Response to NICE Questions Jan 2009

Section A: Clarification on effectiveness data

Systematic review

A1. Please provide a table of all the studies of comparator interventions identified during the review. Please provide the inclusion and exclusion criteria for each study and justification for inclusion/exclusion in subsequent analyses.

Appendix 1 provides an overview of the studies identified for the comparators in the literature review with the reason for inclusion or exclusion in the subsequent indirect treatment comparison (Table 1). The table does not include the inclusion/exclusion criteria for the individual studies as confirmed with NICE on the 27th January 2009.

Appendix 1 also includes an overview of the studies identified for each comparator and reasons for exclusion of studies from the indirect comparison analyses.

PUVA trials

A2. Please provide tabulated details of all 13 identified PUVA studies, including each study's definition of response and efficacy/safety results (including those for the Adams et al 2007 and Grattan et al 1991 studies, which are not currently presented).

Tabulated details are included in appendix 1 table 2.

A3. Please provide the response rates of the PUVA arms for all of the 13 identified studies.

Table 2 of appendix 1 includes this information.

A4. On page 58 it is stated that four of the PUVA trials provide only mean reduction in severity and do not report number of responders. Is it possible for you to synthesise the mean reduction in severity from these trials with the corresponding mean reduction in severity from the alitretinoin trials for comparison and factor these into their model?

The results of the four trials that were not included in the indirect comparison because only mean reduction in disease severity was reported, are shown in appendix 1, table 3.

- In the case of the alitretinoin arm of the model, 4 weekly efficacy ratings by mTLSS reduction could potentially have been used instead of PGA states because matched mTLSS data are available from study visits, however it is not clear how the PUVA arm could be modified to take account of these 4 PUVA trials.
- The 4 PUVA studies use different continuous rating instruments, the results of which would be difficult to synthesise. There are insufficient details regarding corresponding categorical PGA status or similar to allow validation of scores by correlation with categorical disease state.
- Furthermore, CHE is almost certainly of different baseline severity in these PUVA studies. The largest PUVA trial of Coevoorden et al uses a severity score which appears the most similar to mTLSS, however baseline severity is 41% of the maximum score for the instrument used (8.3/21) whereas in the alitretinoin trial baseline severity is 74% of the maximum mTLSS (15.6/21). Because of differences in baseline severity, comparison of mean reductions in severity are potentially misleading even if sufficiently similar instrument ratings could be identified for comparison.

Quality of life data

A5. Please clarify whether quality of life was measured in trials BAP00089 and BAP00091? If so, please provide the results.

- Quality of life was not measured in these phase III trials but was measured in the BAP0003 study from which evidence was presented. Additional evidence of the impact of change in CHE severity on quality of life was presented from an observational study.

DLQI analysis

A6. Please provide further tabulated details of the DLQI analysis in BAP00003 (including population characteristics for DLQI subgroups)

- Thank you for your clarification of question A6 in response to our query. For the sake of clarity we will refer to the two different DLQI analyses performed on BAP0003 study data as follows :

Analysis 1: Treatment effect on DLQI (original protocol specified analysis)
Analysis 2: DLQI analysis independent of treatment effect (conducted for the purposes of NICE submission)

- The population used for analysis 1 was the overall BAP00003 randomised study population but DLQI data was collected only in a subset of the population where a validated DLQI was available in the local language and where matched baseline-12 week questionnaires were completed.
- Please find details of the BAP00003 population characteristics and results of Analysis 1 of treatment effect on DLQI in appendix 2

- As stressed in our submission, alitretinoin doses and patient population in BAP0003 do not match the phase III trial population or the alitretinoin licensed indication because there was no 30mg dose group and the population was mostly of PGA moderate severity at baseline.

- As regards analysis 2 of DLQI independent of treatment effect: As per analysis 1, the population analysed was a subset of all patients based on availability of paired DLQI questionnaires in the right language rather than a particular subgroup. Patient characteristics for patients included in analysis 2 are as per appendix 2 for the DLQI analysis population; analysis 2 was by PGA state rather than treatment group as in analysis 1.

Safety data

A7. Please provide complete tabulated data from the special safety assessments discussed on p.70-71.

Please see appendix 3 for the tables of special safety assessments requested and additional attachments of relevant summaries of special safety findings. The summarised information may provide a better overview of findings in the pooled population exposed to alitretinoin to date and special safety in patients receiving longer periods of intermittent and continuous exposure because of sequential participation in BAP00089 and BAP00091 studies.

A8. On page 93 of your submission it is stated that "The probability associated with withdrawing from treatment had to be estimated for most adverse events since there was no data available." Therefore please clarify the methods used to derive all the withdrawal rate and adverse event estimates, for example were any based on clinical opinion?

- For the comparators azathioprine, ciclosporin and PUVA, because no comparable trial evidence exists in CHE, reliance was placed on reported tolerability in different indications (eg atopic eczema) or on anecdotal experience of these treatments in CHE.

- Comparator adverse event rates were derived from the Summary of Product Characteristics in the case of azathioprine and ciclosporin with reference as far as possible to dermatological doses which are usually lower than doses used in transplant indications.

- In the case of PUVA, adverse event estimates were derived from a published paper (Laube, George. Adverse Effects with PUVA and UVB phototherapy, Journal of Dermatology Treatment 2001, 12, 101-105)

- The probability of withdrawal due to an AE for alitretinoin (20%) was based on the trial observation that headache-related withdrawal occurred in 4% of patients whereas the rate that headache was reported was

approximately 20%, giving a 1 in 5 (20%) probability of withdrawal for this event in the model. In the absence of equivalent data for comparator AEs, a withdrawal probability of 1 in 5 was used for transient AEs (< 4 weeks duration) on the assumption that, like headache, they could be managed without discontinuation in the majority of cases. An arbitrarily higher value of 40% was assumed for permanent AEs such as hypertension (> 4 weeks duration) as it was assumed that the longer term implication of continued drug exposure would prompt discontinuation in a higher proportion of cases. It should be noted that these withdrawal probabilities have minimal influence on the estimated cost-effectiveness ratios as the probability of occurrence is low.

Also please clarify whether any data on withdrawal rates due to adverse events, other than headache in the alitretinoin trial, were available (for example from the other RCTs obtained during the review).

Appendix 4 provides the withdrawal rates from the BAP00089, BAP00091 studies. These data confirm that the main treatment related reason for discontinuation in patients taking alitretinoin was headache and that this is a dose dependent adverse event, being highest in the 40mg group in phase II BAP00003 and lowest in the 10mg group, hence its proposed role in the management of headache on the higher dose.

Sub-group analysis

A9. The report provides a sub-group analysis for hyperkeratotic patients. Please provide the corresponding analysis for the sub-group of non-hyperkeratotic patients.

- Further sub-group analysis has been performed for the following groups of patients:
    - Hyperkeratotic and pompholyx
    - Pompholyx only

- The table below provides the 24 week data for the different sub-groups from BAP00089
- Four weekly data were not available for the sub-group analysis within the time-frame available and therefore the efficacy was modelled linearly over the 24 week period for both the first and subsequent cycles, BAP00089 and BAP00091
- Only 5% of patients had disease that was classified as pompholyx alone. Furthermore, analysis of mTLSS indicates that only 1% of patients had vesicular CHE without also having a significant score for hyperkeratosis. In BAP00091 only one patient classified as pompholyx received 30mg

alitretinoin and therefore it was not felt appropriate to model this patient group

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

Hyperkeratotic and Pompholyx Sub-group analysis

- Tables below provide the transition probabilities for patients with hyperkeratotic and pompholyx disease for alitretinoin and placebo
- For the comparator model – sub-group data are not available for the comparators and therefore the same data were used as in the main comparison
- In BAP00091 patients with hyperkeratotic and pompholyx disease at 24 weeks had either PGA status severe or clear/almost clear. Therefore patients have been moved linearly over 24 weeks through these two PGA states with no patients with mild or moderate disease.
- For the placebo model - In BAP00091 data were not available in the time-frame available for patients that received placebo in BAP00089 and placebo in BAP00091 for this sub-group. Therefore data for the 13 patients in the whole population has been used.

Alitretinoin First Cycle (30mg; BAP00089) – Hyperkeratotic and pompholix					
	Disease Severity				
Week	**Remission**	**Mild**	**Moderate**	**Severe**	**Refractory**
4	0.056	0.030	0.048	0.867	0.000
8	0.111	0.059	0.096	0.733	0.000
12	0.167	0.089	0.145	0.600	0.000
16	0.222	0.119	0.193	0.467	0.000
20	0.278	0.148	0.241	0.333	0.000
24	0.333	0.178	0.289	0.200	0.000

Alitretinoin Subsequent Cycles (30mg; BAP00091) – Hyperkeratotic and pompholyx					
	Disease Severity				
Week	Remission	Mild	Moderate	Severe	Refractory
4	0.125	0.000	0.000	0.875	0.000
8	0.250	0.000	0.000	0.750	0.000
12	0.375	0.000	0.000	0.625	0.000
16	0.500	0.000	0.000	0.500	0.000
20	0.625	0.000	0.000	0.375	0.000
24	0.750	0.000	0.000	0.250	0.000

Placebo – First Cycle (BAP00089) – Hyperkeratotic and Pompholyx					
	Disease Severity				
Week	Remission	Mild	Moderate	Severe	Refractory
4	0.020	0.040	0.032	0.909	0.000
8	0.040	0.079	0.063	0.818	0.000
12	0.060	0.119	0.095	0.727	0.000
16	0.079	0.159	0.127	0.635	0.000
20	0.099	0.198	0.158	0.544	0.000
24	0.119	0.238	0.190	0.453	0.000

Placebo (Responders) - Subsequent cycles (Analysis of 13 patients from BAP00091)					
	Disease Severity				
Week	Remission	Mild	Moderate	Severe	Refractory
4	0.115	0.000	0.051	0.833	0.000
8	0.231	0.000	0.103	0.667	0.000
12	0.346	0.000	0.154	0.500	0.000
16	0.462	0.000	0.205	0.333	0.000
20	0.577	0.000	0.256	0.167	0.000
24	0.692	0.000	0.308	0.000	0.000

Results

- Results are presented below for the base case (including costs of TSH monitoring)

Treatment	Total Costs	Incremental Costs	Total Utility	Incremental Utility	ICER
Placebo (Hyperkeratotic and Pompholyx)	£566.81		1.76		
Alitretinoin (Hyperkeratotic and Pompholyx)	£2,867.43	£2,300.62	1.84	0.08	£26,013.22
PUVA	£3,640.90		1.80		
Alitretinoin (Hyperkeratotic and Pompholyx)	£2,867.43	-£733.47	1.84	0.04	-£19,472.48 (Alitretinoin dominant)
Ciclosporin	£1,683.44		1.80		
Alitretinoin (Hyperkeratotic and Pompholyx)	£2,867.43	£1,183.99	1.84	0.04	£27,950.50
Azathioprine	£845.80		1.76		
Alitretinoin (Hyperkeratotic and Pompholyx)	£2,867.43	£2,012.63	1.84	0.08	£24,631.59

A10. Please provide further detail about how the treatment effect was adjusted for the hyperkeratotic sub-group analysis.
Which trials provided the source of the data and what type of analysis was used to calculate the sub-group specific treatment effect?

- The same analysis was performed as for the overall study population from which the hyperkeratotic subgroup came. See also question 9 above.
- All data were derived from the BAP00089 and BAP00091 study and the subgroup analysis was identical in all respects to the analysis performed for the overall population with the exception that it was performed on patients classified by investigators as hyperkeratotic only, patients classified as hyperkeratotic and pompholyx and patients classified as pompholyx only.

Why do the re-treatment transition probabilities for the hyperketatotic sub-group differ to the re-treatment transition probabilities for the overall patient population, as it seems these were based on the same trial?

- The re-treatment transition probabilities for the hyperkeratotic subgroup were from a subgroup analysis of the trial BAP00091 and therefore differed from the overall patient population. In addition data were only available for the 24 week time point for this sub-group and therefore transition probabilities were back-calculated linearly over the 24 week time period rather than being available at 4 weekly time points.

Sub-group analysis of re-treatment of hyperkeratotic patients from BAP00091

PGA status at 24 weeks	Alitretinoin 30mg N=45
Clear/Almost Clear	80.0%
Mild	8.9%
Moderate	4.4%
Severe	6.7%

Miscellaneous

A11. Please provide full tabulated details of BAP00626 as have been provided for the randomised trials.

These are provided in Appendix 5

A12. On page 77 in paragraph four, two consecutive statements appear to contradict each other. It is stated that "*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.*" The median time to relapse would suggest that 50% of responders had relapsed by five and a half months. Please can you clarify the discrepancy between the figures?

The apparent discrepancy may be explained as follows. The median time to relapse is an estimated value, calculated according to Kaplan-Meier analysis, with patients censored at the time of their last non-relapse assessment. When patients are censored, they are not counted in the numerator of relapsed patients (since they have not relapsed) or in the denominator of all patients (since they have no possibility of contributing to the numerator). This means that the calculation changes with every event of censoring.

A13. To evaluate any potential underlying seasonal effects, please provide details of the monthly response and relapse rates for the placebo arms of BAP00089 or BAP00091.

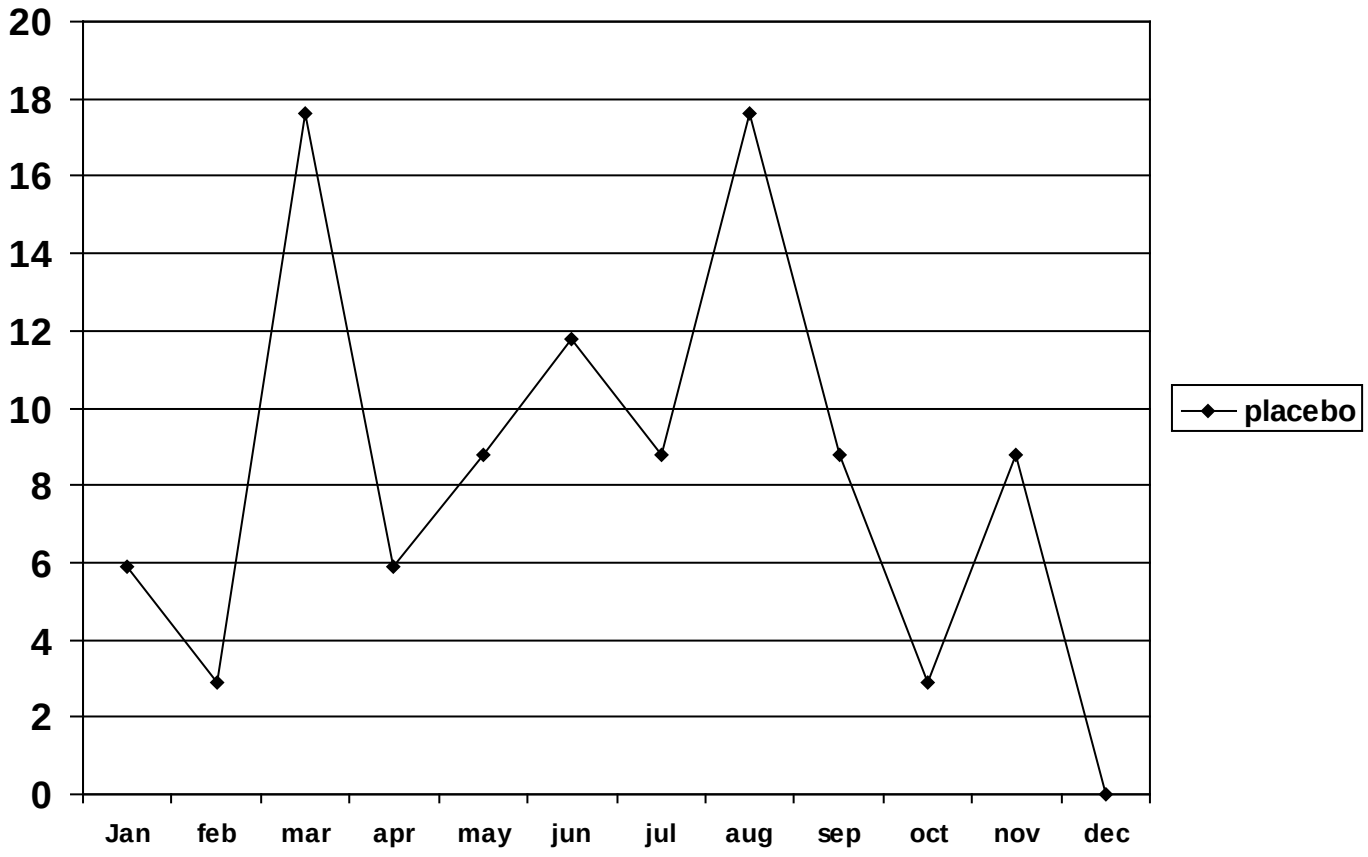
- The best approach to the evaluation of a potential seasonal effect was not immediately clear. We felt that this would require analysis of the probability of response for placebo patients by calendar month relative to time on treatment because peaks in response in any month could be treatment time as well as season-dependent.
- In the time available we have been able to analyse the PGA response by month for the placebo group as requested in the table and accompanying graph below. As regards a potential seasonal effect on relapse, only 15 placebo-responding patients relapsed during the follow up period and this was of six months duration. We have therefore not attempted this analysis but would be happy to do so if considered necessary. As no treatment was given during follow up observation for

relapse, it would seem reasonable to assume that a seasonal effect consistent with the published literature could be presumed.

- From the summary of response by month below it might appear that placebo response rate is indeed lowest in winter and highest in spring/summer, however there are inconsistencies such as the twin peaks of placebo response in late winter and late summer and the potential effect of duration of treatment with placebo in individual patients has not been factored into this analysis.
- We would be happy to discuss options to explore the question of seasonal effect further with NICE as required.

Summary by month of % PGA responses observed in placebo-treated patients in BAP00089 study

	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Placebo	5.9	2.9	17.6	5.9	8.8	11.8	8.8	17.6	8.8	2.9	8.8	0



A14. In the trials of alitretinoin, the time to relapse was approximately the same for alitretinoin and placebo (see p43 and p46). Please can you clarify whether the clinicians on the expert panel were presented with this evidence when they provided estimates of the time to relapse for the comparators, as these are significantly shorter than the time to relapse with alitretinoin (and placebo).

- Expert panel members were provided with the April 2008 BJD publication of the BAP00089 trial and asked to review it as pre-work for the meeting in the meeting invitation. (see appendix 7) Median time to relapse for alitretinoin 10mg, 30mg and placebo was displayed in a table of secondary efficacy parameters of the publication and the median time to relapse in alitretinoin groups is mentioned in the summary and discussion sections of this paper.
- In addition panel invitees were asked to complete and return a brief CHE treatment questionnaire prior to the meeting. This was designed to explore the severity of CHE patients treated with different approaches in their centres and the efficacy and durability of remission produced by such treatments.(see appendix 7 for invite, questionnaire and meeting report and response to B2 below for additional information)
- Question 4 of the pre-meeting questionnaire relating to durability of treatment response was worded as follows:

  Q " Considering those patients achieving a response to systemic therapy or phototherapy (either defined as PGA clear/almost clear or a substantial % improvement); what proportion would have relapsed to at least 75% of their original disease severity by:
  4 weeks
  8 weeks
  12 weeks
  16 weeks
  20 weeks
  24 weeks

  Please specify which agents are associated with any particular period of relapse if possible"

  This was phrased to allow for potential differences in the definition of a meaningful response that could be clarified at the meeting.

- The main features of the BAP00089 trial were briefly presented by the UK Medical Director of Basilea at the panel meeting and questions were invited from the panel of experts; no specific questions about time to relapse in the trial were raised. (see clinical presentation attached)
- In response to a specific question from Basilea the panel agreed that the trial definition was acceptably close to the normal clinical definition of relapse "sufficient to be retreated with systemic therapy or PUVA"
- The estimation of relapse rates for comparators was the main objective of the panel meeting and this is reflected in the information captured in the panel report. There was, in addition, considerable discussion regarding individual agents at the meeting however opinions or background rationale to the expert estimates were not generally included in the report. Further background is therefore provided below.
- Panel consensus was established regarding the relatively rapid rate of relapse associated with ciclosporin and this was illustrated by one dermatologist who used the example of "rebound" exacerbation

sometimes seen with this agent when used in severe psoriasis. For several experts, rapid relapse was stressed as the major reason their use of ciclosporin had declined in CHE whereas for others, safety concerns were the major reason cited.

- Azathioprine was generally considered to have a slower time to relapse than ciclosporin, possibly through different immunological mechanisms as it was noted to also be slower to produce improvement. Precise estimation of time to relapse (as defined in the BAP00089 trial) for azathioprine was felt to be difficult for some experts because of the relatively small number of patients recalled to have fully responded (as per the PGA definition (and therefore observable for a 75% deterioration in severity) and the consequent tendency to treat patients continuously with this agent to maintain control of CHE rather than clear hands

- It was stressed that topical steroids would continue to be used and would probably act to prolong “response” (however defined) for all the comparators discussed.

A15. In the background section, please comment further on the appropriateness and relevance to clinical practice of providing only emollients to patients with severe refractory CHE. This is because we have been informed by a clinical adviser that (in the absence of alitretinoin) the majority of patients with severe hand eczema would continue to use topical steroids even if they no longer received much benefit. In addition, patients ineligible for PUVA or immunosuppressants would also continue to receive topical steroids. Given that alitretinoin is the only licensed treatment for severe chronic hand eczema, a comparison with supportive care/'do nothing' may therefore considered to be warranted.

- The population defined in the NICE final scope for the appraisal of alitretinoin is adult patients with severe CHE refractory to potent topical steroids. It is however appreciated that information from experts may come to light during the consultation process that may throw up additional questions of interest, hence we are happy to provide our perspective on these questions:

<u>Appropriateness</u>

- Eligibility for treatment in the BAP00089 trial depended on the documentation of no benefit (40-48%), inadequate benefit (49-59%) from previous topical steroids or inability to tolerate these agents (1-3%).
- Although topical steroids are unlikely to cause systemic toxicity when used in adults with CHE, topical steroids have well recognised local side effects which include skin atrophy and susceptibility to trauma and

further, a body of opinion supports a role for topical steroids in the perpetuation of CHE by impairment of skin barrier function.

- From the patient perspective it is clear that the application of topical treatments is often considered messy and inconvenient because it interferes with normal life activities.
- In view of these potential drawbacks to topical steroid use there would be no clear justification for their further use (at least at study outset) in the absence of any obvious benefit to be obtained.

Relevance to clinical practice

- It is clear that current clinical practice often does include the use of topical steroids in CHE even in the absence of significant benefit and multiple factors may be responsible for this.
- Without adequately effective systemic or phototherapy treatment for steroid refractory patients there is likely to remain an underlying compulsion to continue to help the patient rather than appear to cease all potentially effective treatment.
- In the absence of a reliable evidence base or guidelines to change long standing practice, continued use of topical steroids in CHE may be easily rationalised because they may be perceived as relatively benign and cheap to provide.
- The placebo arm of the BAP00089 trial provides RCT evidence that meticulous attention to patch testing, allergen avoidance, protection from irritants and optimal emollient therapy can result in reasonable rates of PGA defined response in this population without the use of topical steroids or other active medication. This evidence would tend to refute the necessity of topical steroids in the “supportive care” of patients with severe CHE provided the standard supportive care of CHE can be optimised, although the additional contribution of a truly psychological placebo effect in the trial is difficult to estimate.
- On the other hand, topical steroids are recognised to be associated with tachyphylaxis due to change in skin vascular responsiveness and this may be reversible after a suitable holiday from their use, hence it is possible that intermittent use in clinical practice does produce additional clinical benefit and might have done so in the alitretinoin trials, however there is currently limited evidence to support this.
- Given the potential effects on the skin barrier described above, if topical steroids were to be re-introduced to previously refractory patients it would seem most appropriate to do this once patients had achieved a significant degree of improvement.
- Future trials of alitretinoin may be able to elucidate these questions but for the purposes of the placebo model attached we have not attempted to factor in a potentially beneficial topical steroid effect as it is not possible to quantify this.

Section B: Clarification on cost effectiveness data

The structure of the model

B1. Please could you consider to provide a model that includes a 'supportive care' arm, as this may be considered a relevant alternative (particularly in patients who are no longer eligible for immunosuppressants or PUVA). We are aware that this is not specified in the scope but during the discussion with the clinical adviser this has been described as a possibility. (see A15). The 'supportive care' option could reflect the management of patients in the placebo arm of the clinical trials or may include the ongoing use of topical steroids.

- Please see the placebo controlled model for the overall population and the hyperkeratotic sub population submitted with these responses (CHE Placebo Model v4 and CHE Placebo Model Hyperkeratotic subgroup respectively)

Placebo Model

- Data from BAP00089 and BAP00091 trials for first cycle and subsequent cycles respectively are used to estimate the cost-effectiveness of alitretinoin compared to placebo. The clinical efficacy data is summarised in the tables below.
- For the placebo re-treatment data a separate analysis was performed to understand the efficacy of patients responding to placebo in BAP00089 and then receiving placebo in BAP00091. This represents 13 patients only. In addition these data were only available for the 24 week time-point and therefore the data were linearly allocated over a 4 weekly time period. For the other data 4 weekly data from BAP00089 and BAP00091 were used.
- In the placebo compared to alitretinoin model, both arms were assumed to use supportive treatments – emollients and dermatologist visits. In addition, the alitretinoin arm was assumed to include two blood tests over a 24 week treatment cycle from TSH monitoring. (As requested in question B13) No adverse events were modelled. All other model assumptions, variables and values are the same as the base case analysis.

Placebo – First Cycle (BAP00089)					
	Disease Severity				
Week	**Remission**	**Mild**	**Moderate**	**Severe**	**Refractory**
4	0.020	0.055	0.338	0.587	0.000
8	0.034	0.147	0.373	0.446	0.000
12	0.044	0.225	0.333	0.397	0.000
16	0.093	0.201	0.348	0.358	0.000
20	0.108	0.245	0.299	0.348	0.000
24	0.167	0.196	0.304	0.333	0.000

Placebo (Responders) - Subsequent cycles (Analysis of 13 patients from BAP00091)					
	Disease Severity				
Week	**Remission**	**Mild**	**Moderate**	**Severe**	**Refractory**
4	0.115	0.000	0.051	0.833	0.000
8	0.231	0.000	0.103	0.667	0.000
12	0.346	0.000	0.154	0.500	0.000
16	0.462	0.000	0.205	0.333	0.000
20	0.577	0.000	0.256	0.167	0.000
24	0.692	0.000	0.308	0.000	0.000

Alitretinoin First Cycle (30mg; BAP00089)					
	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

Alitretinoin Subsequent Cycles (30mg; BAP00091)					
	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

Results

Scenarios	Treatment	Total Costs	Incremental Costs	Total Utility	Incremental Utility	ICER
Base Case	**Placebo**	£611.83		1.79		
	Alitretinoin	£3,391.98	£2,780.15	2.01	0.22	£12,930.96
1 year	**Placebo**	£313.55		0.65		
	Alitretinoin	£2,207.96	£1,894.41	0.74	0.09	£21,562.06
6 years	**Placebo**	£995.00		3.32		
	Alitretinoin	£4,432.32	£3,437.32	3.63	0.31	£11,171.56
10 years	**Placebo**	£1,438.95		5.12		
	Alitretinoin	£4,975.34	£3,536.39	5.44	0.32	£10,967.78
20 years	**Placebo**	£2,315.14		8.67		
	Alitretinoin	£5,969.17	£3,594.03	9.01	0.34	£10,765.49

An analysis of Hyperkeratotic patients was conducted using the placebo model.

- A sub-group analysis of patients in BAP00089 and BAP00091 was performed using the same analysis used for the whole patient population of the studies
- 24 week data only were available for the hyperkeratotic sub-group analysis and therefore data have been modelled linearly at 4 weekly time points over the 24 week period
- For the placebo re-treatment data no sub-group analysis were available for patients that received placebo in both BAP00089 and BAP00091. Therefore re-treatment data for the 13 patients used in the main placebo model were used for this sub-group analysis

Hyperkeratotic subgroup – Placebo First Cycle (30mg; BAP00089)					
	Disease Severity				
Week	Remission	Mild	Moderate	Severe	Refractory
4	0.021	0.035	0.060	0.883	0.000
8	0.042	0.071	0.121	0.766	0.000
12	0.063	0.106	0.181	0.650	0.000
16	0.084	0.142	0.241	0.533	0.000
20	0.105	0.177	0.302	0.416	0.000
24	0.126	0.213	0.362	0.299	0.000

Hyperkeratotic subgroup – Placebo Subsequent Cycles (30mg; BAP00091)					
	Disease Severity				
Week	Remission	Mild	Moderate	Severe	Refractory
4	0.115	0.000	0.051	0.833	0.000
8	0.231	0.000	0.103	0.667	0.000
12	0.346	0.000	0.154	0.500	0.000
16	0.462	0.000	0.205	0.333	0.000
20	0.577	0.000	0.256	0.167	0.000
24	0.692	0.000	0.308	0.000	0.000

Hyperkeratotic subgroup – Alitretinoin First Cycle (30mg; BAP00089)					
	Disease Severity				
Week	Remission	Mild	Moderate	Severe	Refractory
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

Hyperkeratotic subgroup – Alitretinoin Subsequent Cycles (30mg; BAP00091)					
	Disease Severity				
Week	Remission	Mild	Moderate	Severe	Refractory
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

Results

Scenarios	Treatment	Total Costs	Incremental Costs	Total Utility	Incremental Utility	ICER
Base Case	**Placebo (Hyperkeratotic)**	£585.44		1.76		
	Alitretinoin (Hyperkeratotic)	£3,419.91	£2834.47	1.95	0.19	£15,018.95

B2. Please provide further details about the use of clinical opinion in estimating parameters for the model. In particular the method used to synthesise the clinicians' estimates, details of how many clinicians were invited to take part, the evidence the clinicians were presented with and the questions the clinicians were required to answer. Were the clinicians asked to provide estimates of uncertainty as well as point estimates? Were the clinicians asked to estimate the distribution of patients between the severe, moderate, and mild and remission states over a series of four week periods? If possible, please provide the full report of the expert panel meeting.

Pre-work for the expert panel meeting and evidence presented to the experts

- Please see appendix 7 for full documentation of the expert panel invite letter, instructions for meeting pre-work, pre-meeting treatment questionnaire and final meeting report showing the panel composition and main estimates generated. In addition, the slides presented at the meeting are attached to this response document. Please note that analysis 2 of DLQI values from the BAP00089 study had not been conducted at the time of the expert panel meeting therefore different preliminary observational DLQI data from the Augustin study is referred to in the WG presentation. The final Augustin data as used in sensitivity analysis in the submission was similarly not available at that point. (see question A6 and B5)
- As per response to question A14, expert panel members were provided with the April 2008 BJD publication of the BAP00089 trial and asked to review it as pre-work for the meeting (see meeting invitation). They were also asked to complete a brief CHE treatment questionnaire prior to the meeting. This was designed to explore the severity of CHE patients treated in different centres and the efficacy and durability of remission produced by the treatments to allow time for detailed discussion at the meeting.
- Questionnaire responses were received in time for the meeting from 4 of the 6 experts and a summary of results was shown in slide format (WG consulting slides). In addition, the summarised results of a similar exercise conducted in Scotland for the purposes of SMC submission were presented in order to explore possible reasons for variability between a larger number of UK centres.

- Some of the variability in questionnaire estimates of efficacy for comparators appeared to result from differences in the proportion of PGA severe CHE treated. In both the Scottish and English/Welsh questionnaire returns, the highest estimate of efficacy for PUVA was from centres treating the highest proportion of patients classified as PGA moderate in response to the questionnaire, which included the PGA classification for reference.
- It was noted from discussion of the published trials of PUVA in CHE that baseline severity was either not clearly stated or appeared lower than in the alitretinoin trials; for example in the studies of Rosen and Coevoorden et al, mean baseline severity was approximately 50% or less of the theoretical maximum of the scoring instruments used, whereas in the BAP00089 study it was 74% of the theoretical maximum for mTLSS.
- Because of the potential effect of case mix, particular care was taken to frame all expert panel questions regarding efficacy carefully with respect to the severity of the baseline population being treated or observed for relapse but it is nonetheless possible that the estimates for PUVA efficacy in particular remain overoptimistic in the model.

Questions the clinicians were required to answer and how the evidence was synthesised

- At key points in the meeting, having provided some background to the question (see WG slides attached), a flip chart exercise was employed to plot individual estimates of the distribution of patients between the severe, moderate, mild and clear/almost clear states at 4 weekly intervals on a grid for the different comparators.
- Any differences in individual estimates were then discussed and consensus was reached on an acceptable nationally representative estimate to enable completion of each cell in the corresponding powerpoint slide. An example (powerpoint slide 33) is given below.
- Clinicians were not asked to provide estimates of uncertainty.
- The full report of the meeting is attached in appendix 7 however as stressed above, the main purpose of this report was to provide a record of the numerical estimates obtained therefore we hope that the additional background information provided is helpful.

Slide 33 of presentation shown at Expert panel meeting 14th October 2008

Is it possible to estimate incremental efficacy at 4 weekly visits? (Aza)

	Clear/almost clear	Mild	Moderate	Severe
Week 4				
Week 8				
Week 12				
Week 16				
Week 20				
?Week 24				
?Week 48				

B3. The results of the clinical trials presented in the submission are based on response versus no response at a fixed point in time (e.g. 24 weeks). Please clarify why you modelled the distribution of patients between health states over four week periods when the relevant treatment periods are 12 and 24 weeks? Is this distribution of patients based on patient-level data from any trial?

- The distribution of patients between health states was modelled over 4 weeks because this was the frequency at which efficacy and safety observations were available from the BAP00089 (on treatment and relapse follow up visits) and BAP00091 studies (on treatment visits).
- Monthly clinical observations in the studies contributed to the calculation of cumulative efficacy endpoint PGA response between week 12 and 24.
- Summarised four weekly efficacy data for the BAP00089 and BAP00091 trials are presented in appendix 6. We would be happy to provide patient level data should this be required

B3 Please can you also clarify why you opted to model the distribution of patients between severe, moderate and mild for the non-responders, but have combined the categories of clear and almost clear for the responders? The combination appears to fix the proportion of responders in the clear and almost clear categories at 50%; is this based on any trial results?

- The primary efficacy endpoint in the BAP00089 and BAP00091 study was the proportion of patients PGA clear or almost clear, counting all other degrees of improvement as non response which is stringent.
- The actual % of clear vs almost clear for 30mg responders at end of alitretinoin treatment was reasonably close to 50:50 for the 30mg group (at 46%:54%) as compared to 34%:56% for the 10mg group and 17%:83% for the placebo group in the trial. This suggests that the proportion of completely clear hands contributing to the overall PGA response figures is alitretinoin dose dependent, in keeping with what would be expected.
- Analysis 2 of the data from BAP00003 study used to determine the change in DLQI (and therefore utilty in the model) was independent of the treatment that patients received. For this reason it was not considered appropriate to apply the split of clear/almost clear associated with alitretinoin study efficacy in the model. A 50:50 split in PGA clear or almost clear utility was applied for patients entering remission in all arms of the model.
- An additional practical consideration was the absence of data to inform the relative proportions of clear/almost clear hands in comparator responders in the model. It was considered fairest and most convenient to assume 50:50 split for all arms.
- In order to understand how this split may affect the cost-effectiveness of alitretinoin the original model submitted to NICE and the model containing TSH monitoring (as requested) were run assuming all patients in remission had the lower utility of almost clear (calculated to be 0.88)
- Alitretinoin was found to remain cost-effective compared to all the comparators when almost clear utility for all responders was assumed.

Change in DLQI based on PGA

PGA	Change in DLQI from PGA severe	P value	95% Confidence intervals	DLQI
Severe	0	<0.0001	(12.20, 17.96)	15.08
Moderate	-5.3	<0.0001	(-7.86, -2.73)	9.78
Mild	-9.15	<0.0001	(-11.92,-6.37)	5.93
Almost Clear	-12.03	<0.0001	(-14.67, -9.40)	3.05
Clear	-14.65	<0.0001	(-18.01, -11.30)	0.43

*Baseline DLQI score (Intercept value) 15.08 (p<0.0001, 95%CI 12.20, 17.96
Test of overall PGA effect df = 4 DDF = 126 F = 30.88 P <0.0001

Change in DLQI and utility score based on PGA

PGA	DLQI	Utility
Severe	15.08	0.582
Moderate	9.78	0.713
Mild	5.93	0.809
Almost Clear	3.05	0.880
Clear	0.43	0.950

Results

Scenario: Base Case Analysis	ICER	
	Without TSH Monitoring	With TSH Monitoring
Alitretinoin vs. Ciclosporin	£9,262.25	£9,298.49
Alitretinoin vs. PUVA	-£500.74 (Alitretinoin dominant)	-£462.64 (Alitretinoin dominant)
Alitretinoin vs. Azathioprine	£11,577.33	£11,609.03
Alitretinoin vs. Placebo	£14,024.85	£14,060.52

B4. Please could you clarify whether the current treatment effects in the model are based on the absolute rates observed in the alitretinoin arm of the trial and that the placebo response has not been adjusted for? Usually, an adjustment for placebo response should be carried out for all of the comparators in the model. Including a 'supportive care" arm would be one way to make the adjustment (as in B1).

- No adjustment for placebo response was made in the initial submission; however we have provided a placebo model to address this particular question (see B1).

B5 Utility mapping methodology

Please provide further detail regarding the mapping between PGA state and DLQI (see page 78).
For example, what was the form of the equation and how were the covariates included?
How were the proportion of patients out of the trial population that were included selected and how representative were they of the whole trial population?
How well do the predicted DLQI scores match the observed DLQI scores in the estimation sample?
The results of BAP00003 trial (shown in Tables 6.4.1 and 6.4.2) indicate that 53% of patients moved to the states of 'clear or almost clear' in the alitretinoin arm as compared to 27% in the placebo arm, yet the difference in mean within-patient change in DLQI between those two groups is only one. This doesn't seem to correspond to an additional 26% of patients in the alitretinoin arm experiencing a change in DLQI of at least 7 (for the two thirds who were moderate at baseline) and 12 (for the one third who were severe at baseline), as indicated by Table 6.9.1. Please can this be clarified?

Mapping
Information on the mapping between PGA state and DLQI are provided on page 103 of the submission as below. These were not cross-referenced on page 78 for which we apologise.

'*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). 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)'

- Although we recognise that the original mapping exercise was conducted in psoriasis, no mapping methodology could be identified for CHE. If you require any further clarification on the mapping of PGA state to DLQI we would be happy to discuss this further.

Selection of population for analysis and how representative of overall population?

- As stated in our submission, DLQI data was not collected in the phase III study.
- In the phase II BAP0003 study, DLQI data was collected but only in a subset of patients determined by the availability of a validated DLQI questionnaire in local language. Only paired baseline and end of treatment questionnaires were analysed in either of the analyses performed (see below)
- The phase II study population did not receive the licenced 30mg dose of alitretinoin as the doses evaluated were 10mg, 20mg and 40mg versus placebo.
- 2/3 of the BAP00003 population were of PGA moderate severity at baseline and only 1/3 were PGA severe as opposed to the phase III population which was required to be PGA severe at baseline.

As described in question A6, the two different analyses performed on the phase II data will be described as follows for the sake of clarity:

Analysis 1: Treatment effect on DLQI (original protocol-specified analysis)
Analysis 2: DLQI analysis independent of treatment effect (conducted for the purposes of NICE submission)

- Only analysis 2 will be discussed in this section as analysis 1 is discussed in response to question A6.

- Prior to conducting analysis 2 for the purposes of NICE submission, the only other DLQI data available in CHE was from an observational study conducted in Germany by Professor Augustin This study examined the DLQI reported by different patients in different disease states and did not examine the DLQI change experienced by patients moving between disease states.
- In an attempt to obtain dynamic DLQI data that would be more reflective of the effect of treatment in a group of patients than static observations in different patients, we conducted analysis 2 of change in DLQI associated with change in PGA state independent of treatment. Table 6.9.1 refers to this treatment-independent analysis whereas tables 6.4.1 and 6.4.2. are treatment-specific. We may not have made this sufficiently clear but is one reason why the different results presented in the tables are not easy to reconcile.
- In the case of both analyses, patients were selected according to the availability of DLQI in the right language and paired completed questionnaires; no subgroup was selected for any particular characteristic. The characteristics of patients analysed for DLQI changes are displayed in appendix 2. Although observations are displayed according to treatment group, the population characteristics would apply equally to analysis 2, the only difference being that patients were allocated to groups for analysis 2 according to the PGA

transitions they made rather than according to which treatment they were taking.

How well do predicted DLQI values match the observed DLQI in the estimation sample?

- We hope that we have been able to clarify the difference between analyses 1 and 2 conducted on the phase II DLQI data.
- There are a number of possible reasons why the predicted DLQI values for PGA transitions generated by analysis 2 (from which utility was mapped) in table 6.9.1 are not well matched with the observed DLQI changes by treatment group according to the original analysis 1 of the BAP00003 data (as per table 6.4.2)
- In the context of the factors discussed in our submission and the inherent variability in the scoring of DLQI and the lack of validation of this instrument in CHE, we would propose that no conclusions can be reached regarding the impact of alitretinoin 30mg treatment on quality of life from the BAP0003 study.
- We do however propose that it would be plausible, in the absence of evidence of drug toxicity or other negative effect to appreciably worsen quality of life, to consider the predicted DLQI values (as per analysis 2) to be achievable for patients moving through the same PGA states as a result of alitretinoin treatment in phase III.
- Recognising the limitations of the data used to calculate utilities for a health economic model we have also run the analysis with the only other DLQI data available in CHE. As mentioned above, the Augustin data is based on static PGA-DLQI correlations and yields reduced estimates of DLQI which were used in a sensitivity analysis in our submission.

Definition of relapse used in the model

B6. Please clarify why relapse was defined in terms of the mTLSS score (as opposed to PGA state)?

- Relapse was defined as a return to 75% of the baseline severity score in the trial. It should be noted that this could correspond to PGA severe or, less commonly PGA moderate (see below)
- An mTLSS definition of relapse was proposed by expert dermatologists who advised Basilea on protocol design. This was considered to reflect clinical practice because it allowed scope for investigators to begin retreatment in anticipation of return to PGA severe once a significant degree of deterioration had occurred rather than be obliged to wait for patients to deteriorate to the most severe state.

- The suitability of this trial definition was also presented as a key question for consideration at 2 expert panel meetings in UK conducted for the purposes of SMC and NICE respectively. In both cases, the trial definition was generally considered to reflect the usual working definition of relapse “sufficient to require re-treatment with systemic agents or phototherapy”.
- Some UK expert clinicians did express the view that they would not re-treat with systemic immunosuppressive agents until the most severe state had been reached again because of safety concerns. The trial threshold for intervention after relapse may therefore be lower than that employed by some dermatologists for current systemic agents.
- Dermatologists consulted agreed they would generally start (or more often simply continue) topical steroids as a matter of course after treatment with current comparators and their estimates of relapse for comparators took this into account, potentially disadvantaging alitretinoin in the comparison as no topical corticosteroids were allowed in the trial observation period for relapse.
- In the models presented to NICE, relapse is assumed to signify a return to the most severe PGA state in all cases, with a median time of 168 days as seen in the pivotal trial

B7. On pages 96-7 of the submission it explains that that the definition of relapse used in the model is based on the one employed in the BAP00089 and BAP00091 trials (PGA clear/almost clear) Please clarify how a definition of relapse as a return to a PGA state other than clear/almost clear influences the results of BAP00089 and BAP00091.

- Thank you for the clarification of this question provided.
- As per response to question B6, in the models presented to NICE, relapse is assumed to signify a return to the most severe PGA state with a median time of 168 days as in the pivotal trial whereas 75% of baseline mTLSS could have represented relapse to PGA moderate or PGA severe.
- The table below shows that at baseline in the retreatment study (ie having just relapsed by attaining 75% of their baseline mTLSS in 089) patients in the 30mg group were 30.6% PGA moderate and 60.4% PGA severe.
- Compared to the actual rate of return to PGA severe state in the trial, the model would thus increase the rate of patient return to PGA severe utility by a third whilst reducing return to the more favourable utility of PGA moderate by the same proportion.
- Expert dermatologists were asked to provide 4 weekly estimates of relapse for comparators based on return to the categorical PGA severe state and were asked to assume this to be equivalent to a return to 75% baseline mTLSS. This was because PGA severe and the accompanying descriptors were considered to provide a more clinically

vivid picture for estimates based on recall than a percentage change in a composite severity score.

- The overall effect of the resulting discrepancy between trial results and the model for alitretinoin would be to produce a conservative estimate of the relative cost effectiveness of alitretinoin versus comparators.

PGA severity and mTLSS for BAP00091 study patients at baseline

	Cohort A Relapse in BAP00089		
	10mg	**30mg**	Placebo
Number of Patients (ITT)	21	49	47
Physician's Global Assessment at Baseline			
Clear	0	0	0
Almost Clear	1 (4.8%)	0	0
Mild Disease	1 (4.8%)	0	0
Moderate Disease	9 (42.9%)	**15 (30.6%)**	18 (38.3%)
Severe Disease	10 (47.6%)	**34 (69.4%)**	29 (61.7%)
mTLSS at Baseline			
n	21	49	47
Mean	12.6	13.3	13.4
SD	3.19	2.36	2.35
Median	12.0	13.0	14.0

Source: B91T09.sas 10may07

- Relapse is equated with return to PGA severe for the purposes of the model but is not defined as such in the trial. PGA severe and mTLSS 75% of baseline (given that baseline was PGA severe) were considered close enough in meaning to reflect the way in which "relapse sufficient to require retreatment" would be decided in clinical practice.
- In the phase II trial, 2/3 of participants were classified as PGA moderate, however efficacy comparable to phase III was achieved in the 20mg and 40mg dose groups suggesting that the efficacy of alitretinoin is not confined to PGA severe patients.
- Whereas in registration clinical trials it is necessary to have a standardised, categorical definition of baseline severity and efficacy endpoint to enable a reliable comparison of treatments and description of the product in accurate labelling, there is no requirement for this in clinical practice.
- Basilea does not assume that diagnosis of severe chronic hand eczema requires the patient to be identified as in PGA category 'severe'.

B8. On page 96 of the submission it explains that "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." Patients with close to 75% of their original mTLSS score are still likely to have severe CHE. Please clarify how the different thresholds (e.g. 50%) influence the results of BAP00089 and BAP00091.

- As shown in the table above and the analysis below, it cannot be assumed that patients with mTLSS close to 75% of their baseline severity would have severe CHE. Having returned to a mTLSS 75% of baseline, one third of patients in the 30mg group were rated as PGA moderate as were a similar proportion in the placebo group.
- It is accepted that the use of different thresholds of mTLSS to define relapse, eg 50% could have influenced the results of the BAP00089 trial.
- As explained in response to question B6, mTLSS 75% was suggested by dermatologists as a suitable clinical definition of relapse requiring retreatment at the outset of the BAP00089 trial and was also confirmed to be similar to the usual working definition in UK by two panels of experts consulted.
- It is notable that where minor disagreement existed among UK clinicians, this was because a higher threshold severity of >75% baseline for retreatment was considered by some dermatologists to better reflect the wish to delay repeated immunosuppressive treatment for as long as possible in clinical practice.
- The lack of topical steroid use to potentially delay return to mTLSS 75% after alitretinoin treatment in the trial was also commented on as an area of potential divergence from current clinical practice-this issue is discussed further in response to question A15.
- To explore the impact of alternative definitions of relapse in the health economic model further is difficult for practical reasons. A dataset for patients defined to be in remission or relapse according to different definitions could be created from existing data from study BAP0089 but not from BAP00091
- BAP00091 efficacy data are based on the retreatment of patients who have previously relapsed to 75%mTLSS therefore by implication results are not available for the efficacy of retreatment commenced at lower mTLSS thresholds.
- As regards the impact of alternative definitions of relapse on the BAP00089 trial results please see the table below. This provides a summary of the time to relapse (days) for median relapse, and for relapse of 25% of the responders (1st quartile). The numbers confirm that the 75% mTLSS criterion results in a population of relapsers with moderate or severe CHE and that a 50% mTLSS criterion results in a population which is mainly of moderate CHE severity.

Time to relapse (days) with different criteria for relapse (BAP00089)

		Placebo	10mg	30 mg
Median	PGA Mild PGA Moderate	86 162 NA	63 162 NA	56 107 NA

	PGA Severe			
	mTLSS 50% mTLSS 75%	165 168	190 190	99 168
1st Quartile	PGA Mild PGA Moderate PGA Severe	29 60 112	30 63 205	29 56 99
	mTLSS 50% mTLSS 75%	64 86	63 147	53 84

- Compared to PGA relapse criteria, the 75%mTLSS falls between PGA moderate and severe for 1st quartile and median relapse rates, while the 50%mTLSS is very close to PGA moderate.

- In conclusion, we believe that the 75%mTLSS is an appropriate criterion for defining relapse of CHE. A less stringent criterion (50%mTLSS) would yield a patient population with moderately severe CHE who would be unlikely to be immediately retreated with systemic therapy. A more stringent criterion (PGA severe) would yield fewer "relapsed" patients, and might have overestimated the duration of therapeutic effect.

B9. Please clarify how time to relapse is operationalised in the model. How is the average time to relapse of 24 weeks converted into a transition probability to move from remission to the severe health state?

Efficacy data was used to calculate the average time to remission for each of the agents during the first treatment cycle. From this point in time patients would begin their weeks of continued treatment once they had entered remission (where applicable) and from this point the average time to relapse was applied; at the end of the time to relapse period patients transition between the health states according to the subsequent cycle transition probabilities.

Assumptions used in the model

B10. Please clarify whether all patients who respond to treatment are assumed to have 'clear' or 'almost clear' hands for the entire period of time in which they do not relapse?

Yes. Patients who respond to alitretinoin or comparators are assumed to be in remission for the entire period of time in which they do not relapse. Once in the remission health state, patients do not consume drug costs. Whilst in remission patients are assumed to continue with the use of supportive treatments (emollients); these are each associated with a unit cost.

B11. Please clarify whether patients are assumed to cease treatment as soon as they enter the remission state, even if this is at four or eight weeks?

The model assumes that once a patient enters the remission state they cease treatment for alitretinoin and PUVA. For ciclosporin and azathioprine treatment is continued for 6 and 8 weeks following clearance respectively based on clinical opinion on how these immunosuppressants are used in practice. This variable can be altered for each treatment on the input page of the cost-effectiveness model ("weeks treated following clearance"). Once in remission patients consume supportive treatments in the management of their CHE.

If so, can you clarify why responders would not complete the full 24 week treatment cycle with alitretinoin.

- It would be difficult to provide a clinical rationale for continued treatment of patients who have attained PGA clear/almost clear hands earlier than 24 weeks with alitretinoin, systemic immunosuppression or PUVA in clinical practice as the required treatment outcome has been achieved.
- It could be argued that patients "almost clear" might continue to be treated until "clear" but this situation probably would not warrant the continued use of a systemic agent or the patient inconvenience of PUVA. Patients in such a situation would most likely be advised to continue topical steroid therapy and emollients only.
- It is not possible to predict precisely what frequency of follow up will be for the follow up of alitretinoin patients (eg. telephone contact or community assessment by specialist nurses, pharmacists or GPs where shared care arrangements can be agreed)
- Although it is not possible to estimate precisely what follow up arrangements will be put in place for alitretinoin patients, Dermatologists are likely to modify existing systems used to follow up of slow acting or continuously used therapies following its introduction as the potential for early and complete response is clear.
- It would appear unlikely that patients whose hands clear rapidly would go undetected and therefore remain on alitretinoin for 24 weeks.

Also, please clarify if in BAP00089 or BAP00091, treatment was discontinued in those patients responding before the end of a treatment cycle.

- Treatment was stopped at the next available study visit in patients who had achieved PGA clear/almost clear in both trials prior to the 24 week on-treatment visit.
- In the majority of cases this protocol determined discontinuation occurred at the week 12 week visit. For example this occurred in 78 of patients assigned to 30mg alitretinoin in the BAP00089 study.

- Patients could also discontinue for “early improvement” at the week 16 or 20 visit and this occurred in 3 patients assigned to 30mg alitretinoin in BAP00089.

If so, what was the impact of early discontinuation on relapse?

- Analysis of time to relapse was performed for responders treated for 12 weeks or less (see below) and a comparable median time to relapse was demonstrated (141 days for alitretinoin 30mg).
- This suggests no clear relationship between the duration of treatment received and the duration of remission obtained.

Time to Relapse of CHE for Responding Patients at End of Therapy
ITT Population in Patients Treated for 12 Weeks or Less

	Alitretinoin 10mg	Alitretinoin 30mg	Placebo
Number of Patients in ITT Population	104	163	59
Number of Patients Responding at End of Therapy	32 (30.8%)	87 (53.4%)	4 (6.8%)
Number of Patients with Confirmed (Calculated) Relapse	8 (7.7%)	35 (21.5%)	3 (5.1%)
Time to Relapse (days)			
Q1 95% Confidence Interval	126.0 (63, -)	69.0 (56, 99)	28.5 (28, 92)
Median 95% Confidence Interval	(149, -)	141.0 (107, -)	60.5 (28, -)
Q3 95% Confidence Interval	(-, -)	(-, -)	(29, -)

Source Data: B89L29
B89TSG25_07_01.sas 18JUN07

In addition, if patients are assumed to cease treatment prior to 24 weeks, do they require a visit with a dermatologist to identify that they are in remission?

In the model, patients see a dermatologist at monthly intervals in all arms because this is the frequency of observation by dermatologists in the alitretinoin trials. In clinical practice, review may be by a dermatologist in a hospital or by dermatology nurses (face to face or potentially by telephone), or others in a community setting such as GPs where shared care arrangements can be established.

Miscellaneous

B12. In the electronic model one hidden sheet is apparent (Sheet 8 – Treatment Cycles). Are any other hidden data of which we should be aware? For example, it is clear that Sheets 6 and 7 were created but subsequently deleted.

There are no hidden data sheets that you need to be aware of. Sheets 6 and 7 were “working sheets” created during the construction of the model.

B13. Please comment on the apparent correlation between increasing alitretinion dose and reduced TSH, and the implications of this for clinical and cost effectiveness. In particular, any costs associated with TSH monitoring should be incorporated into the model. Have these been included? If not, please include.

Changes in TSH in the clinical trial programme were asymptomatic and reversible on cessation of treatment, requiring no intervention. Although T4 was lowered in addition to TSH in some cases, no clinical hypothroidism was reported and no intervention, such as thyroid hormone supplementation, was required.
There is no requirement for thyroid function tests in the SPC for alitretinoin reflecting the regulatory authority view that at the doses and duration of alitretinoin therapy recommended, there are no significant clinical implications expected from temporary and asymptomatic laboratory abnormalities.

It should be noted that there is an appreciable background rate of asymptomatic thyroid laboratory abnormalities in the normal population and that the current UK consensus regarding such abnormalities is that screening is not warranted in the absence of evidence that treatment improves outcomes (Van Der Pump MPJ, Tunbridge MG Thyroid Vol 12;10,2002)

Drug induced thyroid laboratory abnormalities may not be strictly comparable to background subclinical hypothyroidism. In the case of alitretinoin there is clear evidence that stopping treatment leads to reversal of abnormalities. Post trial follow up at one month demonstrated a return to normal TSH levels.

It is however understandable that dermatologists may wish to perform thyroid function tests at least until greater experience with the drug is gained, or if intending to use the agent for longer or at higher doses than the SPC recommends.

To explore this, we have included the costs of two thyroid function tests (TSH) per 24 week cycle for patients in the alitretinoin arm of the economic models at a cost of £3 each.

The effect of including this additional cost is negligible on the cost-effectiveness profile of alitretinoin versus the other agents and when compared to placebo. The incremental cost effectiveness ratio (ICER) of alitretinoin versus the other agents with and without TSH monitoring is summarised in the table below. There are no effects on the estimates of health benefit (utility). The economic model has been updated to include the cost of TSH monitoring (see CHE model v7).

Scenario: Base Case Analysis	ICER	
	Without TSH Monitoring	With TSH Monitoring
Alitretinoin vs. Ciclosporin	£8,614.43	£8,648.13
Alitretinoin vs. PUVA	-£468.98 (Alitretinoin dominant)	-£433.29 (Alitretinoin dominant)
Alitretinoin vs. Azathioprine	£10,611.80	£10,640.85
Alitretinoin vs. Placebo	£12,898.16	£12,930.96

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Appendix 1:

Table 1: Comparator interventions in the treatment of hand eczema or hand dermatoses identified during the systematic review

Study ID Total Enrolment	**Design, Control Type**	**Study & Control Drugs Dose, Route & Regimen**	**Diagnosis**	**Justification for inclusion/exclusion in the indirect treatment comparison**	
				Inclusion criteria	**Exclusion criteria**
PUVA					
Pham et al. 1993[1] N=10	Controlled study	Topical-PUVA	Hand eczema		Outcome measure not efficacy
Rosen et al. 1989[2]	Controlled study	Topical-PUVA versus UVB	Chronic hand eczema		Outcome measure not efficacy
Sjovall et al. 1986[3]	Controlled study	UVB versus UVA	Unclear		Efficacy not the outcome measure
Pozo-Roman et al. 2006[4] N=40	Uncontrolled study	Topical-PUVA	Dermatoses		Not controlled Study not carried out in hand eczema Outcome not adequately described
Douwes et al. 2000[5]	Uncontrolled, prospective study (efficacy in smokers versus non-smokers)	Bath-PUVA	Palmoplantar eczema		Not controlled versus comparator
Behrens et al. 1999[6] N=30	Uncontrolled, prospective study	Bath-PUVA	Palmoplantar eczema		Not controlled

Gritiyarangsan et al. 1998[7] N=17	Uncontrolled, prospective study	Topical-PUVA	Chronic hand eczema		Not controlled
Schempp et al. 1997[8] N=28	Uncontrolled, prospective study	Topical-PUVA	Palmar or plantar eczema		Not controlled No separation of results for hand and foot
De Rie 1995[9] N=2	Uncontrolled, prospective study	Topical-PUVA	Hyperkeratotic eczema		Not controlled
Reichl et al. 2007[10] N=50	Uncontrolled study	Unknown	Hand and foot eczema		Not controlled
Riad et al. 2006[11] N=125	Uncontrolled study	Topical PUVA	Palmoplantar dermatoses		Not controlled
Davis et al. 1998[12] N=35	Uncontrolled study	Topical PUVA	Palmoplantar dermatoses		Not controlled
Tegner et al. 1985[13] N=38	Uncontrolled study	PUVA	Chronic eczema of the palms		Not controlled
Kalimo et al. 1989[14] N=5	Uncontrolled study	Oral PUVA	Chronic hand dermatitis		Not controlled
Mobacken et al. 1983[15] N=5	Uncontrolled study	Oral PUVA	Chronic hyperkeratotic dermatitis of the palms		Not controlled
Bruynzeel et al.1982[16] N=9	Uncontrolled study	Oral PUVA	Allergic contact dermatitis of the hands		Not controlled
Bruynzeel et al.1980[17] N=26	Uncontrolled study	Oral PUVA	Chronic dermatoses of the hands and feet		Not controlled
Morrison et al. 1978[18] N=20	Uncontrolled study	PUVA	Dermatoses (palms and soles)		Not controlled No patients with chronic hand eczema
Tuchinda et al. 2006[19] N=92	Uncontrolled, retrospective study	UVA-1	Hand or foot dermatitis		Not controlled UVA-1 therapy
Schmidt et al. 1998[20]		UVA-1	Chronic vesicular dyshidrotic hand eczema		UVA-1

Polderman et al. 2003[21] N=28	Randomised, double-blind, placebo-controlled study	UVA-1	Dyshidrotic eczema		UVA-1 therapy
Rosen et al. 1988[22]	Controlled study	Topical-PUVA versus UVB	Chronic hand eczema		Results described previously (Rosen et al. 1987)
Sezer et al. 2007	Letter				Not an original study
5 controlled PUVA studies – not considered for indirect comparison					
Schiener et al. 2005[23] N=20	Randomised, single-blinded, prospective	Bath PUVA versus gel-PUVA	Palmoplantar eczema		No separation of results for hand and foot
Grundmann-Kollmann et al. 1999[24] N=4	Randomised, controlled (within-patient) study	Bath-PUVA versus cream-PUVA	Palmoplantar eczema		No separation of results for hand and foot
Engin et al. 2005[25] N=22	Controlled (within-patient) study	Topical PUVA versus UVA	Palmoplantar dermatoses (psoriasis vulgaris, eczema or pustulosis		No separation of results for hand and foot
Shephard et al. 1998[26] N=37	Controlled (within-patient) study	Bath PUVA versus lotion PUVA	Palmoplantar eczema or psoriasis		Inadequately controlled
Moon et al. 2000[27] N=24	Controlled study	Bath PUVA versus topical and oral steroid	Palmoplantar pustular psoriasis and dyshidrotic eczema		Results not adequately described in English (Korean)
4 controlled PUVA studies –included in indirect comparison					
Petering et al. 2003[28]	Controlled (Within patient) trial	UVA-1 or topical PUVA	Chronic vesicular dishydrotic eczema	Controlled study Correct comparator	

N=27				Chronic hand eczema (subtype)	
Sezer et al. 2007[29] N= 15	Open label randomised, within-patient trial	UVB vs topical PUVA	Chronic hand eczema of dry and dishydrotic types of more than 4-month duration Conventional therapies, ineffective	Controlled study Correct comparator Chronic hand eczema (subtypes)	
Rosen et al. 1987[30] N=35	Open label, randomised controlled trial	UVB and oral PUVA with untreated hand controls.	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.	Controlled study Correct comparator Chronic hand eczema (subtypes)	
Simons et al. 1997[31] N=13	Open-label randomised within-patient study	UVB and topical bath PUVA	Bilateral chronic hand dermatitis with vesicles or hyperkeratotic plaques of the hands present for > 6 months.	Controlled study Correct comparator Chronic hand eczema	
4 controlled PUVA studies – considered for but not included in indirect comparison					
Sheehan-Dare et al. 1989[32] N= 25	Double-blind randomised within-patient study	PUVA and superficial radiotherapy	Chronic bilateral constitutional hand eczema with continuous or	Controlled study Correct comparator Chronic hand eczema	Patient level data not recorded – only mean reduction in severity/extent of

			intermittent vesiculation for at least 6 months. Resistant to conventional therapy		disease.
Van Coevorden et al. 2004[33] N=158	Open-label, randomised, controlled study	Oral and bath PUVA	Chronic bilateral or unilateral hand eczema (no subtype exclusions) of at least 1 year duration Moderate to severe hand eczema	Controlled study Correct comparator Chronic hand eczema	Patient level data not recorded – only mean reduction in severity/extent of disease.
Adams et al. 2007[34] N= 15	Prospective randomised (within-patient) study	PUVA and UVA-1.	Dishydrotic eczema (chronic recurrent) for at least 1 month	Controlled study Correct comparator Chronic hand eczema	Patient level data not recorded – only mean reduction in severity/extent of disease.
Grattan et al. 1991[35] N=15	Double-blind randomised within - patient trial	topical PUVA with UVA	Bilateral symmetrical vesicular hand eczema (recurrent disabling) for at least 6 months	Controlled study Correct comparator Chronic hand eczema	Patient level data not recorded – only mean reduction in severity/extent of disease.
Ciclosporin					
Granlund et al. 1997[36] N=41	Randomised controlled study	Ciclosporin	Chronic hand eczema		Outcome measure not efficacy
Bowers et al. 2001[37] N=1	Case study	Ciclosporin	Dogger Bank Itch		Study not carried out in hand eczema
Granlund et al. 1998[38] N=75	Long-term follow-up study	Ciclosporin	Chronic hand eczema		Not controlled

Petersen et al. 1992[39] N=1	Case study	Ciclosporin	Chronic vesicular hand eczema		Not controlled
Kanerva 1996[40] N=1	Case study	Ciclosporin	Allergic contact dermatitis		Not controlled Not hand eczema
Reitamo et al. 1994[41] N=7	Uncontrolled study	Ciclosporin	Chronic dermatitis of the hands		Not controlled
Granlund et al. 1996[42] N=41	Randomised double-blind study	Ciclosporin and placebo cream or topical corticosteroids and placebo capsules	Hand eczema	Controlled study Correct comparator Hand eczema	
Alitretinoin					
Bollag et al. 1999[43]N=38	Open label study	20 or 40mg alitretinoin	Chronic hand eczema, unresponsive to topical steroids		Not controlled
Ruzicka et al. 2004[44] N=319	Double-blind placebo controlled study	10, 20 or 40mg alitretinoin, or placebo capsules	Moderate or severe chronic hand eczema, unresponsive to topical steroids	Controlled study Correct comparator Chronic hand eczema	
Ruzicka et al. 2008[45]N=1032	Double-blind placebo controlled study	10 or 30mg alitretinoin, or placebo capsules	Severe chronic hand eczema, unresponsive to topical steroids	Controlled study Correct comparator Chronic hand eczema	

Figure 1: Overview of the studies identified for each comparator and reasons for exclusion from the indirect comparison analyses

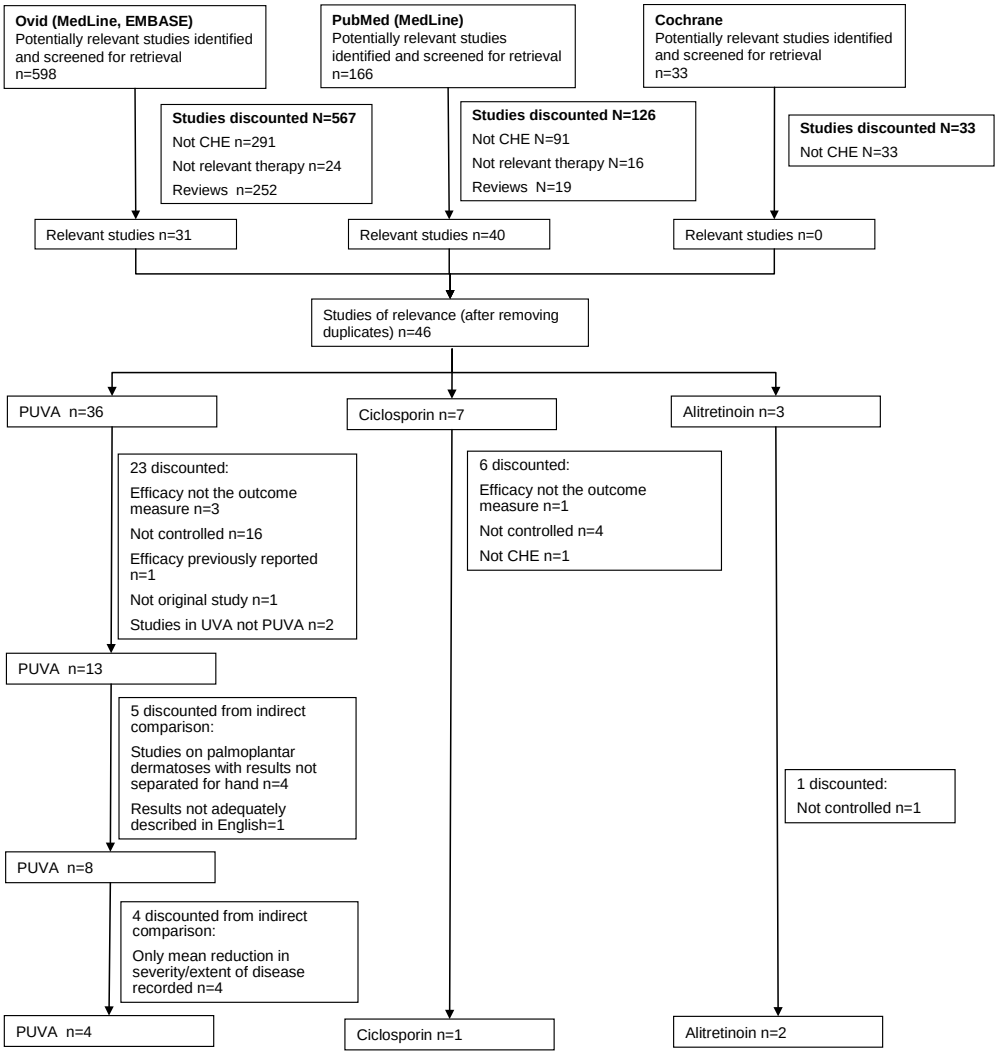

Table 2: Results of the 13 controlled studies on PUVA which were considered for analysis in the indirect comparison.

	Study ID Total Enrolment	**Number of Subjects by Treatment Arm Entered**	**Baseline disease demographics/ severity scoring system**	**Primary endpoint Response/ relapse definition**	**Efficacy Results**	**Safety Results**
5 studies – Not considered for indirect comparison	Scheiner et al. 2005 N=20	Not applicable (within patient trial) PUVA-gel vs. PUVA-bath	Severe recalcitrant dermatoses of the palms or soles and/or local psoriatic plaques (included dyshidrotic eczema, hyperkeratotic eczema, psoriasis vulgaris and lichen rubber) Scored using the Area and Severity Index for palmoplantar dermatoses (ASI_{ppd}) – adapted from the Psoriasis area and severity index (PASI). Median ASI_{ppd} at week 0 = 28 for the body half randomised to PUVA-gel and 26.5 for the body half randomised to PUVA-bath	Change in ASI_{ppd} from baseline to 2, 4 and 6 weeks and at the end of therapy Relapse not reported.	After a median of 33 irradiation sessions ASI_{ppd} was significantly reduced (p=0.00) to 1.5 for both PUVA-gel and PUVA-bath therapies with a median difference in ASI_{ppd} scores of 24 vs. 23 for PUVA-gel vs. PUVA-bath, respectively. Scores were comparable across all diseases.	Severe phototoxic reactions were not observed with any method.
	Grundmann-Kollmann et al. 1999 N=12	Not applicable (within patient trial) PUVA-cream vs. PUVA-bath	Severe recalcitrant dermatoses of the palms and soles (plaque-type psoriasis n=4, atopic eczema n=4, hyperkeratotic eczema n=4).	Improvement weekly, at the end of the study and for 8 weeks afterwards - defined as excellent (total score 0-4), good (5-8), satisfactory (9-12) and poor/no response	33% non-responders for both treatments. 58% and 50% good or excellent responses to PUVA-bath and PUVA-cream, respectively.	No side effects observed.

			Scoring system ranging from 0-20 scoring erythema, scaling, infiltration, pustulation and hyperkeratosis graded from 0 to 4 for each feature. Baseline scores all >16.	(12-20). Relapse not defined.	No relapses at 8 weeks after treatment.	
	Engin et al. 2005 N=22	Not applicable (within patient trial) PUVA vs. UVA	Chronic recurrent palmoplantar dermatoses (psoriasis vulgaris n=11, eczema n=6, pustulosis n=5) Assessment of erythema, scaling, infiltration, pustules and fissures on a 4-point scale (none=0, mild=1, moderate=2, severe=3). Severity index = sum of scores Baseline mean severity index = 7.5 (PUVA) and 6.95 (UVA).	Change in mean severity index at 6 weeks. Relapse not reported.	Baseline mean severity index decreased in both groups to = 2.5 (PUVA) and 3.45 (UVA). These values were significantly different ($p<0.05$)	Phototoxicity
	Shephard et	Not applicable (within	Severe palmoplantar	Efficacy observed at 4	Overall response rate	Erythema,

	al. 1998 N=37	patient trial) PUVA-bath vs. PUVA-lotion	eczema (n=24 eczema, n=13 psoriasis). Efficacy compared using total UVA dose, number of treatment sessions, therapy preference vs. diagnosis, % of responders vs. non-responders, length of lesion free interval following therapy. No baseline scoring.	weeks, as described. Subjective preference for treatment expressed by patient and continued. Relapse not defined.	of 80%. 15 preferred PUVA-bath, 11 preferred PUVA-lotion, 8 had no preference, 5 did not respond at all. Eczema patients preferred PUVA-bath to PUVA-lotion. Results were vice-versa in psoriasis group. Average symptom free interval of 3 months.	hyperpigmentation.
	Moon et al. 2000 N=44 *NB Paper in Korean, observations are from English language abstract and tables*	Steroid treatment (systemic and topical)(N=20) vs. bath-PUVA (N=24)	Palmoplantar pustular psoriasis (PPP), dyshidrotic eczema (DE) and palmoplantar keratoderma (PPK). Objective and subjective scores (not defined in English abstract) Mean objective severity scores in PUVA group at baseline = 10.42	Objective and subjective severity scores before and after treatment. Relapse not defined.	Mean severity scores significantly ($p<0.001$) decreased in both groups after treatment to 4.81 (PUVA) 4.25 and (steroids). Recurrence rate 4% in PUVA group and 11% in steroid group. Majority of patients in both groups reported excellent or good subjective scores after treatment.	Not reported

			Mean objective severity scores in steroid group at baseline = 9.75			
4 studies – Included in indirect comparison	Petering et al. 2003[Error! Bookmark not defined.] N=27	Not applicable (within patient trial) UVA vs. PUVA	Chronic vesicular dyshidrotic eczema for, DASI score10-12 at baseline (out of maximum 60).	Change in DASI score from baseline to completion of therapy.	DASI scores decreased significantly and were reduced to nearly half of the pre-treatment values in both arms. After 3 weeks no relapse was observed in 23 of 27 patients.	Both treatments were well tolerated.
	Sezer et al. 2007 N= 12	Not applicable (within patient trial)	Subtype only CHE of dry and dyshidrotic types, (hyperkeratotic CHE excluded). The following criteria were evaluated: erythema, squamation, induration, fissures and itching, each assessed on a 4 point scale: none 0, mild 1, moderate 2, severe 3. The total clinical score calculated by the sum of each variable. Complete clearance was defined as total clinical score of 0, marked clinical improvement was defined as reduction of 70% or more from baseline at week 9.	Clinical assessment every 3 weeks during the 9-week assessment period,. Further evaluation 10 weeks after treatment cessation with relapse defined as severe (>70% of pre-treatment scores), moderate (30-70% of pre-treatment scores) or mild (<30% of pre-treatment scores).	Significant ($p<0.05$) reductions in total clinical scores for both treatments at each timepoint. 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	Mild xerosis (both groups), hyperpigmentation (PUVA group).

			Mean total clinical scores: UVB – 10.5, PUVA – 9.83 of a maximum possible 15			
	Rosen et al. 1987 N=35	N= 18 PUVA and N=17 UVB	Bilateral hand eczema, symmetrical distribution. Predominantly females (31/35) with vesicular CHE (26/31) enrolled. Clinical assessment of: desquamation, erythema, vesiculation, infiltration and fissures. Each variable was assessed on a four point scale: 0, none; 1, slight; 2, moderate; 3, severe. Mean severity scores 10.3 (PUVA) and 10.5 (UVB) out of maximum 21 possible range (5-18)	Change in combined severity score at 3, 6, 9 and 12 weeks. Global evaluation at the end of treatment (cleared, much improved, somewhat improved, unchanged/worse). Relapse not defined.	PUVA: 92% reduction in severity score at treatment cessation. 14 patients cleared (4 patients at 3 weeks, 5 patients at 6 weeks and 5 patients at 9 weeks, $p<0.001$) UVB: 51% reduction in severity score at treatment cessation. Improvement in both treated and untreated hands, no clearance in either. In 9/14 PUVA patients dermatitis recurred within 3 months (mean) of end of treatment	PUVA: nausea, oedema, pain and itching in the treated hand, hyperpigmentation, soreness and stiffness in the fingers. UVB: Bullae, infection
	Simons et al. 1997 N=13	Not applicable (with-in patient trial) UVB vs. PUVA	Patients with vesicles or hyperkeratotic plaques of the hands present for > 6 months. Mean severity score 8.98 (UVB) and 10.17 (PUVA)	Change in clinical assessment score (based upon area and severity of symptoms) from baseline to 6 weeks. Relapse not reported.	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). Relapse not assessed	During the 6-week observation 2 patients developed UV radiation-induced erythema of the UVB treated side on a total of 3 occasions. Six patients suffered phototoxic reactions

						from PUVA on a total of 9 occasions. The PUVA treated side became more pigmented than the UVB treated side.
Considered for indirect comparison – not included as only mean differences in disease severity reported	Sheehan-Dare et al. 1989 N= 25	Not applicable (with-in patient trial) UVA vs. PUVA	Chronic bilateral constitutional hand eczema ,Week 0, mean severity score 3-4. Assessment of clinical severity: Grade 0, normal skin; Grade 1, mild scaling and erythema; Grade 2, moderate scaling, erythema and shallow fissures; Grade 3, severe scaling, erythema and deep bleeding fissures; Grade 4, active pompholyx. Patient visual analogue scale (0-10) also used to assess symptom severity, mean score 5-6 at baseline for both UVA and PUVA.	Change in clinical severity scores from baseline to 6, 9 and 18 weeks. Changes in VAS scores from baseline to 6, 9 and 18 weeks. Relapse not reported.	Significant improvements in clinical severity scores from baseline to 6, 9 and 18 weeks in both groups (p value not reported). Mean scores reduced to between 2-3 at 6, 9 and 18 weeks. Significant improvements in VAS scores from baseline to 6, 9 and 18 weeks in both groups (p value not reported). Mean scores reduced to between 2-3 at 6, 9 and 18 weeks.	Not reported.

	Van Coevorden et al. 2004 N=158	Oral PUVA at home N=78, Hospital bath PUVA N=80	Chronic bilateral or unilateral hand eczema. Moderate to severe (8.1 out of maximum 20). The following criteria were evaluated: erythema, squamation, vesiculation, fissures, itching and pain each assessed on a 4 point scale	Clinical assessment using the hand eczema score at 10 weeks. Relapse not reported.	Week 10: Oral PUVA mean score 4.8 (mean reduction 3.3), bath PUVA mean score 5.6 (mean reduction 2.5). In the oral PUVA group 72% improved and in the bath PUVA group 61% improved. At 8 weeks follow up scores did not change significantly. 23% and 18% in oral and bath groups respectively worsened by more than 1 point.	Temporary nausea (home group); mild stinging and burning (hospital group)
	Adams et al. 2007**Error! Bookmark not defined.** N= 15 *NB Paper in German, observations are from English language abstract*	N= 11, one hand received PUVA and the other UVA-1	Chronic dyshidrotic hand dermatitis. DASI (dishydrotic eczema area and severity index)	Change in DASI score from baseline to 5 weeks (15 irradiations). Relapse not reported in abstract.	Significant improvement in DASI score with PUVA (p=0.0498) and UVA irradiation (p=0.0039). No significant difference between the two therapies (p=0.3070).	Not reported in abstract
	Grattan et al. 1991 N=15	N=12, one hand received PUVA and the other UVA	Recurrent disabling bilateral symmetrical vesicular hand eczema for at least 6 months. Mean severity score at week 0 = <2.5 (mild to moderate on global	Change in global rating scale from baseline to 8 weeks and 16 weeks. Change in VAS scores from baseline	Significant ($p<0.05$) reduction in mean severity by global rating, at week 8 (to approximately 1.5, minimal to mild). VAS significantly	1 patient experienced a burning episode on his PUVA hand. 2 patients who withdrew experience exacerbations.

			rating scale: clear 0; minimal 1; mild 2; moderate 3; severe 4) for both treatments. Mean visual analogue scale (VAS) score (0-10) at week 0 between 3 and 5 for both treatments. Mean T_{120} score (area and severity scoring system, 0-120) at week 0 = 27.63 (PUVA) and 26.63 (UVA)	to 8 weeks and 16 weeks. Change in T_{120} score from baseline to 8 weeks and 16 weeks. Relapse not reported.	(p<0/05) improved (to 5-7) at week 8. T_{120} significantly (p<0.05) decreased to approximately 7-9) at week 8. No significant change in any scores at 4 or 8 weeks after end of treatment.	

Table 3. PUVA studies that were not included in the indirect comparison because only mean reduction in disease severity was reported

Study ID Total Enrolment	**Number of Subjects by Treatment Arm Entered**	**Baseline disease demographics/ severity scoring system**	**Primary endpoint Response/ relapse definition**	**Efficacy Results**
Sheehan-Dare et al. 1989 N= 25	Not applicable (with-in patient trial) UVA vs. PUVA	Chronic bilateral constitutional hand eczema ,Week 0, mean severity score 3-4. Assessment of clinical severity: Grade 0, normal skin; Grade 1, mild scaling and erythema; Grade 2, moderate scaling, erythema and shallow fissures; Grade 3, severe scaling, erythema and deep bleeding fissures; Grade 4, active pompholyx. Patient visual analogue scale (0-10) also used to assess symptom severity, mean score 5-6 at baseline for both UVA and PUVA.	Change in clinical severity scores from baseline to 6, 9 and 18 weeks. Changes in VAS scores from baseline to 6, 9 and 18 weeks. Relapse not reported.	Significant improvements in clinical severity scores from baseline to 6, 9 and 18 weeks in both groups (p value not reported). Mean scores reduced to between 2-3 at 6, 9 and 18 weeks. Significant improvements in VAS scores from baseline to 6, 9 and 18 weeks in both groups (p value not reported). Mean scores reduced to between 2-3 at 6, 9 and 18 weeks.
Van Coevorden et al. 2004 N=158	Oral PUVA at home N=78, Hospital bath PUVA N=80	Chronic bilateral or unilateral hand eczema. Moderate to severe (8.1 out of maximum 20). The following criteria were evaluated: erythema, squamation, vesiculation, fissures, itching and pain each assessed on a 4 point scale	Clinical assessment using the hand eczema score at 10 weeks. Relapse not reported.	Week 10: Oral PUVA mean score 4.8 (mean reduction 3.3), bath PUVA mean score 5.6 (mean reduction 2.5). In the oral PUVA group 72% improved and in the bath PUVA group 61% improved. At 8 weeks follow up scores did not change significantly. 23% and 18% in oral and bath groups respectively worsened by more than 1 point.
Adams et al. 2007	N= 11, one hand received PUVA and	Chronic dyshidrotic hand dermatitis.	Change in DASI score from baseline to 5 weeks (15	Significant improvement in DASI score with PUVA (p=0.0498) and UVA irradiation (p=0.0039). No significant difference between

N= 15 *NB Paper in German, observations are from English language abstract*	the other UVA-1	DASI (dishydrotic eczema area and severity index)	irradiations). Relapse not reported in abstract.	the two therapies (p=0.3070).
Grattan et al. 1991 N=15	N=12, one hand received PUVA and the other UVA	Recurrent disabling bilateral symmetrical vesicular hand eczema for at least 6 months. Mean severity score at week 0 = <2.5 (mild to moderate on global rating scale: clear 0; minimal 1; mild 2; moderate 3; severe 4) for both treatments. Mean visual analogue scale (VAS) score (0-10) at week 0 between 3 and 5 for both treatments. Mean T_{120} score (area and severity scoring system, 0-120) at week 0 = 27.63 (PUVA) and 26.63 (UVA)	Change in global rating scale from baseline to 8 weeks and 16 weeks. Change in VAS scores from baseline to 8 weeks and 16 weeks. Change in T_{120} score from baseline to 8 weeks and 16 weeks. Relapse not reported.	Significant ($p<0.05$) reduction in mean severity by global rating, at week 8 (to approximately 1.5, minimal to mild). VAS significantly ($p<0/05$) improved (to 5-7) at week 8. T_{120} significantly ($p<0.05$) decreased to approximately 7-9) at week 8. No significant change in any scores at 4 or 8 weeks after end of treatment.

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Appendix 2: Population characteristics and results of DLQI analysis in BAP00003

Contents:

BAL4079/ALITRETINOIN
Additional Table 51 **Response to Previous Treatment: ITT Population -patients with both Baseline and Week 12 DLQI data**

		Alitretinoin			
	Placebo	10mg	20mg	40mg	Total
Number of Patients in ITT population	41	36	43	42	162
Treated for 4 Weeks Previously					
Yes	41 (100%)	36 (100%)	43 (100%)	42 (100%)	162 (100%)
No	0	0	0	0	0
No Response					
Yes	7 (17%)	8 (22%)	9 (21%)	10 (24%)	34 (21%)
No	34 (83%)	28 (78%)	34 (79%)	32 (76%)	128 (79%)
Transient Response					
Yes	35 (85%)	28 (78%)	35 (81%)	33 (79%)	131 (81%)
No	6 (15%)	8 (22%)	8 (19%)	9 (21%)	31 (19%)
Treatment Not Tolerated					
Yes	1 (2%)	1 (3%)	0	0	2 (1%)
No	40 (98%)	35 (97%)	43 (100%)	42 (100%)	160 (99%)
Other					
Yes	0	0	0	1 (2%)	1 (1%)
No	41 (100%)	36 (100%)	43 (100%)	41 (98%)	161 (99%)

Source Data: Listing 9 b3ta51.sas 28JAN2009

BAL4079/ALITRETINOIN

Additional Table 49 **Summary of Demographic Variables: ITT Population (Part 1 of 2)- patients with both Baseline and Week 12 DLQI data**

		Alitretinoin			
	Placebo	10mg	20mg	40mg	Total
Number of Patients in ITT Population	41	36	43	42	162
Age (years)					
N	41	36	43	42	162
Mean	50.1	51.8	49.3	48.4	49.9
Standard Deviation	12.81	11.72	11.93	11.00	11.84
Median	54.0	53.0	50.0	50.0	52.0
Minimum	18	22	18	23	18
Maximum	68	68	76	69	76
Sex					
Male	33 (80%)	23 (64%)	29 (67%)	32 (76%)	117 (72%)
Female	8 (20%)	13 (36%)	14 (33%)	10 (24%)	45 (28%)
Weight (kg)					
N	41	36	43	42	162
Mean	79.07	78.03	76.73	81.36	78.81
Standard Deviation	14.716	12.470	13.816	15.100	14.088
Median	78.00	77.00	77.90	82.00	78.00
Minimum	54.0	53.0	45.0	56.0	45.0
Maximum	125.1	110.0	115.0	140.0	140.0
Height (cm)					
N	41	36	43	42	162
Mean	172.5	170.2	171.4	172.4	171.7
Standard Deviation	7.35	7.01	9.60	9.80	8.57
Median	173.0	170.0	171.0	174.0	172.0
Minimum	157	158	150	150	150
Maximum	188	186	191	196	196

Source Data: Listing 6

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BAL4079/ALITRETINOIN

Additional Table 49 **Summary of Demographic Variables: ITT Population (Part 2 of 2)- patients with both Baseline and Week 12 DLQI data**

		Alitretinoin			
	Placebo	10mg	20mg	40mg	Total
Number of Patients in ITT Population	41	36	43	42	162
Race					
Caucasian/White	39 (98%)	34 (94%)	42 (98%)	41 (98%)	156 (97%)
Black	1 (3%)	0	1 (2%)	0	2 (1%)
Oriental	0	2 (6%)	0	0	2 (1%)
Other	0	0	0	1 (2%)	1 (1%)
Missing	1	0	0	0	1
Normal Occupation					
Employed/Self Employed Full-Time	23 (56%)	21 (58%)	28 (65%)	29 (69%)	101 (62%)
Employed/Self Employed Part-Time	0	2 (6%)	2 (5%)	1 (2%)	5 (3%)
Student	2 (5%)	0	0	1 (2%)	3 (2%)
Homemaker/Housewife	3 (7%)	1 (3%)	4 (9%)	3 (7%)	11 (7%)
Unemployed	4 (10%)	3 (8%)	3 (7%)	2 (5%)	12 (7%)
Retired	9 (22%)	9 (25%)	6 (14%)	6 (14%)	30 (19%)

Note: Details of 'Other' Races and Normal Occupations will be included in the listing

Source Data: Listing 6

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BAL4079/ALITRETINOIN

Additional Table 50 **History of Chronic Hand Dermatitis: ITT Population- patients with both Baseline and Week 12 DLQI data**

		Alitretinoin			
	Placebo	10mg	20mg	40mg	Total
Number of Patients in the ITT Population	41	36	43	42	162
Number of Patients With History of Chronic Hand Dermatitis	41 (100%)	36 (100%)	43 (100%)	42 (100%)	162 (100%)
Type of Disease					
Hyperkeratotic Eczema	35 (85%)	31 (86%)	39 (91%)	35 (83%)	140 (86%)
Pompholyx	9 (22%)	4 (11%)	11 (26%)	13 (31%)	37 (23%)
Fingertip Eczema	11 (27%)	12 (33%)	19 (44%)	13 (31%)	55 (34%)
Other	4 (10%)	4 (11%)		2 (5%)	10 (6%)
Time Since Start of Primary Diagnosis (Years)					
N	41	36	43	42	162
Mean	6.23	6.28	5.86	7.67	6.51
Standard Deviation	5.273	8.386	7.838	8.889	7.671
Median	3.90	2.80	2.70	3.00	2.95
Minimum	0.8	0.4	0.3	0.3	0.3
Maximum	23.8	34.7	34.7	37.1	37.1
Time Since Start of Present Episode (Months)					
N	40	36	43	42	161
Mean	16.23	15.65	28.77	23.98	21.47
Standard Deviation	20.970	23.262	50.640	49.077	39.324
Median	5.20	6.40	10.00	3.85	5.50
Minimum	1.0	0.8	0.9	0.2	0.2
Maximum	78.8	122.4	274.2	260.0	274.2

Note: Patients can have more than one "Type of Disease"
Details of "Other Types of Disease" will be given in the listing
'Time Since Start of Primary Diagnosis' or 'Present Episode' use derived dates if date recorded was partial
except for patient 3606 'Present Episode' as only the year was recorded and the derived date was prior
to the patient starting in the study

Source Data: Listing 8 b3ta50.sas 28JAN2009

BAL4079/ALITRETINOIN

Additional Listing: Patients with Total Dermatology Life Quality Index (DLQI) Score at Baseline and Week 12 By Center, Treatment and Patient
ITT Population

Center/ Investigator	Treatment Group	Pt. No.	Age/ Sex	Population ITT	Population PP	PGA	Total DLQI Baseline	Total DLQI Week 12	Total DLQI Change From Baseline
1/ Prof. J. Lambert	Placebo	102	67/M	Y	Y	Mod. Disease	6	6	0
	Alitretinoin 20mg	104	47/M	Y	Y	Mod. Disease	11	12	1
	Alitretinoin 40mg	101	51/M	Y	N	Mild Disease	25	7	-18
2/ Prof. D. Roseeuw	Placebo	203	21/M	Y	Y	Mod. Disease	1	2	1
	Alitretinoin 20mg	201	53/F	Y	Y	Almost Clear	9	5	-4
	Alitretinoin 40mg	204	23/M	Y	Y	Almost Clear	5	5	0
		205	44/M	Y	Y	Mod. Disease	3	15	12
	Alitretinoin 10mg	202	22/M	Y	Y	Severe Dis.	8	6	-2
		207	45/M	Y	Y	Mod. Disease	3	5	2
3/ Prof. M.F. De La Brassine	Alitretinoin 20mg	301	59/F	Y	Y	Clear	10	0	-10
	Alitretinoin 40mg	303	52/M	Y	Y	Mod. Disease	14	14	0
	Alitretinoin 10mg	302	51/M	Y	Y	Almost Clear	2	0	-2
4/ Prof. M. Heenen	Placebo	401	34/M	Y	Y	Almost Clear	4	2	-2
7/ Dr. F. Larsen	Placebo	704	58/M	Y	Y	Mod. Disease	12	2	-10
		715	27/M	Y	Y	Mod. Disease	6	13	7
		720	51/F	Y	Y	Mild Disease	7	1	-6
		726	43/M	Y	Y	Almost Clear	3	0	-3
	Alitretinoin 20mg	702	50/M	Y	Y	Almost Clear	9	0	-9
		709	40/M	Y	Y	Mild Disease	2	3	1
		712	29/M	Y	Y	Mod. Disease	7	13	6
		723	50/F	Y	Y	Mild Disease	10	2	-8
	Alitretinoin 40mg	701	53/F	Y	Y	Clear	8	1	-7
		711	26/M	Y	Y	Mod. Disease	6	3	-3
		717	57/M	Y	Y	Mod. Disease	4	7	3
		725	41/M	Y	Y	Mod. Disease	6	5	-1
		727	47/M	Y	Y	Almost Clear	14	0	-14
	Alitretinoin 10mg	705	48/F	Y	Y	Mild Disease	5	1	-4
		713	59/M	Y	N	Mod. Disease	19	19	0
		719	68/F	Y	Y	Almost Clear	4	0	-4
		722	65/F	Y	Y	Almost Clear	8	0	-8
9/ Prof. J.P. Ortonne	Placebo	902	26/M	Y	Y	Mild Disease	3	4	1
		906	51/M	Y	Y	Almost Clear	16	10	-6
		916	58/F	Y	Y	Clear	5	0	-5
	Alitretinoin 10mg	907	51/M	Y	Y	Mild Disease	11	10	-1
		909	57/F	Y	Y	Mod. Disease	8	12	4

Note: Total DLQI Score is the sum of the scores for the responses given at the specified visit

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Additional Listing: Patients with Total Dermatology Life Quality Index (DLQI) Score at Baseline and Week 12 By Center, Treatment and Patient
ITT Population

Center/ Investigator	Treatment Group	Pt. No.	Age/ Sex	Population ITT	Population PP	PGA	Total DLQI Baseline	Total DLQI Week 12	Total DLQI Change From Baseline
9/ Prof. J.P. Ortonne	Alitretinoin 20mg	904	45/F	Y	Y	Mod. Disease	24	6	-18
		905	65/F	Y	Y	Mod. Disease	9	14	5
		911	18/M	Y	Y	Mild Disease	9	6	-3
		915	76/F	Y	N	Mild Disease	0	0	0
	Alitretinoin 40mg	903	43/M	Y	Y	Mod. Disease	10	13	3
		908	52/M	Y	Y	Almost Clear	3	6	3
		912	51/F	Y	N	Clear	5	0	-5
	Alitretinoin 10mg	914	62/M	Y	N	Almost Clear	4	6	2
10/ Prof. F. Cambazard	Placebo	1005	50/F	Y	Y	Almost Clear	11	4	-7
		1006	62/M	Y	N	Severe Dis.	6	10	4
	Alitretinoin 20mg	1004	55/M	Y	Y	Mild Disease	14	4	-10
	Alitretinoin 40mg	1001	69/M	Y	Y	Severe Dis.	13	13	0
		1008	54/M	Y	Y	Mild Disease	10	7	-3
	Alitretinoin 10mg	1003	52/F	Y	N	Almost Clear	19	2	-17
11/ Prof. B. Dreno	Placebo	1102	55/M	Y	Y	Mod. Disease	9	9	0
	Alitretinoin 20mg	1104	29/M	Y	Y	Almost Clear	5	1	-4
	Alitretinoin 40mg	1103	51/M	Y	Y	Clear	5	0	-5
	Alitretinoin 10mg	1101	40/M	Y	Y	Mod. Disease	5	3	-2
12/ Prof. L. Dubertret	Placebo	1204	59/M	Y	Y	Mild Disease	2	2	0
	Alitretinoin 20mg	1203	56/F	Y	Y	Almost Clear	5	1	-4
	Alitretinoin 10mg	1202	55/F	Y	N	Severe Dis.	21	23	2
15/ Prof. G. Wozel	Placebo	1501	43/M	Y	Y	Mild Disease	6	10	4
	Alitretinoin 20mg	1505	54/M	Y	Y	Mod. Disease	10	16	6
	Alitretinoin 40mg	1502	47/M	Y	Y	Mod. Disease	9	8	-1
	Alitretinoin 10mg	1503	41/M	Y	N	Mild Disease	5	4	-1
16/ Prof. Th. Ruzicka	Placebo	1601	52/M	Y	Y	Severe Dis.	13	14	1
		1608	61/M	Y	Y	Almost Clear	15	10	-5
		1611	47/M	Y	Y	Almost Clear	16	7	-9
		1616	68/M	Y	Y	Mod. Disease	6	9	3
	Alitretinoin 20mg	1602	42/F	Y	Y	Almost Clear	3	2	-1
	Alitretinoin 10mg	1604	38/M	Y	Y	Almost Clear	8	9	1
		1607	48/M	Y	N	Mod. Disease	20	19	-1
		1609	29/M	Y	Y	Mod. Disease	8	19	11
		1613	57/F	Y	Y	Mod. Disease	18	19	1
		1619	48/F	Y	Y	Almost Clear	13	5	-8

Note: Total DLQI Score is the sum of the scores for the responses given at the specified visit

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Additional Listing: Patients with Total Dermatology Life Quality Index (DLQI) Score at Baseline and Week 12 By Center, Treatment and Patient
ITT Population

Center/ Investigator	Treatment Group	Pt. No.	Age/ Sex	Population ITT	Population PP	PGA	Total DLQI Baseline	Total DLQI Week 12	Total DLQI Change From Baseline
16/ Prof. Th. Ruzicka	Alitretinoin 20mg	1605	50/F	Y	Y	Clear	19	0	-19
		1617	52/M	Y	Y	Almost Clear	23	0	-23
	Alitretinoin 40mg	1603	57/M	Y	Y	Clear	16	1	-15
		1606	49/M	Y	Y	Mild Disease	19	16	-3
		1612	60/F	Y	Y	Almost Clear	27	0	-27
		1614	55/F	Y	Y	Mild Disease	30	23	-7
		1618	33/M	Y	Y	Almost Clear	12	9	-3
17/ Prof. H-U. Peter	Placebo	1703	56/M	Y	Y	Mod. Disease	9	4	-5
	Alitretinoin 20mg	1701	60/M	Y	Y	Mod. Disease	22	12	-10
	Alitretinoin 40mg	1702	65/M	Y	Y	Mild Disease	3	3	0
	Alitretinoin 10mg	1705	65/F	Y	Y	Severe Dis.	9	9	0
18/ Prof. T. Zuberbier	Placebo	1807	65/M	Y	Y	Severe Dis.	8	8	0
		1810	18/M	Y	Y	Almost Clear	9	7	-2
	Alitretinoin 20mg	1804	41/M	Y	Y	Mod. Disease	4	7	3
		1806	62/M	Y	N	Clear	2	0	-2
	Alitretinoin 40mg	1805	61/F	Y	Y	Almost Clear	11	6	-5
		1808	56/M	Y	Y	Clear	13	0	-13
	Alitretinoin 10mg	1802	62/M	Y	Y	Almost Clear	9	0	-9
		1809	57/F	Y	Y	Clear	6	2	-4
19/ Prof. Ch. Zouboulis	Placebo	1902	32/M	Y	Y	Almost Clear	7	3	-4
	Alitretinoin 20mg	1901	46/F	Y	Y	Mod. Disease	13	15	2
		1907	37/F	Y	N	Mod. Disease	14	17	3
	Alitretinoin 40mg	1903	43/F	Y	Y	Almost Clear	2	3	1
	Alitretinoin 10mg	1904	49/F	Y	Y	Severe Dis.	15	25	10
		1906	61/F	Y	Y	Mild Disease	15	3	-12
24/ Prof. P.J. Coenraads	Placebo	2403	44/M	Y	Y	Mod. Disease	10	4	-6
		2405	54/M	Y	Y	Severe Dis.	14	15	1
		2410	57/M	Y	Y	Mod. Disease	3	4	1
		2416	58/M	Y	Y	Almost Clear	7	1	-6
	Alitretinoin 20mg	2404	54/M	Y	N	Severe Dis.	15	6	-9
		2406	35/M	Y	Y	Severe Dis.	12	19	7
	Alitretinoin 10mg	2401	53/M	Y	Y	Severe Dis.	27	24	-3
		2408	58/F	Y	Y	Almost Clear	20	0	-20
		2411	35/M	Y	Y	Mild Disease	6	0	-6
		2414	50/M	Y	Y	Mod. Disease	5	0	-5

Note: Total DLQI Score is the sum of the scores for the responses given at the specified visit

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Additional Listing: Patients with Total Dermatology Life Quality Index (DLQI) Score at Baseline and Week 12 By Center, Treatment and Patient
ITT Population

Center/ Investigator	Treatment Group	Pt. No.	Age/ Sex	Population ITT	Population PP	PGA	Total DLQI Baseline	Total DLQI Week 12	Total DLQI Change From Baseline
24/ Prof. P.J. Coenraads	Alitretinoin 20mg	2412	59/M	Y	Y	Mild Disease	3	1	-2
		2415	55/M	Y	Y	Mild Disease	7	0	-7
	Alitretinoin 40mg	2402	45/M	Y	Y	Almost Clear	13	0	-13
		2407	32/M	Y	Y	Mild Disease	21	2	-19
		2409	59/F	Y	Y	Almost Clear	3	0	-3
		2413	56/M	Y	Y	Clear	2	0	-2
25/ Prof. Th. Starink	Alitretinoin 20mg	2501	59/F	Y	Y	Mod. Disease	14	5	-9
26/ Dr. H.B. van der Walle	Placebo	2602	45/M	Y	Y	Severe Dis.	8	11	3
		2606	60/M	Y	Y	Severe Dis.	17	13	-4
	Alitretinoin 20mg	2603	60/M	Y	N	Mild Disease	19	21	2
	Alitretinoin 40mg	2604	62/F	Y	Y	Clear	15	0	-15
	Alitretinoin 10mg	2605	67/M	Y	Y	Almost Clear	8	0	-8
27/ Dr. P. van der Valk	Placebo	2707	61/F	Y	Y	Mod. Disease	12	6	-6
		2709	41/F	Y	Y	Mild Disease	4	1	-3
	Alitretinoin 20mg	2702	56/M	Y	Y	Mod. Disease	7	2	-5
		2711	64/M	Y	Y	Mod. Disease	9	13	4
	Alitretinoin 40mg	2708	32/M	Y	N	Severe Dis.	9	9	0
		2712	47/M	Y	Y	Severe Dis.	13	17	4
35/ Prof. G. Burg	Placebo	3504	61/M	Y	Y	Severe Dis.	23	24	1
	Alitretinoin 20mg	3503	61/M	Y	Y	Mod. Disease	10	16	6
	Alitretinoin 40mg	3502	39/M	Y	Y	Mod. Disease	16	16	0
36/ Prof. J-H. Saurat	Placebo	3606	52/M	Y	Y	Mod. Disease	11	10	-1
	Alitretinoin 20mg	3603	40/M	Y	N	Mod. Disease	3	5	2
		3604	45/M	Y	N	Clear	10	0	-10
	Alitretinoin 40mg	3602	48/M	Y	Y	Mild Disease	10	15	5
		3605	58/F	Y	Y	Mod. Disease	9	8	-1
	Alitretinoin 10mg	3601	53/M	Y	Y	Mild Disease	11	3	-8
37/ Dr. C.J. Flemming	Placebo	3702	55/M	Y	N	Severe Dis.	9	9	0
	Alitretinoin 20mg	3701	60/F	Y	Y	Mod. Disease	2	3	1
	Alitretinoin 10mg	3703	63/M	Y	Y	Mod. Disease	16	17	1
38/ Dr. A.D. Burden	Alitretinoin 40mg	3802	53/M	Y	N	Clear	5	1	-4
39/ Dr. R. Ratnavel	Alitretinoin 20mg	3902	48/F	Y	Y	Mod. Disease	7	3	-4
		3905	42/M	Y	Y	Almost Clear	12	1	-11
	Alitretinoin 40mg	3901	49/F	Y	Y	Mod. Disease	8	4	-4
	Alitretinoin 10mg	3903	24/M	Y	Y	Mod. Disease	5	3	-2

Note: Total DLQI Score is the sum of the scores for the responses given at the specified visit

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Additional Listing: Patients with Total Dermatology Life Quality Index (DLQI) Score at Baseline and Week 12 By Center, Treatment and Patient
ITT Population

Center/ Investigator	Treatment Group	Pt. No.	Age/ Sex	Population ITT	Population PP	PGA	Total DLQI Baseline	Total DLQI Week 12	Total DLQI Change From Baseline
40/ Dr. R.D. Aldridge	Placebo	4001	48/M	Y	Y	Mod. Disease	3	3	0
		4007	60/M	Y	Y	Mild Disease	7	3	-4
	Alitretinoin 20mg	4002	46/M	Y	Y	Mild Disease	2	1	-1
	Alitretinoin 40mg	4003	39/M	Y	Y	Mild Disease	4	1	-3
	Alitretinoin 10mg	4004	50/M	Y	N	Mod. Disease	7	2	-5
41/ Prof. D. Abeck	Placebo	4103	55/F	Y	N	Severe Dis.	22	21	-1
	Alitretinoin 40mg	4101	37/M	Y	N	Almost Clear	12	4	-8
	Alitretinoin 10mg	4102	64/M	Y	N	Mod. Disease	7	11	4
42/ Dr. Ch. Willers	Placebo	4205	55/F	Y	Y	Almost Clear	19	1	-18
	Alitretinoin 20mg	4203	19/M	Y	Y	Clear	13	1	-12
	Alitretinoin 40mg	4204	35/M	Y	Y	Mod. Disease	7	0	-7
43/ Prof. R. Kaufmann	Placebo	4302	30/M	Y	Y	Mild Disease	14	6	-8
	Alitretinoin 20mg	4301	42/M	Y	Y	Mod. Disease	21	19	-2
44/ Dr. B.J. Halioua	Placebo	4405	68/F	Y	Y	Almost Clear	0	0	0
		4408	47/M	Y	Y	Mod. Disease	14	4	-10
	Alitretinoin 20mg	4403	55/M	Y	Y	Mild Disease	5	2	-3
		4407	48/M	Y	Y	Clear	2	0	-2
	Alitretinoin 40mg	4404	34/M	Y	Y	Clear	3	0	-3
	Alitretinoin 10mg	4401	53/M	Y	Y	Almost Clear	6	0	-6
46/ Prof. H. Degreef	Alitretinoin 20mg	4602	58/M	Y	Y	Mild Disease	7	0	-7
	Alitretinoin 40mg	4603	68/M	Y	N	Almost Clear	2	0	-2
	Alitretinoin 10mg	4601	66/M	Y	Y	Severe Dis.	14	3	-11

Note: Total DLQI Score is the sum of the scores for the responses given at the specified visit

The following 4 tables are provided as commercial in confidence

Appendix A10 Dermatology Life Quality Index (DLQI) Results: ITT Population

	Placebo		Alitretinoin 10mg		Alitretinoin 20mg		Alitretinoin 40mg	
	Baseline	Week 12*	Baseline	Week 12*	Baseline	Week 12*	Baseline	Week 12*
Number of Patients in ITT Population in Countries Assessing DLQI	49	44	48	39	48	43	50	45
Number of Patients With Available Data	48	41	48	36	48	43	50	42
Question 1								
Very Much	14 (29%)	6 (15%)	13 (27%)	5 (14%)	15 (31%)	5 (12%)	11 (22%)	1 (2%)
A Lot	15 (31%)	6 (15%)	18 (38%)	6 (17%)	18 (38%)	7 (16%)	20 (40%)	13 (31%)
A Little	15 (31%)	24 (59%)	16 (33%)	14 (39%)	11 (23%)	16 (37%)	19 (38%)	14 (33%)
Not at All	4 (8%)	5 (12%)	1 (2%)	11 (31%)	4 (8%)	15 (35%)	0	14 (33%)
Missing	1	3	0	3	0	0	0	3
Question 2								
Very Much	11 (23%)	3 (7%)	7 (15%)	2 (6%)	7 (15%)	5 (12%)	6 (12%)	3 (7%)
A Lot	14 (29%)	3 (7%)	17 (35%)	5 (14%)	19 (40%)	7 (16%)	20 (40%)	8 (19%)
A Little	13 (27%)	22 (54%)	17 (35%)	14 (39%)	16 (33%)	9 (21%)	15 (30%)	11 (26%)
Not at All	10 (21%)	13 (32%)	7 (15%)	15 (42%)	6 (13%)	22 (51%)	9 (18%)	20 (48%)
Missing	1	3	0	3	0	0	0	3
Question 3								
Very Much	13 (27%)	7 (17%)	13 (27%)	5 (14%)	6 (13%)	5 (12%)	8 (16%)	2 (5%)
A Lot	13 (27%)	9 (22%)	12 (25%)	6 (17%)	14 (29%)	8 (19%)	14 (29%)	8 (19%)
A Little	10 (21%)	6 (15%)	13 (27%)	10 (28%)	14 (29%)	11 (26%)	19 (39%)	9 (21%)
Not at All	11 (23%)	17 (41%)	7 (15%)	14 (39%)	11 (23%)	18 (42%)	7 (14%)	23 (55%)
Not Relevant	1 (2%)	2 (5%)	3 (6%)	1 (3%)	3 (6%)	1 (2%)	1 (2%)	0
Missing	1	3	0	3	0	0	1	3

Note: Week 12* refers to Week 12 or treatment discontinuation
All percentages have been calculated out of the number of patients with available data for that question
Patients 1802 and 1806 answered the second part of Question 7 when it was not applicable to them. However, their data has been included in the table

Appendix A10 (cont) Dermatology Life Quality Index (DLQI) Results: ITT Population

	Placebo		Alitretinoin 10mg		Alitretinoin 20mg		Alitretinoin 40mg	
	Baseline	Week 12*	Baseline	Week 12*	Baseline	Week 12*	Baseline	Week 12*
Number of Patients in ITT Population in Countries Assessing DLQI	49	44	48	39	48	43	50	45
Number of Patients With Available Data	48	41	48	36	48	43	50	42
Question 4								
Very Much	1 (2%)	0	3 (6%)	1 (3%)	1 (2%)	0	4 (8%)	1 (2%)
A Lot	1 (2%)	2 (5%)	7 (15%)	3 (8%)	4 (8%)	1 (2%)	2 (4%)	2 (5%)
A Little	15 (31%)	5 (12%)	3 (6%)	2 (6%)	9 (19%)	6 (14%)	16 (32%)	11 (26%)
Not at All	29 (60%)	33 (80%)	28 (58%)	25 (69%)	28 (58%)	34 (79%)	25 (50%)	26 (62%)
Not Relevant	2 (4%)	1 (2%)	7 (15%)	5 (14%)	6 (13%)	2 (5%)	3 (6%)	2 (5%)
Missing	1	3	0	3	0	0	0	3
Question 5								
Very Much	6 (13%)	1 (2%)	5 (10%)	4 (11%)	7 (15%)	2 (5%)	5 (10%)	1 (2%)
A Lot	10 (21%)	7 (17%)	8 (17%)	7 (19%)	7 (15%)	5 (12%)	5 (10%)	6 (14%)
A Little	16 (33%)	12 (29%)	20 (42%)	4 (11%)	8 (17%)	9 (21%)	15 (30%)	11 (26%)
Not at All	13 (27%)	20 (49%)	13 (27%)	21 (58%)	24 (50%)	26 (60%)	22 (44%)	23 (55%)
Not Relevant	3 (6%)	1 (2%)	2 (4%)	0	2 (4%)	1 (2%)	3 (6%)	1 (2%)
Missing	1	3	0	3	0	0	0	3
Question 6								
Very Much	3 (6%)	1 (2%)	6 (13%)	5 (14%)	4 (8%)	1 (2%)	7 (14%)	1 (2%)
A Lot	5 (10%)	5 (12%)	5 (10%)	4 (11%)	4 (8%)	1 (2%)	3 (6%)	4 (10%)
A Little	11 (23%)	7 (17%)	12 (25%)	5 (14%)	5 (10%)	6 (14%)	10 (20%)	6 (14%)
Not at All	18 (38%)	18 (44%)	12 (25%)	16 (44%)	20 (42%)	24 (56%)	19 (38%)	23 (55%)
Not Relevant	11 (23%)	10 (24%)	13 (27%)	6 (17%)	15 (31%)	11 (26%)	11 (22%)	8 (19%)
Missing	1	3	0	3	0	0	0	3

Note: Week 12* refers to Week 12 or treatment discontinuation
All percentages have been calculated out of the number of patients with available data for that question
Patients 1802 and 1806 answered the second part of Question 7 when it was not applicable to them. However, their data has been included in the table

Appendix A10 (cont) Dermatology Life Quality Index (DLQI) Results: ITT Population

	Placebo		Alitretinoin 10mg		Alitretinoin 20mg		Alitretinoin 40mg	
	Baseline	Week 12*	Baseline	Week 12*	Baseline	Week 12*	Baseline	Week 12*
Number of Patients in ITT Population in Countries Assessing DLQI	49	44	48	39	48	43	50	45
Number of Patients With Available Data	48	41	48	36	48	43	50	42
Question 7								
Yes	10 (21%)	5 (12%)	11 (23%)	4 (11%)	8 (17%)	6 (14%)	8 (16%)	5 (12%)
No	26 (54%)	30 (73%)	32 (67%)	27 (75%)	32 (67%)	32 (76%)	35 (70%)	31 (74%)
Not Relevant	12 (25%)	6 (15%)	5 (10%)	5 (14%)	8 (17%)	4 (10%)	7 (14%)	6 (14%)
Missing	1	3	0	3	0	1	0	3
If no:								
A Lot	5 (20%)	2 (7%)	8 (26%)	6 (22%)	14 (44%)	4 (12%)	9 (28%)	2 (7%)
A Little	12 (48%)	10 (34%)	12 (39%)	3 (11%)	12 (38%)	6 (18%)	15 (47%)	9 (30%)
Not at All	8 (32%)	17 (59%)	11 (35%)	18 (67%)	6 (19%)	23 (70%)	8 (25%)	19 (63%)
Missing	1	1	1	1	0	0	3	1
Question 8								
Very Much	2 (4%)	0	3 (6%)	4 (11%)	2 (4%)	2 (5%)	4 (8%)	0
A Lot	7 (15%)	3 (7%)	4 (8%)	2 (6%)	4 (8%)	5 (12%)	2 (4%)	3 (7%)
A Little	12 (25%)	10 (24%)	14 (29%)	7 (19%)	14 (29%)	6 (14%)	19 (38%)	11 (26%)
Not at All	24 (50%)	26 (63%)	23 (48%)	22 (61%)	25 (52%)	28 (65%)	24 (48%)	28 (67%)
Not Relevant	3 (6%)	2 (5%)	4 (8%)	1 (3%)	3 (6%)	2 (5%)	1 (2%)	0
Missing	1	3	0	3	0	0	0	3

Note: Week 12* refers to Week 12 or treatment discontinuation
All percentages have been calculated out of the number of patients with available data for that question
Patients 1802 and 1806 answered the second part of Question 7 when it was not applicable to them. However, their data has been included in the table

Appendix A10 (cont) Dermatology Life Quality Index (DLQI) Results: ITT Population

	Placebo		Alitretinoin 10mg		Alitretinoin 20mg		Alitretinoin 40mg	
	Baseline	Week 12*	Baseline	Week 12*	Baseline	Week 12*	Baseline	Week 12*
Number of Patients in ITT Population in Countries Assessing DLQI	49	44	48	39	48	43	50	45
Number of Patients With Available Data	48	41	48	36	48	43	50	42
Question 9								
Very Much	2 (4%)	1 (2%)	1 (2%)	4 (11%)	1 (2%)	1 (2%)	4 (8%)	0
A Lot	1 (2%)	1 (2%)	5 (10%)	1 (3%)	5 (10%)	5 (12%)	2 (4%)	2 (5%)
A Little	10 (21%)	9 (22%)	5 (10%)	6 (17%)	5 (10%)	4 (9%)	8 (16%)	6 (14%)
Not at All	28 (58%)	26 (63%)	27 (56%)	22 (61%)	27 (56%)	29 (67%)	25 (50%)	28 (67%)
Not Relevant	7 (15%)	4 (10%)	10 (21%)	3 (8%)	10 (21%)	4 (9%)	11 (22%)	6 (14%)
Missing	1	3	0	3	0	0	0	3
Question 10								
Very Much	2 (4%)	4 (10%)	1 (2%)	3 (8%)	3 (6%)	1 (2%)	2 (4%)	0
A Lot	6 (13%)	1 (2%)	6 (13%)	2 (6%)	7 (15%)	2 (5%)	5 (10%)	3 (7%)
A Little	18 (38%)	6 (15%)	14 (30%)	4 (11%)	5 (10%)	7 (16%)	20 (40%)	10 (24%)
Not at All	20 (42%)	26 (63%)	20 (43%)	23 (64%)	22 (46%)	30 (70%)	20 (40%)	27 (64%)
Not Relevant	2 (4%)	4 (10%)	6 (13%)	4 (11%)	11 (23%)	3 (7%)	3 (6%)	2 (5%)
Missing	1	3	1	3	0	0	0	3

Note: Week 12* refers to Week 12 or treatment discontinuation
All percentages have been calculated out of the number of patients with available data for that question
Patients 1802 and 1806 answered the second part of Question 7 when it was not applicable to them. However, their data has been included in the table

Appendix 3: special safety assessments from the Alitretinoin studies

The entire appendix 3 is commercial in confidence

Psychiatric disorders

Psychiatric disorders: BAP00089 study

The following tables and figures are from the BAP00089 Clinical Study Report – Efficacy and Safety of Alitretinoin in the Treatment of Severe Refractory Chronic Hand Dermatitis (Protocol BAP00089) / Report BAP00997 / 25 July 2007

Table 34 Patients with CES-D Total Score of ≥ 20 and a Change from Baseline ≥ 4 (Safety Population)

	Alitretinoin					
	10 mg		30 mg		Placebo	
Number of Patients in Safety Population	418		410		203	
Number of Patients with Available Observations	405	(96.9%)	406	(99.0%)	199	(98.0%)
Number of Patients with CES-D total score >=20 and a Change from Baseline >= 4 at any time During Active Treatment	33	(7.9%)	27	(6.6%)	12	(5.9%)

Note: Baseline is last available assessment before and including Baseline visit.

Appendix A 48 Summary of CES-D Questionnaire (Safety Population)

ALITRETINOIN 10 mg

	CES-D Total Score (N=418)				
	N	Mean	SD	Median	Minimum	Maximum
Raw score						
Pre-scre	6	4.7	4.18	5.5	0	11
Screening	384	6.0	5.89	4.0	0	38
Baseline	395	5.6	5.58	4.0	0	30
Week 4	371	5.6	5.48	4.0	0	38
Week 8	354	5.3	5.80	3.0	0	33
Week 12	303	4.5	5.08	3.0	0	25
Week 16	287	4.3	5.16	3.0	0	36
Week 20	274	4.6	6.02	3.0	0	36
Week 24	394	5.3	6.99	3.0	0	36
End of Therapy	405	5.4	6.98	3.0	0	36
Fu Week 4	222	4.9	6.37	3.0	0	41
Fu Week 8	6	5.2	2.93	5.5	2	9
Fu Week 16	2	0.0	0.00	0.0	0	0
Change from Baseline						
Week 4	368	-0.0	3.99	0.0	-16	23
Week 8	351	-0.2	4.66	0.0	-21	26
Week 12	301	-1.2	4.42	-1.0	-16	15
Week 16	284	-1.5	4.91	-1.0	-20	16
Week 20	271	-1.0	5.68	-1.0	-18	31
Week 24	391	-0.4	6.33	0.0	-22	33
End of Therapy	402	-0.4	6.27	0.0	-22	33
Fu Week 4	219	-0.9	6.55	0.0	-20	41
Fu Week 8	6	-5.2	9.52	-3.0	-23	4
Fu Week 16	2	-1.0	0.00	-1.0	-1	-1

Appendix A 48 (cont.) Summary of CES-D Questionnaire (Safety Population)

ALITRETINOIN 30 mg

	CES-D Total Score (N=410)				
	N	Mean	SD	Median	Minimum	Maximum
Raw score						
Pre-scre	4	2.8	3.10	2.0	0	7
Screening	384	6.4	6.27	5.0	0	38
Baseline	383	6.1	6.51	4.0	0	35
Week 4	363	6.0	6.13	4.0	0	38
Week 8	340	5.5	6.14	3.0	0	34
Week 12	240	5.3	5.91	4.0	0	36
Week 16	218	4.6	5.43	3.0	0	33
Week 20	209	4.8	5.95	3.0	0	36
Week 24	392	5.6	6.63	3.0	0	34
End of Therapy	406	5.7	6.82	3.0	0	36
Fu Week 4	256	5.3	6.79	3.0	0	33
Fu Week 8	10	7.3	6.96	5.0	0	17
Fu Week 16	1	34.0		34.0	34	34
Fu Week 24	1	15.0		15.0	15	15
Change from Baseline						
Week 4	358	-0.3	4.84	0.0	-29	15
Week 8	335	-0.7	5.39	0.0	-32	33
Week 12	236	-0.8	4.76	0.0	-29	12
Week 16	215	-1.5	5.14	-1.0	-32	12
Week 20	206	-1.2	5.29	0.0	-29	12
Week 24	386	-0.4	5.82	0.0	-35	24
End of Therapy	399	-0.4	5.79	0.0	-35	24
Fu Week 4	254	-0.9	5.93	0.0	-32	29
Fu Week 8	10	-2.4	11.36	0.0	-32	9
Fu Week 16	1	3.0		3.0	3	3
Fu Week 24	1	-16.0		-16.0	-16	-16

PLACEBO

	CES-D Total Score (N=203)				
	N	Mean	SD	Median	Minimum	Maximum
Raw score						
Pre-scre	1	24.0		24.0	24	24
Screening	191	6.1	5.70	5.0	0	31
Baseline	192	5.4	5.58	3.0	0	35
Week 4	178	5.4	5.88	3.0	0	35
Week 8	163	5.1	5.27	3.0	0	23
Week 12	145	4.9	5.34	3.0	0	30
Week 16	131	4.5	5.33	3.0	0	29
Week 20	130	4.1	5.30	3.0	0	33
Week 24	189	5.0	6.64	3.0	0	47
End of Therapy	199	5.2	6.71	3.0	0	47
Fu Week 4	112	4.7	5.72	3.0	0	27
Fu Week 8	4	4.0	5.48	2.0	0	12
Fu Week 16	1	1.0		1.0	1	1
Change from Baseline						
Week 4	178	0.0	5.01	0.0	-21	33
Week 8	163	-0.2	4.81	0.0	-17	18
Week 12	144	-0.5	5.26	0.0	-17	28
Week 16	130	-0.8	5.00	0.0	-17	27
Week 20	130	-1.0	5.61	0.0	-17	31
Week 24	188	-0.5	5.94	0.0	-17	24
End of Therapy	198	-0.4	5.90	0.0	-17	24
Fu Week 4	111	-1.0	5.46	0.0	-18	16
Fu Week 8	4	-3.5	4.73	-2.0	-10	0
Fu Week 16	1	-4.0		-4.0	-4	-4

Note: Baseline is last available assessment before and including Baseline visit.
End of Therapy is last available non-missing total score during treatment period, excluding unscheduled visits.

Appendix A 49 Summary of CES-D Highest Total Score (Safety Population)

	Alitretinoin		
	10 mg	30 mg	Placebo
Number of Patients in Safety Population	418	410	203
CES-D Higest Total Score at any on Treatment Post Baseline Assessment			
n	405	406	199
Mean	8.6	8.5	8.2
SD	7.95	7.63	7.51
Q1	3.0	3.0	3.0
Median	6.0	6.5	7.0
Q3	13.0	12.0	12.0
Minimum	0	0	0
Maximum	38	38	47

Note: Baseline is last available assessment before and including Baseline visit.

Appendix A 50 Analysis of Covariance of the Change from Baseline in CES-D Total Score (Safety Population)

	Alitretinoin		
	10 mg	30 mg	Placebo
Number of Patients in Safety Population	418	410	203
Change from Baseline in CES-D Total Score at End of Therapy			
n	402	399	198
Mean	-0.4	-0.4	-0.4
SD	6.27	5.79	5.90
Q1	-3.0	-3.0	-3.0
Median	0.0	0.0	0.0
Q3	1.0	2.0	1.0
Minimum	-22	-35	-17
Maximum	33	24	24
LSMeans	-0.48	-0.30	-0.61
95% CI	(-1.06, 0.10)	(-0.86, 0.25)	(-1.44, 0.22)
litretinoin Dose-Placebo			
Difference in LSMean	0.12	0.30	
95% CI	(-0.84, 1.09)	(-0.69, 1.29)	
p-value	0.802	0.552	

Note: Baseline is last available assessment before and including Baseline visit.
End of Therapy is last available non-missing total score during treatment period.
The analysis of covariance model includes treatment, CES-D total score at baseline and PGA response at end of therapy as covariates.

Psychiatric disorders: BAP00091 study

The following tables and figures are from the BAP00091 Clinical Study Report - Follow-Up Efficacy and Safety Study of BAL4079 in the Treatment of Chronic Hand Dermatitis Refractory to Topical Therapy (Protocol BAP00091) / Clinical Study Report BAP00998 / 30 July 2007

Table 30: Patients with CES-D Total Score of ≥ 20 and a Change from Baseline ≥ 4

	Cohort B Non Responder in BAP89	Cohort A Relapse in BAP89		
	30mg	10mg	30mg	Placebo
Number of Patients (Safety)	243	21	50	46
Number of Patients with Available Observations	243 (100.0%)	20 (95.2%)	49 (98.0%)	45 (97.8%)
Number of Patients with CES-D Total Score ≥20 and a Change from Baseline ≥ 4 at any time During Active Treatment	14 (5.8%)	0	4 (8.0%)	2 (4.3%)

Source: B91T55.sas 10may07
Note: Baseline is last available assessment before and including baseline visit.

Appendix A 32 Summary of CES-D Questionnaire (Safety Population)

Non Responder in BAP89 - Alitretinoin 30mg

	CES-D Total Score (N=243)					
	N	Mean	SD	Median	Minimum	Maximum
Raw score						
Screening	219	4.5	5.04	3.0	0	25
Baseline	166	4.0	4.72	3.0	0	31
Treatment Week4	227	4.3	5.05	3.0	0	26
Treatment Week8	223	4.4	5.38	3.0	0	32
Treatment Week12	184	4.2	5.01	3.0	0	24
Treatment Week16	181	4.0	5.12	3.0	0	27
Treatment Week20	170	4.1	4.84	3.0	0	22
Treatment Week24	238	4.6	6.07	3.0	0	31
End of Therapy	243	4.7	6.13	3.0	0	31
Follow Up Week 4	35	5.3	6.48	3.0	0	22
Change from Baseline						
Treatment Week4	227	-0.0	3.17	0.0	-11	15
Treatment Week8	223	0.1	3.24	0.0	-9	16
Treatment Week12	184	-0.3	3.03	0.0	-10	14
Treatment Week16	181	-0.4	3.08	0.0	-10	11
Treatment Week20	170	-0.5	3.42	0.0	-17	12
Treatment Week24	237	0.5	4.76	0.0	-12	22
End of Therapy	242	0.4	4.75	0.0	-12	22
Follow Up Week 4	35	-0.5	3.89	0.0	-11	8

Source Data: B91L37.1, B91L37.2 B91T54.sas 10MAY07
Note: Baseline is last available assessment before and including baseline visit.
End of Therapy is last available non-missing total score up to end of therapy, excluding unscheduled visits.

Appendix A32 (continued) Summary of CES-D Questionnaire (Safety Population)

Relapse in BAP89 - Alitretinoin 10mg

	CES-D Total Score (N=21)				
	N	Mean	SD	Median	Minimum	Maximum
Raw score						
Screening	18	4.5	4.50	3.5	0	16
Baseline	17	4.2	5.04	3.0	0	16
Treatment Week4	18	4.1	4.40	3.0	0	14
Treatment Week8	18	3.8	4.54	2.5	0	15
Treatment Week12	16	3.6	3.16	3.0	0	11
Treatment Week16	12	2.7	2.99	2.0	0	8
Treatment Week20	16	3.3	2.63	3.0	0	9
Treatment Week24	18	3.2	4.95	1.5	0	19
End of Therapy	20	3.2	4.70	2.0	0	19
Follow Up Week 4	1	3.0		3.0	3	3
Change from Baseline						
Treatment Week4	16	-0.7	2.15	-0.5	-3	3
Treatment Week8	16	-0.3	1.69	0.0	-3	3
Treatment Week12	14	-0.3	2.09	0.0	-3	5
Treatment Week16	10	-1.0	2.94	-1.5	-5	6
Treatment Week20	14	-0.6	2.21	0.0	-5	4
Treatment Week24	17	-0.5	2.76	0.0	-6	6
End of Therapy	18	-0.7	2.89	-0.5	-6	6
Follow Up Week 4	1	-1.0		-1.0	-1	-1

Appendix A32 (continued) Summary of CES-D Questionnaire (Safety Population)

Relapse in BAP89 - Alitretinoin 30mg

	CES-D Total Score (N=50)					
	N	Mean	SD	Median	Minimum	Maximum
Raw score						
Screening	45	5.0	5.78	3.0	0	24
Baseline	34	5.5	5.95	3.0	0	19
Treatment Week4	48	5.7	6.29	3.5	0	23
Treatment Week8	43	4.9	5.29	3.0	0	20
Treatment Week12	36	4.6	5.06	2.5	0	20
Treatment Week16	34	5.1	6.18	2.5	0	24
Treatment Week20	34	5.4	7.46	2.0	0	36
Treatment Week24	47	5.6	6.63	2.0	0	22
End of Therapy	49	5.7	6.51	4.0	0	22
Follow Up Week 4	10	3.4	4.12	2.0	0	12
Change from Baseline						
Treatment Week4	47	-0.6	4.98	0.0	-18	16
Treatment Week8	42	-1.2	5.07	0.0	-19	9
Treatment Week12	35	-1.2	4.78	0.0	-19	9
Treatment Week16	33	-0.5	5.67	0.0	-19	15
Treatment Week20	33	-0.8	5.61	0.0	-19	10
Treatment Week24	46	-0.7	4.39	0.0	-19	8
End of Therapy	48	-0.6	4.32	0.0	-19	8
Follow Up Week 4	10	-2.1	4.70	0.0	-12	2

Appendix A32 (continued) Summary of CES-D Questionnaire (Safety Population)

Relapse in BAP89 - Placebo

	CES-D Total Score (N=46)					
	N	Mean	SD	Median	Minimum	Maximum
Raw score						
Screening	43	4.7	4.26	4.0	0	17
Baseline	38	4.7	4.43	4.0	0	18
Treatment Week4	41	6.7	6.52	5.0	0	30
Treatment Week8	38	5.7	5.63	5.5	0	24
Treatment Week12	35	5.7	6.07	4.0	0	27
Treatment Week16	33	4.8	5.60	3.0	0	26
Treatment Week20	32	4.4	4.54	3.0	0	17
Treatment Week24	43	5.3	6.84	4.0	0	34
End of Therapy	45	5.4	6.86	4.0	0	34
Follow Up Week 4	10	3.5	4.12	2.0	0	12
Change from Baseline						
Treatment Week4	40	1.4	4.71	0.0	-7	18
Treatment Week8	37	0.2	3.59	0.0	-9	12
Treatment Week12	34	-0.1	4.75	0.0	-12	15
Treatment Week16	33	-0.8	3.70	0.0	-9	14
Treatment Week20	32	-1.2	3.66	0.0	-11	9
Treatment Week24	42	0.2	5.94	0.0	-12	22
End of Therapy	44	0.4	5.87	0.0	-12	22
Follow Up Week 4	10	-2.2	3.05	-1.0	-10	0

Appendix A 33 Patients with CES-D Total Score ≥20 and a Change from Baseline ≥4 (Safety Population)

	Non Responder in BAP89		Relapse in BAP89					
	Alitretinoin 30mg		Alitretinoin 10mg		Alitretinoin 30mg		Placebo	
Number of Patients in Safety Population	243		21		50		46	
Number of Patients with Available Observations	243	(100.0%)	20	(95.2%)	49	(98.0%)	45	(97.8%)
Number of Patients with CES-D Total Score >=20 and a Change from Baseline >= 4 at any time During Active Treatment	14	(5.8%)	0		4	(8.0%)	2	(4.3%)

Appendix A 34 Analysis of Covariance of the Change from Baseline in CES-D Total Score (Safety Population)

	Non Responder in BAP89	Relapse in BAP89		
	Alitretinoin 30mg	Alitretinoin 10mg	Alitretinoin 30mg	Placebo
Number of Patients in Safety Population	243	21	50	46
Change from Baseline in CES-D Total Score at End of Therapy				
n	242	18	48	44
Mean	0.4	-0.7	-0.6	0.4
SD	4.75	2.89	4.32	5.87
Q1	-1.0	-2.0	-2.0	-1.5
Median	0.0	-0.5	0.0	0.0
Q3	1.0	0.0	1.5	1.0
Minimum	-12	-6	-19	-12
Maximum	22	6	8	22
LSMeans		-0.88	-1.36	1.01
95% CI		(-3.03, 1.28)	(-2.82, 0.10)	(-0.45, 2.47)
Alitretinoin Dose-Placebo				
Difference in LSMean		-1.89	-2.37	
95% CI		(-4.47, 0.69)	(-4.58,-0.15)	
p-value		0.150	0.036	

Source Data: B91L37.1, B91L37.2 B91T57.sas 10MAY07
Note: Baseline is last available assessment before and including Baseline visit.
End of Therapy is last available non-missing total score during treatment period.
The analysis of covariance model includes treatment, CES-D total score at baseline and PGA response at end of therapy as covariates

Psychiatric disorders: BAP00200 study

The following table and figure are from the BAP00200 Clinical Study Report – Pharmacokinetics, efficacy and safety of alitretinoin in patients with severe or moderate chronic hand dermatitis refractory to topical therapy (Protocol BAP00200) / Report BAP00983 / 31 July 2007

Figure 18 **Maximum Change from Baseline against Maximum CES-D Total Score (Safety Population)**

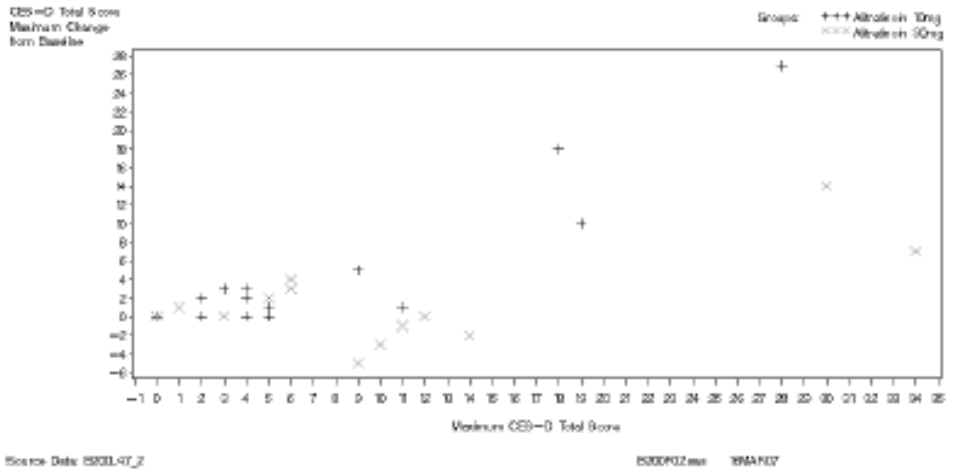

Table 30 Patients with CES-D Total Score ≥20 and a Change from Baseline ≥4 (Safety Population)

	Alitretinoin 10 mg		30 mg	
Number of Patients in Safety Population	16		16	
Number of Patients with Available Observations	15	(93.8%)	16	(100.0%)
Number of Patients with CES-D total score >=20 and a Change from Baseline >= 4 at any time During Active Treatment	1	(6.3%)	2	(12.5%)

Derived from source: B200T41.sas 16MAR07

Psychiatric disorders: BAP00626 study

The following table is from the BAP00626 Clinical Study Report – Safety and Efficacy of Alitretinoin in the Treatment of Severe Refractory Chronic Hand Dermatitis (Protocol BAP00626) / Report BAP01366 / 7 December 2007

Table 36 Patients with CES-D Total Score ≥20 and a change from baseline ≥4: Safety Population

	Alitretinoin 30mg	
Number of Patients in Safety Population	248	
Number of Patients with Available Observations	241	(97.2%)
Number of Patients with CES-D total score >=20 and a Change from Baseline >= 4	20	(8.1%)

Source: B626T55.sas 02OCT07
Note: Baseline is last available assessment before and including baseline visit.

Ophthalmologic examinations

Ophthalmologic examinations: BAP00089

Please see attached report "*Assessment of Ophthalmologic Findings after Oral Alitretinoin Therapy in Patients with Severe Refractory Chronic Hand Dermatitis - Protocol BAP00089: Efficacy and Safety of Alitretinoin in the Treatment of Severe Refractory Chronic Hand Dermatitis*" 20 July 2007.

Ophthalmologic examinations: BAP00091

The following tables and figures are from the BAP00091 Clinical Study Report - Follow-Up Efficacy and Safety Study of BAL4079 in the Treatment of Chronic Hand Dermatitis Refractory to Topical Therapy (Protocol BAP00091) / Clinical Study Report BAP00998 / 30 July 2007

Please also see Appendix A36 "Reports on special safety assessments" from the abovementioned Clinical Study Report for the report "*Assessment of Ophthalmologic Findings after Oral Alitretinoin Therapy in Patients with Severe Refractory Chronic Hand Dermatitis Protocol BAP00091: Follow-up Efficacy and Safety Study of BAL4079 in the Treatment of Chronic Hand Dermatitis Refractory to Topical Treatment*" 20 July 2007.

Appendix A 31 Summary of Ophthalmological Evaluations (Safety Population)
Visual Disturbances (Part 1)

	Non Responder in BAP89 Alitretinoin 30mg		Relapse in BAP89 Alitretinoin 10mg		Relapse in BAP89 Alitretinoin 30mg		Relapse in BAP89 Placebo	
Number of Patients in Safety Population	243		21		50		46	
Number of Patients with Ophthalmological Evaluations	13	(100.0%)	2	(100.0%)	6	(100.0%)	2	(100.0%)
Patients with an adverse change:								
Overall								
No	9	(69.2%)	0		6	(100.0%)	1	(50.0%)
Yes	1	(7.7%)	0		0		0	
Missing	3	(23.1%)	2	(100.0%)	0		1	(50.0%)
Vision Loss								
No	9	(69.2%)	0		6	(100.0%)	1	(50.0%)
Yes	1	(7.7%)	0		0		0	
Missing	3	(23.1%)	2	(100.0%)	0		1	(50.0%)
Decreased Night Vision								
No	9	(69.2%)	0		6	(100.0%)	1	(50.0%)
Yes	1	(7.7%)	0		0		0	
Missing	3	(23.1%)	2	(100.0%)	0		1	(50.0%)
Visual Obscuring								
No	8	(61.5%)	0		6	(100.0%)	1	(50.0%)
Yes	0		0		0		0	
Missing	5	(38.5%)	2	(100.0%)	0		1	(50.0%)
Other Visual Disturbances								
No	7	(53.8%)	0		5	(83.3%)	1	(50.0%)
Yes	0		0		0		0	
Missing	6	(46.2%)	2	(100.0%)	1	(16.7%)	1	(50.0%)

Source Data: B91L33_2 B91T58_01.sas 10MAY07
Note: An adverse change is defined as a change from normal at baseline to abnormal at EOT, for either or both eyes. A missing adverse change is defined as missing results at baseline and EOT, or missing result at baseline and abnormal at EOT, or normal at baseline and missing result at EOT, for both eyes. Other changes from baseline to EOT are considered as no adverse change.

Appendix A31 (continued) Summary of Ophthalmological Evaluations (Safety Population)
Visual Disturbances (Part 2)

	Non Responder in BAP89 Alitretinoin 30mg		Relapse in BAP89 Alitretinoin 10mg		Relapse in BAP89 Alitretinoin 30mg		Relapse in BAP89 Placebo	
Number of Patients in Safety Population	243		21		50		46	
Number of Patients with Ophthalmological Evaluations	13	(100.0%)	2	(100.0%)	6	(100.0%)	2	(100.0%)
Vision Loss at Baseline								
No	12	(92.3%)	2	(100.0%)	3	(50.0%)	2	(100.0%)
Yes	1	(7.7%)	0		3	(50.0%)	0	
Vision Loss at End of Therapy								
No	9	(69.2%)	0		3	(50.0%)	1	(50.0%)
Yes	1	(7.7%)	0		3	(50.0%)	0	
Missing	3	(23.1%)	2	(100.0%)	0		1	(50.0%)
Decreased Night Vision at Baseline								
No	13	(100.0%)	2	(100.0%)	4	(66.7%)	2	(100.0%)
Yes	0		0		2	(33.3%)	0	
Decreased Night Vision at End of Therapy								
No	9	(69.2%)	0		4	(66.7%)	1	(50.0%)
Yes	1	(7.7%)	0		2	(33.3%)	0	
Missing	3	(23.1%)	2	(100.0%)	0		1	(50.0%)
Visual Obscuring at Baseline								
No	12	(92.3%)	2	(100.0%)	3	(50.0%)	2	(100.0%)
Yes	0		0		3	(50.0%)	0	
Missing	1	(7.7%)	0		0		0	
Visual Obscuring at End of Therapy								
No	8	(61.5%)	0		3	(50.0%)	1	(50.0%)
Yes	0		0		2	(33.3%)	0	
Missing	5	(38.5%)	2	(100.0%)	1	(16.7%)	1	(50.0%)

Source Data: B91L33_2 B91T58_02.sas 10MAY07
Note: Each type of visual disturbance is counted once if it is reported for either or both eyes.

Appendix A31 (continued) Summary of Ophthalmological Evaluations (Safety Population)
Visual Disturbances (Part 2)

	Non Responder in BAP89 Alitretinoin 30mg		Relapse in BAP89 Alitretinoin 10mg		Relapse in BAP89 Alitretinoin 30mg		Relapse in BAP89 Placebo	
Other Visual Disturbances at Baseline								
No	9	(69.2%)	2	(100.0%)	5	(83.3%)	2	(100.0%)
Yes	1	(7.7%)	0		1	(16.7%)	0	
Missing	3	(23.1%)	0		0		0	
Other Visual Disturbances at End of Therapy								
No	6	(46.2%)	0		4	(66.7%)	1	(50.0%)
Yes	1	(7.7%)	0		1	(16.7%)	0	
Missing	6	(46.2%)	2	(100.0%)	1	(16.7%)	1	(50.0%)

Appendix A31 (continued) Summary of Ophthalmological Evaluations (Safety Population)
Refraction – End of Therapy compared to Baseline

	Non Responder in BAP89		Relapse in BAP89					
	Alitretinoin		Alitretinoin					
	30mg		10mg		30mg		Placebo	
Number of Patients in Safety Population	243		21		50		46	
Number of Patients with Ophthalmological Evaluations	13	(100.0%)	2	(100.0%)	6	(100.0%)	2	(100.0%)
Refraction								
No change	1	(7.7%)	0		2	(33.3%)	1	(50.0%)
Minor change	4	(30.8%)	1	(50.0%)	1	(16.7%)	0	
Major change	1	(7.7%)	0		1	(16.7%)	0	
Missing	7	(53.8%)	1	(50.0%)	2	(33.3%)	1	(50.0%)

Source Data: B91L33_2 B91T58_03.sas 10MAY07
For refraction, a change in absolute value <0.5 diopter is counted as no change, a change in absolute value 0.5 to 1 diopter change Is counted as minor, and a change in absolute value >1 diopter is counted as a major change. The largest change in absolute value (any plane in either eye) is counted in the summary.

Appendix A31 (continued) Summary of Ophthalmological Evaluations (Safety Population)
Peripheral Visual Field

	Non Responder in BAP89		Relapse in BAP89					
	Alitretinoin		Alitretinoin					
	30mg		10mg		30mg		Placebo	
Number of Patients in Safety Population	243		21		50		46	
Number of Patients with Ophthalmological Evaluations	13	(100.0%)	2	(100.0%)	6	(100.0%)	2	(100.0%)
Patients with an adverse change								
No	9	(69.2%)	2	(100.0%)	5	(83.3%)	1	(50.0%)
Yes	1	(7.7%)	0		0		0	
Missing	3	(23.1%)	0		1	(16.7%)	1	(50.0%)
Peripheral visual field at baseline								
Normal	11	(84.6%)	2	(100.0%)	6	(100.0%)	1	(50.0%)
Abnormal	2	(15.4%)	0		0		1	(50.0%)
Peripheral visual field at end of therapy								
Normal	8	(61.5%)	2	(100.0%)	5	(83.3%)	1	(50.0%)
Abnormal	2	(15.4%)	0		0		0	
Missing	3	(23.1%)	0		1	(16.7%)	1	(50.0%)

Source Data: B91L33_2 B91T58_04.sas 10MAY07
Note: An adverse change is defined as a change from normal at baseline to abnormal at EOT, for either or both eyes. A missing adverse change is defined as missing results at baseline and EOT, or missing result at baseline and abnormal at EOT, or normal at baseline and missing result at EOT, for both eyes. Other changes from baseline to EOT are considered as no adverse change.
An abnormality is counted once in this summary if it is reported in either or both eyes.

Appendix A31 (continued) Summary of Ophthalmological Evaluations (Safety Population)
Ocular Motility

	Non Responder in BAP89 Alitretinoin 30mg		Relapse in BAP89 Alitretinoin 10mg		Relapse in BAP89 Alitretinoin 30mg		Relapse in BAP89 Placebo	
Number of Patients in Safety Population	243		21		50		46	
Number of Patients with Ophthalmological Evaluations	13	(100.0%)	2	(100.0%)	6	(100.0%)	2	(100.0%)
Patients with an adverse change								
No	10	(76.9%)	2	(100.0%)	6	(100.0%)	1	(50.0%)
Yes	0		0		0		0	
Missing	3	(23.1%)	0		0		1	(50.0%)
Ocular Motility at baseline								
Normal	13	(100.0%)	2	(100.0%)	5	(83.3%)	2	(100.0%)
Abnormal	0		0		1	(16.7%)	0	
Ocular Motility at end of therapy								
Normal	10	(76.9%)	2	(100.0%)	5	(83.3%)	1	(50.0%)
Abnormal	0		0		1	(16.7%)	0	
Missing	3	(23.1%)	0		0		1	(50.0%)

Source Data: B91L33_2 B91T58_05.sas 10MAY07
Note: An adverse change is defined as a change from normal at baseline to abnormal at EOT, for either or both eyes. A missing adverse change is defined as missing results at baseline and EOT, or missing result at baseline and abnormal at EOT, or normal at baseline and missing result at EOT, for both eyes. Other changes from baseline to EOT are considered as no adverse change.
An abnormality is counted once in this summary if it is reported in either or both eyes.

Appendix A31 (continued) Summary of Ophthalmological Evaluations (Safety Population)
Anterior Segment (Part 1)

	Non Responder in BAP89 Alitretinoin 30mg		Relapse in BAP89 Alitretinoin 10mg		Relapse in BAP89 Alitretinoin 30mg		Relapse in BAP89 Placebo	
Number of Patients in Safety Population	243		21		50		46	
Number of Patients with Ophthalmological Evaluations	13	(100.0%)	2	(100.0%)	6	(100.0%)	2	(100.0%)
Patients with an adverse change:								
Overall								
No	9	(69.2%)	2	(100.0%)	4	(66.7%)	1	(50.0%)
Yes	1	(7.7%)	0		2	(33.3%)	1	(50.0%)
Missing	3	(23.1%)	0		0		0	
Lid Margin								
No	10	(76.9%)	2	(100.0%)	5	(83.3%)	1	(50.0%)
Yes	0		0		1	(16.7%)	0	
Missing	3	(23.1%)	0		0		1	(50.0%)
Conjunctiva								
No	10	(76.9%)	2	(100.0%)	5	(83.3%)	0	
Yes	0		0		1	(16.7%)	1	(50.0%)
Missing	3	(23.1%)	0		0		1	(50.0%)
Cornea								
No	10	(76.9%)	2	(100.0%)	6	(100.0%)	1	(50.0%)
Yes	0		0		0		0	
Missing	3	(23.1%)	0		0		1	(50.0%)
Anterior Chamber								
No	10	(76.9%)	2	(100.0%)	6	(100.0%)	1	(50.0%)
Yes	0		0		0		0	
Missing	3	(23.1%)	0		0		1	(50.0%)

Source Data: B91L33_2 B91T58_06.sas 10MAY07
Note: An adverse change is defined as a change from normal at baseline to abnormal at EOT, for either or both eyes. A missing adverse change is defined as missing results at baseline and EOT, or missing result at baseline and abnormal at EOT, or normal at baseline and missing result at EOT, for both eyes. Other changes from baseline to EOT are considered as no adverse change.

Appendix A31 (continued) Summary of Ophthalmological Evaluations (Safety Population)
Anterior Segment (Part 1)

	Non Responder in BAP89		Relapse in BAP89					
	Alitretinoin		Alitretinoin					
	30mg		10mg		30mg		Placebo	
Iris								
No	10	(76.9%)	2	(100.0%)	6	(100.0%)	1	(50.0%)
Yes	0		0		0		0	
Missing	3	(23.1%)	0		0		1	(50.0%)
Lens								
No	9	(69.2%)	2	(100.0%)	5	(83.3%)	2	(100.0%)
Yes	1	(7.7%)	0		1	(16.7%)	0	
Missing	3	(23.1%)	0		0		0	
Dry Eyes Symptoms								
No	10	(76.9%)	2	(100.0%)	4	(66.7%)	0	
Yes	0		0		2	(33.3%)	1	(50.0%)
Missing	3	(23.1%)	0		0		1	(50.0%)
Ocular Discomfort								
No	10	(76.9%)	2	(100.0%)	5	(83.3%)	1	(50.0%)
Yes	0		0		1	(16.7%)	0	
Missing	3	(23.1%)	0		0		1	(50.0%)

Source Data: B91L33_2 B91T58_06.sas 10MAY07
Note: An adverse change is defined as a change from normal at baseline to abnormal at EOT, for either or both eyes. A missing adverse change is defined as missing results at baseline and EOT, or missing result at baseline and abnormal at EOT, or normal at baseline and missing result at EOT, for both eyes. Other changes from baseline to EOT are considered as no adverse change.

Appendix A31 (continued) Summary of Ophthalmological Evaluations (Safety Population)
Anterior Segment (Part 2)

	Non Responder in BAP89		Relapse in BAP89					
	Alitretinoin		Alitretinoin					
	30mg		10mg		30mg		Placebo	
Number of Patients in Safety Population	243		21		50		46	
Number of Patients with Ophthalmological Evaluations	13	(100.0%)	2	(100.0%)	6	(100.0%)	2	(100.0%)
Lid Margin at Baseline								
Normal	12	(92.3%)	2	(100.0%)	6	(100.0%)	2	(100.0%)
Abnormal	1	(7.7%)	0		0		0	
Lid Margin at End of Therapy								
Normal	9	(69.2%)	2	(100.0%)	5	(83.3%)	1	(50.0%)
Abnormal	1	(7.7%)	0		1	(16.7%)	0	
Missing	3	(23.1%)	0		0		1	(50.0%)
Conjunctiva at Baseline								
Normal	12	(92.3%)	2	(100.0%)	6	(100.0%)	2	(100.0%)
Abnormal	1	(7.7%)	0		0		0	
Conjunctiva at End of Therapy								
Normal	9	(69.2%)	2	(100.0%)	5	(83.3%)	0	
Abnormal	1	(7.7%)	0		1	(16.7%)	1	(50.0%)
Missing	3	(23.1%)	0		0		1	(50.0%)
Cornea at Baseline								
Normal	9	(69.2%)	1	(50.0%)	6	(100.0%)	2	(100.0%)
Abnormal	4	(30.8%)	1	(50.0%)	0		0	
Cornea at End of Therapy								
Normal	6	(46.2%)	2	(100.0%)	6	(100.0%)	1	(50.0%)
Abnormal	4	(30.8%)	0		0		0	
Missing	3	(23.1%)	0		0		1	(50.0%)

Source Data: B91L33_2 B91T58_07.sas 10MAY07
Note: An abnormality is counted once in this summary if it is reported for either or both eyes.

Appendix A31 (continued) Summary of Ophthalmological Evaluations (Safety Population)
Anterior Segment (Part 2)

	Non Responder in BAP89		Relapse in BAP89					
	Alitretinoin		Alitretinoin					
	30mg		10mg		30mg		Placebo	
Anterior Chamber at Baseline								
Normal	13	(100.0%)	2	(100.0%)	6	(100.0%)	2	(100.0%)
Abnormal	0		0		0		0	
Anterior Chamber at End of Therapy								
Normal	10	(76.9%)	2	(100.0%)	6	(100.0%)	1	(50.0%)
Abnormal	0		0		0		0	
Missing	3	(23.1%)	0		0		1	(50.0%)
Iris at Baseline								
Normal	12	(92.3%)	2	(100.0%)	6	(100.0%)	2	(100.0%)
Abnormal	1	(7.7%)	0		0		0	
Iris at End of Therapy								
Normal	9	(69.2%)	2	(100.0%)	6	(100.0%)	1	(50.0%)
Abnormal	1	(7.7%)	0		0		0	
Missing	3	(23.1%)	0		0		1	(50.0%)
Lens at Baseline								
Normal	10	(76.9%)	1	(50.0%)	3	(50.0%)	1	(50.0%)
Abnormal	3	(23.1%)	1	(50.0%)	3	(50.0%)	1	(50.0%)
Lens at End of Therapy								
Normal	6	(46.2%)	1	(50.0%)	2	(33.3%)	1	(50.0%)
Abnormal	4	(30.8%)	1	(50.0%)	4	(66.7%)	0	
Missing	3	(23.1%)	0		0		1	(50.0%)
Dry Eyes Symptoms at Baseline								
Normal	11	(84.6%)	1	(50.0%)	3	(50.0%)	2	(100.0%)
Abnormal	2	(15.4%)	1	(50.0%)	3	(50.0%)	0	

Source Data: B91L33_2 B91T58_07.sas 10MAY07
Note: An abnormality is counted once in this summary if it is reported for either or both eyes.

Appendix A31 (continued) Summary of Ophthalmological Evaluations (Safety Population)
Anterior Segment (Part 2)

	Non Responder in BAP89		Relapse in BAP89					
	Alitretinoin		Alitretinoin					
	30mg		10mg		30mg		Placebo	
Dry Eyes Symptoms at End of Therapy								
Normal	8	(61.5%)	2	(100.0%)	1	(16.7%)	0	
Abnormal	2	(15.4%)	0		5	(83.3%)	1	(50.0%)
Missing	3	(23.1%)	0		0		1	(50.0%)
Ocular Discomfort at Baseline								
Normal	12	(92.3%)	2	(100.0%)	4	(66.7%)	2	(100.0%)
Abnormal	1	(7.7%)	0		2	(33.3%)	0	
Ocular Discomfort at End of Therapy								
Normal	9	(69.2%)	2	(100.0%)	3	(50.0%)	1	(50.0%)
Abnormal	1	(7.7%)	0		3	(50.0%)	0	
Missing	3	(23.1%)	0		0		1	(50.0%)

Source Data: B91L33_2 B91T58_07.sas 10MAY07
Note: An abnormality is counted once in this summary if it is reported for either or both eyes.

Appendix A31 (continued) Summary of Ophthalmological Evaluations (Safety Population)
Fundoscopy (Part 1)

	Non Responder in BAP89		Relapse in BAP89					
	Alitretinoin 30mg		Alitretinoin 10mg		Alitretinoin 30mg		Placebo	
Number of Patients in Safety Population	243		21		50		46	
Number of Patients with Ophthalmological Evaluations	13	(100.0%)	2	(100.0%)	6	(100.0%)	2	(100.0%)
Patients with an adverse change:								
Overall								
No	9	(69.2%)	2	(100.0%)	6	(100.0%)	1	(50.0%)
Yes	1	(7.7%)	0		0		0	
Missing	3	(23.1%)	0		0		1	(50.0%)
Optic disc								
No	9	(69.2%)	2	(100.0%)	6	(100.0%)	1	(50.0%)
Yes	1	(7.7%)	0		0		0	
Missing	3	(23.1%)	0		0		1	(50.0%)
Macula								
No	10	(76.9%)	2	(100.0%)	6	(100.0%)	1	(50.0%)
Yes	0		0		0		0	
Missing	3	(23.1%)	0		0		1	(50.0%)
Retinal Periphery								
No	10	(76.9%)	2	(100.0%)	6	(100.0%)	1	(50.0%)
Yes	0		0		0		0	
Missing	3	(23.1%)	0		0		1	(50.0%)

Source Data: B91L83_2 B91T58_08.sas 10MAY07
Note: An adverse change is defined as a change from normal at baseline to abnormal at EOT, for either or both eyes. A missing adverse change is defined as missing results at baseline and EOT, or missing result at baseline and abnormal at EOT, or normal at baseline and missing result at EOT, for both eyes. Other changes from baseline to EOT are considered as no adverse change.

Appendix A31 (continued) Summary of Ophthalmological Evaluations (Safety Population)
Fundoscopy (Part 2)

	Non Responder in BAP89		Relapse in BAP89					
	Alitretinoin 30mg		Alitretinoin 10mg		Alitretinoin 30mg		Placebo	
Number of Patients in Safety Population	243		21		50		46	
Number of Patients with Ophthalmological Evaluations	13	(100.0%)	2	(100.0%)	6	(100.0%)	2	(100.0%)
Optic disc at Baseline								
Normal	12	(92.3%)	1	(50.0%)	4	(66.7%)	2	(100.0%)
Abnormal	1	(7.7%)	1	(50.0%)	2	(33.3%)	0	
Optic disc at End of Therapy								
Normal	9	(69.2%)	1	(50.0%)	4	(66.7%)	1	(50.0%)
Abnormal	1	(7.7%)	1	(50.0%)	2	(33.3%)	0	
Missing	3	(23.1%)	0		0		1	(50.0%)
Macula at Baseline								
Normal	11	(84.6%)	2	(100.0%)	5	(83.3%)	2	(100.0%)
Abnormal	2	(15.4%)	0		1	(16.7%)	0	
Macula at End of Therapy								
Normal	8	(61.5%)	2	(100.0%)	5	(83.3%)	1	(50.0%)
Abnormal	2	(15.4%)	0		1	(16.7%)	0	
Missing	3	(23.1%)	0		0		1	(50.0%)
Retinal Periphery at Baseline								
Normal	11	(84.6%)	2	(100.0%)	6	(100.0%)	2	(100.0%)
Abnormal	2	(15.4%)	0		0		0	
Retinal Periphery at End of Therapy								
Normal	9	(69.2%)	2	(100.0%)	6	(100.0%)	1	(50.0%)
Abnormal	1	(7.7%)	0		0		0	
Missing	3	(23.1%)	0		0		1	(50.0%)

Source Data: B91L83_2 B91T58_09.sas 10MAY07
Note: An abnormality is counted once in this summary if it is reported for either or both eyes.

Ophthalmologic examinations: BAP00200

Please see the attached Appendix A17 from the BAP00200 Clinical Study Report – Pharmacokinetics, efficacy and safety of alitretinoin in patients with severe or moderate chronic hand dermatitis refractory to topical therapy (Protocol BAP00200) / Report BAP00983 / 31 July 2007 for the report "*Assessment of Ophthalmologic Findings after Oral Alitretinoin Therapy in Patients with Severe Refractory Chronic Hand Dermatitis - Protocol BAP00200: Pharmacokinetics, Efficacy and Safety Study of BAL4079 in Patients with Severe or Moderate Chronic Hand Dermatitis refractory to Topical Therapy*" 20 July 2007

Skeletal abnormalities

Skeletal abnormalities: BAP00089 study

Please see attached report "*Assessment of Skeletal Radiographs after Oral Alitretinoin Therapy in Patients with Severe Refractory Chronic Hand Dermatitis - Protocol BAP00089 : Efficacy and Safety of Alitretinoin in the Treatment of Severe Refractory Chronic Hand Dermatitis*". 10 July 2007.

Please also see attached report "*Assessment of Bone Mineral Density by DXA after Oral Alitretinoin Therapy in Patients with Severe Refractory Chronic Hand Dermatitis - Protocol BAP00089: Efficacy and Safety of Alitretinoin in the Treatment of Severe Refractory Chronic Hand Dermatitis*". 10 July 2007.

Skeletal abnormalities: BAP00091 study

The following table is from the BAP00091 Clinical Study Report - Follow-Up Efficacy and Safety Study of BAL4079 in the Treatment of Chronic Hand Dermatitis Refractory to Topical Therapy (Protocol BAP00091) / Clinical Study Report BAP00998 / 30 July 2007

Table 29: Summary of Overall Change from Baseline for X-Ray Evaluations

	Cohort B Non Responder in BAP89 30mg	Cohort A Relapse in BAP89 10mg	30mg	Placebo
Number of Patients (Safety)	243	21	50	46
Number of Patients with X-ray evaluations	8 (100.0%)	1 (100.0%)	5 (100.0%)	2 (100.0%)
End of Treatment				
No change	8 (100.0%)	1 (100.0%)	5 (100.0%)	2 (100.0%)
Progression	0	0	0	0
Improvement	0	0	0	0
Unable to assess	0	0	0	0

Source: B91T59_7.sas 10may07

Please also see Appendix A36 "Reports on special safety assessments" from the abovementioned Clinical Study Report for the report "*Assessment of Skeletal Radiographs after Oral Alitretinoin Therapy in Patients with Severe Refractory Chronic Hand Dermatitis - Protocol BAP00091: Follow-up Efficacy and Safety Study of BAL4079 in the Treatment of Chronic Hand Dermatitis Refractory to Topical Treatment*" 10 July 2007

Please also see Appendix A36 "Reports on special safety assessments" from the abovementioned Clinical Study Report for the report "*Assessment of Bone Mineral Density by DXA after Oral Alitretinoin Therapy in Patients with Severe Refractory Chronic Hand Dermatitis - Protocol BAP00091: Follow-up Efficacy and Safety Study of BAL4079 in the Treatment of Chronic Hand Dermatitis Refractory to Topical Treatment*" 17 July 2007

Skeletal abnormalities: BAP00626 study

The following tables and figures are from the BAP00626 Clinical Study Report – Safety and Efficacy of Alitretinoin in the Treatment of Severe Refractory Chronic Hand Dermatitis (Protocol BAP00626) / Report BAP01366 / 7 December 2007

Table 37 X-ray Evaluations - Spine - Number of Patients with a Change in Grade from Baseline (by Worst Change): Safety Population

	Alitretinoin 30mg	
Number of Patients in Safety Population	248	
Number of Patients with X-ray evaluations	9	(100.0%)
End of Treatment		
Spondylosis		
No deterioration	8	(88.9%)
+1 grade	1	(11.1%)
+2 grades	0	
+3 grades	0	
Missing	0	
Syndesmophytes		
No deterioration	8	(88.9%)
+1 grade	1	(11.1%)
+2 grades	0	
+3 grades	0	
Missing	0	

Source: B626T57_4.sas 02OCT07
Note: The worst change in grade is tabulated.

Table 38 Summary of Decreases from Baseline in Bone Mineral Density (DXA Evaluations) – BMD: Safety Population

	Overall		Alitretinoin 30mg End of Treatment Male and Female <=45 years		Female >45 years	
Number of patients in the Safety Population	248		166		82	
Lumbar Spine						
N	3	(100.0%)	1	(100.0%)	2	(100.0%)
No decrease	1	(33.3%)	0		1	(50.0%)
Decrease of]0%-2%]	0		0		0	
Decrease of]2%-5%[	1	(33.3%)	0		1	(50.0%)
Decrease >=5%	0		0		0	
Missing	1	(33.3%)	1	(100.0%)	0	
Femur						
N	3	(100.0%)	1	(100.0%)	2	(100.0%)
No decrease	2	(66.7%)	0		2	(100.0%)
Decrease of]0%-2%]	0		0		0	
Decrease of]2%-5%[	0		0		0	
Decrease >=5%	0		0		0	
Missing	1	(33.3%)	1	(100.0%)	0	

Source: B626T58_2.sas 02OCT07

Appendix A 31 X-ray Evaluations - Technical Adequacy of Images: Safety Population

		Alitretinoin 30mg
Number of Patients in Safety Population	248	
Number of Patients with X-ray evaluations	9	(100.0%)
Baseline		
Lateral C-Spine		
Optimal	7	(77.8%)
Readable, but not optimal	2	(22.2%)
Not readable	0	
Lateral T-Spine		
Optimal	3	(33.3%)
Readable, but not optimal	6	(66.7%)
Not readable	0	
Calcaneus		
Optimal	9	(100.0%)
Readable, but not optimal	0	
Not readable	0	
End of Treatment		
Lateral C-Spine		
Optimal	7	(77.8%)
Readable, but not optimal	2	(22.2%)
Not readable	0	
Lateral T-Spine		
Optimal	5	(55.6%)
Readable, but not optimal	4	(44.4%)
Not readable	0	
Calcaneus		
Optimal	9	(100.0%)
Readable, but not optimal	0	
Not readable	0	

Source: B626T57_1.sas 02OCT07
Note: The worst case reading is used.

Appendix A 32 Summary of Bone Mineral Density (DXA Evaluations, BMD): Safety Population

	Alitretinoin 30mg	
	Baseline	EOT
Number of Patients in Safety Population	248	248
Raw Score		
Lumbar Spine		
n	3	2
Mean	1.16	1.13
SD	0.116	0.191
Q1	1.03	0.99
Median	1.21	1.13
Q3	1.25	1.26
Minimum	1.0	1.0
Maximum	1.3	1.3
Femur		
n	3	2
Mean	1.06	1.12
SD	0.068	0.037
Q1	0.97	1.10
Median	1.08	1.12
Q3	1.14	1.15
Minimum	1.0	1.1
Maximum	1.1	1.2
Change from Baseline		
Lumbar Spine		
n		2
Mean		-0.01
SD		0.035
Q1		-0.04
Median		-0.01
Q3		0.01
Minimum		-0.0
Maximum		0.0
Femur		
n		2
Mean		0.01
SD		0.003
Q1		0.01
Median		0.01
Q3		0.02
Minimum		0.0
Maximum		0.0
Percentage Change from Baseline		
Lumbar Spine		
n		2
Mean		-1.35
SD		3.323
Q1		-3.70
Median		-1.35
Q3		1.00
Minimum		-3.7
Maximum		1.0
Femur		
n		2
Mean		1.30
SD		0.283
Q1		1.10
Median		1.30
Q3		1.50
Minimum		1.1
Maximum		1.5

Source: B626T58_1.sas 02OCT07

Appendix 4 : Patient withdrawals from study BAP00089 and BAP00091 studies

Table 4 **Reasons for Premature Withdrawal from Treatment and Follow-up (ITT Population)**

Patients	Alitretinoin				Placebo	
	10 mg		30 mg			
	n	%	n	%	n	%
Enrolled	418	100	409	100	205	100
Withdrawn from treatment	99	23.7	106	25.9	68	33.2
Insufficient response	35	8.4	32	7.8	42	20.5
Adverse events / intercurrent illness	24	5.7	39	9.5	11	5.4
Refused treatment / lack of cooperation	24	5.7	16	3.9	12	5.9
Failure to return	6	1.4	8	2.0	0	0
Administrative reasons	5	1.2	3	0.7	1	0.5
Early improvement	2	0.5	3	0.7	0	0
Withdrawn from follow-up	27	23.5	54	27.7	7	20.6
Administrative reasons	16	13.9	40	20.5	5	14.7
Failure to return	11	9.6	14	7.2	2	5.9

Table 29 summarizes the AEs leading to treatment discontinuation. Overall, 71 (6.9%) patients reported 105 AEs that led to treatment discontinuation. The frequency of treatment-emergent AEs leading to treatment discontinuation was higher in the alitretinoin 30 mg group than the alitretinoin 10 mg group. The most frequent treatment-emergent AEs leading to treatment discontinuation, i.e., those occurring in at least 5 patients overall, were headache, various skin and subcutaneous tissue disorders, and depression.

One patient was withdrawn from study treatment because of pregnancy (see also 0 and patient narrative in Appendix A 43).

Table 29 **Summary of Treatment-Emergent Adverse Events Leading to Treatment Discontinuation (Safety Population)**

	Alitretinoin				Placebo	
	10 mg		30 mg			
Number of Patients in Safety Population	418	(100.0%)	410	(100.0%)	203	(100.0%)
ALL BODY SYSTEMS						
Number of Patients Reporting at Least One Treatment Emergent Adverse Event	22	(5.3%)	38	(9.3%)	11	(5.4%)
Total Number of Treatment Emergent Adverse Events	36		57		12	
NERVOUS SYSTEM DISORDERS						
Number of Patients Reporting at Least One Treatment Emergent Adverse Event	7	(1.7%)	18	(4.4%)	1	(0.5%)
HEADACHE	6	(1.4%)	17	(4.1%)	1	(0.5%)
DIZZINESS	0		1	(0.2%)	0	
DYSGEUSIA	0		1	(0.2%)	0	
ISCHEMIC STROKE	1	(0.2%)	0		0	
PARAESTHESIA	0		1	(0.2%)	0	
Total Number of Treatment Emergent AEs	7		20		1	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS						
Number of Patients Reporting at Least One Treatment Emergent Adverse Event	6	(1.4%)	8	(2.0%)	4	(2.0%)
ECZEMA	2	(0.5%)	1	(0.2%)	1	(0.5%)
DERMATITIS	0		1	(0.2%)	1	(0.5%)
DERMATITIS CONTACT	0		2	(0.5%)	0	
URTICARIA	1	(0.2%)	1	(0.2%)	0	
DERMATITIS ATOPIC	1	(0.2%)	0		0	
DERMATITIS EXFOLIATIVE	1	(0.2%)	0		0	
ECZEMA NUMMULAR	1	(0.2%)	0		0	
ERYTHEMA	0		1	(0.2%)	0	
PHOTOSENSITIVITY REACTION	0		0		1	(0.5%)
PSORIASIS	0		0		1	(0.5%)
RASH	0		1	(0.2%)	0	
SKIN ULCER	0		1	(0.2%)	0	
Total No. of Treatment Emergent AEs	6		8		4	
GASTROINTESTINAL DISORDERS						
Number of Patients Reporting at Least One Treatment Emergent Adverse Event	4	(1.0%)	2	(0.5%)	1	(0.5%)
NAUSEA	2	(0.5%)	1	(0.2%)	0	
ABDOMINAL PAIN UPPER	1	(0.2%)	0		0	
DRY MOUTH	1	(0.2%)	0		0	
GASTROINTESTINAL DISORDER	0		1	(0.2%)	0	
PANCREATITIS ACUTE	0		0		1	(0.5%)
VOMITING	1	(0.2%)	0		0	
Total No. of Treatment Emergent AEs	5		2		1	

Table 29 (cont.) **Summary of Treatment-Emergent Adverse Events Leading to Treatment Discontinuation (Safety Population)**

	Alitretinoin 10 mg		Alitretinoin 30 mg		Placebo	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
Number of Patients Reporting at Least One Treatment Emergent Adverse Event	1	(0.2%)	5	(1.2%)	0	
FATIGUE	0		2	(0.5%)	0	
IRRITABILITY	1	(0.2%)	1	(0.2%)	0	
ASTHENIA	0		1	(0.2%)	0	
DISEASE PROGRESSION	0		1	(0.2%)	0	
FACE OEDEMA	0		1	(0.2%)	0	
Total Number of Treatment Emergent Adverse Events	1		6		0	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS						
Number of Patients Reporting at Least One Treatment Emergent Adverse Event	2	(0.5%)	3	(0.7%)	1	(0.5%)
MUSCULOSKELETAL PAIN	1	(0.2%)	1	(0.2%)	0	
ANKYLOSING SPONDYLITIS	0		1	(0.2%)	0	
BACK PAIN	0		1	(0.2%)	0	
PAIN IN EXTREMITY	0		0		1	(0.5%)
POLYMYALGIA	1	(0.2%)	0		0	
Total Number of Treatment Emergent Adverse Events	2		3		1	
PSYCHIATRIC DISORDERS						
Number of Patients Reporting at Least One Treatment Emergent Adverse Event	3	(0.7%)	2	(0.5%)	1	(0.5%)
DEPRESSION	3	(0.7%)	2	(0.5%)	1	(0.5%)
Total Number of Treatment Emergent Adverse Events	3		2		1	
VASCULAR DISORDERS						
Number of Patients Reporting at Least One Treatment Emergent Adverse Event	1	(0.2%)	3	(0.7%)	2	(1.0%)
FLUSHING	1	(0.2%)	2	(0.5%)	0	
HOT FLUSH	0		1	(0.2%)	0	
HYPERTENSIVE CRISIS	0		0		1	(0.5%)
PHLEBITIS	0		0		1	(0.5%)
Total Number of Treatment Emergent Adverse Events	1		3		2	
INFECTIONS AND INFESTATIONS						
Number of Patients Reporting at Least One Treatment Emergent Adverse Event	2	(0.5%)	3	(0.7%)	0	
ABSCESS LIMB	1	(0.2%)	0		0	
BRONCHITIS ACUTE	1	(0.2%)	0		0	
GASTROENTERITIS	0		1	(0.2%)	0	
PNEUMONIA	0		1	(0.2%)	0	
VULVOVAGINAL MYCOTIC INFECTION	0		1	(0.2%)	0	
Total Number of Treatment Emergent Adverse Events	2		3		0	
INVESTIGATIONS						
Number of Patients Reporting at Least One Treatment Emergent Adverse Event	2	(0.5%)	2	(0.5%)	1	(0.5%)
BLOOD CREATINE PHOSPHOKINASE INCREASED	0		1	(0.2%)	1	(0.5%)
BLOOD CHOLESTEROL INCREASED	0		1	(0.2%)	0	
BLOOD CREATININE INCREASED	1	(0.2%)	0		0	
BLOOD PRESSURE INCREASED	1	(0.2%)	0		0	
BLOOD TRIGLYCERIDES INCREASED	0		1	(0.2%)	0	
Total Number of Treatment Emergent Adverse Events	2		3		1	

Table 29 (cont.) Summary of Treatment-Emergent Adverse Events Leading to Treatment Discontinuation (Safety Population)

	Alitretinoin 10 mg		Alitretinoin 30 mg		Placebo	
EYE DISORDERS						
Number of Patients Reporting at Least One Treatment Emergent Adverse Event	2	(0.5%)	2	(0.5%)	0	
ABNORMAL SENSATION IN EYE	0		1	(0.2%)	0	
DRY EYE	1	(0.2%)	0		0	
VISION BLURRED	0		1	(0.2%)	0	
XEROPHTHALMIA	1	(0.2%)	0		0	
Total Number of Treatment Emergent Adverse Events	2		2		0	
METABOLISM AND NUTRITION DISORDERS						
Number of Patients Reporting at Least One Treatment Emergent Adverse Event	1	(0.2%)	3	(0.7%)	0	
DECREASED APPETITE	0		2	(0.5%)	0	
HYPERTRIGLYCERIDAEMIA	0		1	(0.2%)	0	
INCREASED APPETITE	1	(0.2%)	0		0	
OVERWEIGHT	0		1	(0.2%)	0	
Total Number of Treatment Emergent Adverse Events	1		4		0	
CARDIAC DISORDERS						
Number of Patients Reporting at Least One Treatment Emergent Adverse Event	2	(0.5%)	0		0	
MYOCARDIAL INFARCTION	1	(0.2%)	0		0	
PALPITATIONS	1	(0.2%)	0		0	
Total Number of Treatment Emergent Adverse Events	2		0		0	
EAR AND LABYRINTH DISORDERS						
Number of Patients Reporting at Least One Treatment Emergent Adverse Event	2	(0.5%)	0		0	
EAR PAIN	1	(0.2%)	0		0	
VERTIGO	1	(0.2%)	0		0	
Total Number of Treatment Emergent Adverse Events	2		0		0	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS						
Number of Patients Reporting at Least One Treatment Emergent Adverse Event	0		1	(0.2%)	0	
DRUG EXPOSURE DURING PREGNANCY	0		1	(0.2%)	0	
Total Number of Treatment Emergent Adverse Events	0		1		0	
RENAL AND URINARY DISORDERS						
Number of Patients Reporting at Least One Treatment Emergent Adverse Event	0		0		1	(0.5%)
DYSURIA	0		0		1	(0.5%)
Total Number of Treatment Emergent Adverse Events	0		0		1	

BAP00091 study withdrawal information

Table 5: Summary of Reasons for Premature Withdrawal from Treatment

	Cohort B Non Responder in BAP89 30mg	Cohort A Relapse in BAP89 10mg	30mg	Placebo	Total
Number of Patients (ITT)	243	21	49	47	360
Withdrawn from treatment	48 (19.8%)	4 (19.0%)	6 (12.2%)	14 (29.8%)	72 (20.0%)
Primary reason for withdrawal:					
Adverse event/intercurrent illness	11 (4.5%)	1 (4.8%)	2 (4.1%)	2 (4.3%)	16 (4.4%)
Death	0	1 (4.8%)	0	0	1 (0.3%)
Insufficient therapeutic response	13 (5.3%)	0	2 (4.1%)	8 (17.0%)	23 (6.4%)
Failure to return	4 (1.6%)	0	0	2 (4.3%)	6 (1.7%)
Other protocol violation	1 (0.4%)	0	0	0	1 (0.3%)
Refused trt/did not cooperate/ withdrew consent	12 (4.9%)	1 (4.8%)	2 (4.1%)	1 (2.1%)	16 (4.4%)
Administrative/other	7 (2.9%)	1 (4.8%)	0	1 (2.1%)	9 (2.5%)

Source: B91T05.sas 10MAY07

Table 26: Summary of Adverse Events Leading to Treatment Discontinuation

	Cohort B Non Responder in BAP89 30mg	Cohort A Relapse in BAP89 10mg	30mg	Placebo	Total
Number of Patients (Safety)	243	21	50	46	360
Number of Patients Reporting at Least One AE Leading to Treatment Discontinuation:					
All Body Systems	11 (4.5%)	2 (9.5%)	2 (4.0%)	2 (4.3%)	17 (4.7%)
Nervous System Disorders	5 (2.1%)	0	1 (2.0%)	0	6 (1.7%)
Headache	3 (1.2%)	0	1 (2.0%)	0	4 (1.1%)
Dizziness	3 (1.2%)	0	0	0	3 (0.8%)
Disturbance In Attention	1 (0.4%)	0	0	0	1 (0.3%)
Skin and Subcutaneous Tissue Disorders	3 (1.2%)	1 (4.8%)	0	1 (2.2%)	5 (1.4%)
Dermatitis	1 (0.4%)	1 (4.8%)	0	0	2 (0.6%)
Alopecia Effluvium	1 (0.4%)	0	0	0	1 (0.3%)
Eczema	0	0	0	1 (2.2%)	1 (0.3%)
Rash Maculo-Papular	1 (0.4%)	0	0	0	1 (0.3%)
Psychiatric Disorders	1 (0.4%)	0	0	1 (2.2%)	2 (0.6%)
Depression	1 (0.4%)	0	0	0	1 (0.3%)
Dysthymic Disorder	0	0	0	1 (2.2%)	1 (0.3%)
Cardiac Disorders	0	1 (4.8%)	0	0	1 (0.3%)
Cardiac Failure Acute	0	1 (4.8%)	0	0	1 (0.3%)
Gastrointestinal Disorders	1 (0.4%)	0	0	0	1 (0.3%)
Nausea	1 (0.4%)	0	0	0	1 (0.3%)
Vomiting	1 (0.4%)	0	0	0	1 (0.3%)
General Disorders and Administration Site Conditions	0	0	1 (2.0%)	0	1 (0.3%)
Systemic Inflammatory Response Syndrome	0	0	1 (2.0%)	0	1 (0.3%)
Injury, Poisoning and Procedural Conditions	1 (0.4%)	0	0	0	1 (0.3%)
Forearm Fracture	1 (0.4%)	0	0	0	1 (0.3%)
Metabolism and Nutritional Disorders	1 (0.4%)	0	0	0	1 (0.3%)
Hypercholesterolaemia	1 (0.4%)	0	0	0	1 (0.3%)
Musculoskeletal and Connective Tissue Disorders	1 (0.4%)	0	0	0	1 (0.3%)
Compartment Syndrome	1 (0.4%)	0	0	0	1 (0.3%)
Vascular Disorders	0	0	1 (2.0%)	0	1 (0.3%)
Aortic Aneurysm	0	0	1 (2.0%)	0	1 (0.3%)

Source: B91T35_***_10may07

Appendix 5: Tabulated details of the BAP00626 study

Study	Recruitment/ Trial	Intervention/Duration	Study Type/ Design	Randomisation Method	Blinding Method
BAP00626	First patient enrolled April 13th 2006. Last patient assessment May 10th 2007..	Intervention: 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 30mg once daily. 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. Duration: Trial treatment was given once daily for 24 weeks, with a 4 week post-treatment safety follow-up period. All patients were evaluated for PGA and mTLSS every 4 weeks during treatment. PaGA and extent of disease assessments were performed at the end of therapy. The QTO-HE was completed at baseline and at the end of treatment. At each visit, patients indicated the intensity of pain and pruritus on a VAS. In addition, pruritus was assessed in categorical terms. AEs were recorded at each visit until 4 weeks after the end of therapy. Laboratory safety tests were performed at screening and every 4 weeks until 4 weeks after the end of therapy. Serious adverse events (SAEs) were to be reported if they occurred up to 4 weeks after the end of therapy.	The phase III study was conducted in patients with severe CHE unresponsive to topical steroids. The study took place at 38 centres in Germany, Poland and Canada. Consenting patients were screened for enrollment eligibility (including compliance with contraceptive measures) within 4 weeks before the start of therapy. Enrolled patients received 30 mg of Alitretinoin (BAL4079) once daily to be administered with food. Efficacy and safety were evaluated every 4 weeks, and treatment duration was 24 weeks. During follow-up, patients were evaluated for safety and efficacy 4 weeks after the end of treatment. Primary objective Primary objective was to assess the safety of Alitretinoin. Secondary objectives Secondary objectives were to assess treatment efficacy according to the following endpoints: – proportion of patients with response at end of therapy (patient global assessment [PGA] rating of “clear” or “almost clear”), – proportion of patients with at least partial response at end of therapy (PGA rating of “clear”, “almost clear” or “mild”), – time from start of treatment to first PGA assessment of “clear” or “almost clear” (Time to response) for responders, – patient global assessment at the end of therapy, – questionnaire on treatment objectives in hand dermatitis (QTOHE), – percentage change from baseline in modified Total Lesion Symptom Score (mTLSS) at the end of therapy, – extent of disease at the end of therapy, – percentage change from baseline in visual analogue scale (VAS) for pain and pruritus, and – categorical assessment of pruritus.	Open-label study. Enrolled patients received 30 mg of Alitretinoin (BAL4079) once daily to be administered with food.	N/A

Appendix 6- data from 4 weekly study visits in BAP00089 and BAP00091 studies

Appendix A10 (cont.) **Summary of Physician Global Assessment by Visit (OC / LOCF)**
ITT Population

ALITRETINOIN 30 mg

		Week 4		Week 8		Week 12		Week 16		Week 20		Week 24	
Number of Patients in ITT Population		409		409		409		409		409		409	
Number of Patients Rated (OC)													
Responder	Total	29	(7.1%)	93	(22.7%)	103	(25.2%)	51	(12.5%)	67	(16.4%)	96	(23.5%)
	Clear	1	(0.2%)	24	(5.9%)	51	(12.5%)	23	(5.6%)	25	(6.1%)	37	(9.0%)
	Almost Clear	28	(6.8%)	69	(16.9%)	52	(12.7%)	28	(6.8%)	42	(10.3%)	59	(14.4%)
Non responder	Total	380	(92.9%)	316	(77.3%)	306	(74.8%)	358	(87.5%)	342	(83.6%)	313	(76.5%)
	Mild Disease	65	(15.9%)	77	(18.8%)	87	(21.3%)	83	(20.3%)	64	(15.6%)	48	(11.7%)
	Moderate Disease	151	(36.9%)	129	(31.5%)	93	(22.7%)	80	(19.6%)	65	(15.9%)	64	(15.6%)
	Severe Disease	159	(38.9%)	66	(16.1%)	49	(12.0%)	22	(5.4%)	18	(4.4%)	16	(3.9%)
	Missing	5		44		77		173		195		185	
Number of Patients Rated (LOCF)													
Responder	Total	29	(7.1%)	96	(23.5%)	114	(27.9%)	138	(33.7%)	166	(40.6%)	195	(47.7%)
	Clear	1	(0.2%)	24	(5.9%)	54	(13.2%)	70	(17.1%)	77	(18.8%)	90	(22.0%)
	Almost Clear	28	(6.8%)	72	(17.6%)	60	(14.7%)	68	(16.6%)	89	(21.8%)	105	(25.7%)
Non responder	Total	380	(92.9%)	313	(76.5%)	295	(72.1%)	271	(66.3%)	243	(59.4%)	214	(52.3%)
	Mild Disease	65	(15.9%)	83	(20.3%)	95	(23.2%)	99	(24.2%)	78	(19.1%)	59	(14.4%)
	Moderate Disease	151	(36.9%)	140	(34.2%)	116	(28.4%)	100	(24.4%)	94	(23.0%)	88	(21.5%)
	Severe Disease	159	(38.9%)	87	(21.3%)	82	(20.0%)	70	(17.1%)	69	(16.9%)	66	(16.1%)
	Missing	5		3		2		2		2		1	

Note: OC refers to observed cases, LOCF refers to last observation carried forward.

Appendix A 10 (cont.) Summary of Physician Global Assessment by Visit (OC / LOCF) ITT Population

PLACEBO

		Week 4		Week 8		Week 12		Week 16		Week 20		Week 24	
Number of Patients in ITT Population		205		205		205		205		205		205	
Number of Patients Rated (OC)													
Responder	Total	4	(2.0%)	7	(3.4%)	9	(4.4%)	15	(7.3%)	16	(7.8%)	29	(14.1%)
	Clear	3	(1.5%)	2	(1.0%)	3	(1.5%)	3	(1.5%)	1	(0.5%)	4	(2.0%)
	Almost Clear	1	(0.5%)	5	(2.4%)	6	(2.9%)	12	(5.9%)	15	(7.3%)	25	(12.2%)
Non responder	Total	201	(98.0%)	198	(96.6%)	196	(95.6%)	190	(92.7%)	189	(92.2%)	176	(85.9%)
	Mild Disease	11	(5.4%)	28	(13.7%)	45	(22.0%)	38	(18.5%)	46	(22.4%)	38	(18.5%)
	Moderate Disease	68	(33.2%)	70	(34.1%)	59	(28.8%)	56	(27.3%)	47	(22.9%)	48	(23.4%)
	Severe Disease	118	(57.6%)	70	(34.1%)	56	(27.3%)	28	(13.7%)	21	(10.2%)	19	(9.3%)
	Missing	4		30		36		68		75		71	
Number of Patients Rated (LOCF)													
Responder	Total	4	(2.0%)	7	(3.4%)	9	(4.4%)	19	(9.3%)	22	(10.7%)	34	(16.6%)
	Clear	3	(1.5%)	2	(1.0%)	3	(1.5%)	5	(2.4%)	3	(1.5%)	6	(2.9%)
	Almost Clear	1	(0.5%)	5	(2.4%)	6	(2.9%)	14	(6.8%)	19	(9.3%)	28	(13.7%)
Non responder	Total	201	(98.0%)	198	(96.6%)	196	(95.6%)	186	(90.7%)	183	(89.3%)	171	(83.4%)
	Mild Disease	11	(5.4%)	30	(14.6%)	46	(22.4%)	41	(20.0%)	50	(24.4%)	40	(19.5%)
	Moderate Disease	68	(33.2%)	76	(37.1%)	68	(33.2%)	71	(34.6%)	61	(29.8%)	62	(30.2%)
	Severe Disease	118	(57.6%)	91	(44.4%)	81	(39.5%)	73	(35.6%)	71	(34.6%)	68	(33.2%)
	Missing	4		1		1		1		1		1	

Note: OC refers to observed cases, LOCF refers to last observation carried forward.

Appendix A 10 Summary of Physician Global Assessment by Visit (OC / LOCF) ITT Population

ALITRETINOIN 10 mg

		Week 4		Week 8		Week 12		Week 16		Week 20		Week 24	
Number of Patients in ITT Population		418		418		418		418		418		418	
Number of Patients Rated (OC)													
Responder	Total	8	(1.9%)	28	(6.7%)	45	(10.8%)	41	(9.8%)	52	(12.4%)	77	(18.4%)
	Clear	0		2	(0.5%)	15	(3.6%)	5	(1.2%)	8	(1.9%)	22	(5.3%)
	Almost Clear	8	(1.9%)	26	(6.2%)	30	(7.2%)	36	(8.6%)	44	(10.5%)	55	(13.2%)
Non responder	Total	410	(98.1%)	390	(93.3%)	373	(89.2%)	377	(90.2%)	366	(87.6%)	341	(81.6%)
	Mild Disease	34	(8.1%)	74	(17.7%)	106	(25.4%)	93	(22.2%)	101	(24.2%)	88	(21.1%)
	Moderate Disease	144	(34.4%)	152	(36.4%)	144	(34.4%)	132	(31.6%)	111	(26.6%)	98	(23.4%)
	Severe Disease	221	(52.9%)	116	(27.8%)	64	(15.3%)	39	(9.3%)	26	(6.2%)	31	(7.4%)
	Missing	11		48		59		113		128		124	
Number of Patients Rated (LOCF)													
Responder	Total	8	(1.9%)	29	(6.9%)	47	(11.2%)	69	(16.5%)	90	(21.5%)	115	(27.5%)
	Clear	0		2	(0.5%)	16	(3.8%)	17	(4.1%)	23	(5.5%)	39	(9.3%)
	Almost Clear	8	(1.9%)	27	(6.5%)	31	(7.4%)	52	(12.4%)	67	(16.0%)	76	(18.2%)
Non responder	Total	410	(98.1%)	389	(93.1%)	371	(88.8%)	349	(83.5%)	328	(78.5%)	303	(72.5%)
	Mild Disease	34	(8.1%)	77	(18.4%)	108	(25.8%)	103	(24.6%)	109	(26.1%)	92	(22.0%)
	Moderate Disease	144	(34.4%)	159	(38.0%)	154	(36.8%)	154	(36.8%)	137	(32.8%)	125	(29.9%)
	Severe Disease	221	(52.9%)	145	(34.7%)	102	(24.4%)	85	(20.3%)	75	(17.9%)	79	(18.9%)
	Missing	11		8		7		7		7		7	

Note: OC refers to observed cases, LOCF refers to last observation carried forward

Appendix A 11 (cont.) Summary of Physician Global Assessment by Visit (OC / LOCF)
PP Population

ALITRETINOIN 30 mg

		Week 4		Week 8		Week 12		Week 16		Week 20		Week 24	
Number of Patients in Per-Protocol Population		364		364		364		364		364		364	
Number of Patients Rated (OC)													
Responder	Total	24	(6.6%)	86	(23.6%)	99	(27.2%)	48	(13.2%)	64	(17.6%)	94	(25.8%)
	Clear	1	(0.3%)	22	(6.0%)	49	(13.5%)	21	(5.8%)	23	(6.3%)	36	(9.9%)
	Almost Clear	23	(6.3%)	64	(17.6%)	50	(13.7%)	27	(7.4%)	41	(11.3%)	58	(15.9%)
Non responder	Total	340	(93.4%)	278	(76.4%)	265	(72.8%)	316	(86.8%)	300	(82.4%)	270	(74.2%)
	Mild Disease	60	(16.5%)	70	(19.2%)	83	(22.8%)	80	(22.0%)	60	(16.5%)	42	(11.5%)
	Moderate Disease	136	(37.4%)	118	(32.4%)	87	(23.9%)	78	(21.4%)	62	(17.0%)	62	(17.0%)
	Severe Disease	142	(39.0%)	60	(16.5%)	48	(13.2%)	21	(5.8%)	18	(4.9%)	16	(4.4%)
	Missing	2		30		47		137		160		150	
Number of Patients Rated (LOCF)													
Responder	Total	24	(6.6%)	88	(24.2%)	105	(28.8%)	128	(35.2%)	155	(42.6%)	184	(50.5%)
	Clear	1	(0.3%)	22	(6.0%)	51	(14.0%)	65	(17.9%)	71	(19.5%)	84	(23.1%)
	Almost Clear	23	(6.3%)	66	(18.1%)	54	(14.8%)	63	(17.3%)	84	(23.1%)	100	(27.5%)
Non responder	Total	340	(93.4%)	276	(75.8%)	259	(71.2%)	236	(64.8%)	209	(57.4%)	180	(49.5%)
	Mild Disease	60	(16.5%)	75	(20.6%)	88	(24.2%)	92	(25.3%)	70	(19.2%)	50	(13.7%)
	Moderate Disease	136	(37.4%)	124	(34.1%)	101	(27.7%)	87	(23.9%)	81	(22.3%)	74	(20.3%)
	Severe Disease	142	(39.0%)	76	(20.9%)	70	(19.2%)	57	(15.7%)	58	(15.9%)	56	(15.4%)
	Missing	2		1		0		0		0		0	

Note: OC refers to observed cases, LOCF refers to last observation carried forward.

Appendix A 11 (cont.) Summary of Physician Global Assessment by Visit (OC / LOCF)
PP Population

PLACEBO

		Week 4		Week 8		Week 12		Week 16		Week 20		Week 24	
Number of Patients in Per-Protocol Population		179		179		179		179		179		179	
Number of Patients Rated (OC)													
Responder	Total	4	(2.2%)	7	(3.9%)	9	(5.0%)	14	(7.8%)	15	(8.4%)	28	(15.6%)
	Clear	3	(1.7%)	2	(1.1%)	3	(1.7%)	3	(1.7%)	1	(0.6%)	4	(2.2%)
	Almost Clear	1	(0.6%)	5	(2.8%)	6	(3.4%)	11	(6.1%)	14	(7.8%)	24	(13.4%)
Non responder	Total	175	(97.8%)	172	(96.1%)	170	(95.0%)	165	(92.2%)	164	(91.6%)	151	(84.4%)
	Mild Disease	11	(6.1%)	28	(15.6%)	44	(24.6%)	37	(20.7%)	44	(24.6%)	36	(20.1%)
	Moderate Disease	62	(34.6%)	63	(35.2%)	57	(31.8%)	54	(30.2%)	45	(25.1%)	48	(26.8%)
	Severe Disease	100	(55.9%)	63	(35.2%)	49	(27.4%)	26	(14.5%)	19	(10.6%)	18	(10.1%)
	Missing	2		18		20		48		56		49	
Number of Patients Rated (LOCF)													
Responder	Total	4	(2.2%)	7	(3.9%)	9	(5.0%)	18	(10.1%)	21	(11.7%)	33	(18.4%)
	Clear	3	(1.7%)	2	(1.1%)	3	(1.7%)	5	(2.8%)	3	(1.7%)	6	(3.4%)
	Almost Clear	1	(0.6%)	5	(2.8%)	6	(3.4%)	13	(7.3%)	18	(10.1%)	27	(15.1%)
Non responder	Total	175	(97.8%)	172	(96.1%)	170	(95.0%)	161	(89.9%)	158	(88.3%)	146	(81.6%)
	Mild Disease	11	(6.1%)	30	(16.8%)	45	(25.1%)	40	(22.3%)	48	(26.8%)	37	(20.7%)
	Moderate Disease	62	(34.6%)	68	(38.0%)	62	(34.6%)	65	(36.3%)	56	(31.3%)	58	(32.4%)
	Severe Disease	100	(55.9%)	74	(41.3%)	63	(35.2%)	56	(31.3%)	54	(30.2%)	51	(28.5%)
	Missing	2		0		0		0		0		0	

Note: OC refers to observed cases, LOCF refers to last observation carried forward.

Appendix A 11 Summary of Physician Global Assessment by Visit (OC / LOCF)
PP Population

ALITRETINOIN 10 mg

		Week 4		Week 8		Week 12		Week 16		Week 20		Week 24	
Number of Patients in Per-Protocol Population		378		378		378		378		378		378	
Number of Patients Rated (OC)													
Responder	Total	8	(2.1%)	26	(6.9%)	42	(11.1%)	41	(10.8%)	52	(13.8%)	75	(19.8%)
	Clear	0		2	(0.5%)	15	(4.0%)	5	(1.3%)	8	(2.1%)	22	(5.8%)
	Almost Clear	8	(2.1%)	24	(6.3%)	27	(7.1%)	36	(9.5%)	44	(11.6%)	53	(14.0%)
Non responder	Total	370	(97.9%)	352	(93.1%)	336	(88.9%)	337	(89.2%)	326	(86.2%)	303	(80.2%)
	Mild Disease	32	(8.5%)	69	(18.3%)	102	(27.0%)	89	(23.5%)	96	(25.4%)	83	(22.0%)
	Moderate Disease	133	(35.2%)	144	(38.1%)	140	(37.0%)	127	(33.6%)	108	(28.6%)	96	(25.4%)
	Severe Disease	202	(53.4%)	107	(28.3%)	60	(15.9%)	38	(10.1%)	24	(6.3%)	30	(7.9%)
	Missing	3		32		34		83		98		94	
Number of Patients Rated (LOCF)													
Responder	Total	8	(2.1%)	27	(7.1%)	44	(11.6%)	67	(17.7%)	88	(23.3%)	112	(29.6%)
	Clear	0		2	(0.5%)	16	(4.2%)	17	(4.5%)	23	(6.1%)	39	(10.3%)
	Almost Clear	8	(2.1%)	25	(6.6%)	28	(7.4%)	50	(13.2%)	65	(17.2%)	73	(19.3%)
Non responder	Total	370	(97.9%)	351	(92.9%)	334	(88.4%)	311	(82.3%)	290	(76.7%)	266	(70.4%)
	Mild Disease	32	(8.5%)	72	(19.0%)	103	(27.2%)	97	(25.7%)	102	(27.0%)	85	(22.5%)
	Moderate Disease	133	(35.2%)	150	(39.7%)	145	(38.4%)	142	(37.6%)	127	(33.6%)	116	(30.7%)
	Severe Disease	202	(53.4%)	127	(33.6%)	85	(22.5%)	71	(18.8%)	60	(15.9%)	64	(16.9%)
	Missing	3		2		1		1		1		1	

Note: OC refers to observed cases, LOCF refers to last observation carried forward.

Appendix 7: Methods for obtaining expert panel estimates of efficacy and relapse for comparators

Expert Panel Invite

WG House
2 Cressex Road
High Wycombe
HP12 4TY
Tel: 01494 470760
Fax: 01494 472498
www.wg-group.co.uk

Dear xxxxx,

WG Consulting is an independent management consultancy specialising in health care, and we advise clients in both the public sector and the pharmaceutical industry. We are organising an advisory panel meeting on behalf of Basilea Pharmaceuticals Ltd.

Basilea are the manufacturer of oral alitretinoin, developed for the treatment of patients with severe Chronic Hand Eczema (CHE) unresponsive to potent topical corticosteroids for which a UK marketing licence is anticipated in September 2008.

In anticipation of the requirement to submit to NICE, Basilea would like to fully understand the range of existing treatments for CHE and how alitretinoin is likely to be used in clinical practice. Panel members will be drawn from throughout England and Wales and we would be delighted if you could attend.

It is particularly important for Basilea to seek the input of Consultant Dermatologists at this stage for several reasons:

- No studies of alitretinoin have been conducted against comparator treatments, therefore indirect comparisons against best current standard of care in England and Wales will be required
- There is currently considerable variation in approach to the treatment of CHE. Also, no reliable published evidence base or guidelines exist to indicate what the appropriate standard of care for cost effectiveness assessments should be

The objectives of this NICE advisory panel meeting for alitretinoin will be:

- To gain feedback on the intended strategy and positioning for alitretinoin in CHE to maximise the chances of a successful NICE submission
- To gain feedback from panel members on the key clinical and quality of life data that we propose to present to NICE
- To explore potential methods of economic modelling and appropriate comparator data in this therapy area

Basilea would like to stress that their purpose in organising this advisory board is to seek guidance from experts in the field that will help Basilea construct a credible health economic case for alitretinoin. Should you feel that attendance would create a conflict of interest because of a current or future NICE expert advisory role, please decline our invitation as we would not wish interaction with Basilea to disqualify you from this essential function.

The meeting will be held on one of the following dates: (Please indicate which date would suit you)

- Monday 13th October 2008
- Tuesday 14th October 2008

The meeting will be held from 10am until 3.30pm at The Royal College of Obstetricians and Gynaecologists (RCOG), or other similar venue in London.

So that we can devote as much time as possible to discussion in the meeting , which will be run as a series of workshop sessions, we propose to send you some background reading and a brief questionnaire about current practice that we would like you to complete and return to us in advance. In recognition of your input to the prework and meeting itself, an honorarium of £700 will be available. We will gladly reimburse reasonable travel expenses for mileage, taxis & train/air fares. If you have any queries regarding travel arrangements please contact us prior to booking.

All discussions at the meeting will be non-attributable and confidentiality agreements will be required.

I will call you in the next few days to discuss this in more detail. Alternatively please feel free to contact me on alexisc@wg-group.com. I will look forward to speaking with you.

Yours sincerely,

ALI080050
Innovators in Healthcare Solutions

VAT Number : GB 913 5045 50

Date of preparation 04/08/08
WG Consulting Healthcare Limited
Registered Office: The Johnson Building, 77 Hatton Garden, London. EC1N 8JS
Registered No. 3024760, Registered in England

Pre-meeting Questionnaire

Chronic Hand Eczema (CHE) Questionnaire

Please note that this should take no more than 10-15 minutes to complete.
The information collected will help Basilea to formulate appropriate indirect comparisons between alitretinoin and alternative treatments for the purposes of NICE submission.
Please return to george.stanley@basilea.com as soon as possible by e mail to allow collation of responses in advance of the Advisory Board meeting. If this is not possible, please bring the completed questionnaire to the meeting and we will attempt to incorporate your feedback on the day

Thank You

1. Severity of CHE population treated

Q: The Physicians Global Assessment (PGA) as below was used to rate severity in the alitretinoin clinical trials, with all patients "PGA severe" at baseline in the phase III trial.

PGA severity	Features	Intensity	Area involved*
Severe	Erythema, scaling, hyperkeratosis/lichenification	At least one moderate or severe	> 30% of affected hand surface
	Vesiculation, oedema, fissures, pruritus/pain	At least one severe	
Moderate	Erythema, scaling, hyperkeratosis/lichenification	At least one mild or moderate	10%–30% of affected hand surface
	Vesiculation, oedema, fissures, pruritus/pain	At least one moderate	
Mild	Erythema, scaling, hyperkeratosis/lichenification	At least one mild	Less than 10% of affected hand surface
	Vesiculation, oedema, fissures, pruritus/pain	At least one mild	
Almost clear	Erythema, scaling, hyperkeratosis/lichenification	At least one mild	Less than 10% of affected hand surface
	Vesiculation, oedema, fissures, pruritus/pain	Absent	
Clear	Erythema, scaling, hyperkeratosis/lichenification	Absent	Not detectable
	Vesiculation, oedema, fissures, pruritus/pain	Absent	

*% total of dorsal and palmar areas involved

If this classification were to be used to categorise the baseline severity of the CHE patients you treat with systemic agents or phototherapy, what proportion would be classified as:

Moderate?----------

Severe?----------

2. Treatment approach

Q: Considering the "PGA severe" CHE patients that you see who show no or poor response to topical corticosteroids, what proportion would you initially treat with the following therapies? -please indicate patient/disease factors in choice where possible.

a. Oral corticosteroids:

b. PUVA/UVB (please specify which, or relative proportions if use both)

c. Oral immunosuppressants (please specify approximate % treated with ciclosporin, methotrexate, azathioprine, MMF or other)

d. Topical immunomodulators

e. Retinoids (please specify)

f. Other (eg Re-PUVA please specify):

Q: If patients showed no or unsatisfactory response to your first line of treatment, what would be the 2nd line approach in your centre? (Again indicating patient/disease factors in choice where possible)

3. Definition of Efficacy

Q: Using your current treatment approaches as above, what proportion of CHE patients with severe, steroid unresponsive CHE would you expect to become "PGA clear/almost clear" after:

12 weeks treatment?

24 weeks treatment?

Q: In trials of systemic agents and phototherapy in CHE, efficacy has usually been expressed as a % improvement in severity score. What % overall improvement in signs and symptoms would you consider to be a meaningful "response" in current clinical practice?

4. Durability of Treatment Response

Q: Considering those patients achieving a response to systemic therapy or phototherapy (either defined as PGA clear/almost clear or a substantial % improvement); what proportion would have relapsed to at least 75% of their original disease severity by:

4 weeks
8 weeks
12 weeks
16 weeks
20 weeks
24 weeks

Please specify which agents are associated with any particular period of relapse if possible.

Thank you for completing this survey

Expert Panel Meeting report

DATA ON FILE reference sheet: Excerpt from England & Wales Advisory board meeting report

Reference number	DOF-ALI08020
Date created	11 December 2008
Source reference	Basilea / WG Consulting England & Wales advisory board meeting report

Meeting date: Tuesday 14th October, 2008

Venue: The Royal College of Physicians, London

Aim
To understand clinical practice in the treatment of chronic hand eczema (CHE), in order to inform a NICE single technology appraisal for alitretinoin (Toctino).

Objectives
To define the current treatment pathway for CHE
To gain an understanding of current clinical practice for treatment of CHE
Main focus on PUVA, ciclosporin and azathioprine as these are the comparators that have been chosen by NICE
To understand where alitretinoin would fit in the treatment pathway
To understand how alitretinoin will be used in clinical practice

Current treatment options for CHE unresponsive to topical steroids

Treatment chosen would to an extent depend on the severity & disease morphology:

It was felt that the characteristics seen in the BACH study reflect clinical experience, where hyperkeratosis is associated with more chronic disease.

Topical immunomuodulators, such as protopic, are sometimes tried when the patient is not responding to topical steroids. However, expectations for success were low and these were seen as a last resort before progressing to systemics.

In some cases, a short course of oral steroids may be used to control flares, often before starting on other treatments.

Proportion of treatments currently used for CHE

Centre	PUVA	Ciclosporin	Azathioprine	Other
1	60%	20%	10%	10%
2	50%	15%	35%	
3	80%	5%	5%	10%
4	70%	5%	15%	10%
5	70%	10%	20%	
6		40%	40%	20%
7	80%		20%	

The panel came to agreement that of the comparators chosen by NICE, the proportion of patients treated with PUVA would be approximately 70%, ciclosporin 10% and azathioprine 20%.

It was felt that it was important to understand the definition of response and that it is difficult to determine a clinically meaningful response as this is so patient dependent i.e. A patient may have a 75% response (improvement in symptoms) but if they haven't returned to work that this is not very meaningful whereas for other patients a small response can make a big difference. However after discussion, a 50% improvement in symptoms was considered to be clinically meaningful overall by approximately half the attendees.

Azathioprine
Dose: start at 100mg/day and titrate to 150mg/day depending on response/tolerance
However tapering the dose makes therapy more complicated and requires frequent patient review, including blood monitoring in early weeks
Treatment duration 6-12 months, if no improvement by 3 months would withdraw treatment
Approx. 30% withdraw due to gastro intestinal disturbances or non-symptomatic reasons

Monitoring:
Initial TPMT monitoring is required to minimise risk of marrow suppression
Every week for the first month, then fortnightly for the next month:
Liver function tests
Full blood tests

Toxicities:
Lymphoma (Long term)
Liver toxicity, hepatitis
Bone marrow suppression
There is substantial cost associated with managing side-effects of azathioprine.
The trials identified in which azathioprine was used to treat atopic dermatitis were not considered to be suitable for a comparison with treatment of CHE, due to the different nature of the conditions.

Efficacy of azathioprine at 4-weekly visits

	Disease severity				Withdraw from treatment
Week	Clear/almost	Mild	Moderate	Severe	
4	0%	0%	0%	100%	0%
8	0%	0%	5-10%	90-95%	0%
12	0%	10%	40%	50%	0%
16	5%	15%	30%	0%	50%
20	5%	20%	25%	0%	50%
24	10%	20%	20%	0%	60%
48	10%	10%	10%	0%	70%

NB. 20% of patients would drop out between 20-48 weeks, due to side-effects/ lack of response
Based on combination therapy with topical corticosteroids
Patients would be kept on therapy for approx. 2 months following complete response as maintenance therapy

Relapse:
Difficult to estimate as patients often do not return - possibly decide to live with the condition, move or go and see someone else rather than because they are in remission. However the panel estimated 2-3 months to relapse.
Would potentially retreat with azathioprine, if the patient had initially responded well.

Contraindications:
Previous malignancy
Hepatitis
Homozygous for TPMT enzyme deficiency

Ciclosporin
2.5mg/kg total daily dose (low) up to 5mg/kg if severe eczema
Would use for 3 months duration
Would not generally use more than 2 treatments per year, if patients were relapsing quickly then would try an alternative (eg aza or PUVA)

Monitoring – fortnightly for 2 months
Renal function
Blood pressure

Contraindications: hypertension and renal disease, drug-drug interactions

Efficacy of ciclosporin at 4-weekly visits

	Disease severity			
Week	Clear/almost	Mild	Moderate	Severe
4	10%	10%	10%	70%
8	30%	20%	20%	30%
12	50%	10%	10%	0%
16	50%	10%	10%	0%

Patients who achieve clear/almost clear hands would either remain on the same dose or a lower dose as maintenance for 1-2 months following clearance, or treatment would be stopped.
Time to relapse: (i.e. return to 75% of baseline severity) 30% by week 4, 50% by week 8, 80% by week 12.

PUVA
UVB is not generally used in the representative centres in Engand/Wales.
Retinoid - PUVA treatment is very rarely used.
PUVA treatment is almost always topical and not oral for localised hand eczema.

Efficacy of PUVA at 4-weekly intervals

	Disease severity			
Week	Clear/almost	Mild	Moderate	Severe
4	0%	0%	10%	90%
8	15%	5%	10%	70%
12	40%	5%	5%	50%
16	50%	10%	10%	30%

NB: Assumes 30 sessions of PUVA, over an average of 16 weeks

Contraindications:
No medical, but 20% of patients decide not to use
There are cohorts of patients in which PUVA could not be used due to lack of access or hand-specific equipment
10-15% would drop out before treatment completion of therapy
Would very rarely reach an upper limit of sessions (i.e. 200 considered max), so do not really consider this, though in any case considered that risk of cancer after 200 sessions related to whole body PUVA for atopic eczema, not localised hand PUVA.

Relapse rates:

Week 4	10%	
Week 8		20%
Week 12	40%	
Week 16	60%	
Week 20		80%

Positioning of alitretinoin and expected market share

If alitretinoin were approved by NICE then the following uptake would be expected:

Year	Alitretinoin	PUVA	Ciclosporin/azathioprine
0	0%	70%	30%
1	20%	60%	20%
2	25%	55%	20%
3	35%	50%	15%

Some panel members felt that if alitretinoin were an approved treatment then they would be little justification to prescribe unlicensed treatments, especially currently available systemics which are highly toxic.

However prescription would be carefully considered in women of child-bearing age.

In the initial year, the largest cohort of patients treated with alitretinoin would be those who had failed on every other treatment. New patients may be kept on PUVA/currently available immunosuppressants until clinical experience with alitretinoin is gained, so total % might not increase that much in second year but would probably be made up of a greater proportion of "new" patients. After that, how many treated would depend on the referral rate to dermatologists. Some felt this would increase because GPs would become more educated about a new treatment and patients would become more aware that a new option existed.

Some patients who are unable to attend clinics for PUVA would be treated with alitretinoin.

General
It was felt that the figure of 10% of the adult population suffering from hand eczema was too high (maybe more like 5%).