SmPC this should be presented as a separate scenario, by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- the costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required)

- the robustness and plausibility of the endpoint on which the rule is based
- whether the 'response' criteria defined in the rule can be reasonably achieved
- the appropriateness and robustness of the time at which response is measured
- whether the rule can be incorporated into routine clinical practice
- whether the rule is likely to predict those patients for whom the technology is particularly cost effective
- issues with respect to withdrawal of treatment from non-responders and other equity considerations.

- Treatment continuation rules have been assumed for each of the treatment strategies. Patients are assumed to continue treatment (whilst having breaks in treatment between treatment cycles) until one of the following conditions are met; they reach the remission state, are unresponsive to treatment (i.e. have entered refractory group), have withdrawn from treatment following an adverse event, have reached the maximum number of allowed treatment cycles or the time horizon of the model has expired.

- For alitretinoin, PUVA, ciclosporin and azathioprine, once patients in the model enter the severe state they discontinue treatment and will enter the refractory state. The time at which this switch occurs during a treatment cycle is variable across the four agents. Once a patient enters refractory they remain there for the remainder of their time in the model.

- For each of the agents, patients with mild or moderate CHE (e.g. partial response to treatment) will switch to a refractory status at the end of the treatment cycle. This assumption was applied because patients in the alitretinoin study BAP00089 who achieved only mild or moderate PGA status were not subsequently retreated in BAP00091.

- For each of the agents, therefore, at the end of the first cycle, only patients in remission (who then relapse) will be treated in subsequent cycles. At the end of the first treatment cycle, those patients in remission are assumed to relapse after a variable time and begin re-treatment. All patients requiring re-treatment are assumed to enter subsequent treatment cycles as severe, and following re-treatment will respond in part (enter mild or moderate health states) or in full (remission). As in the first treatment cycle, patients in the severe state during the cycle who are assumed to be refractory to treatment (at a pre-specified time point) and patients at the end of the cycle who are still mild or moderate are assumed to have not responded adequately to treatment and are considered to be refractory.

- For each of the agents, once patients are refractory to their initial treatment, or reach the maximum number of allowed treatment cycles, they are switched to supportive care – the use of emollients and topical steroids.

- Feedback from clinicians suggests that in some cases patients will be switched to supportive care upon failure of second line therapy but in other cases patients may continue to receive repeated or different treatments until it is perceived that the risks no longer justify the partial benefits being obtained. This will be influenced by a complex mix of factors including individual patient risk factors, comorbidity, and CHE impact and whether the treating dermatologist is predominantly safety or efficacy focussed. A treatment model depicting the "average" long term scenario for refractory patients is thus highly uncertain and therefore has not been attempted.

7.2.2 Patients

7.2.2.1 What group(s) of patients is/are included in the economic evaluation? Do they reflect the licensed indication? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem?

Adults with severe CHE that are refractory to treatment with potent topical corticosteroids were included in the study. This reflects the licensed indication.

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7.2.2.2 Was the analysis carried out for any subgroups of patients? If so, how were these subgroups identified? If subgroups are based on differences in relative treatment effect, what clinical information is there to support the biological plausibility of this approach? For subgroups based on differences in baseline risk of specific outcomes, how were the data to quantify this identified? How was the statistical analysis undertaken?

Subgroup analysis was carried out on the following subgroups of patients:

Hyperkeratotic patients – The SPC emphasises that patients in whom the CHE has predominantly hyperkeratotic features are more likely to respond to alitretinoin treatment than those in whom the CHE predominantly presents as pompholyx. This subgroup was modelled by adjusting the efficacy data for alitretinoin to reflect the improved efficacy that has been observed in trials of predominantly hyperkeratotic patients treated with alitretinoin. Four weekly trial data were not available for the hyperkeratotic patient group and therefore the data were modelled linearly over the 24 week period. Re-treatment data was based 4 weekly data for the overall population from BAP00091 because hyperkeratotic analysis was not available.

Table 7.2.1: Hyperkeratotic First Cycle Treatment Probabilities[53]

Alitretinoin 30 mg First cycle					
	Disease Severity				
Week	**Remission**	**Mild**	**Moderate**	**Severe**	**Refractory**
0	0.000	0.000	0.000	1.000	0.000
4	0.090	0.025	0.028	0.856	0.000
8	0.181	0.050	0.057	0.712	0.000
12	0.271	0.076	0.085	0.568	0.000
16	0.362	0.101	0.114	0.424	0.000
20	0.452	0.126	0.142	0.280	0.000
24	**0.543**	**0.151**	**0.171**	**0.136**	**0.000**

Table 7.2.2: Hyperkeratotic Efficacy Data Treatment Probabilities[42]

Alitretinoin 30 mg subsequent cycles					
	Disease Severity				
Week	**Remission**	**Mild**	**Moderate**	**Severe**	**Refractory**
0	0.000	0.000	0.000	1.000	0.000
4	0.133	0.015	0.007	0.844	0.000
8	0.267	0.030	0.015	0.689	0.000
12	0.400	0.044	0.022	0.533	0.000
16	0.533	0.059	0.030	0.378	0.000
20	0.667	0.074	0.037	0.222	0.000
24	**0.800**	**0.089**	**0.044**	**0.067**	**0.000**

Women of child bearing potential have been modelled as a separate subgroup. This subgroup was identified and chosen for analysis because of the teratogenic effect of alitretinoin. To address this issue, women of child bearing potential treated with alitretinoin receive additional monitoring and must adhere to strict pregnancy prevention rules as specified in the SPC. The efficacy data was therefore the same as in the base case. The costs associated with additional monitoring were applied. These were:

- The use of an oral contraceptive during alitretinoin treatment and for two months after discontinuation
- Pregnancy consultation one month prior to start and at start of treatment and then every 28 days during treatment and 5 weeks following the end of treatment
- Pregnancy test one month prior to and at start of treatment then every 28 days for the duration of alitretinoin treatment and at 5 weeks following the end of treatment

7.2.2.3 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Refer to the subgroups identified in the scope.

A subgroup analysis was not considered for patients at high risk of cardiovascular disease. Depending on clinical interpretation of what constitutes acceptable risk for individual patients with severe CHE, it was felt that patients with existing risk factors would either; not be started on alitretinoin therapy or would start on 10mg and then titrate up to 30mg as per the SPC (by implication upon evidence of unchanged lipid profile or after satisfactory control had been achieved with statins). It is currently not possible to predict the relative proportion of patients who would be managed in these different ways, nor the rate at which elevated lipids would be brought under control during therapy with 10mg allowing the greater efficacy of 30mg to be modelled for subsequent treatment.
The management of patients developing hyperlipidaemia on treatment with alitretinoin was built into the adverse event costs included in the model.

7.2.2.4 At what points do patients 'enter' and 'exit' the evaluation? Do these points differ between treatment regimens? If so, how and why?

Patients enter the evaluation initially as severe sufferers of CHE. Patients in all treatment regimens begin treatment immediately. Patients exit the evaluation when they are deemed unresponsive to treatment (refractory) or when the remission state is reached. Patients re-enter treatment following a relapse from remission.

7.2.3 Comparator technology

What comparator(s) was/were used and why was it/were they chosen? The choice of comparator should be consistent with the summary of the decision problem (Section A).

The comparators used for the model were ciclosporin, azathioprine and PUVA. These comparators were chosen because they best represent the usual care of patients with severe CHE that is refractory to topical emollients and corticosteroids.

7.2.4 Study perspective

If the perspective of the study did not reflect NICE's reference case, provide further details and a justification for the approach chosen.

The perspective of the study is from the National Health Service (NHS) and Personal Social Services (PSS).

7.2.5 Time horizon

The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared.

What time horizon was used in the analysis, and what was the justification for this choice?

The time horizon chosen for the model is 3 years. This time horizon was chosen as it reflects the period over which the health outcomes and costs of patients are likely to differ between the treatment and comparator arms.

Since the treatments are not curative and are used to manage the symptoms of CHE, a lifetime model was considered. A lifetime model would however imply that currently available treatments could be used repeatedly over an indefinite period and this is not the case. In the case of the comparators, ciclosporin in particular, there are recommendations on the number of treatment cycles that patients can receive on the grounds of safety.[9]

The effect of adhering to these recommendations would be that after the maximum number of treatment cycles has been reached, only the effects of the supportive treatments (such as emollients) could be modelled.

Although comparable recommended limits do not exist for azathioprine and topical PUVA lifetime use is similarly not generally considered safe by dermatologists because of their potential for increasing the rate of malignancy, particularly of the skin. Furthermore, indefinite

treatment with courses of azathioprine or PUVA is unlikely to be acceptable to patients because of their requirement for frequent monitoring and hospital attendance.

7.2.6 Framework

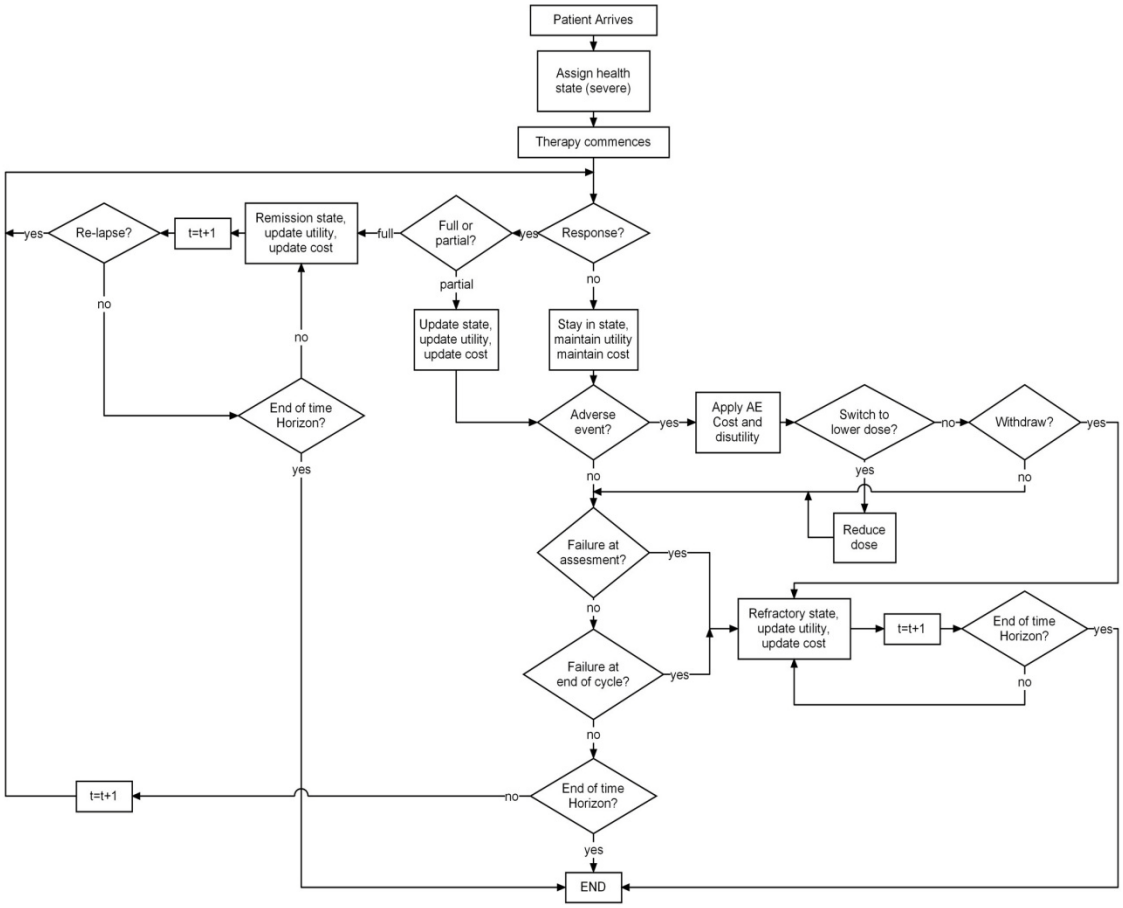
The purpose of this section is to provide details of the framework of the analysis. Section a) below relates to model-based evaluations, and section b) below relates to evaluations conducted alongside clinical trials. Please complete the section(s) relevant to the analysis.

a) Model-based evaluations

7.2.6.1 Please provide the following.

- A description of the model type.
- A schematic of the model. For models based on health states, direction(s) of travel should be indicated on the schematic on all transition pathways.
- A list of all variables that includes their value, range (distribution) and source.
- A separate list of all assumptions and a justification for each assumption.

The model is a Markov Based Simulation. The flow diagram below illustrates the structure of the model.



Variables

The table below outline all the variables used in the model, their values, range and source.

Table 7.2.3: Utility Values

Health State	Value	Source
Remission	0.913	See 7.2.8.
Mild	0.809	
Moderate	0.713	
Severe	0.582	
Refractory (Alitretinoin)	0.582	
Refractory (Ciclosporin)	0.582	
Refractory (PUVA)	0.582	
Refractory (Azathioprine)	0.582	

Table 7.2.4: Drug acquisition and resource costs

Variable	Cost (£)	Calculation	Description	Cost Source	Dose Source
Alitretinoin	383.88	(13.71*7*4)	Daily dose multiplied by time period	Basilea Pharmaceuticals	Basilea Summary of Product Characteris

					tics[53]
Ciclosporin	164.64	(5.88*7*4)	Daily dose multiplied by time period	BNF 56[75]	Advisory panel[18]
PUVA	514.65	(68.62*30)/16*4	Cost per session multiplied by sessions per week, multiplied by number of weeks	See Table 8.5.2	Advisory panel[18]
Azathioprine	16.80	0.60*7*4	Daily dose multiplied by time period	BNF 56[75]	Advisory panel[18]
Refractory costs (per 4 weeks)					
Alitretinoin	11.04	(5.20+5.84)	Cost of topical steroids and emollients	BNF 56[75]	
Ciclosporin	11.04	(5.20+5.84)	Cost of topical steroids and emollients	BNF 56[75]	
PUVA	11.04	(5.20+5.84)	Cost of topical steroids and emollients	BNF 56[75]	
Azathioprine	11.04	(5.20+5.84)	Cost of topical steroids and emollients	BNF 56[75]	
Supportive Costs (per 4 weeks)					
Alitretinoin	54.63				
		(5.20)	Emollients,	BNF 56[75]	
		(5.84)	Topical steroids	BNF 56[75]	
		(38.00)	Dermatological visit	PSSRU[76]	Not applicable
		(1.00 *0.15)	Contraceptives	BNF 56[75]	
		(0.61*0.15)	Pregnancy test	Guest Medical Ltd.[77]	Basilea Summary of Product Characteristics[53]
		(10.00*0.15)	Consultation	PSSRU[76]	Not applicable
		((1.00*2+0.61*3+10.00*3)*0.15)*(4/24)	Contraceptives for an additional 2 months, pregnancy test and consultation an extra 3 times over the treatment cycle	BNF 56[75] PSSRU[76]	Basilea Summary of Product Characteristics[53]
		3.00	Lipid monitoring	Reference Cost Schedules 2006-2007[78]	Basilea Summary of Product Characteristics[53]
Ciclosporin	53.54				
		5.20	Emollients	BNF 56[75]	
		5.84	Topical steroids	BNF 56[75]	
		38.00	Dermatological visit	PSSRU[76]	Not applicable
		(3.00*6)*(4/16)	6 serum creatine monitoring tests over the treatment cycle.	Reference Cost Schedules 2006-2007[78]	British Association of Dermatologists[9]

PUVA	49.04	5.20	Emollients,	BNF 56[75]	
		5.84	Topical steroids	BNF 56[75]	
		38.00	Dermatological visit	PSSRU[76]	Not applicable
Azathioprine	51.04		.		
		5.20	Emollients,	BNF 56[75]	
		5.84	Topical steroids	BNF 56[75]	
		38.00	Dermatological visit	PSSRU[76]	Not applicable
		3.00*(4/48)	1 TMPT cost over the treatment cycle	Reference Cost Schedules 2006-2007[78]	Anstey et al. (on behalf of British Association of Dermatologists)[32]
		(3.00*7)(4/48)	7 liver function tests over the treatment cycle	Reference Cost Schedules 2006-2007[78]	Anstey et al. (on behalf of British Association of Dermatologists)[32]
Remission costs (per 4 weeks)					
Alitretinoin	5.20	5.20	Cost of emollients	BNF 56[75]	
Ciclosporin	11.04	(5.20+5.84)	Cost of topical steroids and emollients	BNF 56[75]	
PUVA	11.04	(5.20+5.84)	Cost of topical steroids and emollients	BNF 56[75]	
Azathioprine	11.04	(5.20+5.84)	Cost of topical steroids and emollients	BNF 56[75]	

Table 7.2.5 Adverse event management costs

Alitretinoin 30mg				
	Treatment period	**AE frequency**	**Dosage**	**Cost**
Headache	4 week	20%[6]	A total of 30 tablets of paracetomol over 4 week cycle	Paracetamol cost = £1.91 for 100 tablets **Total for 30 tablets = £0.57 (BNF 56[75])**
Hyperlipidemia	Treatment cycle	14% (Based on raised cholesterol)[6]	Daily statin cost (pravastatin 10mg daily) + GP visit x 2 over 24 week cycle	Statin cost for 4 weeks = £3.07 (BNF 56[75]) GP visit costs (PSSRU[76]) = £68/6 = £ 11.33 **Total = £14.40**

Alitretinoin 10mg				
Headache	4 week	11%[6]	A total of 30 tablets of paracetomol over 4 week cycle	Paracetamol cost (BNF 56[75]) = £1.91 for 100 tablets **Total for 30 tablets = £0.57**
Hyperlipidemia	Treatment cycle	3% (Based on raised cholesterol)[6]	Daily statin cost (pravastatin 10mg daily) + GP visit x 2 over 24 week cycle	Statin cost for 4 weeks (BNF 56[75]) = £3.07 GP visit costs (PSSRU[76]) = £68/6 = £11.33 **Total = £14.40**
Ciclosporin				
Headache	4 week	10% Based on lowest estimate in SPC (very common frequency ≥ 1/10)[79]	A total of 30 tablets of paracetomol over 4 week cycle	Paracetamol cost (BNF 56[75]) = £1.91 for 100 tablets **Total for 30 tablets = £0.57**
Infection	4 week	10% (URTI/LRTI/urinary infection) Based on lowest estimate in SPC (very common frequency ≥ 1/10)[79]	Average cost of broad spectrum antibiotics; amoxicillin, erythromycin and co-amoxiclav GP visit – over 4 week cycle	Amoxicillin 250mg TDS for 7 days = £0.85 (BNF 56[75]) Erythromycin 250mg QDS for 7 days = £5.95 (BNF 56[75]) Co-amoxiclav 250/125 TDS for 7 days = £4.15 (BNF 56[75]) Average antibiotic cost = £3.65 GP visit cost = £34 (PSSRU[76]) Total = £ 37.65
Fatigue	4 week	5% Based on midpoint estimate from SPC (common frequency ≥ 1/100 and ≤ 1/10) (BNF 56[75])	No additional cost	
Muscle cramps	4 week	5% Based on midpoint estimate from SPC (common frequency ≥ 1/100 and ≤ 1/10) (BNF 56[75])	No additional cost	
Nausea	4 week	5% Based on midpoint estimate from SPC (common frequency ≥ 1/100 and ≤ 1/10)[79]	No additional cost	
Paraesthesia	Treatment cycle	5% Based on midpoint estimate from SPC (common	No additional cost	

		frequency ≥ 1/100 and ≤ 1/10)[79]		
Hyperlipidemia	Treatment cycle	10% Based on lowest estimate in SPC (very common frequency ≥ 1/10)[79]	Daily statin cost (pravastatin 10mg daily) + GP visit x 2 over 16 week cycle	Statin cost for 4 weeks = £3.07 (BNF 56[75]) GP visit costs (PSSRU[76]) = £68/4 = £17 **Total = £20.07**
Liver dysfunction	Treatment cycle	5% Based on midpoint estimate from SPC (common frequency ≥ 1/100 and ≤ 1/10) [79]	Additional 2 blood tests on top of standard monitoring costs over 16 weeks	(£3x2)/4 = **£1.50 (**Reference Cost Schedules 2006-2007[78])
Hypertension	Treatment cycle	10% Based on lowest estimate in SPC (very common frequency ≥ 1/10) [79]	Treat with nifedipine (recommended antihypertensive) with 2 GP visits over 16 weeks	Nifidipress MR 10mg BD = £9.23 (BNF 56[75]) GP visit costs (PSSRU[76]) =(£34x2)/4 = £17 **Total = £ 26.23**
Nephrotoxicity	Treatment cycle	10%	Additional 2 blood tests on top of standard monitoring costs over 16 weeks	(£3x2)/4 = £1.50 (Reference Cost Schedules 2006-2007[78])
PUVA				
Dry, itchy skin	4 week	25%	No additional cost – treated with existing emollients	
Azathioprine				
Nausea	4 week	51%[31]	No cost associated with this adverse event	
Abdominal pain	4 week	10%[31]	No cost associated with this adverse event	
Headache	4 week	12%[31]	A total of 30 tablets of paracetomol over 4 week cycle	Paracetamol cost = £1.91 for 100 tablets (BNF 56[75]) Total for 30 tablets = = £0.57
Lymphopenia	Treatment cycle	43%[31]	Additional 6 blood tests on top of standard monitoring costs over 48 weeks	=(£3*6)/12 = 1.50 (Reference Cost Schedules 2006-2007[78])
URTI/LRTI	Treatment cycle	5%[31]	Average cost of broad spectrum antibiotics; amoxicillin, erythromycin and co-amoxiclav GP visit – over 4	Amoxicillin 250mg TDS for 7 days = £0.85 Erythromycin 250mg QDS for 7 days = £5.95 Co-amoxiclav 250/125 TDS for 7

			week cycle	days = £4.15 Average antibiotic cost = £3.65 GP visit cost = £34 Total = £ 37.65
Neutropenia	Treatment cycle	5%[31]	Additional 6 blood tests on top of standard monitoring over 48 weeks	=(£3*6)/12 = £1.50 (Reference Cost Schedules 2006-2007[78])
Liver dysfunction	Treatment cycle	10%[31]	Additional 6 blood tests on top of standard monitoring costs over 48 weeks	=(£3*6)/12 = £1.50 (Reference Cost Schedules 2006-2007[78])

Probability of withdrawal and utility decrements

The probability associated with withdrawing from treatment had to be estimated for most adverse events since there was no data available. The alitretinoin trial showed that headache led to withdrawal in 1 in 5 cases, therefore a probabilty of 20% was used for this event.[6] The assumption has been made that patients experiencing an adverse event lasting 4 weeks or less have a 20% probability of withdrawal, whilst patients experiencing an adverse event lasting longer than a the 4 weekly treatment cycle, such as a hypertension have a higher probability of withdrawal at 40%. The disutility associated with an AE has been set to 0 in the absence of referenceable values.

Sources

The tables below show the transition probabilities for alitretinoin for each dosage option in the first cycle and subsequent cycles:

The tables below show the efficacy data for alitretinoin and the comparators at four week intervals. These data were used to populate the model. The efficacy of alitretinoin (for each dosage option) in the first cycle and subsequent cycles was obtained from the clinical trials, BAP00089 for the first treatment cycle and BAP00091 for subsequent treatment cycles.[42, 47] The efficacy of comparators was informed by clinical opinion.[18]

Table 7.2.6: Response rates for alitretinoin (30mg) – first cycle

	Disease severity				
Week	Remission	Mild	Moderate	Severe	Refractory
4	0.072	0.161	0.374	0.394	0.000
8	0.236	0.204	0.345	0.214	0.000
12	0.280	0.233	0.285	0.201	0.000
16	0.339	0.243	0.246	0.172	0.000
20	0.408	0.192	0.231	0.170	0.000
24	0.478	0.145	0.216	0.162	0.000

Table 7.2.7: Response rates for alitretinoin (30mg) – subsequent cycles

	Disease severity				
Week	Remission	Mild	Moderate	Severe	Refractory
4	0.191	0.362	0.340	0.106	0.000
8	0.479	0.313	0.188	0.021	0.000
12	0.429	0.469	0.061	0.041	0.000
16	0.714	0.184	0.061	0.041	0.000

20	0.694	0.163	0.102	0.041	0.000
24	0.796	0.082	0.041	0.082	0.000

Table 7.2.8: Response rates for alitretinoin (10mg) – first cycle

	Disease severity				
Week	Remission	Mild	Moderate	Severe	Refractory
4	0.020	0.084	0.354	0.543	0.000
8	0.071	0.188	0.388	0.354	0.000
12	0.114	0.263	0.375	0.248	0.000
16	0.168	0.251	0.375	0.207	0.000
20	0.219	0.265	0.333	0.182	0.000
24	0.280	0.224	0.304	0.192	0.000

Table 7.2.9: Response rates for alitretinoin (10mg) – subsequent cycle

	Disease severity				
Week	Remission	Mild	Moderate	Severe	Refractory
4	0.053	0.421	0.316	0.211	0.000
8	0.050	0.600	0.350	0.000	0.000
12	0.150	0.300	0.450	0.100	0.000
16	0.250	0.400	0.200	0.150	0.000
20	0.250	0.450	0.200	0.100	0.000
24	0.500	0.300	0.150	0.050	0.000

Table 7.2.10: Response rates for ciclosporin

	Disease severity				
Week	Remission	Mild	Moderate	Severe	Refractory
4	0.100	0.100	0.100	0.700	0.000
8	0.300	0.200	0.200	0.300	0.000
12	0.500	0.100	0.100	0.300	0.000
16	0.500	0.100	0.100	0.300	0.300

Table 7.2.11: Response rates for PUVA

	Disease severity				
Week	Remission	Mild	Moderate	Severe	Refractory
4	0.000	0.000	0.100	0.900	0.000
8	0.150	0.050	0.100	0.700	0.000
12	0.400	0.050	0.050	0.500	0.000
16	0.500	0.100	0.100	0.300	0.000

Table 7.2.12: Response rates for azathioprine

	Disease severity				
Week	Remission	Mild	Moderate	Severe	Refractory
4	0.000	0.000	0.000	1.000	0.000
8	0.000	0.000	0.075	0.925	0.000
12	0.000	0.100	0.400	0.500	0.000
16	0.050	0.150	0.300	0.500	0.000
20	0.050	0.200	0.250	0.500	0.000
24	0.100	0.200	0.200	0.500	0.000
28	0.100	0.200	0.200	0.500	0.000
32	0.100	0.175	0.175	0.550	0.000
36	0.100	0.150	0.150	0.600	0.000
40	0.100	0.125	0.125	0.650	0.000
44	0.100	0.100	0.100	0.700	0.000
48	0.100	0.100	0.100	0.700	0.000

Treatment cycle lengths in the model vary depending on the treatment option. Alitretinoin has a cycle length of 24 weeks,[6] azathioprine has a cycle length of 48 weeks, whilst Ciclosporin and PUVA have cycle lengths of 16 weeks. These treatment periods reflect the average time that patients are treated in standard clinical practice.[18]

The table below shows the characteristics of the treatment cycles for each of the treatment options.

Table 7.2.13: Treatment cycle information

Treatment	Treatment length (weeks)	Maximum cycles	Average time to re-treatment (weeks)
Alitretinoin	24	-	24
Ciclosporin	16	4	9.6
PUVA	16	-	18
Azathioprine	48	-	10

Assumptions

The list below outlines all the assumptions that have been made to develop the model:

Patients in the severe group will discontinue treatment at a specified time point during the treatment cycle (except for PUVA where patients with severe CHE continue treatment). Once this time point is reached patients are considered to be refractory to treatment.

- 12 weeks for alitretinoin
- 12 weeks for ciclosporin
- 16 weeks for azathioprine
- 16 weeks for PUVA

Patients that reach the remission state will enter subsequent treatment cycles when they relapse.

Patients that reached the mild or moderate groups by the end of the first treatment cycle will begin enter the refractory state.

Patients that reached the refractory group will remain in this group in all subsequent cycles i.e. the refractory group is an absorbing state.

The average time to remission was calculated for each treatment option using the efficacy data.

No mortality has been assumed because there is no expected difference in mortality between the treatment options and the time horizon is short.

7.2.6.2 Why was this particular type of model used?

This model was selected on the basis that it adequately characterised the natural epidemiology of the disease (the health states) and the mitigating effects of patient response to treatment. It also enables the costs and benefits associated with different treatment strategies to be calculated in assessing the relative cost-effectiveness of the treatment options.

7.2.6.3 What was the justification for the chosen structure? How was the course of the disease/condition represented? Please state why any possible other structures were rejected.

The model's structure reflects the progression of the disease and the cyclical nature of treatment. The course of the disease was modelled using different health states to describe the severity of the disease at different stages. Patients could be in one of the following health states at one time; 'severe', 'moderate', 'mild', 'remission' or 'refractory'. All patients begin the simulation in the severe health state. Through treatment, the patient should move to a less severe health state, in which disease features will be less marked or absent. Since the drug is not curative, the ultimate goal for patients receiving treatment is to reach the remission state of clear/almost clear hands. Patients will however eventually relapse (disease features reappear to a level sufficient to warrant retreatment) and it has been assumed for this model that they at that point re-enter the severe state.

The refractory health state is used to describe those patients that have not responded adequately to treatment. These are patients that remain severe after a certain time point (dependent on the treatment and how quickly it typically exerts its maximum effect) and also those patients who still have mild/moderate disease at the end of the defined treatment period. Depending on the treatment option, the refractory state is populated by using rules that move non-responsive patients from their current state to the refractory state.

These health states were considered appropriate since they are based upon the Physician's Global Assessment (PGA) classifications of the disease and the disease activity score (mTLSS) used in the BAP00089 and BAP00091 studies for alitretinoin The refractory state is equivalent to the trial definition of non-responder (PGA state still mild, moderate or severe after treatment). Patients who have met the trial definition of response (PGA clear/almost clear), have discontinued treatment but have not met the criteria for retreatment (return to 75% of baseline mTLSS) are considered to be in the remission state.

The cyclical nature of treatment is also well represented in this structure by separating treatment into distinct treatment cycles. Patients will receive treatment until the end of the cycle at which point treatment will cease, all those patients that did not reach the remission stage by this time will be classed as refractory to this treatment and will receive supportive care for the remainder of their time in the model. Those patients that did reach the remission stage will continue treatment in subsequent cycles after the remission period is over.

7.2.6.4 What were the sources of information used to develop and inform the structure of the model?

Clinical trials and expert opinion were used to develop and inform the structure of the model.

The phase III clinical trials, BAP00089 and BAP00091 were used to populate the efficacy of alitretinoin in the first treatment cycle and subsequent treatment cycles respectively.

The output of an expert panel of dermatologists was used to populate the efficacy, time to treatment withdrawal and time to treatment relapse of ciclosporin, PUVA and azathioprine. It was necessary to use clinical opinion due to the paucity of data for the comparators as outlined in section 6.6 of this submission.

7.2.6.5 Does the model structure reflect all essential features of the condition that are relevant to the decision problem? If not, why not?

Yes, the model reflects all essential features of the condition that are relevant to the decision problem.

7.2.6.6 For discrete time models, what was the model's cycle length, and why was this length chosen? Does this length reflect a minimum time over which the pathology or symptoms of a disease could differ? If not, why not?

The model operates on monthly intervals and this was chosen due to the variability in treatment cycle length and time to re-treatment for each treatment option. Furthermore, the clinical data for alitretinoin was collected on a 4 weekly basis therefore it is rational that the model utilises the same intervals and therefore remains consistent with the timing of the clinical observations.[47]

Treatment cycle lengths in the model vary depending on the treatment option. Alitretinoin has a cycle length of 24 weeks;[6] azathioprine has a cycle length of 48 weeks, whilst ciclosporin and PUVA have cycle lengths of 16 weeks. These treatment periods reflect the average time that patients are treated in standard clinical practice based on clinical opinion.[18]

7.2.6.7 Was a half-cycle correction used in the model? If not, why not?

A half cycle correction was not used in the model. It was judged that a half cycle correction would not be informative in light of the uncertainty surrounding patients' transitions through the model.

7.2.6.8 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what

assumption was used about the longer-term difference in effectiveness between the technology and its comparator?

Clinical outcomes have been extrapolated beyond the clinical trial follow up period in the case of alitretinoin. The assumption made is that the efficacy of treatment in future treatment cycles (beyond the scope of the clinical trials) is the same as the efficacy data observed in the re-treatment clinical trial (BAP00091).[42]

In the case of the comparator drugs i.e. ciclosporin, PUVA and azathioprine, because no adequate trials in CHE exist, expert opinion has been used to populate all efficacy data and subsequent treatment cycles have been modelled on the same efficacy data as the first cycle.

b) Non-model-based economic evaluations

7.2.6.9 Was the evaluation based on patient-level economic data from a clinical trial or trials?

N/A

7.2.6.10 Provide details of the clinical trial, including the rationale for its selection.

N/A

7.2.6.11 Were data complete for all patients included in the trial? If not, what were the methods employed for dealing with missing data for costs and health outcomes?

N/A

7.2.6.12 Were all relevant economic data collected for all patients in the trial? If some data (for example, resource-use or health-related utility data) were collected for a subgroup of patients in the trial, was this subgroup prespecified and how was it identified? How do the baseline characteristics and effectiveness results of the subgroup differ from those of the full trial population? How were the data extrapolated to a full trial sample?

N/A

7.2.6.13 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what

assumption was used about any longer-term differences in effectiveness between the technology and its comparator?

N/A

7.2.7 Clinical evidence

Where relevant, answers to the following questions should be derived from, and consistent with, the clinical evidence section of the submission (section 5). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided and a justification for the approach provided.

7.2.7.1 How was the baseline risk of disease progression estimated? Also state which treatment strategy represents the baseline.

Data on disease progression was extracted from relevant clinical trials.[42, 47] The baseline treatment strategy is the treatment of CHE with alitretinoin, compared to treatment with azathioprine, ciclosporin or PUVA.

7.2.7.2 How were the relative risks of disease progression estimated?

N/A

7.2.7.3 Were intermediate outcome measures linked to final outcomes (such as patient survival and quality-adjusted life years [QALYs])? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

No. Patients were assumed to be treated with one of alitretinoin, azathioprine, ciclosporin or PUVA. Patient outcomes were described using utility values for each of the modelled health states (see 7.2.6.1).

7.2.7.4 Were the health effects or adverse effects associated with the technology included in the economic evaluation? If not, would their inclusion increase or decrease the estimated cost effectiveness of this technology?

Adverse effects for the technology and comparators were included. For alitretinoin both headache and hyperlipidemia were included at frequencies recorded in rigorous randomised controlled trials in the disease population specified in the decision problem.

For the comparators azathioprine, ciclosporin and PUVA, because no comparable trial evidence exists in CHE, reliance was placed on reported safety of use in different indications (eg atopic eczema) or on anecdotal experience of these agents in CHE. Only those adverse events considered relevant to the doses used in dermatology were considered. It was also assumed that there is a low threshold for discontinuation or dose reduction of systemic immunosuppressive agents in dermatology therefore no long-term costs associated with adverse events such as nephrotoxicity for ciclosporin were included. (See section 7.2.6.1).

Similarly, for both the systemic immunosuppressants and PUVA, no costs associated with malignancy were included because of the probable lead time to its development after accumulated exposure, and the existence of insufficient data on precise risk.

7.2.7.5 Was expert opinion used to estimate any clinical parameters? If so, how were the experts identified, to which variables did this apply, and what was the method of elicitation used?

All the clinical parameters for alitretinoin were taken from the phase III studies BAP00089 and BAP00091.

The data for the comparators was based on clinical expert opinion. A panel meeting was held with a group of 7 invited clinical dermatologists from England and Wales, selected on the basis of known special interest in chronic hand eczema or contact dermatitis. The clinicians were provided with the alitretinoin trial definitions of the PGA categories several weeks in advance of the meeting and asked to consider which of the comparators they would use to treat patients with PGA severe CHE that was unresponsive to topical steroids. At the meeting itself the panel were asked to estimate the 4 weekly efficacies for the comparators in patients with severe CHE expressed as PGA severe, moderate, mild or clear/almost clear, time to relapse and the time at which treatment would be stopped in patients remaining PGA severe. Where published trial data for comparators was available from related indications (e.g. atopic eczema) or from trials in hand eczema of varying severity or unresponsiveness to steroids this was presented in summarised form at the meeting. Feedback was invited from the panel as to how closely reported trial results reflected their own clinical experience in severe CHE that was unresponsive to topical steroids. A report from this meeting was circulated to clinicians to gain their agreement on the outputs.

7.2.7.6 What remaining assumptions regarding clinical evidence were made? Why are they considered to be reasonable?

No further assumptions were made.

7.2.8 Measurement and valuation of health effects

The value of health effects should be expressed in terms of QALYs for the appropriate time horizon. For the reference case, the measurement of changes in HRQL should be reported directly from patients and the value of changes in patients' HRQL (that is, utilities) should be based on public preferences using a choice-based method. The EQ-5D is the preferred measure of HRQL in adults. The methods to elicit EQ-5D utility values should be fully described. When EQ-5D data are not available or are inappropriate for the condition or effects of treatment, the valuation methods should be fully described and comparable to those used for the EQ-5D. Data collected using condition-specific, preference-based measures may be presented in separate analyses. The use of utility estimates from published literature must be supported by evidence that demonstrates that they have been identified and selected systematically.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

7.2.8.1 If health effects were not expressed using QALYs, what health outcome measure was used and what was the justification for this approach?

Health effects were expressed using the expected difference in utility accumulated over the modelled time horizon for the selected cohort size. As there is no expected affect of treatment on mortality and because of the relatively short time horizon for which the expected costs and benefits of treatment are likely to differ, quantity of life was not modelled.

7.2.8.2 Which health effects were measured and valued? Health effects include both those that have a positive impact and those with a negative impact, such as adverse events.

The health effects modelled were the utility of a reduction in disease severity (see 7.2.6.1).

7.2.8.3 How were health effects measured and valued? Consideration should be given to all of the following:

- State whether the EQ-5D was used to measure HRQL or provide a description of the instrument/s used.
- Provide details of the population in which health effects were measured. Include information on recruitment of sample, sample size, patient characteristics and response rates.
- Were the data collected as part of a RCT? Refer to section 5.3 as necessary and provide details of respondents.
- How were health effects valued? If taken from the published literature, state the source and describe how and why these values were selected. What other values could have been used instead?
- Was a mapping mechanism (or 'cross-walk') generated to estimate health-related utilities of patients in the trials? Provide details of the rationale for the analysis, the instruments used, the sample from which the data were derived and the statistical properties of the mapping mechanism.
- Were health states directly valued? If so, provide details of the rationale for the analysis, the HRQL measures that were valued, the population who produced the values and full details of the methods used. Explain the rationale for the analysis and the choice of instruments used.

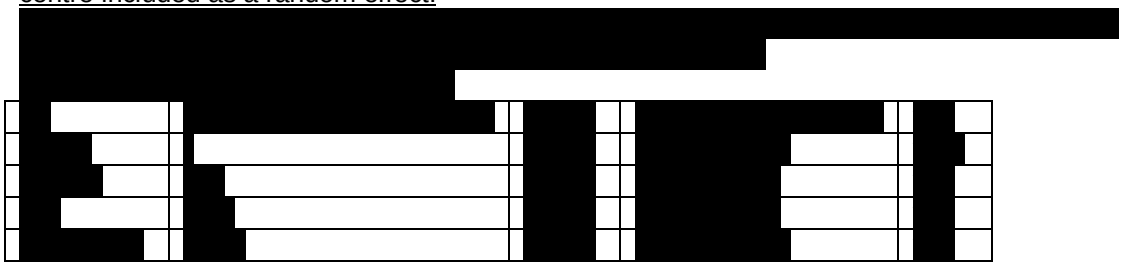
Utility values were derived using values from the Dermatology Life Quality Index (DLQI) and a published mapping exercise, which converted the values into EQ-5D data.

The DLQI is a widely used measure of the quality of life in patients with dermatological diseases such as psoriasis and eczema. It is calculated by summing the results of a 10 question quality of life questionnaire, resulting in a maximum score of 30 and a minimum score of 0. The higher the DLQI score, the more quality of life has been impaired.

The DLQI was used in the phase II dose ranging study of alitretinoin but not in the subsequent phase III study. The phase II data allows the effect of improvement in PGA status on DLQI to be examined. This study did not however include the 30mg dose of interest. Although trends to improved DLQI were seen in the alitretinoin treated groups, the study was not sufficiently powered to demonstrate statistical differences in DLQI between the 10mg; 20mg, 40mg groups and placebo at the end of treatment (see section 6.4).

An analysis of change in DLQI associated with change in PGA status was performed using data from the phase II BAP00003 study population.[66]

Data from 162 patients were available and were analysed using a generalized mixed model, including treatment group and PGA score at 3 months as fixed effects, with investigational centre included as a random effect.



[redacted]

A published method of converting DLQI scores into EQ-5D data was identified and employed. A regression analysis undertaken by Woolacott et al found a statistically significant relationship between psoriasis-related quality of life (as measured by the DLQI) and utility (as measure by the EQ-5D).[80] Furthermore, a one point increase in the DLQI was found to be associated with a fall of 0.0248 in patient utility. Therefore, DLQI scores could be converted into EQ-5D scores using the following algorithm:

EQ-5D utility score = 0.956 – (0.0248 x DLQI Total Score)

Based on the analysis of the data from BAP0003 the following utilities were calculated.

Table 7.2.15: Change in DLQI and utility score based on PGA

PGA	[redacted]	[redacted]
Severe	[redacted]	[redacted]
Moderate	[redacted]	[redacted]
Mild	[redacted]	[redacted]
Almost Clear	[redacted]	[redacted]
Clear		

7.2.8.4 Were any other generic or condition-specific preference based measures used in the clinical trials? Provide a description of the data below. The results should be considered in a sensitivity analysis (see Section 6.2.11).

No other preference based measures were used in the BAP00089 and BAP00091 studies used in the economic evaluation. Patient preference data are available from the open label study BAP00626 (see section 6.8). However, this study does not directly address the impact of alitretinoin treatment on a recognised quality of life measure.

7.2.8.5 Were any health effects excluded from the analysis? If so, why were they excluded?

No.

7.2.9 Resource identification, measurement and valuation

For the reference case, costs should relate to resources that are under the control of the NHS and PSS when differential effects on costs between the technologies under comparison are possible. These resources should be valued using the prices relevant to the NHS and PSS. Evidence should be

presented to demonstrate that resource use and cost data have been identified systematically.

Some technologies may have a substantial impact on the costs (or cost savings) to other government bodies. In these exceptional circumstances, costs to other government bodies may be included if this has been specifically agreed with the Department of Health, usually before referral of the topic. When non-reference-case analyses include these broader costs, explicit methods of valuation are required. In all cases, these costs should be reported separately from NHS/PSS costs. These costs should not be combined into an incremental cost-effectiveness ratio (ICER; where the QALY is the outcome measure of interest).

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

7.2.9.1 What resources were included in the evaluation? (The list should be comprehensive and as disaggregated as possible.)

The resources included in the analysis were the resource costs associated with patient treatment; monitoring and adverse events (see 7.2.6).

7.2.9.2 How were the resources measured?

The unit costs associated with each of the resource categories were identified from published sources (see 7.2.1.6). Costs were converted to monthly costs, where required, to reflect the monthly cycles of the economic model.

7.2.9.3 Were the resources measured using the same source(s) of evidence as the baseline and relative risks of disease progression?

No. Drug costs and costs of supportive treatments were identified and applied from published sources as none were available from the trials used as the basis of the clinical efficacy profiles.

7.2.9.4 Were resources used to treat the disease/condition included for all relevant years (including those following the initial treatment period)?

Provide details and a justification for any assumptions that were made (for example, assumptions regarding types of subsequent treatment).

Yes. Justification – see 7.2.1.2.

7.2.9.5 What source(s) of information were used to value the resources? Were alternative sources of information available? Provide a justification for the preferred source and explain any discrepancies between the alternatives.

See 7.2.9.3.

7.2.9.6 What is the unit cost (excluding VAT) of the intervention(s) included in the analysis? Does this differ from the (anticipated) acquisition cost reported in section 1? If price discounts are presented in sensitivity analyses provide details of formal agreements regarding the discount including the period over which the discount is agreed and confirmation of national organisations with which the discount has been agreed for the whole of the NHS in England and Wales.

Unit costs are summarised in section 7.2.6.1. The cost of Alitretinoin is £13.71 per day, for both 10mg and 30mg doses. This cost is not expected to differ from the acquisition cost. No price discounts are assumed or modelled.

7.2.9.7 Does the technology require additional infrastructure to be put in place? Provide details of data sources used to inform resource estimates and values.

Alitretinoin does not require any additional infrastructure in this disease area. The requirements of the pregnancy prevention programme for alitretinoin use in women of childbearing potential are identical to those for isotretinoin used in the treatment of acne. A variety of clinic based service models exist to meet the pregnancy prevention requirements of isotretinoin therapy and no service redesign will be needed for the introduction of alitretinoin.

7.2.9.8 Were the resources measured and valued in a manner consistent with the reference case? If not, how and why do the approaches differ?

Yes.

7.2.9.9 Were resource values indexed to the current price year?

Prices were taken from the most recent published evidence. In the case of the drug costs the prices are taken from the BNF 56 (2008),[75] costs for staff resource and monitoring were taken from the latest available figures (PSSRU Unit costs of Health and Social Care 2007,[76] Primary Care Trusts Reference Cost Schedules 2006-2007[78]).

7.2.9.10 Provide details of and a justification for any assumptions that were made in the estimation of resource measurement and valuation.

Daily costs were multiplied to monthly costs using a 4 week period as reflective of one month. The cost of supportive care and adverse events were calculated as these would be applied in routine clinical practice.[18]

7.2.10 Time preferences

Were costs and health benefits discounted at the rates specified in NICE's reference case?

Yes. Costs and utility values were discounted at 3.5%, this is consistent with NICE's reference case.

7.2.11 Sensitivity analysis

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

7.2.11.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated including a description of alternative scenarios included in the analysis.

The economic model assumes patients with CHE experience decreases and increases in disease activity in response to treatment. These movements are described by changes in the health states that correspond to treatment successes (remission), treatment success in part (mild or moderate CHE) and treatment failures (refractory to treatment). This structure reflects the natural history of the disease. Threshold analysis was used to assess the influence of different clinical efficacy data on the relative cost-effectiveness of alitretinoin versus the comparator interventions. The percentage of patients in remission (e.g. fully responsive to treatment) was varied for alitretinoin and the comparators such that the base case ICERs moved towards £20,000 (if initially below) or below £20,000 (if initially above) – where ICERs below £20,000 are consistent with alitretinoin being a cost effective use of societal resources. This has been termed “threshold analysis 1” and “threshold analysis 2” in the results section.

7.2.11.2 Which variables were subject to sensitivity analysis? How were they varied and what was the rationale for this?

The modelled time horizon in the base case was 3 years. This was varied to consider the incremental cost-effectiveness of the treatments over 1, 6, 10 and 20 years. The rationale for this is to explore the expected costs and benefits associated with the different treatments, given the assumed treatment algorithms.

[redacted]

Drug costs were considered deterministic and were not subject to sensitivity analysis. The exception to this is PUVA where a range of per session costs was identified from clinical centres. In the sensitivity analysis the cost of PUVA was varied from £49 (the minimum observed cost of a single PUVA session) and £100 (the maximum observed cost).

The cost of supportive treatments was consistent across alitretinoin, azathioprine, ciclosporin and PUVA. Varying these costs would be applied equally. On this basis sensitivity analysis was not conducted on these parameters.

7.2.11.3 Was probabilistic sensitivity analysis (PSA) undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated; including the derivation and value of 'priors'.

PSA was not undertaken. There is considerable uncertainty regarding the clinical efficacy data for comparators in this evaluation. The clinical efficacy data which is used to describe patient responses to alitretinoin treatment at 4 weekly intervals is sourced from a single trial (for alitretinoin) whereas it is sourced from a single panel of clinical experts for azathioprine, ciclosporin and PUVA. This data is highly uncertain and does not permit a meaningful characterisation of the uncertainty surrounding patient response to treatment. No other clinical efficacy data was available. Assessing the joint uncertainty surrounding the input parameters would therefore be made against a backdrop of clinical data that may or may not reflect patients' response to the different therapies in normal clinical practice.

On this basis it was considered that PSA would not give an intuitive or meaningful representation of the uncertainty surrounding the input values. We considered univariate sensitivity analysis and "threshold" analysis to be more meaningful in order to assess the impact on ICERs of changes to the value of key model variables.

7.2.12 Statistical analysis

7.2.12.1 How were rates or probabilities based on intervals transformed into (transition) probabilities?

The transition probabilities were based upon the efficacy observed at the end of the treatment cycles. The probabilities were applied in a similar fashion in the model, where patients were modelled to be in the same states at the end of the treatment cycle as observed in the trials (or to reflect clinical opinion in the case of the comparators).

7.2.12.2 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

Yes this is reflected in the clinical data used in the evaluation.

7.2.13 Validity

Describe the measures that have been undertaken in order to validate and check the model.

The economic model has been double coded and each reviewed by a person other than the person who constructed the model.

The model was subjected to an extreme value analysis where parameter values were varied beyond what would be considered "reasonable" and the effects on the simulated costs and utilities observed to ascertain if the model was consistent with the structural assumptions (i.e. the clinical efficacy data) and a priori expected differences in costs and benefits between the treatments modelled.

7.3 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following:

- costs, QALYs and incremental cost per QALY
- disaggregated results such as life years gained, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- a statement as to whether the results are based on a probabilistic sensitivity analysis
- cost-effectiveness acceptability curves including a representation of the cost-effectiveness acceptability frontier
- scatterplots on cost-effectiveness quadrants
- a tabulation of the mean results (costs, QALYs, ICERs) the probability that the treatment is cost-effectiveness a thresholds of £20,000-£30,000 per QALY gained and the error probability.

7.3.1 Base-case analysis

7.3.1.1 What were the results of the base-case analysis?

Probabilistic sensitivity analysis (and hence cost-effectiveness acceptability curves, scatterplot on cost-effectiveness quadrants) were not generated. This rationale in support of this is detailed in section 7.2.11.3.

Threshold analysis is presented to assess the effect of changes in the proportion of patients in remission at the end of the treatment cycle such that the base case ICER moves above or below the £20,000 - £30,000 threshold. Changes to the efficacy of alitretinoin are labelled

“Threshold analysis 1” and changes to the efficacy of the comparator treatment “Threshold analysis 2”.

The main findings of the base case analysis and sensitivity analyses (time horizon, utility values) are provided as a single table (see below) for the comparison of alitretinoin to ciclosporin, PUVA and azathioprine, respectively. The results for the subgroup analysis (hyperkeratotic patients and women of child bearing age) are presented thereafter.

Results are reported as summarised in disaggregated form for the total and incremental costs and benefits and the ICER.

Table 7.3.1 Base case and sensitivity analysis: Alitretinoin versus Ciclosporin

Scenarios	Treatment	Total Costs	Incremental Costs	Total Utility	Incremental Utility	ICER
Base Case	**Ciclosporin**	£1,580.72		1.79		
	Alitretinoin	£3,388.33	£1,807.62	2	0.21	**£8,614.43**
1 Year	**Ciclosporin**	£1,142.62		0.67		
	Alitretinoin	£2,207.65	£1,065.04	0.74	0.07	**£15,936.24**
6 Years	**Ciclosporin**	£1,854.65		3.31		
	Alitretinoin	£4,346.33	£2,491.67	3.61	0.3	**£8,269.40**
10 Years	**Ciclosporin**	£2,346.25		5.11		
	Alitretinoin	£4,982.05	£2,635.81	5.43	0.33	**£8,051.30**
20 Years	**Ciclosporin**	£3,203.10		8.66		
	Alitretinoin	£5,864.73	£2,661.62	8.98	0.33	**£8,118.26**
Alternative Utility Values	**Ciclosporin**	£1,580.71		2.04		
	Alitretinoin	£3,388.33	£1,807.62	2.15	0.11	**£16,756.47**
Threshold analysis 1 (Reduce efficacy by 30%)	**Ciclosporin**	£1,490.25		1.79		
	Alitretinoin	£2,866.25	£1,376.00	1.85	0.07	**£19,833.18**
Threshold analysis 2 (Increase efficacy by 50%)	**Ciclosporin**	£1,438.65		1.85		
	Alitretinoin	£3,388.33	£1,949.68	2.00	0.14	**£13,503.59**

Table 7.3.2 Base case and sensitivity analysis:Alitretinoin versus PUVA

Scenarios	Treatment	Total Costs	Incremental Costs	Total Utility	Incremental Utility	ICER
Base Case	**PUVA**	£3,481.28		1.8		
	Alitretinoin	£3,388.33	-£92.94	2	0.2	**-£468.98**
1 Year	**PUVA**	£2,670.40		0.67		
	Alitretinoin	£2,207.65	-£462.75	0.74	0.07	**-£6,745.10**
6 Years	**PUVA**	£3,881.76		3.32		
	Alitretinoin	£4,346.33	£464.56	3.61	0.29	**£1,614.25**
10 Years	**PUVA**	£4,296.68		5.11		
	Alitretinoin	£4,982.05	£685.38	5.43	0.32	**£2,171.75**
20 Years	**PUVA**	£5,186.25		8.67		
	Alitretinoin	£5,864.73	£678.47	8.98	0.31	**£2,160.60**
Alternative Utility Values	**PUVA**	£3,481.28		2.05		
	Alitretinoin	£3,388.33	-£92.94	2.15	0.11	**-£884.00**
Cost of PUVA = £49 per session	**PUVA**	£2,665.15		1.80		
	Alitretinoin	£3,388.33	£723.18	2.00	0.20	**£3,649.13**
Cost of PUVA = £100 per session	**PUVA**	£4,786.58		1.80		
	Alitretinoin	£3,388.33	-£1,398.24	2.00	0.20	**-£7,055.44**
Threshold analysis 1 (Reduce efficacy by 30%)	**PUVA**	£3,480.07		1.80		
	Alitretinoin	£2,866.25	-£613.82	1.85	0.06	**-£10,665.51**
Threshold analysis 2 (Increase efficacy by 50%)	**PUVA**	£2,836.47		1.93		
	Alitretinoin	£3,388.33	£551.87	2.00	0.07	**£8,281.12**

Table 7.3.3: Base case and sensitivity analysis:Alitretinoin versus Azathioprine

Scenarios	Treatment	Total Costs	Incremental Costs	Total Utility	Incremental Utility	ICER
Base Case	**Azathioprine**	£805.25		1.75		
	Alitretinoin	£3,388.33	£2,583.09	2	0.24	**£10,611.80**
1 Year	**Azathioprine**	£509.41		0.64		
	Alitretinoin	£2,207.65	£1,698.24	0.74	0.1	**£17,756.02**
6 Years	**Azathioprine**	£1,176.71		3.27		
	Alitretinoin	£4,346.33	£3,169.61	3.61	0.33	**£9,477.51**
10 Years	**Azathioprine**	£1,626.58		5.07		
	Alitretinoin	£4,982.05	£3,355.48	5.43	0.36	**£9,324.35**
20 Years	**Azathioprine**	£2,508.03		8.63		
	Alitretinoin	£5,864.73	3,356.70	8.98	0.36	**£9,359.44**
Alternative Utility Values	**Azathioprine**	£805.25		2.03		
	Alitretinoin	£3,388.33	£2,583.09	2.15	0.12	**£22,312.07**
Threshold analysis 1 (Reduce efficacy by 30%)	**Azathioprine**	£804.45		1.75		
	Alitretinoin	£2,866.25	£2,061.80	1.85	0.10	**£20,063.14**
Threshold analysis 2 (Increase efficacy by 50%)	**Azathioprine**	£1,003.44		1.91		
	Alitretinoin	£3,388.33	£2,384.89	2.00	0.09	**£26,746.02**

Interpretation of base case results:

Alitretinoin versus Ciclosporin

In the base case analysis alitretinoin is more effective and more expensive than ciclosporin. The difference in effectiveness is due to better efficacy (response to treatment) with more patients with alitretinoin achieving remission of CHE. The additional cost of alitretinoin (£1,807.32) is due to the difference in the monthly cost of alitretinoin (£383.88) versus Ciclosporin (£164.64) at the assumed mg/kg dose. The base case ICER of £8,614 is well within the £20,000 - £30,000 threshold.

Alitretinoin versus PUVA

In the base case analysis alitretinoin is more effective and costs less than PUVA. The difference in effectiveness is due to better efficacy with more alitretinoin patients achieving remission of CHE. The negative net cost of alitretinoin to PUVA (-£92.94) is due to the difference in the monthly cost of alitretinoin (£383.88) versus PUVA (£514.65). The base case ICER of £468.98 is well within the £20,000 - £30,000 threshold and is consistent with alitretinoin being the dominant therapy.

Alitretinoin versus azathioprine

In the base case analysis alitretinoin is more effective and more expensive when compared to azathioprine. The difference in effectiveness is due to better efficacy with more alitretinoin patients achieving remission of CHE. The additional cost of alitretinoin (£2,583.09) is due to the difference in the monthly cost of alitretinoin (£383.88) versus azathioprine (£16.80). The base case ICER of £10,611.80 is well within the £20,000 - £30,000 threshold.

7.3.2 Subgroup analysis

7.3.2.1 What were the results of the subgroup analysis/analyses if conducted?

For women of childbearing potential there was very little change in the ICERs, reflecting the minimal additional impact of pregnancy prevention measures and pregnancy tests.

For the hyperkeratotic subgroup the ICERs appear to increase slightly although they remain well within the £20-£30k range. Given that the alitretinoin SPC emphasises greater efficacy in this hyperkeratotic subgroup, the effect on ICERs would appear counterintuitive. This finding is explained by two effects: Firstly the model can take into account only the increase in efficacy seen in the hyperkeratotic subgroup treated with 30mg alitretinoin (from 47.7% to 54%), not the parallel decrease in efficacy seen for placebo treated hyperkeratotic patients in the trial (decreases from 16.6% to 12%), both of which underlie the SPC statement regarding increased efficacy in the hyperkeratotic subgroup. Secondly, cumulative efficacy was not calculated for each of the 4 weekly visits for the hyperkeratotic subgroup as this was not requested by regulatory authorities; only the final 12-24 week efficacy figure of 54% PGA clear/almost clear is available. For the purposes of the model, efficacy was therefore assumed to have accumulated in linear fashion over the 4 week periods and this appears to have led to some artefacts in the way PGA disease states and associated utilities are generated versus the situation observed in the overall population, and therefore in the base case model.

In summary, it would be plausible to assume that alitretinoin will be more cost effective in the hyperkeratotic subgroup but it has not been possible to estimate precisely what the resultant ICERs might be using the same model. Given that the ICERs demonstrated for the overall population are well within the £20-30K range, further attempts to model the hyperkeratotic subgroup were not considered to be warranted.

Table 7.3.4: Subgroup analysis: Patients with hyperkeratotic CHE at baseline

Treatment	Total Costs	Incremental Costs	Total Utility	Incremental Utility	ICER
Ciclosporin	£1,579.54		1.79		
Alitretinoin (Hyperkeratotic)	£3,451.20	£1,871.66	1.95	0.17	**£11,176.87**

PUVA	£3,479.64		1.80		
Alitretinoin (Hyperkeratotic)	£3,451.20	-£28.44	1.95	0.16	**-£182.73**
Azathioprine	£804.87		1.75		
Alitretinoin (Hyperkeratotic)	£3,451.20	£2,646.33	1.95	0.20	**£13,174.24**

Table 7.3.5: Subgroup analysis: Women of child bearing potential (women % set to 100%, child bearing proportion set to 100%)

Treatment	Total Costs	Incremental Costs	Total Utility	Incremental Utility	ICER
Ciclosporin	£1,580.72		1.79		
Alitretinoin (WCBA)	£3,492.03	£1,911.32	2.00	0.21	**£9,108.62**
PUVA	£3,481.28		1.80		
Alitretinoin (WCBA)	£3,492.03	£10.76	2.00	0.20	**£54.27**
Azathioprine	£805.25		1.75		
Alitretinoin (WCBA)	£3,492.03	£2,686.78	2.00	0.24	**£11,037.81**

7.3.3 Sensitivity analyses

The sensitivity analyses have been provided in the tables above.

7.3.3.1 What were the main findings of the sensitivity analyses?

Time horizon:

At time horizons less than 3 years (e.g. 1 year) the cost effectiveness of alitretinoin compared to ciclosporin and azathioprine decreases (the ICER increases). This is due to less difference in the incremental benefits and the incremental costs decreasing (as alitretinoin, the more expensive of the two therapies, is used for a shorter period of time). At time horizons less than 3 years the cost effectiveness of alitretinoin compared to PUVA is better (the ICER decreases); under this scenario the incremental utility is still positive and at the same time there is a further reduction in the cost of alitretinoin versus PUVA.

Over time horizons greater than 3 years (6, 10 and 20 years) the ICERs are stable for the comparisons of alitretinoin to ciclosporin, PUVA and azathioprine. The expected difference in the costs and benefits are stable because over a longer term the majority of patients will enter into a health state of refractory and in this refractory state treatment is modelled as a combination of emollients and steroids – i.e. over the longer term the ICERs reflect the use of supportive treatments.

Alternative utility values:

To assess the impact on the ICERs of alternative values for the health states mild, moderate, severe, remission and refractory, alternative utility values were assumed. These values place a higher utility on the health states severe, mild and moderate and a lower utility on the remission health state. The results suggest (see tables 7.2.1.3) that the ICER of alitretinoin versus ciclosporin is £16,756.47 (as the utility difference is approximately halved); the ICER of alitretinoin versus PUVA is -£884 (as the incremental utility is approximately halved); the ICER of alitretinoin versus azathioprine is £22,312.07 (as the incremental utility is approximately halved). All the ICERS remain within the £20,000-£30,000 threshold.

Threshold analysis – changing the efficacy of alitretinoin:

In the base case analysis alitretinoin is associated with ICERs that are always below the £20,000 threshold. The efficacy data is the key structural basis of the model and a key determinant of cost effectiveness (see 7.3.3.2). To assess the impact of changes to the efficacy data the proportion of the alitretinoin cohort responding to treatment (the remission health sate) is varied to assess the point at which alitretinoin is above the £20,000 - £30,000 threshold.

The base case analysis models the proportion of the alitretinoin cohort in remission at each cycle (4 weeks) according to the clinical trial data. These values for remission were varied by reducing these proportions (making alitretinoin less effective) and re-distributing this proportion of patients to the severe health state; a simplifying and conservative assumption for the purpose of this sensitivity analysis, as in reality some will be in the mild or moderate health states. Varying the proportion in remission downwards by 30% at each 4 weeks and re-distributing this proportion to the severe health state results in ICERs of £19,833.18 and £20,063.14 for alitretinoin compared to ciclosporin and azathioprine, respectively. The increase in the ICERs is attributed to lower efficacy for alitretinoin. The ICER for alitretinoin compared to PUVA is -£10,655.51. The comparison to PUVA requires further interpretation as the ICER is more negative: when the efficacy of alitretinoin is reduced by 30%, this proportion is re-distributed to the severe health state. In the severe health state patients ultimately become refractory to treatment; hence patients come off treatment and onto supportive care (where the former is more expensive). The utility gain associated with alitretinoin also reduces but this reduction is outweighed by the reduction in costs.

Threshold analysis – changing the efficacy of the comparators:

In the base case analysis alitretinoin is cost-effective at £8,614.43 (below the £20,000 threshold) compared to ciclosporin; cost-effective (dominant) at -£468.98 (below the £20,000 threshold) compared to PUVA and cost-effective at £10,611.80 (below the £20,000 threshold) compared to azathioprine. To assess the impact of changes to the efficacy data the proportion of the comparator cohorts responding to treatment (the remission health state) is varied to assess the point at which alitretinoin is above the £20,000 - £30,000 threshold.

The base case analysis models the proportion of the comparator cohorts in remission at each cycle (4 weeks) according to elicited expert opinion. These values for severe were varied by reducing these proportions (making the comparators more effective) and re-distributing this proportion of patients to the remission health state. Varying the proportion in severe downwards by 50% at each 4 weeks and re-distributing this proportion to the remission health state results in ICERs of £13,503.59, £8,281.12 and £26,746.02 for alitretinoin compared to ciclosporin, PUVA and azathioprine, respectively. The increase in the ICERs is attributed to higher efficacy of the comparators.

Cost of PUVA sessions

As no published costs were available for PUVA a range of costs were obtained from UK dermatology centres. Although the average PUVA cost was used in the base-case analysis a sensitivity analysis was performed by varying the cost of PUVA from £49 (the minimum observed cost of a single PUVA session) and £100 (the maximum observed cost). A priori this is expected to increase and decrease the ICER of alitretinoin versus PUVA. The modelled results are consistent with expectation – as summarised in the results table (see 7.3.1.1).

7.3.3.2 What are the key drivers of the cost effectiveness results?

The model is sensitive to the expected difference in utilities between the treatment and comparator therapies.

The drug costs are considered deterministic although variation in the estimates of PUVA costs were considered; these costs account for the majority of the expected costs associated with alitretinoin and the comparator treatments.

The structural assumption underlying the economic model (treatment efficacy) is a core determinant of cost-effectiveness. The model ascribes utility values to the different health states associated with CHE, where the highest health-related quality of life is observed in the health state remission (clear/almost clear hands assessed by PGA), the lowest in the health state severe and in between these two bounds are the utility values associated with mild and moderate forms of CHE; thus, the efficacy data, which determines the proportion of patients in each health state at different time points during and between treatment cycles, is a key driver of cost-effectiveness.

7.3.4 Interpretation of economic evidence

7.3.4.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

There were no published economic evaluations to make this comparison.

7.3.4.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology?

Yes. The economic evaluation considered the use of alitretinoin and therapies currently used in clinical practice (ciclosporin, azathioprine and PUVA) to treat patients with severe CHE unresponsive to potent topical steroids.

7.3.4.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The strengths of the model are its ability to characterise the current treatment of CHE and relate this to the use of alitretinoin as an alternative treatment option. The available clinical

data is accurately reflected in the model; the biology of CHE is reflected in the health states and treatment effects are translated as decreases and increases in the severity of CHE and its relation to quality of life.

The model does not consider mortality, although this was a modelling choice given no expected differences in mortality are expected and the short time horizon of the model. The inclusion of mortality would not affect the ICER as the estimate of the incremental benefit would be the same. PSA could not be meaningfully undertaken given the paucity of data on clinical effects from treatment of CHE. If PSA was undertaken the interpretation of the results would, as argued, be made more difficult as there is no evidence to support the modelling of a distribution of values. In place of PSA, deterministic sensitivity analysis of key model parameters and threshold analysis was undertaken to assess the change in ICER that would result from different assumptions. This approach is posited as a better way of addressing the decision makers uncertainty, in this evaluation.

7.3.4.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Further modelling of clinical responses of patients with CHE to different treatments would be informative. When such information becomes available this should be assessed within a cost-effectiveness framework and would add to the robustness of the estimated ICERs.

8 Assessment of factors relevant to the NHS and other parties

8.1 What is the estimated annual budget impact for the NHS in England and Wales?

Patients with severe CHE may receive one or more different treatments during a single year due to several factors including the functional or occupational impact of CHE in the individual, the responsiveness of CHE to different forms of treatment, the associated relapse rate and the experience of adverse events on treatment. Therefore, the impact of alitretinoin introduction has been calculated based on its share of the total number of treatments received by the eligible population, rather than the number of patients suffering from severe CHE.

The total estimated number of patients in England and Wales with severe CHE unresponsive to topical steroids is 127,321. Of patients receiving medical treatment for severe CHE, a percentage will be referred to consultant dermatologists whereas the remainder will be managed with topical treatments prescribed in primary care. Once referred to secondary care, patients will usually be investigated for aetiological factors by way of a complete medical and occupational history and patch testing. Initial management is likely to concentrate on avoidance, where possible, of contact allergens or irritants and the optimisation of emollient and topical corticosteroid therapy; even though these approaches may have been tried in primary care, it is assumed that management will not always have been optimal. If standard initial measures are not successful following 6-8 weeks of treatment in secondary care, second line agents are introduced only if the patients medical history, co-morbidity, lack of consent or ability to comply does not preclude their use. A proportion of patients will be discharged back to the care of their GP with advice from the dermatologist regarding use of topical immunomodulators, topical corticosteroids or protective or avoidance measures. Clinical opinion estimates that 25% of patients with severe CHE unresponsive to topical steroids will receive 2nd line treatments outlined in the decision problem in secondary care, which equates to 31,830 patients being treated in line with the decision problem in one year.

To estimate the annual budget impact, treatment lengths and market share were used to calculate the total number of treatments administered in a given year for each treatment. For a more detailed description see Box 8.1.1. Prior to introduction of alitretinoin it is calculated that the 31,830 patients treated with 2nd line agents will in total receive 62,198 treatments, comprising a mixture of PUVA, ciclosporin and azathioprine (Table 8.1.1). As clinician experience and confidence in the prescribing of a new agent such as alitretinoin grows, it is anticipated that there will be a gradual increase in its market share over time. Due to the longer time to retreatment observed in patients treated with alitretinoin, there is a decrease in the total number of treatments administered in a given population.

The budget impact of the replacement of current therapies with alitretinoin is shown in table 8.1.2. The net budget impact in the 5 years following alitretinoin is an estimated saving of £23.99 million. A further breakdown of the treatment costs is provided in table 8.5.1.

Table 8.1.1 Estimated market share of second-line therapies and corresponding number of treatments in the first five years following alitretinoin treatment

		Alitretinoin		PUVA		Immunosuppressants	
Total Estimated Treatments	**Year**	**Share of treatments %**	**Number of treatments**	**Share of treatments %**	**Number of treatments**	**Share of treatments %**	**Number of treatments**
62,198	0	0%	0	70%	43,539	30%	18,659
58,727	1	20%	11,745	60%	35,236	20%	11,745
57,526	2	25%	14,381	55%	31,639	20%	11,505
55,791	3	35%	19,527	50%	27,895	15%	8,369
55,791	4	35%	19,527	50%	27,895	15%	8,369
55,791	5	35%	19,527	50%	27,895	15%	8,369

Table 8.1.2 Potential cost savings following the introduction of alitretinoin

Treatment	**Cost per treatment £**	**Acquisition cost (£000)**						
		Year 0	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Alitretinoin	1502.90	0	£17,652	£21,614	£29,347	£29,347	£29,347	**£127,306**
PUVA	2058.68	£89,628	£72,538	£65,132	£57,425	£57,425	£57,425	**£399,574**
Other 2nd line agents	291.40	£5,437	£3,423	£3,353	£2,439	£2,439	£2,439	**£19,528**
Total		£95,066	**£93,613**	**£90,099**	**£89,210**	**£89,210**	**£89,210**	**£546,409**
Potential savings to NHS			**£1,453**	**£4,967**	**£5,855**	**£5,855**	**£5,855**	**£23,986**

Box 8.1.1 Description of the budget impact calculations

- The average time to retreatment for each therapy was calculated based on patient response and relapse rates
- The proportion of treatments currently administered and estimated uptake of alitretinoin and replacement of current therapies were based on a consensus of dermatologist opinion
- The market share and average time to retreatment was then used to calculate how many treatments in total would be administered in a given year for a particular population
- The market share for each treatment was then used to calculate the number of treatments administered for each individual treatment. So for example of the 58,727 treatments administered in year 1 following introduction of alitretinoin, 11,745 of those treatments would be alitretinoin (20% of treatments).
- The net budget impact in the 5 years following introduction of alitretinoin is an estimated saving of £23.99 million.

8.2 What numbers of patients were assumed to be eligible? How was this figure derived?

The number of patients eligible is estimated based on the adult population of England and Wales and epidemiological data from published studies.

Table 8.2.1 outlines the eligible population in England and Wales estimated to have severe CHE that is unresponsive to topical corticosteroids.

Since the incidence of severe CHE is not known and severe CHE should not affect patient survival rates we have assumed the patient pool to be largely static, with deaths equalling the incident rate of severe CHE.

Table 8.2.1: Patient numbers in England and Wales

		Reference source
English population aged 18 or over	40,097,200	National Statistics[81]
Welsh population aged 18 or over	2,343,000	National Statistics[81]
English and Welsh population	42,440,200	
Prevalence of chronic hand eczema in England and Wales	10%	Diepgen et al. 2007[1] Meding et al. 2002[1, 10]
Total estimated number of patients with hand eczema in England and Wales	4,244,020	
Prevalence of severe CHE	6%	Diepgen et al. 2007[1]
Total estimated number of patients with severe CHE	254,641	
Proportion of patients with severe CHE who are resistant to topical corticosteroids	50%	Diepgen et al. 2007[1]
Total estimated number of patients with severe CHE who are resistant to topical corticosteroids	127,321	
Proportion of patients that will receive 2nd line therapy	25%	UK clinician opinion
Total estimated number of patients with severe CHE who are resistant to topical corticosteroids who receive 2nd line therapy	**31,830**	

8.3 What assumption(s) were made about current treatment options and uptake of technologies?

The proportions of treatments used currently to treat severe CHE unresponsive to topical steroids were taken from consensus expert clinical opinion.[18] Similarly, uptake of alitretinoin over the first three years following introduction and the proportions of current treatments replaced by alitretinoin were estimated by dermatologists.[18]

Table 8.3.1 Estimated uptake of alitretinoin and replacement of current therapies

Year	**Share of treatments %**		
	Alitretinoin	**PUVA**	**Immunosuppressants**
Year 0	0%	70%	30%
Year 1	20%	60%	20%
Year 2	25%	55%	20%
Year 3	35%	50%	15%
Year 4	35%	50%	15%
Year 5	35%	50%	15%

8.4 What assumption(s) were made about market share (where relevant)?

See table 8.3.1 above.

8.5 What unit costs were assumed? How were these calculated?

Costs used in the budget impact model used to calculate the resource impact of introducing alitretinoin are shown in table 8.5.1 below.

Table 8.5.1: Direct cost of treating severe CHE with alitretinoin and alternative therapies

Treatment	Cost per dose/ treatment £	Dosing regimen	Treatment lengths (weeks)	Cost per patient per treatment course £	Weighted average base	Total Cost
Alitretinoin						**£1,502.90**
Alitretinoin drug cost	13.71	30mg/10mg daily	15.43	1,481.12		
Oral contracep-tives	0.04	Microgynon 30 for duration of alitretinoin treatment plus two months[75]		0.89	15% for female patients of child bearing age only	
Pregnancy testing consul-tation	10.00	Pregnancy consultation one month prior to and at start of treatment, then every 28 days for duration of alitretinoin treatment and at 5 weeks following end of treatment[76]		8.79		
Pregnancy test	0.61	Pregnancy test one month prior to and at start of treatment, then every 28 days for duration of alitretinoin treatment and at 5 weeks following end of treatment[77]		0.54		
Lipid monitoring	3.00	Every 28 days during treatment[78]		11.57		
PUVA						**£1,650**
Oral PUVA	68.62	30 sessions per treatment	16.00	2058.60	5%	
Topical PUVA	68.62	30 sessions per treatment	16.00	2058.60	95%	
Other 2nd line agents						**£291.40**
Ciclosporin	5.88	Based on average daily dose of 275mg (3.75mg/kilo daily assumes 75kg average adult body weight) split 125mg om, 150mg on[75]	14.20	604.12	33%	
plus serum creatinine monitoring	3.00	Baseline, then repeated fortnightly for 8				

		weeks, then monthly until treatment completion[9, 78]				
Azathio-prine	0.60	Based on average daily dose of 150mg assumes 2mg/kg body weight per day for 3 months (75kg average adult body weight)[18, 75]	27.20	135.04	67%	
TMPT monitoring	3.00	Baseline[32, 78]				
plus blood counts	3.00	Weekly for first 4 weeks, then 3 monthly[32, 78]				

[16] Advisory board meeting (England/Wales)
[28] Guidelines for prescribing azathioprine in dermatology (Anstey 2004)
[67] Ciclosporin: Clinical Guidelines for the use in treatment of psoriasis (British Association of Dermatologists)
[74] British National Formulary 56
[75] PSSRU Unit costs of health and social care 2007
[76] Primary Care Trusts Reference Cost Schedules 2006-2007

In the absence of published data on the costs of PUVA treatment and with no current National Tariff price available in England and Wales for PUVA treatments, healthcare professionals (usually dermatology consultants or pharmacists involved in dermatology) were contacted in a range of UK dermatology centres in order to ascertain a cost per session for the provision of topical hand PUVA. From 28 centres surveyed, 3 had no PUVA services available to them for the treatment of CHE and in 7 centres those asked could not provide estimates of costs. Table 8.5.2 below shows the range of responses from the 18 centres that provided an estimate. The average cost was £68.62.

Table 8.5.2: Range of responses for estimation of PUVA costs

Centre	Estimate of PUVA cost per session	Cost for averaging (£)
1	£70	£70
2	£60-70	£65
3	£49	£49
4	£70 initial session £55 subsequent sessions	£55.5
5	£100 for first session then £80 thereafter	£80.67
6	£60	£60
7	£70	£70
8	£100	£100
9	£60 (consultant)-£80 (Dermatology Sister)	£70
10	£70	£70
11	£85	£85
12	£90	£90
13	£80 (consultant)-£90 (SPR)	£85
14	£60	£60
15	£60-£70 (Dermatology Consultants)	£65
16	£50 per session	£50

17	£60 (2 -3 sessions per week for 12 weeks)	£60
18	£40-60	£50
Average estimated cost of one hand PUVA session		**£68.62**

8.6 In addition to drug costs, consider other significant costs associated with treatment?

In the case of alitretinoin, additional costs associated with treatment include implementation of the pregnancy prevention programme measures that are required as a condition of licencing and the monitoring of lipids. These costs have been incorporated into the budget impact model. The most common side effects (occurring in >1/10 patients) observed in clinical trials were headache, increased levels of triglycerides and increased cholesterol. These reversible adverse drug reactions are dose dependent and may therefore a proportion may be alleviated by dose reduction.

The treatment of severe CHE with PUVA tends to require a large number of outpatient visits: treatment for this condition would be expected to entail 30 sessions of outpatient PUVA over a 16 week period,[18] making it a resource intensive treatment. This also makes treatment highly inconvenient for the patient, with travelling and treatment time necessitating time off from work (assuming patients are employed) and out of pocket costs for public transport or fuel and hospital parking.

Ciclosporin treatment requires monitoring of renal function and blood pressure at 2 weekly intervals for the first 2 months of treatment.[18] Azathioprine also requires frequent monitoring, particularly during up-titration of initial doses and dose adjustments to limit toxicity will further complicate therapy. Initial assessment of thiopurine methyltransferase (TPMT) is required to detect common polymorphisms in 6 mercaptopurine metabolism that may be responsible for life threatening pancytopenia (1 in 300 patients) and significant myelosuppression (11% of patients) during azathioprine treatment.[32] Liver function tests and full blood tests are recommended every week for the first month of treatment and would then be required at minimum on a three monthly basis until completion of treatment.[32]

8.7 Were there any estimates of resource savings? If so, what were they?

The budget impact of alitretinoin has been calculated to take into account savings from the reduction in number of treatments currently used, that is PUVA and immunosuppressants such as azathioprine and ciclosporin. Due to the increased time to re-treatment demonstrated by alitretinoin, it is anticipated that in addition to cost savings there will be an overall reduction in the number of treatments used to manage CHE.

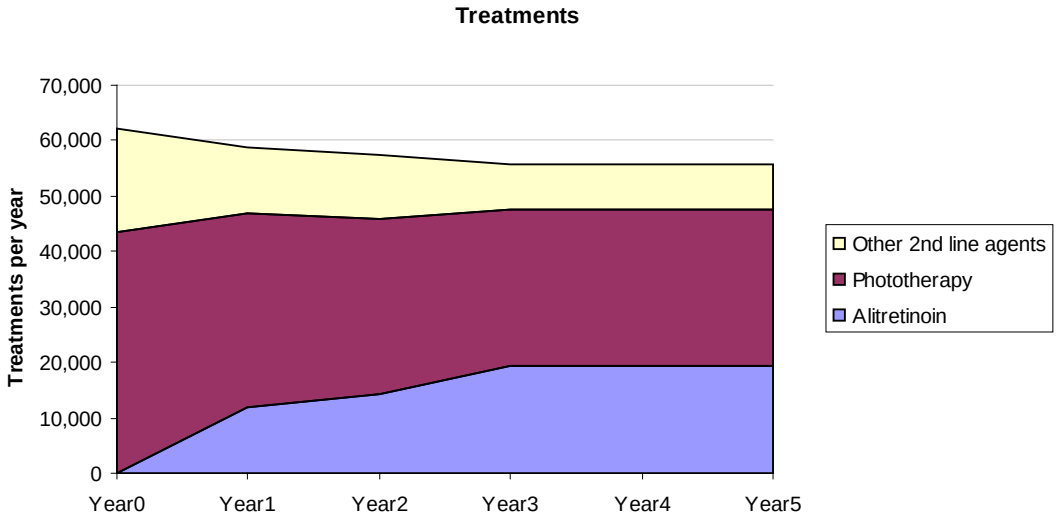
The introduction of alitretinoin as a licensed treatment option for patients with severe CHE unresponsive to topical steroids is expected to lead to a reduction in costs with total cost savings estimated at £23.99 million during the 5 years following alitretinoin introduction.

Due to the increased time to retreatment demonstrated by alitretinoin, it is anticipated that there will be an overall reduction in the number of treatments used to manage CHE within the NHS. In time this may translate into a reduction in burden on existing dermatology services, as demonstrated in Table 8.7.1/ Figure 8.7.1.

Table 8.7.1 Reduction in number of treatments for CHE following introduction of alitretinoin

Treatment	Year 0 Treat-ments	Year 1 Treat-ments	Year 2 Treat-ments	Year 3 Treat-ments	Year 4 Treat-ments	Year 5 Treatments
Alitretinoin	0	11,745	14,381	19,527	19,527	19,527
Phototherapy	43,539	35,236	31,639	27,895	27,895	27,895
Other 2nd line agents	18,659	11,745	11,505	8,369	8,369	8,369
Total	**62,198**	**58,727**	**57,526**	**55,791**	**55,791**	**55,791**

Figure 8.7.1: Reduction in number of treatments for CHE following introduction of alitretinoin



Impact of the Cost of PUVA

The net resource implications are shown in Table 8.1.2, and depend on which treatments are displaced by the introduction of alitretinoin. The estimated resource implications are also dependent on the cost of PUVA, for which precise costs are difficult to obtain. Although an average cost of £68.62 was used for the budget impact and cost effectiveness models estimates from UK centres ranged from £49 to £100. To allow for the variation in estimates a sensitivity analysis was carried out to demonstrate the budget impact of alitretinoin with the upper and lower limit of PUVA cost (Table 8.7.1).

At the lower limit of PUVA cost there would be a net cost of introducing alitretinoin of £15.5 million pounds over 5 years, whereas at the upper limit of PUVA cost savings of £87.2 million could be achieved over 5 years following alitretinoin introduction.

In the absence of published PUVA related costs in the UK there is uncertainty in the true cost of PUVA to the NHS. The only published estimate of PUVA costs that could be found were from a Spanish paper on the use in patients with psoriasis.[82] Although this includes additional costs not seen in CHE the cost per treatment is much higher than the estimates from UK centres, €383.36 or £339.30. The overall costs, taking into consideration indirect costs, is

much higher at €899.70 or £796.20. It is therefore possible that the direct NHS cost of PUVA has been underestimated.

Table 8.7.2: Sensitivity analysis for the cost of PUVA in the budget impact analysis

Cost of PUVA session	Treatment	Cost per treatment £	Acquisition cost (£000) Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
£49	Alitretinoin	1502.90	£0	£17,652	£21,614	£29,347	£29,347	£29,347
	PUVA	1470.00	£64,002	£51,798	£46,510	£41,006	£41,006	£41,006
	Other 2nd line agents	291.40	£5,437	£3,423	£3,353	£2,439	£2,439	£2,439
	Total Potential savings to NHS		**£69,439**	**£72,873**	**£71,476**	**£72,791**	**£72,791**	**£72,791**
				-£3,434	**-£2,037**	**-£3,352**	**-£3,352**	**-£3,352**
£68.62	Alitretinoin	1502.90	£0	£17,652	£21,614	£29,347	£29,347	£29,347
	PUVA	2058.60	£89,628	£72,538	£65,132	£57,425	£57,425	£57,425
	Other 2nd line agents	291.40	£5,437	£3,423	£3,353	£2,439	£2,439	£2,439
	Total Potential savings to NHS		**£95,066**	**£93,613**	**£90,099**	**£89,210**	**£89,210**	**£89,210**
				£1,453	**£4,967**	**£5,855**	**£5,855**	**£5,855**
£100	Alitretinoin	1502.90	£0	£17,652	£21,614	£29,347	£29,347	£29,347
	PUVA	3000,00	£130,616	£105,709	£94,918	£83,686	£83,686	£83,686
	Other 2nd line agents	291.40	£5,437	£3,423	£3,353	£2,439	£2,439	£2,439
	Total Potential savings to NHS		**£136,053**	**£126,784**	**£119,884**	**£115,471**	**£115,471**	**£115,471**
				£9,269	**£16,169**	**£20,582**	**£20,582**	**£20,582**

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Initiation and supervision of oral alitretinoin therapy could in the future be carried out by Dermatology Consultants in a primary care setting, provided that effective arrangements existed to ensure the prevention of teratogenicity, the main risk of alitretinoin therapy. Alternatively, initiation of alitretinoin may remain within secondary care with patients discharged back to primary care for follow up where shared care protocols are agreed. Whereas changes in the setting for alitretinoin treatment are potentially feasible in the future, use of PUVA and systemic immunosuppression are almost certain to remain confined to the hospital setting.

Should the current NHS shift towards primary care provision of services deliver the anticipated cost savings and expand further, the availability of alitretinoin as a treatment option would facilitate the realisation of savings within dermatology.

Hand eczema has been shown to be a major cause of prolonged sick-leave and job loss: 20% of patients reported taking sick-leave and 23% reported they had lost their job at least once in a 12 month period due to their hand eczema.[3] It is therefore to be expected that effective treatment of severe CHE by alitretinoin may enable patients to return to employment and should reduce more temporary work absenteeism due to hospital attendance or sick leave. These effects may lead to important benefits to the wider economy even though they are considered outside the scope of NICE cost effectiveness appraisal for the NHS.

9 References

References are listed at the end of this document.

10 Appendices

10.1 Appendix 1

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product
Toctino®▼ 10mg soft capsules.
Toctino®▼ 30mg soft capsules.

2. Qualitative and quantitative composition
Each soft capsule contains 10mg or 30mg of alitretinoin.
This medicinal product contains the excipients soya-bean oil and sorbitol.
For a full list of excipients, see section 6.1 “List of excipients”.

3. Pharmaceutical form
Soft capsule
The Toctino 10mg capsule is an opaque brown soft capsule imprinted with “A1” in white.
The Toctino 30mg capsule is an opaque red-brown soft capsule imprinted with “A3” in white.

4. Clinical Particulars

4.1 Therapeutic indications
Toctino is indicated for use in adults who have severe chronic hand eczema that is unresponsive to treatment with potent topical corticosteroids.
Patients in whom the eczema has predominantly hyperkeratotic features are more likely to respond to treatment than in those in whom the eczema predominantly presents as pompholyx (See section 5.1 “Pharmacodynamic properties”).

4.2 Posology and method of administration
Toctino should only be prescribed by dermatologists, or physicians with experience in the use of systemic retinoids who have full understanding of the risks of systemic retinoid therapy and monitoring requirements. Prescriptions of Toctino for women of childbearing potential should be limited to 30 days of treatment and continuation of treatment requires a new prescription. Ideally, pregnancy testing, issuing a prescription and dispensing of Toctino should occur on the same day. Dispensing of Toctino should occur within a maximum of 7 days of the prescription.
The recommended dose range for Toctino is 10mg-30mg once daily.
The recommended start dose for Toctino is 30mg once daily. A dose reduction to 10mg once daily may be considered in patients with unacceptable adverse reactions to the higher dose. In studies investigating 10mg and 30mg daily doses, both doses resulted in clearing of the disease. The 30mg dose provided a more rapid response and a higher response rate. The 10mg daily dose was associated with fewer adverse events (see section 4.4 “Special warnings and precautions for use” and section 5.1 “Pharmacodynamic Properties”).
A treatment course of Toctino may be given for 12 to 24 weeks depending on response. Discontinuation of therapy should be considered for patients who still have severe disease after the initial 12 weeks of treatment. In the event of relapse, patients may benefit from further treatment courses of Toctino.
The capsules should be taken with a meal once daily.

Toctino should not be prescribed if the patient's eczema can be adequately controlled by standard measures, including skin protection, avoidance of allergens and irritants, and treatment with potent topical corticosteroids.

Children
Toctino is not recommended for use in patients under 18 years of age.

4.3 Contraindications
Pregnancy is an absolute contraindication to treatment with Toctino (see section 4.6 "Pregnancy and lactation").
Toctino is contraindicated in woman of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met (see section 4.4 "Special warnings and special precautions for use").
Toctino contains soya oil. Patients who are allergic to peanut, soya or with rare hereditary fructose intolerance should not take this medicine.
Toctino is contraindicated in breastfeeding.
Toctino is also contraindicated in patients

- With hepatic insufficiency
- With severe renal insufficiency
- With uncontrolled hypercholesterolaemia
- With uncontrolled hypertriglyceridaemia
- With uncontrolled hypothyroidism
- With hypervitaminosis A
- With hypersensitivity either to alitretinoin, to other retinoids or to any of the excipients, in particular in case of allergies to peanut or soya
- Receiving concomitant treatment with tetracyclines (see section 4.5 "Interactions with other medicinal products and other forms of interactions")

4.4 Special warnings and precautions for use

Pregnancy Prevention Programme
This medicinal product is **TERATOGENIC.**

Toctino is contraindicated in women of childbearing potential unless all of the following conditions of the Pregnancy Prevention Programme are met:

- She understands the teratogenic risk
- She understands the need for rigorous follow-up, on a monthly basis
- She understands and accepts the need for effective contraception, without interruption, 1 month before starting treatment, throughout the duration of treatment and 1 month after the end of treatment. At least one and preferably two complementary forms of contraception including a barrier method should be used
- Even if she has amenorrhoea she must follow all of the advice on effective contraception
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy
- She understands the need and accepts to undergo pregnancy testing before, during and 5 weeks after the end of treatment
- She has acknowledged that she has understood the hazards and necessary precautions associated with the use of Toctino

These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.
The prescriber must ensure that:

- The patient complies with the conditions for pregnancy prevention as listed above, including confirmation that she has an adequate level of understanding
- The patient has acknowledged the aforementioned conditions

- The patient has used at least one and preferably two methods of effective contraception including a barrier method for at least 1 month prior to starting treatment and is continuing to use effective contraception throughout the treatment period and for at least 1 month after cessation of treatment
- Negative pregnancy test results have been obtained before, during and 5 weeks after the end of treatment. The dates and results of pregnancy tests should be documented

Contraception
Female patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception.
As a minimum requirement, female patients at potential risk of pregnancy must use at least one effective method of contraception. Preferably the patient should use two complementary forms of contraception including a barrier method. Contraception should be continued for at least 1 month after stopping treatment with Toctino, even in patients with amenorrhea.

Pregnancy testing
According to local practice, medically supervised pregnancy tests with a minimum sensitivity of 25mIU/mL are recommended to be performed in the first 3 days of the menstrual cycle, as follows:

One month prior to starting therapy
In order to exclude the possibility of pregnancy prior to starting contraception, it is recommended that an initial medically supervised pregnancy test should be performed and its date and result recorded. In patients without regular menses, the timing of this pregnancy test should reflect the sexual activity of the patient and should be undertaken approximately 3 weeks after the patient last had unprotected sexual intercourse. The prescriber should educate the patient about contraception.

At the start of therapy
A medically supervised pregnancy test should also be performed during the consultation when Toctino is prescribed or in the 3 days prior to the visit to the prescriber, and should have been delayed until the patient had been using effective contraception for at least 1 month. This test should ensure the patient is not pregnant when she starts treatment with Toctino.

Follow-up visits
Follow-up visits should be arranged at 28 day intervals. The need for repeated medically supervised pregnancy tests every month should be determined in consideration amongst other of the patient's sexual activity and recent menstrual history (abnormal menses, missed periods or amenorrhea). Where indicated, follow-up pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.

End of treatment
Five weeks after stopping treatment, women should undergo a final pregnancy test to exclude pregnancy.

Prescribing and dispensing restrictions
Prescriptions of Toctino for women of childbearing potential should be limited to 30 days of treatment and continuation of treatment requires a new prescription. Ideally, pregnancy testing, issuing a prescription and dispensing of Toctino should occur on the same day. Dispensing of Toctino should be completed within a maximum of 7 days of the prescription.

Male patients
Small amounts of alitretinoin have been detected in the semen of healthy volunteers receiving 40 mg of alitretinoin and there is no indication of drug accumulation in semen. Assuming complete vaginal absorption of these amounts would have a negligible effect on the endogenous plasma levels of the female partner and therefore does not appear to pose a risk to the foetus if the partner is

pregnant. Based on non-clinical findings, male fertility may be compromised by treatment with Toctino (see section 5.3 “Preclinical safety data”).
Male patients should be reminded that they must not share their medication with anyone, particularly not females.

Additional precautions
Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of treatment.
Patients should not donate blood during therapy and for 1 month following discontinuation of Toctino because of the potential risk to the foetus of a pregnant transfusion recipient.

Educational material
In order to assist prescribers, pharmacists and patients in avoiding foetal exposure to alitretinoin, the Marketing Authorisation Holder will provide educational material to reinforce the warnings about the teratogenicity of Toctino, to provide advice on contraception before therapy is started and to provide guidance on the need for pregnancy testing. Full patient information about the teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme should be given by the physician to all patients, both male and female.

Psychiatric disorders
Depression, aggravated depression, anxiety, aggressive tendencies, mood alterations, psychotic symptoms, and very rarely, suicidal ideation, suicide attempts and suicide have been reported in patients treated with systemic retinoids. Particular care needs to be taken in patients with a history of depression and patients on alitretinoin treatment should therefore be observed for signs of depression and referred for appropriate treatment if necessary. However, discontinuation of alitretinoin may be insufficient to alleviate symptoms and therefore further psychiatric or psychological evaluation may be necessary.

UV light
The effects of UV light are enhanced by retinoid therapy, therefore patients should avoid excessive exposure to sunlight and the unsupervised use of sun lamps. Where necessary a sun-protection product with a high protection factor of at least SPF 15 should be used.
Patients who experience dryness of the skin and lips should be advised to use a skin moisturising ointment or cream and a lip balm.

Musculo-skeletal and connective tissue disorders
Treatment with other systemic retinoids has been associated with bone changes including premature epiphyseal closure, hyperostosis, and calcification of tendons and ligaments.
Myalgia, arthralgia and increased serum creatinine phosphokinase values have been observed in patients treated with alitretinoin.

Eye disorders
Treatment with alitretinoin has been associated with dry eyes. The symptoms usually resolve after discontinuation of therapy. Dry eyes can be helped by the application of a lubricating eye ointment or by the application of tear replacement therapy. Intolerance to contact lenses may occur which may necessitate the patient wearing glasses during treatment.
Treatment with systemic retinoids has been associated with corneal opacities and keratitis.
Decreased night vision has been observed in patients treated with alitretinoin. These effects usually resolve after discontinuation of therapy.
Patients experiencing visual difficulties should be referred to an ophthalmologist. Withdrawal of alitretinoin may be necessary.

Benign intracranial hypertension
Treatment with systemic retinoids, including alitretinoin, has been associated with the occurrence of benign intracranial hypertension, some of which involved concomitant use of tetracyclines (see section 4.3 “Contraindications” and section 4.5 “Interaction with other

medicinal products and other forms of interaction"). Signs and symptoms of benign intracranial hypertension include headache, nausea and vomiting, visual disturbances and papilloedema. Patients who develop signs of benign intracranial hypertension should discontinue alitretinoin immediately.

Lipid Metabolism
Alitretinoin has been associated with an increase in plasma cholesterol and triglyceride levels. Serum cholesterol and triglycerides (fasting values) should be monitored.
Alitretinoin should be discontinued if hypertriglyceridaemia cannot be controlled at an acceptable level or if symptoms of pancreatitis occur (see section 4.8 "Undesirable effects"). Triglyceride levels in excess of 800mg/dL (9mmol/L) are sometimes associated with acute pancreatitis, which may be fatal.

Thyroid function
Changes in thyroid function tests have been observed in patients receiving alitretinoin, most often noted as a reversible reduction in thyroid stimulating hormone (TSH) levels and T4 (free thyroxine).

Hepatobiliary disorders
Treatment with other systemic retinoids has been associated with transient and reversible increases in liver transaminases. In the event of persistent clinically relevant elevation of transaminase levels, reduction of the dose or discontinuation of treatment should be considered.

Gastrointestinal disorders
Systemic retinoids have been associated with IBD (inflammatory bowel disease, including regional ileitis) in patients without a history of intestinal disorders. If severe diarrhoea is observed, diagnosis of IBD should be considered and alitretinoin should be discontinued immediately.

Allergic reactions
Anaphylactic reactions have been rarely reported in systemic retinoids, in some cases after previous topical exposure to retinoids. Allergic cutaneous reactions are reported infrequently. Serious cases of allergic vasculitis, often with purpura (bruises and red patches) of the extremities and extracutaneous involvement have been reported. Severe allergic reactions necessitate interruption of therapy and careful monitoring.

High risk patients
In patients with diabetes, obesity, cardiovascular risk factors or a lipid metabolism disorder undergoing treatment with alitretinoin, more frequent checks of serum values for lipids may be necessary. It is recommended that these patients are started with 10mg once daily and titrated up to the maximum dose of 30mg if necessary.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interaction
Alitretinoin is metabolised by cytochrome P450 3A4 (CYP3A4).
Patients should be prospectively cautioned not to self-medicate with the herbal supplement St. John's Wort because a possible interaction has been suggested with hormonal contraceptives based on reports of breakthrough bleeding on oral contraceptives shortly after starting St. John's Wort. Pregnancies have been reported by users of combined hormonal contraceptives who also used some form of St. John's Wort.
Co-administration with CYP3A4 inhibitors such as ketoconazole increases the plasma level of alitretinoin and dose reduction may be required. The effects of other inhibitors of CYP3A4 have not been studied. Alitretinoin did not affect the pharmacokinetics of ketoconazole.
A 16% reduction of simvastatin plasma levels was observed when co-administered with alitretinoin.
The effects on other similar medicinal products have not been studied. Simvastatin did not affect the pharmacokinetics of alitretinoin.

No pharmacokinetic interactions were observed when alitretinoin was co-administered with ciclosporin or the oral contraceptive ethinyl estradiol and norgestimate.

Pharmacodynamic interactions
Patients should not take vitamin A or other retinoids as concurrent medication due to the risk of hypervitaminosis A.
Cases of benign intracranial hypertension (pseudotumour cerebri) have been reported with concomitant use of retinoids and tetracyclines. Therefore, concomitant treatment with tetracyclines must be avoided (see sections 4.3 “Contraindications” and section 4.4 “Special warnings and precautions for use”).

4.6 Pregnancy and lactation

Pregnancy is an absolute contraindication to treatment with Toctino (see section 4.3, “Contraindications”). If pregnancy does occur in spite of the pregnancy prevention precautions during treatment with Toctino or in the month following discontinuation of therapy, there is a great risk of very severe and serious malformation of the foetus.

Alitretinoin is a retinoid and therefore is a potent teratogen. The foetal malformations associated with exposure to retinoids include central nervous system abnormalities (hydrocephalus, cerebellar malformation/ abnormalities, microcephaly), facial dysmorphia, cleft palate, external ear abnormalities (absence of external ear, small or absent external auditory canals), eye abnormalities (microphthalmia), cardiovascular abnormalities (conotruncal malformations such as tetralogy of Fallot, transposition of great vessels, septal defects), thymus gland abnormality and parathyroid gland abnormalities. There is also an increased incidence of spontaneous abortion.
If pregnancy occurs in a woman treated with Toctino, treatment must be stopped and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice.

Lactation
Alitretinoin is highly lipophilic, therefore the passage of alitretinoin into human milk is very likely. Due to the potential risk for the exposed child, the use of alitretinoin is contraindicated during breastfeeding.

Fertility
Small amounts of alitretinoin have been detected in the semen of healthy volunteers receiving 40mg of alitretinoin and there is no indication of drug accumulation in semen. In the event of complete vaginal absorption of these amounts, this would have a negligible effect on the endogenous plasma levels of the female partner and therefore does not appear to pose a risk to the foetus if the partner is pregnant. Based on non-clinical findings, male fertility may be compromised by treatment with Toctino (see section 5.3 “Preclinical safety data”).

4.7 Effects on ability to drive and use machines
Decreased night vision has been reported in patients treated with alitretinoin and other retinoids. Patients should be advised of this potential problem and warned to be cautious when driving or operating machines.

4.8 Undesirable effects
The most frequent adverse drug reactions (ADRs) observed under alitretinoin therapy are headache (30mg: 21%; 10mg: 11%), flushing (30mg: 5.9%; 10mg: 1.6%), and laboratory changes consisting of increased levels of triglycerides (30mg: 35.4%; 10mg: 17.0%), increased cholesterol (30mg: 27.8%; 10mg: 16.7%), decreased levels of thyroid stimulating hormone (TSH, 30mg: 8.4%; 10mg: 6.0%) and decreased levels of free T4 (30mg: 10.5%; 10mg: 2.9%). These reversible ADRs are dose dependent and may therefore be alleviated by dose reduction.

	Very common (≥ 1/10)	Common (≥ 1/100 < 1/10)	Uncommon (≥ 1/1000, < 1/100)	Rare (≥ 1/10.000 < 1/1000)
Blood and lymphatic system disorders		Anaemia, increased iron binding capacity, monocytes decreased; thrombocytes increased		
Endocrine Disorders		TSH decreased, free T4 decreased		
Nervous system disorders	Headache			Benign intracranial hypertension
Eye disorders		Conjunctivitis, dry eye, eye irritation	Blurred vision, cataract	
Vascular disorders		Flushing		Vasculitis
Respiratory, thoracic and mediastinal disorders			Epistaxis	
Hepatobiliary disorders		Transaminase increased[1)]		
Skin and subcutaneous tissues disorders		Dry skin, dry lips, cheilitis, eczema[1)], dermatitis[1)] , erythema, alopecia	Pruritus, rash, skin exfoliation, asteatotic eczema	
Musculo-skeletal and connective tissue disorders		Arthralgia[1)], myalgia[1]	Exostosis, (hyperostosis), ankylosing spondylitis	
Investigations	Hypertriglyceridemia, high density lipoprotein decreased, hypercholesterolemia	Blood creatinine phosphokinase increased		

[1)] The incidence of adverse events was not higher than those observed in the corresponding placebo group.

Psychiatric effects, in particular depression, and mood changes and suicidal ideation, have been associated with retinoids. In clinical studies, where patients with a history or active psychiatric disorders were excluded patients have been monitored for depression using the CES-D (Center for Epidemiological Studies - Depression) score. Treatment with alitretinoin was not associated with changes in the CES-D score.

The following adverse events have not been observed in clinical trials with alitretinoin, but have been observed with other retinoids: inflammatory bowel disease, diabetes mellitus, colour blindness (colour vision deficiencies), and contact lens intolerance (see section 4.4 “Special warnings and precautions for use”).

Changes in bone mineralisation and extra-osseous calcifications have been associated with systemic retinoid treatment. In clinical studies with alitretinoin, degenerative changes of the

spine and ligamentous calcifications were frequent findings in patients with chronic hand eczema before treatment (baseline), with minor progression in a small number of patients during treatment. These observations were consistent with age dependent degenerative changes. Assessments of bone density (DXA) did not indicate a dose dependent effect on bone mineralisation.

4.9 Overdose

Alitretinoin is a derivative of vitamin A. Alitretinoin has been administered in oncological clinical studies at dosages of more than 10 times the therapeutic dosage given for chronic hand eczema. The adverse effects observed were consistent with retinoid toxicity, and included severe headache, diarrhoea, facial flushing, hypertriglyceridaemia. These effects were reversible.

5. Pharmacological properties

5.1 Pharmacodynamic properties

ATC code: D11AX19

Mechanism of action

The pharmacological action of retinoids may be explained by their effects on cell proliferation, cell differentiation, apoptosis, angiogenesis, keratinisation, sebum secretion and immunomodulation. Unlike other retinoids, which are specific agonists of either RAR or RXR receptors, alitretinoin binds to members of both receptor families. The mechanism of action of alitretinoin in chronic hand eczema is unknown. Alitretinoin has demonstrated immunomodulatory and anti-inflammatory effects that are relevant to skin inflammation. CXCR3 ligands and CCL20 chemokines, expressed in eczematous skin lesions, are down-regulated by alitretinoin in cytokine-stimulated keratinocytes and dermal endothelial cells. In addition, alitretinoin suppresses the expansion of cytokine-activated leucocyte subsets and antigen presenting cells.

It has been observed that in humans alitretinoin only minimally affects sebum secretion.

Clinical efficacy

The safety and efficacy of Toctino in patients with severe chronic hand eczema (CHE) refractory to topical corticosteroids has been established in two randomised, double blind, placebo-controlled Phase 3 studies.

The primary endpoint in these studies was the proportion of patients achieving Physicians Global Assessment (PGA) ratings of clear or almost clear hands at the end of therapy. The treatment duration was 12 to 24 weeks.

The BACH (Benefit of Alitretinoin in Chronic Hand Dermatitis Study) included 1032 severe CHE patients who had no response or a transient response (initial improvement and worsening of disease despite continued treatment) to potent topical corticosteroids or who were intolerant of potent topical corticosteroids. All phenotypes of CHE were included: hyperkeratosis (87%), pompholyx (27%), fingertip dermatitis (43%), and other (15%). Essentially all patients had signs of skin inflammation, comprising of erythema and/or vesicles. Treatment with alitretinoin led to a significantly higher proportion of patients with clear/almost clear hands, compared to placebo. The response was dose dependent (see Table 2). Response rates for different CHE subtypes were also dose dependent, except for patients with pompholyx (see Table 3).

Table 2: Primary Efficacy Parameter - Results

	Alitretinoin		
Primary Endpoint	**10 mg**	**30 mg**	**Placebo**
ITT Population	**N=418**	**N=409**	**N=205**
PGA at end of study			
Total Response Rate	115 (27.5%)	195 (47.7%)	34 (16.6%)
Clear	39 (9.3%)	90 (22.0%)	6 (2.9%)
Almost clear	76 (18.2%)	105 (25.7%)	28 (13.7%)
Comparison to placebo	P=0.004	P=<0.001	N/A

Table 3: Response rate by CHE subtype

CHE subtype	**Hyperkeratotic**	**Hyperkeratotic/**	**Pompholyx**

(% of ITT population)	(64%)	Pompholyx (22%)	(5%)
Response rate (PGA)	30mg: 54% 10 mg: 30% Placebo: 12%	30mg: 33% 10 mg: 23% Placebo: 12%	30mg: 33% 10 mg: 22% Placebo: 30%

Secondary endpoints included the proportion of patients achieving at least mild disease, time to achieving clear to almost clear hands, reduction in total lesion symptom score, patient global assessment (PaGA) of disease severity, reduction in extent of disease (see Table 4). Patients with clear/almost clear hands at end of treatment were followed up for 24 weeks. During that period no active drug treatment for CHE was allowed. Relapse was defined as 75% of the initial total lesion symptom score.

Table 4: Secondary Efficacy Parameters - Results

	Alitretinoin		
Efficacy Variable	**10 mg**	**30 mg**	**Placebo**
ITT Population	**N=418**	**N=409**	**N=205**
Partial Response Rate (clear, almost clear or mild disease)	207 (49.5%)	254 (62.1%)	74 (36.1%)
PaGA (clear or almost clear)	101 (24.2%)	163 (39.9%)	31 (15.1%)
mTLSS (mean % change from baseline)	-50.79 (n=411)	-60.80 (n=408)	-37.30 (n=204)
Extent of disease (mean % change from baseline)	-40.01 (n=402)	-54.15 (n=391)	-31.93 (n=197)

The numbers of responding patients without observed relapse at the end of the 24-weeks follow-up period is given in Table 5 below. In this analysis, the majority of responders given 10mg and 30mg alitretinoin did not relapse by the end of the follow-up period.

Table 5: Relapse Rates* at the End of Follow-up

	Alitretinoin		Placebo
	10 mg N=418	**30 mg N=409**	**N=205**
Responders	115 (100%)	195 (100%)	34 (100%)
No Relapse	81 (70.4%)	122 (62.6%)	19 (55.9%)

* Corresponds to a last-observation-carried-forward (LOCF) computation

A follow-up study (the second Phase 3 study) investigated the efficacy and safety of a second course of treatment both in patients who previously responded (Cohort A) and in patients who did not (Cohort B). Cohort A patients who responded in the previous study but who relapsed were randomised to the same dose they received in their initial treatment (10 or 30mg) or to placebo in a 2:1 ratio. 80% of relapsing patients who again received the 30 mg dose achieved clear/almost clear hands vs. 8% of the corresponding placebo group ($p<0.001$). 48% of relapsing patients who again received the 10 mg dose achieved clear/almost clear hands vs. 10% of the corresponding placebo group ($p=0.1$). Patients who responded to treatment with placebo in the previous study also received placebo in this follow-up study. Many of these patients responded again to treatment with placebo (69.2%).

5.2 Pharmacokinetic Properties

Absorption

The absorption of alitretinoin from the gastro-intestinal tract is variable and dose-proportional over the therapeutic range from 10-30mg. The absolute bioavailability of alitretinoin has not been determined. When alitretinoin is taken with food, the systemic exposure is enhanced by a factor of 4 and the variability of exposure is decreased. Therefore, alitretinoin should be taken with a meal.

Distribution
Alitretinoin strongly binds to plasma proteins. The volume of distribution of alitretinoin in man has not been determined, but animal studies indicate a volume of distribution greater than the extracellular volume.

Metabolism
Alitretinoin is metabolised by oxidation in the liver by CYP3A4 isoenzymes into 4-oxo-alitretinoin. Both compounds undergo isomerisation into all-trans retinoic acid and 4-oxo-all-trans retinoic acid. After oral administration, the contribution of the metabolites in plasma to the systemic exposure of alitretinoin is approximately 35% to 80% for 4-oxo-alitretinoin. The major metabolite 4-oxo-alitretinoin is further glucuronidated and eliminated in urine. Alitretinoin is degraded similarly to vitamin A by sequential cleavage of the carbon-side chain.
During a 12-to 24-week treatment period with 10 or 30mg, the exposure to alitretinoin remained stable.

Elimination
Alitretinoin is an endogenous retinoid. Alitretinoin concentrations return to normal range within 1 to 3 days after treatment cessation.
Excretion of radio-labelled alitretinoin was complete with approximately 94% of the dose recovered. Radio-labelled material was eliminated mainly in urine and a smaller fraction (approx. 30%) in faeces. The most abundant excretion compound is the glucuronide of 4-oxo-alitretinoin amounting to 6.5% of the dose in urine.
Elimination half-life of unchanged alitretinoin ranges between 2 to 10 hours. Alitretinoin and its 4-oxo-metabolite do not accumulate.

Pharmacokinetic in special populations
In a pharmacokinetic study in patients, gender, weight and age did not affect the pharmacokinetics of alitretinoin.
The pharmacokinetics of alitretinoin in CHE patients was similar to that in healthy volunteers.
Alitretinoin kinetics have not been studied in patients with hepatic or with severe renal insufficiency or in patients below 18 years (see section 4.3).

5.3 Preclinical safety data

Acute toxicity
As with other retinoids, the acute toxicity of alitretinoin was low in mice and rats. The LD_{50} after intraperitoneal administration was >4000 mg/kg after 24 hours and 1400 mg/kg after 10 days. The approximate LD_{50} after oral administration in rats was 3000 mg/kg.

Chronic toxicity
Alitretinoin was tested in long-term studies up to 9 months in dogs and 6 months in rats. Signs of toxicity were dose-related and occurred at exposures similar to the human therapeutic exposure based on AUC. Effects were characteristic for retinoids (consistent with hypervitaminosis A), and were generally spontaneously reversible.

Teratogenicity
Like other retinoids, alitretinoin has been shown to be teratogenic *in vitro* and *in vivo*.
Due to the teratogenic potential of alitretinoin, women of childbearing potential must adhere to strict pregnancy prevention measurers during and 1 month following alitretinoin therapy (see section 4.3 “Contraindications”, section 4.4 “Special warnings and special precautions for use” and section 4.6 “Pregnancy and lactation”).

Fertility
Alitretinoin was tested in a study of fertility and early embryonic development in rats. No effects on male or female reproductive parameters were observed at the highest dose tested. However, systemic exposure in this study did not reach the level observed in patients.
As with other retinoids reversible effects on male reproductive organs were observed in experimental animals in the form of disturbed spermatogenesis and associated degenerative

lesions of the testes. The safety margin in dogs with regard to the no-effect level of toxicity to male reproductive organs was 1-6 for a human dose of 30mg.

Mutagenicity
In *in vitro* or *in vivo* tests, alitretinoin has been shown not to be mutagenic.

Carcinogenicity
Alitretinoin was tested in 2-year carcinogenicity studies in rats and mice. Dose-related retinoid-specific toxicity was seen at higher doses, but no carcinogenic potential was noted.

Phototoxicity
Alitretinoin was found to be phototoxic *in vitro* and *in vivo.*

6. Pharmaceutical properties

6.1 List of excipients
Capsule content:
Soya-bean oil, refined
Partially hydrogenated soya-bean oil
Triglycerides, medium chain
Beeswax, yellow
All-rac-□-tocopherol
Capsule shell:
Gelatin
Glycerol
Sorbitol, liquid (non-crystallising)
Water purified
Iron oxide (E 172)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store in the original package. Keep the blister in the outer carton to protect from light.

6.5 Nature and contents of container
PVC/PE/PVDC/Aluminum or COC (cycloolefin copolymer)/Aluminum blisters. Pack sizes of 30 capsules.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed in accordance with local requirements.

7. Marketing authorisation holder
Basilea Medical Ltd, 14/16 Frederick Sanger Road, The Surrey Research Park, Guildford, Surrey GU2 7YD

8. Marketing authorisation number

10mg, 30 capsules	PL 32205/0001
30mg, 30 capsules	PL 32205/0002

9. Date of first authorisation/renewal of the authorisation

5 SEPTEMBER 2008

10. Date of revision of the text
5 SEPTEMBER 2008

10.2 Appendix 2: search strategy for section 5

10.2.1 The specific databases searched and the service provider used

The databases and dates searched are shown below. MedLine was searched using Ovid and PubMed. Embase was searched using Ovid.

Database	**Date span**
Medline (R)	1950 to Oct Week 2 2008
MedLine (R) In Process	1950 to Oct 21, 2008
EMBASE	1974 to 2008 (Week 24)
Cochrane Library	1950 to 2008

10.2.2 The date on which the search was conducted.

The latest search was carried out on the 22nd October 2008.

10.2.3 The date span of the search.

Shown in section 10.2.1.

10.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Table 10.2.1 MedLine and EMBASE (Ovid)

	Searches	**Results**
1	exp Skin Diseases, Eczematous/	106071
2	exp Eczema/	16840
3	exp Dermatitis/	130310
4	(contact or allergic or irritant).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm]	440935
5	(eczema$ or dermatitis or tylotic or pompholyx or cheiropompholyx).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm]	118756
6	(pulpitis or pulpite or dyshidro$ or dyshydro$ or dishidro$ or dishydro$	84726

	or hyperkerato$ or kerato$).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm]	
7	exp Hand/	83760
8	(hand or hands or acra or acral or acras or finger or fingers or fingertip$).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm]	558514
9	(dors$ or apron or palm or palms or palmal or palmar or palmoplant$).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm]	235929
10	1 or 2 or 3 or 4 or 5 or 6	610132
11	7 or 8 or 9	776535
12	10 and 11	32235
13	(treat$ or therap$).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm]	7544825
14	12 and 13	8920
15	Hand Dermatoses/	7614
16	hand disease/	1939
17	13 and 15	2212
18	13 and 16	834
19	14 or 17 or 18	10505
20	(trial$ or random$ or placebo$ or control$ or prospectiv$ or volunteer$).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm]	7322407
21	19 and 20	3633
22	(trial or clinical trial or controlled clinical or controlled clinical trial or randomized controlled or review or meta analysis or multicenter study or multicentre or practice guideline or consensus or cohort).pt.	2894412
23	19 and 22	1992
24	(blind$ or mask$ or crossover$ or cross-over$ or factorial).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm]	533630
25	19 and 24	537
26	(controlled or singl$ or doubl$ or trebl$).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm]	5098362
27	19 and 26	2371
28	21 or 23 or 25 or 27	4841
29	exp Azathioprine/	59968
30	azathioprine.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm]	66095

31	(ciclosporin$ or cyclosporin$).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm]	131124
32	exp Cyclosporine/	62918
33	exp immunosuppressive agents/	528740
34	immunosuppres$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm]	246155
35	exp phototherapy/ or exp photochemotherapy/ or exp ultraviolet therapy/ or exp puva therapy/ or exp puva/	44676
36	alitretinoin.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm]	1810
37	9-cis retinoic acid.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm]	2129
38	36 or 34 or 33 or 35 or 31 or 32 or 29	684650
39	28 and 38	773
40	limit 39 to human	694
41	remove duplicates from 40	598
42	from 41 keep 1-598	598

Table 10.2.2 Terms used to search the Cochrane library

Connector	**Search term**		**Results**
	eczema or dermatitis or eczema* or dermat* or tylotic or pompholyx or cheiropompholyx or pulpitis or pulpite or dyshidro* or dyshydro* or dishidro* or dishydro* or hyperkerat*	Search all text	
AND	hand or hands or finger* or acra* or palm* or dors* or apron	Search all text	
AND	PUVA or psoralen* or UVA or phototherapy or photochemotherapy or azathioprine or ciclosporin* or cyclosporine* or alitretinoin or 9-cis retinoic acid	Search all text	**33**

MedLine (PubMed) search terms

(eczema or dermatitis or eczema* or dermat* or tylotic or pompholyx or cheiropompholyx or pulpitis or pulpite or dyshidro* or dyshydro* or dishidro* or dishydro* or hyperkerat*) and (hand or hands or finger* or acra* or palm* or dors* or apron) and (PUVA or psoralen* or UVA or phototherapy or photochemotherapy or azathioprine or ciclosporin* or cyclosporine* or alitretinoin or 9-cis retinoic acid)

10.2.5 Details of any additional searches, for example searches of company databases (include a description of each database).

No additional searches were carried out.

10.2.6 The inclusion and exclusion criteria.

Inclusion criteria

- Although in the search strings listed above all types of trials were included in the strategy, the inclusion criteria for the literature search was as follows: all randomised controlled trials (RCTs) comparing alitretinoin, PUVA, ciclosporin or azathioprine to an alternative treatment (including placebo) when used for the treatment of CHE.

Exclusion criteria

- Reviews
- Studies carried out in disease areas other than CHE (studies on palmoplantar dermatoses were also excluded, these studies include all types of dermatoses that affect the hands and feet such as psoriasis and did not separate results by hand and foot)
- Studies which did not compare relevant therapies.

10.2.7 The data abstraction strategy.

The relevant search terms were entered into the database being searched and the terms were then combined to form search strings as detailed in section 10.2.4. The titles and abstracts (if available) of all papers revealed at this stage were then reviewed and eliminated manually if they were not relevant to the search – as per the inclusion and exclusion criteria. Results from the Ovid, PubMed and Cochrane searches were cross-checked and duplicates removed. 46 studies were further reviewed for potential relevance and full texts retrieved if necessary, papers were eliminated as per the inclusion and exclusion criteria.

10.3 Appendix 3: search strategy for section 6

The following information should be provided.

10.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

The following databases were searched:

- MEDLINE (R) – 1950 to November week 2 2008
- MEDLINE (R) - In process
- EMBASE – 1947 to 2008 week 46
- NHS Economic Evaluation Database
- DARE – Database of Abstracts of Reviews and Effectiveness
- HTA – Health Technology Assessment

10.3.2 The date on which the search was conducted.

The search of Medline and Embase databases was carried out on 12.11.08.

The searches for the remaining databases were carried out on 01.12.08.

10.3.3 The date span of the search.

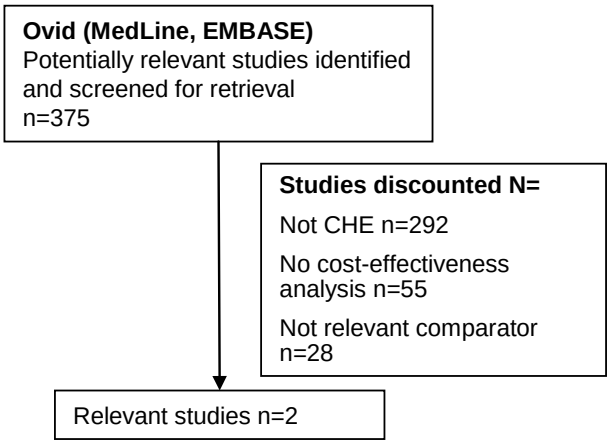
Please see section 10.3.1

10.3.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Search strategy for Medline and Embase (via Ovid)

	Search term	**Number of results**
1	exp skin diseases, eczematous/	(120511)
2	exp eczema/	(21771)
3	exp dermatitis/	(144776)
4	(contact or allergic or irritant).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm]	(482697)
5	(eczema$ or dermatitis or tylotic or pompholyx or cheiropompholyx).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm]	(132283)
6	(pulpitis or pulpite or dyshidro$ or dyshydro$ or dishidro$ or dishydro$ or hyperkerato$ or kerato$).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm]	(92316)
7	exp Hand/	(88126)
8	(hand or hands or acra or acral or acras or finger or fingers or fingertip$).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm]	(610703)
9	(dors$ or apron or palm or palms or palmal or palmar or palmoplant$).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm]	(253764)
10	6 or 4 or 1 or 3 or 2 or 5	(669402)
11	8 or 7 or 9	(844854)
12	11 and 10	(36052)
13	(treat$ or therap$).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm]	(8023056)
14	13 and 12	(10171)
15	Hand Dermatoses/	(7637)
16	hand disease/	(1960)
17	13 and 15	(2223)
18	16 and 13	(844)
19	economics/	(32078)
20	exp "Costs and Cost Analysis"/	(269590)
21	VALUE OF LIFE/	(39021)
22	economics, dental/	(12882)
23	exp economics, hospital/	(247932)
24	economics, medical/	(18419)
25	economics, nursing/	(14946)
26	24 or 21 or 20 or 23 or 25 or 22 or 19	(473869)
27	(econom$ or cost$ or costs or costly or costing or fee$ or budget$ or resource or price or prices or pricing or	(2538009)

	pharmacoeconom$ or effective$).ti,ab.	
28	(expenditure$ not energy).ti,ab.	(24182)
29	(value adj1 money).ti,ab.	(32)
30	budget$.ti,ab.	(23001)
31	27 or 29 or 30 or 28	(2546441)
32	26 or 31	(2787691)
33	letter.pt.	(1124102)
34	editorial.pt.	(476256)
35	historical article.pt.	(257952)
36	34 or 33 or 35	(1847416)
37	exp Azathioprine/	(61385)
38	azathioprine.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm]	(67552)
39	(ciclosporin$ or cyclosporin$).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm]	(131598)
40	exp Cyclosporine/	(63143)
41	exp immunosuppressive agents/	(541680)
42	immunosuppres$.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm]	(250294)
43	exp phototherapy/ or exp photochemotherapy/ or exp ultraviolet therapy/ or exp puva therapy/ or exp puva/	(45156)
44	alitretinoin.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm]	(1819)
45	9-cis retinoic acid.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm]	(2135)
46	18 or 17 or 14	(11764)
47	32 not 36	(2711713)
48	39 or 40 or 41 or 38 or 42 or 45 or 37 or 43 or 44	(703079)
49	46 and 48 and 47	(409)
50	limit 49 to human	(375)
51	from 50 keep 1-375	(375)



Search strategy for NHS EED, DARE and HTA databases through the Centre for Reviews and Dissemination

Search: Eczema

- 72 results (37 DARE; 24 NHS EED; 11 HTA)
- A hand search of these 72 studies identified 13 (2 DARE; 8 NHS EED; 3 HTA) studies relating to the economic evaluation of eczema. The following terms formed the basis of selection: cost-utility, cost-effectiveness, cost-consequence, and cost-minimisation, economic evaluation, economic assessment, health technology assessment, HTA, cost-benefit analysis.

- Of these 13 studies the following 7 studies were excluded:
    - Two duplicates, abstract and full publication of same studies
    - One study on the treatment of childhood asthma
    - One study on the treatment of peritoneal dialysis
    - One study on the treatment of deep vein thrombosis following hip replacement
    - One study on the treatment of chronic pain
    - One study: project ongoing (Transmural care for hand eczema).

The remaining 6 studies were in atopic eczema or psoriasis and did not address the cost-effectiveness of relevant comparators.

10.3.5 Details of any additional searches, for example searches of company databases (include a description of each database).

No additional searches were carried out.

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