1. TITLE

Randomised, double-blind, placebo-controlled study of topical GW842470X formulation in adult patients with moderate atopic dermatitis.

GW842470X is an inhibitor of phosphodiesterase 4, the major phosphodiesterase isoenzyme in inflammatory cells. Inhibition of phosphodiesterase 4 results in relevant anti-inflammatory effects and a topical formulation of GW842470X is being developed for atopic dermatitis (AD). The purpose of this study was to investigate the clinical efficacy of 3% (w/w) GW842470X cream applied to involved skin of adult patients with moderate AD using the Eczema Area Severity Index (EASI) assessment of disease severity, and to investigate the safety and tolerability of 3% GW842470X cream on diseased skin of adult patients with moderate AD in support of subsequent Phase II and III studies.

2. INVESTIGATOR

Dr [redacted]

3. STUDY CENTRE

There were 18 centres in total: 11 in Germany, three in Netherlands and four in UK.

4. PUBLICATIONS

None at the time of this report.

5. STUDY PERIOD

21 March 2006 – 22 September 2006.

6. PHASE OF DEVELOPMENT

II

7. OBJECTIVES

7.1. Primary

- To investigate clinical efficacy of 3% GW842470X cream applied to involved skin of adult patients with moderate AD using the EASI.

7.2. Secondary

- To investigate the safety and tolerability of 3% GW842470X cream on diseased skin of adult patients with moderate AD.
- To investigate the clinical efficacy of 3% GW842470X cream applied to involved skin of adult patients with moderate AD using the SCORing atopic dermatitis score (SCORAD) and the Investigator's Global Assessment scale (IGA) for AD.
- To characterise the systemic exposure to GW842470X following 21 day dosing of 3% GW842470X cream on diseased skin of adult patients with AD.
- To investigate histological biomarkers in a subgroup of adult patients with moderate AD.

8. ENDPOINTS

8.1. Primary

- Difference in change from baseline EASI scores between GW842470X Cohort versus placebo (vehicle) Cohort.

8.2. Secondary

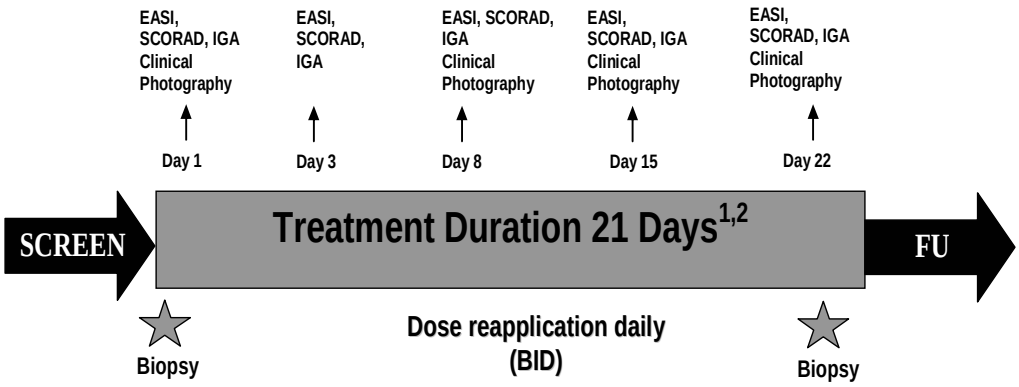
- Safety parameters included physical examination findings, vital signs, 12-lead electrocardiograms (ECGs), clinical laboratory tests, and clinical monitoring/observation for adverse events (AEs).
- Secondary efficacy endpoints included clinical evaluation of AD using the IGA, assessment of clinical signs and symptoms according to the SCORAD system, in addition to a patient-based assessment of disease control.
- Atopic dermatitis symptoms pruritus and sleep loss were recorded daily using patient diary cards over the duration of treatment.
- Plasma concentrations of GW842470X were determined on Days 1, 8 (pre-dose), 15 (pre-dose), 22, and at the follow up visit. Area under the plasma concentration-time curve over the dosing interval (AUC(0–τ)) and maximal observed plasma concentration (Cmax) were evaluated on Days 1 and 22, as data permitted.
- Exploratory pharmacodynamic endpoints included: clinical photography, and investigation of histological biomarkers in skin biopsy sections.

9. METHODOLOGY

This was a double-blind, placebo (vehicle) controlled, randomised (with respect to placebo administration), parallel group, out-patient study to evaluate the safety, efficacy and tolerability of GW842470X following repeat applications (twice-daily (BID) for 21 days) on involved skin of adult patients with moderate AD, as assessed using the IGA at baseline.

Subjects were screened 10 days prior to the first dose of study medication. Successfully screened subjects underwent a 10-day washout period of their current medication between screening and the day of the first dose. It was planned that 140 male and female subjects would be enrolled and randomised in equal numbers to one of two cohorts (70 subjects per cohort). The ratio of subjects receiving active: placebo drug in each group was to be 1:1. GW842470X (3% w/w) or matching placebo was provided as a yellow smooth water-in-oil cream. During the 21-day treatment phase, patients were instructed to apply a thin layer of cream twice daily to all involved areas of skin as present on Day 1 regardless of whether the patient felt the disease had improved or healed. Patients were also instructed to apply cream to new lesions if they arose during the treatment phase. Patients were assessed at Day 1 then returned for further assessments on days 3, 8, 15 and 22. The treatment duration of 21 days was selected to maximise percutaneous delivery of GW842470X to the skin and was deemed a sufficient duration to show superiority over vehicle treatment. A schematic of the study design is presented in Figure 1.

Figure 1 Study design



1. Safety was monitored for the duration of the study.
2. Pharmacokinetic Sampling on Day 1, Day 8, Day 15, Day 22 and at follow-up.

EASI = eczema area severity index, SCORAD = SCORing atopic dermatitis, IGA = investigator's global assessment
BID = twice-daily, FU = follow-up.

Subjects attended a follow-up visit within 7 to 10 days after removal of the last dose of study medication. The total study duration was expected to be approximately 6 weeks for any subject. Time and events tables are presented in Attachment 1.

10. NUMBER OF SUBJECTS

10.1. Disposition of Subjects

A summary of end of study record is presented in Table 1.

Table 1 Summary of end of study record

Number of Subjects	GW842470X	Placebo
Planned, N	70	70
Randomised, N	72	71
Completed, n (%)	65 (90)	64 (90)
Total Withdrawn (any reason), n (%)	7 (10)	7 (10)
Withdrawn due to Serious Adverse Events, n (%)	0	0
Withdrawn due to Adverse Events, n (%)	2 (3)	3 (4)
Lost to Follow-Up, n (%)	0	1 (1)
Protocol Violation, n (%)	0	1 (1)
Subject Decided to Withdraw, n (%)	2 (3)	0
Lack of Efficacy, n (%)	2 (3)	1 (1)
Disease Progression, n (%)	1 (1)	1 (1)

Source Data: Table 9.06

11. DIAGNOSIS AND CRITERIA FOR INCLUSION

Key inclusion criteria included: adult (aged 18 to 65 years) men or women with body weight ≥ 50 kg (110 lbs) and body mass index within the range of 17.5 – 32 kg/m^2 inclusive. Women were not to be pregnant, nursing or of child-bearing potential. If a woman was of child-bearing potential she was to use an appropriate method of contraception with a documented failure rate of less than 1% per year for the duration of the study and for 1 month after the last administration of investigational product. Subjects had a diagnosis of moderate AD as defined by an IGA score of 3 and presented with at least one index lesion (≥1 cm^2 in size) with a sumscore of ≥4 and ≤6 for erythema and oedema/papulations and excoriations using a system of grading from 0 to 3 (0 = absent, 1 = mild, 2 = moderate, 3 = severe). The index lesion was selected from the subject's neck, hands or flexural sites of the elbow or knees and represented common lesions i.e., not the most or least severe lesions. Subjects had a body surface area (BSA) disease involvement of >5% as assessed by the rule of nines method and were willing to wash out from current active therapy for at least 10 days prior to Day 1.

Key exclusion criteria included: any systemic disorder or active skin disease (other than AD, e.g., psoriasis) that would in any way confound interpretation of the study results or subjects who presented with scars, moles, tattoos, body piercing, sunburn in the test area which could have interfered with the assessment of lesions at screening. Subjects whose AD was restricted to the face, the feet or the hands only. If the subject had a current complication of AD such as erythroderma or overt bacterial or viral infection for which treatment with anti-infectives were indicated they were not to be included in the study.

12. TREATMENT AND ADMINISTRATION

Active GW842470X treatment and a matching placebo (vehicle control) formulation were provided as a yellow smooth water-in-oil cream packaged in collapsible aluminium tubes with reverse taper puncture tip caps (fill weight 50 g per tube) free of visible

evidence of contamination. The drug product contained 30 mg of GW842470X per gram (i.e., 3% w/w of free base equivalent to 3% GW842470X).

The proposed applied doses of GW842470X, the concentration of GW842470X cream and the surface area of application (for active or placebo cream) for this study are outlined inTable 2.

Dosing in this study used finger tip units (FTU) to ensure consistent load (weight of formulation per unit area) of application across all subjects. Dosing a cream using FTUs corresponded to approximately 0.49 g of cream applied to 312 cm^2 area of skin [Long, 1991]. This definition of clinical loading for a topical formulation corresponded to a loading rate of 1.6 mg/cm^2, which approximated the loading of 2 mg/cm^2 used in the previous pharmacokinetic/safety study (TPD102031) and also correlated with previously reported load encountered in normal clinical use [NDA-21-32]. In Table 2, the proposed applied dose of GW842470X is illustrated as a function of load and concentration. For the purposes of calculating maximum dose applied, a more conservative 2 mg/cm^2 load was used to account for potential variability in the use of FTUs.

Table 2 Proposed applied dose, load, concentration and body surface area of application

Dose	Weight of formulation (active or placebo)	Load (mg/cm^2)	Concentration (% w/w)	BSA (cm^2)	Approximate BSA (%)[a]
GW842470X or placebo 60 – 480 mg BID	2 – 16 g BID	2	3 % or placebo	1000 – 8000	5 – 40

a. An assumption was made that an 80 kg subject would have a BSA of 20,000 cm^2.
BID = twice-daily; BSA = body surface area.

13. CRITERIA FOR EVALUATION

Efficacy analysis included: EASI, SCORAD, IGA. Safety analysis included: AEs, supine vital signs, 12-lead ECGs, laboratory safety tests (clinical chemistry, haematology and urinalysis). Pharmacokinetic parameters derived included: AUC (0–τ) and Cmax on days 1 and 22. In addition, the trough (pre-dose) concentration (Cτ) was assessed on days 8, 15, and 22, and the observed accumulation ratio (Ro), average steady-state concentration (C_{ave}), minimum steady-state concentration (Cmin) and degree of fluctuation (Df) were assessed on Day 22, as the data permitted. Exploratory pharmacodynamic parameters included: clinical photography and biopsies of index lesions. All study assessments were performed at the time points specified in Attachment 1.

14. STATISTICAL METHODS

14.1. Sample Size

A sample size of 56 subjects on GW842470X and 42 subjects on placebo provided >85% power to detect a 35% difference (an absolute difference of 2.56) in EASI score following 21 days of treatment, based on a two sample t-test and a two-sided 5% level of significance. This sample size assumed a baseline EASI score of 8.6 with a standard deviation of 4, and a 15% placebo effect at Day 22 (an absolute reduction in EASI score of 1.29). In order to obtain the desired sample size for the analysis of the per protocol population, 70 subjects per group (140 subjects in total) were planned to be randomised. This number allowed for the anticipated drop-out rate of 20% in the GW842470X group and 40% in the placebo group to yield the desired number of subjects for each treatment group.

Baseline EASI scores and variability in published studies varies as these studies encompass a wide range of disease severity, cover both adult and paediatric populations, and vary greatly in sample size. For the purposes of calculating sample size for this study, a baseline EASI of 8.6 and standard deviation of 4 from the most recent study [Meurer, 2004] was assumed to be the most appropriate choice, because EASI was measured in an adult population with moderate AD, where eligibility in terms of disease severity was defined using an IGA cut-off of 3 (moderate). This same eligibility criterion was used to define severity in this study.

Assuming a baseline EASI score of 8.6 with a standard deviation of 4.81 (the upper 95% confidence interval of the standard deviation from the Meurer study), the sample size for the per protocol population of 56 subjects on GW842470X and 42 subjects on placebo would have 73.2% power to detect a 35% difference (an absolute difference of 2.56) in EASI score following 21 days of treatment, based on a two sample t-test and a two-sided 5% level of significance. This calculation also assumed a 15% placebo effect at Day 22 and an anticipated drop-out rate of 20% in the GW842470X group and 40% in the placebo group.

14.2. Analysis Populations

- Per protocol population: the primary population for the efficacy analysis. All patients who completed the study and had data for both baseline and Day 22 were included in this population.
- Safety population: all subjects who received at least one dose of a study drug.
- Pharmacokinetic concentration population: patients from whom a pharmacokinetic sample was obtained and analysed.
- Pharmacokinetic parameter population: all subjects in the pharmacokinetic concentration population who provided pharmacokinetic parameters.
- Efficacy population: all subjects who completed the study and had data for both baseline and Day 22.

- Biomarker population: all subjects who provided biomarker data.

14.3. Interim Analyses

In order to increase confidence that the study sample size was sufficient to deliver the protocol objectives an interim data look at the blinded baseline (Day 1 pre-dose) EASI data for the first 70 patients randomised into the study was performed. The mean and standard deviation of this data were calculated and used to re-estimate the sample size. The results ensured enough power to detect 35% difference between active and placebo groups, assuming that such difference existed.

14.4. Final Analyses

All analyses are fully described in the Reporting and Analysis Plan for this study.

Efficacy Analysis

The primary focus of efficacy analyses was to compare the effects of GW842470X with the effects of placebo.

Primary efficacy analyses: changes from baseline to each post-dose assessment in the composite EASI scores were analysed using mixed models, repeated-measures analysis of variance (ANOVA), with Day (i.e., 3, 8, 15 and 22), group (active, placebo), centre, baseline (i.e., Day 1 pre-dose), group-by-day and baseline-by-day interactions as fixed effects, and subject as a random effect. Other covariates such as BSA coverage of the diseased skin were added into the model. Point estimates and 95% confidence intervals (CIs) were derived for the difference in the composite EASI scores at Day 22 and EASI change from baseline to Day 22, respectively, between GW842470X and placebo.

Secondary efficacy analyses: changes from baseline to each post-dose assessment in full SCORAD, objective SCORAD (with symptomatic scores omitted) scores, and the absolute IGA score were separately analysed using mixed models, repeated-measures ANOVA, with Day (i.e., 3, 8, 15 and 22), group (active, placebo), centre, baseline (i.e., Day 1 pre-dose), group-by-day and baseline-by-day interactions as fixed effects, and subject as a random effect. Other covariates such as BSA coverage of the diseased skin were added into the model. Point estimates and 95% CIs were derived for the difference in SCORAD (full and objective) change from baseline and IGA, respectively, between GW842470X and placebo.

In addition, IGA at Day 22 was dichotomised at each time point post first dose into a success (IGA score of 0 or1) or a failure (2 – 5 inclusive). Differences in the proportion of successes between treatment groups at Day 22 were assessed using Fisher's exact test. A second definition for the treatment success based on IGA was used: success (IGA score of 0, 1, or 2) and treatment failure (IGA score of 3, 4, or 5). Similar outputs were produced for both definitions for IGA.

Efficacy parameters (i.e., both raw values and changes from baseline [i.e., expressed as a difference change and % change) were listed and summarised descriptively (e.g., n,

arithmetic mean and corresponding 95% CIs, standard deviation, median, minimum, maximum) by day, where appropriate, for each treatment.

Safety Analysis

No formal statistical analysis of the safety data was planned or conducted.

Pharmacokinetic Analysis

As appropriate to the data, pharmacokinetic parameters were listed and summarised descriptively (e.g., n, arithmetic mean and corresponding 95% CI, standard deviation, median, minimum, maximum, CVb(%), geometric mean with its 95% CI and SD logs where appropriate) for each day. Standard stick plots and mean/SE plots were produced by day.

Body surface area relationship to systemic exposure (i.e., AUC, Cmax) was evaluated. Subjects were grouped in BSA categories (i.e., 5–10%, 10–20%, 20–30%, etc) and AUC and Cmax were summarised descriptively (e.g., n, arithmetic and geometric means with the corresponding 95% CI, standard deviation, median, minimum, maximum, CVb(%), sdlog) for each category.

Pharmacodynamic Analysis

No formal statistical analysis of the pharmacodynamic endpoints was planned or performed. Exploratory pharmacodynamic analyses were performed.

Body surface area and FTU units at baseline were summarised by headache incidence group (i.e., headache or no headache) for patients who received active treatment. Appropriate graphical representations were produced to indicate the relationship between dose applied (i.e., BSA and/or FTU) and incidence of headache in the active treatment group.

To investigate how the data might vary with disease severity, change from baseline EASI data were summarised by the baseline EASI range group. Subjects were grouped in baseline EASI ranges (e.g., 1 – 6, 6 – 11, 11 – 16, and 16 – 51.2).

14.5. Changes in the Conduct of the Study or Planned Analyses

No skin biopsy data was received.

15. SUMMARY

15.1. Demographics

The demographic characteristics of the subjects in this study are presented in Table 3.

Table 3 Demographic Characteristics

	GW842470X N=72	Placebo N=71	Total N=143
Age, years			
Mean (range)	34.4 (18 – 65)	32.4 (18 – 65)	33.3 (18 – 65)
Sex n (%)			
Female:	39 (54)	30 (42)	69 (48)
Male:	33 (46)	41 (58)	74 (52)
Ethnicity n (%)			
Hispanic or Latino:	0	0	0
Not Hispanic or Latino:	72 (100)	71 (100)	143 (100)
Race n (%)			
African American/African Heritage:	2 (3)	0	2 (1)
Japanese Heritage:	1 (1)	1 (1)	2 (1)
Central/South Asian Heritage:	1 (1)	0	1 (<1)
White/Caucasian/European Heritage:	64 (94)	70 (99)	138 (97)
Height, cm			
Mean (range)	172.0 (157 – 190)	175.6 153 – 197)	173.8 (153 - 197)
Weight, kg			
Mean (range)	72.84 (48.0 – 112.5)	75.38 (50.0 – 108.0)	74.10 (48.0 – 112.5)
Body mass index, kg/m^2			
Mean (range)	24.51 (18.5 – 32.0)	24.43 (18.3 – 34.7)	24.47 (18.3 – 34.7)

Source Data: Table 9.01 and Table 9.04

15.2. Protocol Violations

The following subjects had protocol waivers or violations recorded:

- [redacted]
- [redacted]
- [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted] This subject should have been a screen failure, however met the eligibility criteria at baseline. Subject's data was included in analysis.
- [redacted] She was not withdrawn from the study; however this subject's data was excluded from analysis.
- [redacted]

15.3. Efficacy

15.3.1. Eczema Area Severity Index

Reductions from baseline in EASI score of increasing magnitude were observed from Day 1 to Day 22 in the GW842470X group and for placebo. A summary of EASI scores and change from baseline by treatment and visit are presented in Table 4.

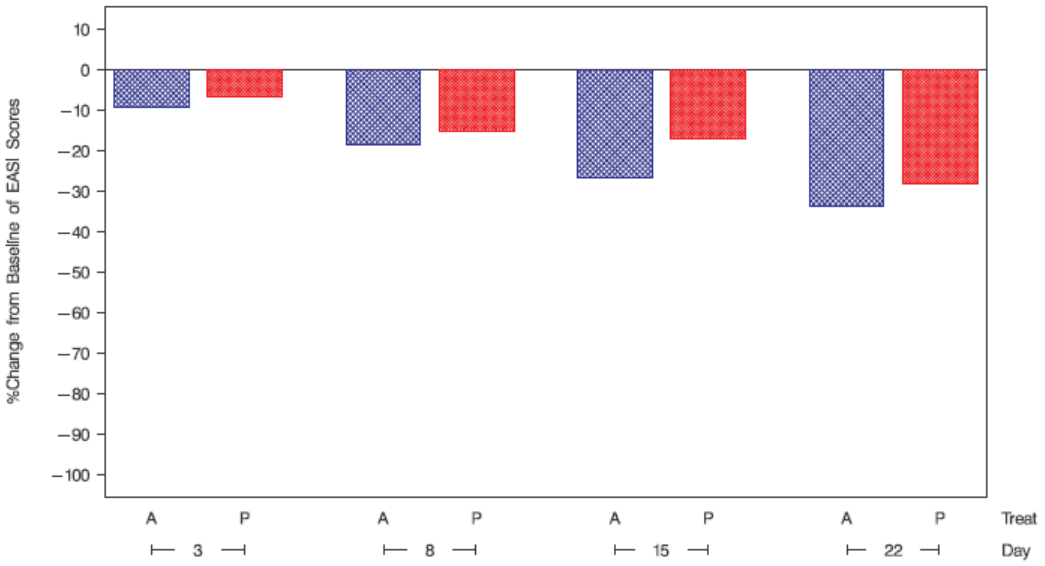
Table 4 Mean eczema area sensitivity index (95% confidence intervals) score by treatment and visit

Mean (95% Confidence Intervals)				
	GW842470X (3% w/w) (N =72)		Placebo (N = 71)	
Day	EASI Score	Change from Baseline	EASI Score	Change from Baseline
1	11.31 (9.42, 13.20)		9.38 (7.99, 10.76)	
3	10.25 (8.32, 12.18)	-1.06 (-1.74, -0.38)	8.56 (7.23, 9.88)	-0.82 (-1.57, -0.07)
8	9.10 (7.11, 11.10)	-2.21 (-3.22, -1.19)	8.06 (6.44, 9.68)	-1.32 (-2.39, -0.24)
15	8.25 (6.39, 10.11)	-3.06 (-4.26, -1.86)	7.93 (5.99, 9.87)	-1.44 (-2.87, -0.01)
22	7.59 (5.68, 9.50)	-3.71 (-4.94, -.2.48	7.01 (5.06, 8.95)	-2.37 (-3.86, -0.88)

Source Data: Table 1 and Table 2
EASI = eczema area severity index

The percentage change from baseline in EASI scores is presented in Figure 2.

Figure 2 Percentage change from baseline in eczema area severity index scores



Source Data: Figure 1
A = GW842470X (3% w/w), P = placebo

There were no statistically significant differences in EASI scores between GW842470X and placebo on days 3, 8, 15 or 22. A summary of point estimates and associated 95% CIs for the comparison of interest in EASI score is presented in Table 5.

Table 5 Summary of point estimates and associated 95% confidence intervals for eczema area severity index scores

Parameter	Day	Comparison	PE	95% C.I.	SDb
Δ in EASI	Day 3	GW842470X – Placebo	-0.18	(-1.36, 0.99)	3.10
	Day 8	GW842470X – Placebo	-0.71	(-1.89, 0.46)	
	Day 15	GW842470X – Placebo	-1.01	(-2.19, 0.16)	
	Day 22	GW842470X – Placebo	-0.99	(-2.16, 0.19)	

Source Data: Table 4
Δ in EASI = Change from baseline in EASI score.
EASI = eczema area severity index, PE = point estimate, CI = confidence interval, SDb = standard deviation

15.3.2. SCORing Atopic Dermatitis

Objective SCORing atopic dermatitis

In general, reductions from baseline in objective SCORAD scores of increasing magnitude were observed from Day 1 to Day 22 in the GW842470X group and for placebo. A summary of objective SCORAD scores and change from baseline by treatment and visit is presented in Table 6.

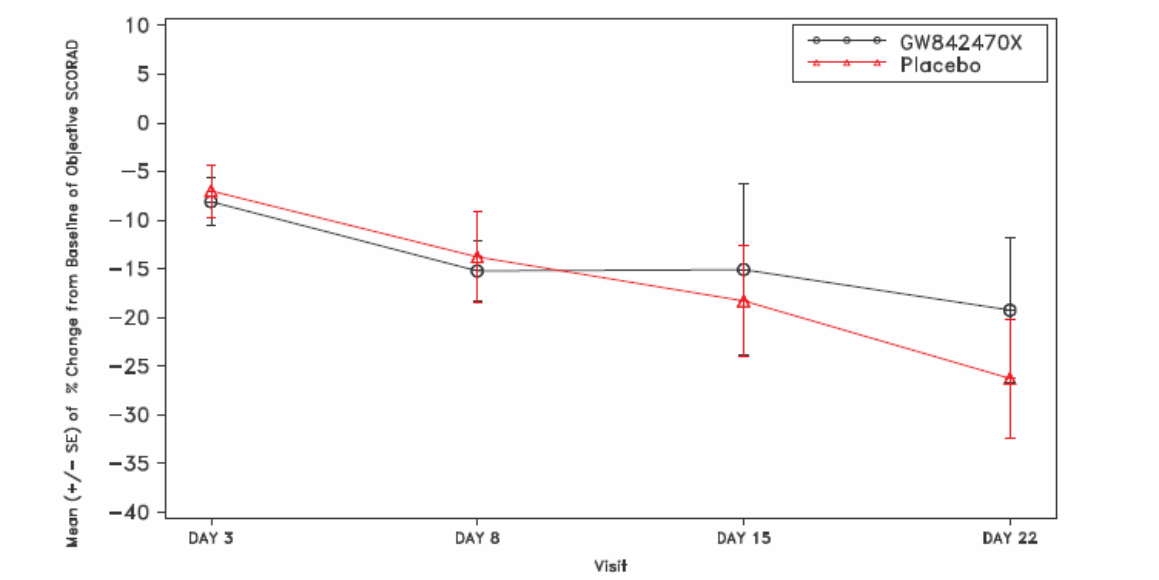
Table 6 Mean objective SCORing atopic dermatitis (95% confidence intervals) score by treatment and visit

Mean (95% Confidence Intervals)				
	GW842470X (3% w/w) (N =72)		Placebo (N = 71)	
Day	SCORAD Score	Change from Baseline	SCORAD Score	Change from Baseline
1	36.23 (32.73, 39.73)	-	36.13 (31.09, 41.17)	-
3	32.83 (29.49, 36.18)	-3.55 (-5.57, -1.52)	32.78 (28.55, 37.0)	-3.35 (-5.57, -1.12)
8	29.96 (26.56, 33.36)	-6.27 (-8.81, -3.73)	30.50 (25.73, 35.26)	-5.63 (-9.04, -2.22)
15	30.18 (23.58, 36.79)	-6.05 (-11.96, -0.13)	30.29 (23.07, 37.51)	-6.05 9-11.07, -1.03)
22	28.98 (23.0, 34.96)	-7.12 (-12.17, -2.07)	27.17 (20.32, 34.02)	-8.96 (-14.33, -3.59)

Source Data: Table 8 and Table 9
SCORAD = SCORing atopic dermatitis

The mean percentage change from baseline of objective SCORAD is presented in Figure 3.

Figure 3 Mean percentage change from baseline of objective SCORing atopic dermatitis



Source Data: Figure 23

There were no statistically significant differences in objective SCORAD scores between GW842470X and placebo on Days 3, 8, 15 or 22. A summary of point estimates and associated 95% CIs for the comparison of interest in objective SCORAD score is presented in Table 7.

Table 7 Summary of point estimates and associated 95% confidence intervals for objective SCORing atopic dermatitis scores

Parameter	Day	Comparison	PE	95% C.I.	SDb
Δ in objective SCORAD	Day 3	GW842470X – Placebo	-3.98	(-8.61, 0.65)	12.28
	Day 8	GW842470X – Placebo	-4.04	(-8.66, 0.57)	
	Day 15	GW842470X – Placebo	-2.50	(-7.14, 2.14)	
	Day 22	GW842470X – Placebo	-2.01	(-6.64, 2.61)	

Source Data: Table 7
Δ in objective = Change from baseline in objective SCORAD score.
SCORAD = SCORing atopic dermatitis, PE = point estimate, CI = confidence interval, SDb = standard deviation.

Full SCORing atopic dermatitis

Reductions from baseline in full SCORAD scores of increasing magnitude were observed from Day 1 to Day 22 in the GW842470X group and for placebo. A summary of full SCORAD scores and change from baseline by treatment and visit is presented in Table 8.

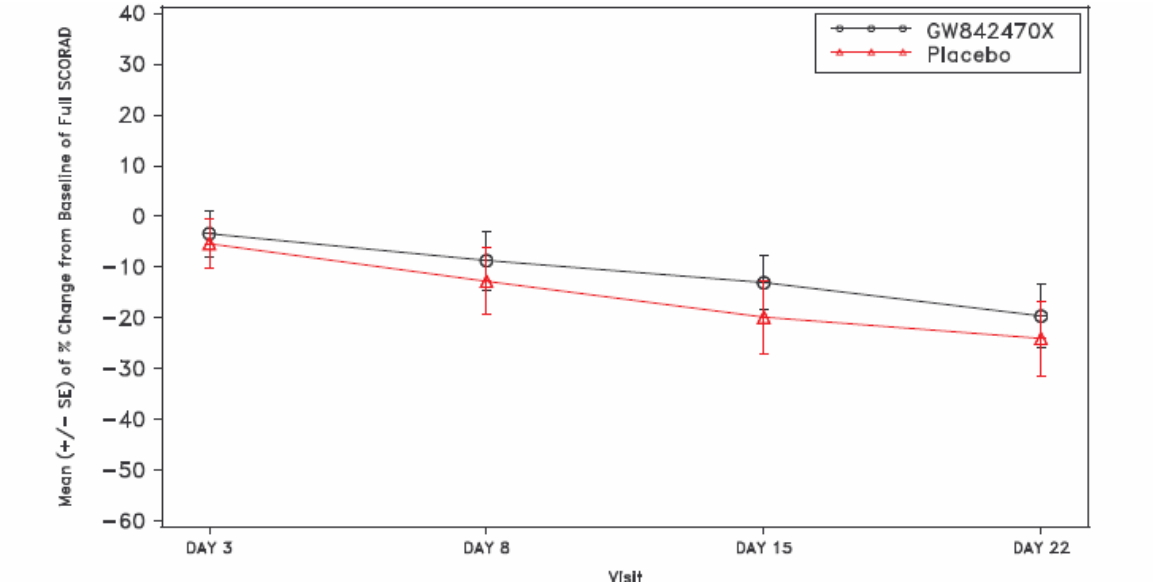
Table 8 Mean full SCORing atopic dermatitis (95% confidence intervals) score by treatment and visit

	Mean (95% Confidence Intervals)			
	GW842470X (3% w/w) (N =72)		Placebo (N = 71)	
Day	SCORAD Score	Change from Baseline	SCORAD Score	Change from Baseline
1	133.98 (124.68, 143.27)		134.64 (121.91, 147.38)	
3	125.34 (113.87, 136.80)	-9.46 (-20.87, -1.95)	120.68 (108.14, 133.22)	-14.17 (-26.22, -2.12)
8	116.36 (104.18, 128.54)	-18.29 (-31.26, -5.33)	110.73 (95.51, 125.95)	-24.20 (-40.26, -8.14)
15	114.52 (98.55, 130.50)	-19.45 (-33.99, -4.92)	100.93 (83.34, 118.52)	-32.89 (-51.84, -13.95)
22	105.81 (89.18, 122.45)	-28.77 (-44.18, -13.36)	94.67 (77.21, 112.14)	-38.66 (-58.13, -19.18)

Source Data: Table 11 and Table 12
SCORAD = SCORing atopic dermatitis

The mean percentage change from baseline of full SCORAD is presented in Figure 4.

Figure 4 Mean percentage change from baseline of full SCORing atopic dermatitis



Source Data: Figure 15

There were no statistically significant differences in full SCORAD scores between GW842470X and placebo on days 3, 8, 15 or 22. A summary of point estimates and associated 95% CIs for the comparison of interest in full SCORAD score is presented in Table 9.

Table 9 Summary of point estimates and associated 95% confidence intervals for full SCORing atopic dermatitis scores

Parameter	Day	Comparison	PE	95% C.I.	SDb
Δ in full SCORAD	Day 3	GW842470X – Placebo	-0.93	(-19.00, 17.14)	47.42
	Day 8	GW842470X – Placebo	0.66	(-17.38, 18.70)	
	Day 15	GW842470X – Placebo	9.99	(- 8.24, 28.23)	
	Day 22	GW842470X – Placebo	6.27	(-11.94, 24.47)	

Source Data: Table 7
Δ in full = Change from baseline in full SCORAD score.
SCORAD = SCORing atopic dermatitis, PE = point estimate, CI = confidence interval, SDb = standard deviation

15.3.3. Investigator's Global Assessment

Sleep Quality

Sleep quality - case report forms

In general, reductions from baseline of increasing magnitude in visual analogue scale (VAS) scores in sleep quality from case report forms (CRFs) were observed from Day 1 to Day 22 in the GW842470X group (except Day 15) and for placebo. A summary of

VAS scores from CRFs and change from baseline by treatment and visit is presented in Table 10.

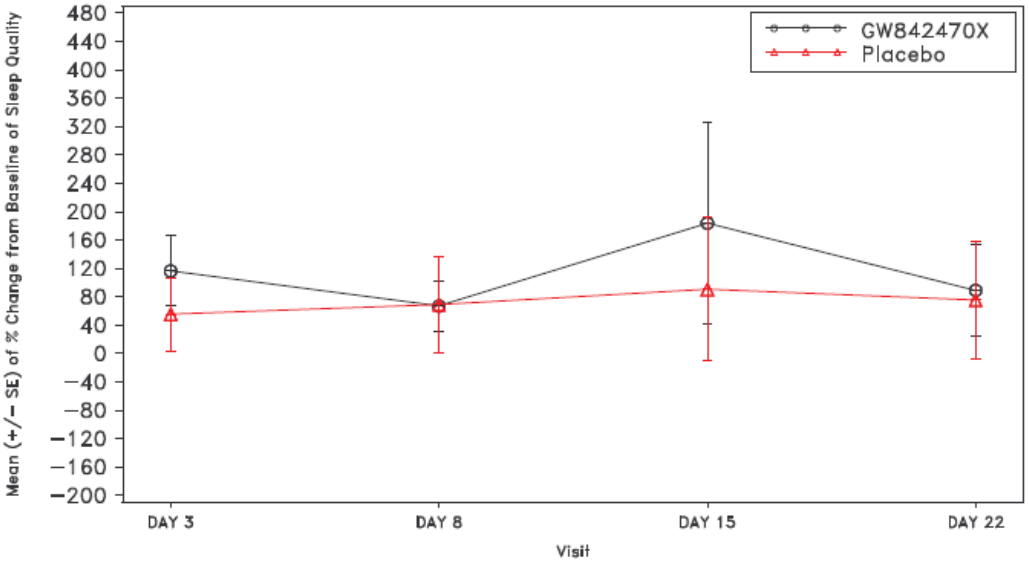
Table 10 Summary of mean visual analogue scale scores in sleep quality (95% confidence intervals) from case report forms

	Mean (95% Confidence Intervals)			
	GW842470X (3%w/w) (N =72)		Placebo (N = 71)	
Day	VAS Score	Change from Baseline	VAS Score	Change from Baseline
1	42.32 (35.64, 48.99)		45.66 (38.74, 52.59)	
3	42.76 (36.80, 48.72)	0.07 (-7.57, 7.71)	39.96 (33.51, 46.41)	-6.00 (-13.11, 1.11)
8	40.12 (33.81, 46.43)	-2.58 (-10.37, 5.22)	36.93 (29.53, 44.32)	-9.11 (-17.64, -0.59)
15	41.07 (33.91, 48.22)	-1.25 (-9.18, 6.68)	31.04 (23.69, 38.38)	-14.13 (-23.45, -4.82)
22	35.33 (28.32, 42.34)	-7.24 (-15.53, 1.05)	32.03 (24.68, 39.38)	-13.08 (-22.92, -3.24)

Source Data: Table 21 and Table 22

The mean percentage change from baseline of VAS scores in sleep quality is presented in Figure 5.

Figure 5 Mean percentage change from baseline in visual analogue scale score in sleep quality



Source Data: Figure 26

Sleep quality - patient diary cards

There did not appear to be any notable differences in sleep quality between GW842470X (3% w/w) and placebo. A summary of VAS scores from patient diary cards in sleep quality by treatment and visit is presented in Table 11.

Table 11 Summary of mean visual analogue scale scores in sleep quality (95% confidence intervals) from patient diary cards

	Mean (95% Confidence Intervals)			
	GW842470X (3% w/w) (N =72)		Placebo (N = 71)	
Day	VAS Score	Change from Baseline	VAS Score	Change from Baseline
1	44.26 (37.91, 50.62)	-	43.80 (36.90, 50.70)	-
2	43.48 (37.46, 49.49)	-0.79 (-7.19, 5.61)	42.82 (35.80, 49.84)	-1.09 (-7.32, 5.14)
3	44.30 (37.94, 50.66)	0.82 (-6.39, 8.02)	35.82 (29.77, 41.87)	-7.98 (-14.12, -1.85)
4	38.84 (32.70, 44.98)	-5.43 (-12.13, 1.28)	35.79 (29.14, 42.43)	-8.33 (-14.52, -2.13)
5	35.97 (30.53, 41.40)	-7.80 (-14.14, -1.46)	35.84 (28.72, 42.96)	-7.73 (-15.51, 0.06)
6	32.82 (27.61, 38.03)	-11.44 (-17.86, -5.02)	35.39 (28.96, 41.83)	-8.69 (-16.61, -0.77)
7	34.39 (28.32, 40.46)	-10.11 (-17.15, -3.07)	37.88 (30.71, 45.04)	-6.98 (-13.84, -0.12)
8	35.87 (29.20, 42.53)	-7.19 (-14.30, -0.09)	35.92 (27.96, 43.88)	-7.92 (-16.01, 0.17)
9	37.41 (30.92, 43.90)	-6.85 (-13.02, -0.68)	35.58 (28.58, 42.59)	-9.93 (-17.27, -2.58)
10	36.56 (30.03, 43.09)	-7.70 (-14.04, -1.37)	37.58 (30.00, 45.16)	-7.98 (-16.28, 0.32)
11	36.33 (30.37, 42.29)	-7.93 (-14.67, -1.20)	36.66 (29.07, 44.26)	-8.11 (-16.36, 0.14)
12	38.39 (31.40, 45.39)	-5.87 (-12.80, 1.06)	36.18 (28.97, 43.39)	-8.45 (-16.53, -0.38)
13	35.30 (28.89, 41.70)	-8.97 (-16.24, -1.69)	39.46 (32.25, 46.68)	-4.80 (-12.52, 2.92)
14	33.25 (27.15, 39.34)	-11.02 (-18.08, -6.05)	33.61 (26.59, 40.63)	-10.75 (-19.26, -2.23)
15	37.56 (30.51, 44.62)	-6.75 (-14.59, 1.09)	34.27 (26.86, 41.69)	-11.84 (-20.46, -3.22)
16	36.67 (29.77, 43.57)	-7.59 (-15.21, 0.03)	34.77 (27.45, 42.08)	-9.67 (-18.38, -0.96)
17	32.20 (26.08, 38.32)	-12.07 (-18.08, -6.05)	32.79 (25.46, 40.11)	-11.95 (-20.75, -3.14)
18	35.28 (28.61, 41.95)	-8.98 (-16.03, -1.94)	33.63 (26.17, 41.08)	-11.38 (-20.12, -2.64)
19	35.20 (28.40, 42.00)	-9.07 (-16.21, -1.92)	33.89 (26.44, 41.34)	-11.11 (-20.17, -2.05)
20	37.92 (31.14, 44.70)	-6.34 (-14.18, 1.50)	35.02 (27.43, 42.60_	-9.69 (-18.25, -1.13)
21	36.46 (29.41, 43.51)	-7.80 (-15.68, 0.07)	34.80 (26.78, 42.82)	-10.07 (-18.32, -1.83)
22	38.30 (30.51, 46.09)	-5.19 (-14.14, 3.77)	31.12 (23.77, 38.47)	-12.75 (-21.12, -4.38)

Source Data: Table 14 and Table 15
VAS = visual analogue scale

Itch Severity

Itch severity - case report form

Reductions from baseline of increasing magnitude in VAS scores in itch severity were observed from Day 1 to Day 22 in the GW842470X group and for placebo. No notable differences were observed between GW842470X and placebo. A summary of VAS scores in itch severity and change from baseline by treatment and visit from CRFs is presented in Table 12.

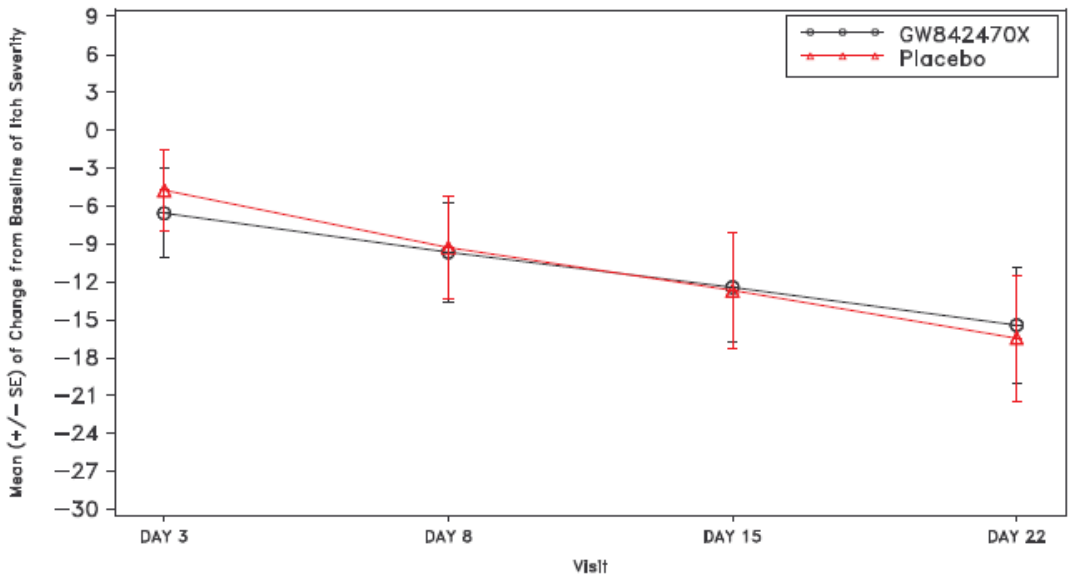
Table 12 Summary of mean visual analogue scale scores in itch severity (95% confidence intervals) from case report forms: change from baseline in actual score

	Mean (95% Confidence Intervals)			
	GW842470X (3% w/w) (N =72)		Placebo (N = 71)	
Day	VAS Score	Change from Baseline	VAS Score	Change from Baseline
1	55.71 (49.11, 62.31)		52.86 (46.11, 59.61)	
3	49.42 (43.05, 55.80)	-6.57 (-13.63, 0.50)	48.16 (41.67, 54.66)	-4.76 (-11.21, 1.69)
8	46.34 (39.76, 52.91)	-9.65 (-17.46, -1.84)	43.61 (35.97, 51.25)	-9.28 (-17.56, -1.00)
15	43.28 (35.47, 51.10)	-12.43 (-21.13, -3.72)	39.45 (31.39, 47.52)	-12.68 (-21.96, -3.40)
22	40.67 (32.84, 48.51)	-15.42 (-24.57, -6.27)	35.73 (27.95, 43.51)	-16.45 (-26.45, -6.46)

Source Data: Table 24 and Table 25
VAS = visual analogue scale

The mean change from baseline of VAS scores in severity of itch from case report forms is presented in Figure 6.

Figure 6 Mean change from baseline in visual analogue scale score in itch severity from case report forms



Source Data: Figure 28

Itch severity - patient diary cards

No apparent differences in itch severity scores were observed between GW842470X and placebo. A summary of VAS scores from patient diary cards in itch severity by treatment and visit are presented in Table 13.

Table 13 Summary of mean visual analogue scale scores in itch severity (95% confidence intervals) from patient diary cards

	Mean (95% Confidence Intervals)			
	GW842470X (3% w/w) (N =72)		Placebo (N = 71)	
Day	VAS Score	Change from Baseline	VAS Score	Change from Baseline
1	53.72 (47.74,59.70)	-	48.32 (41.75, 54.89)	-
2	51.41 (45.62, 57.20)	-2.31 (-7.23, 2.60)	47.07 (40.48, 53.66)	-1.25 (-5.97, 3.47)
3	52.97 (46.67, 59.26)	-0.75 (-5.33, 3.82)	44.73 (38.58, 50.88)	-3.59 (-9.21, 2.03)
4	52.67 (46.42, 58.93)	-1.05 (-6.46, 4.36)	49.02 (42.39, 55.65)	0.70 (-6.12, 7.51)
5	45.69 (39.49, 51.88)	-8.03 (-14.48, -1.59)	48.02 (40.86, 55.17)	-0.30 (-8.33, 7.72)
6	47.62 (41.12, 54.13)	-6.10 (-13.10, 0.90)	44.82 (37.19, 52.54)	-3.50 (-11.76, 4.76)
7	45.83 (38.81, 52.84)	-7.73 (-14.43, -1.02)	44.45 (37.35, 51.54)	-3.88 (-11.60, 3.85)
8	44.61 (37.32, 51.89)	-8.93 (-16.61, -1.26)	44.78 (36.87, 52.68)	-3.02 (-11.46, 5.42)
9	45.25 (38.31, 52.18)	-8.48 (-15.34, -1.61)	45.93 (38.39, 53.47)	-3.11 (-11.30, 5.08)
10	45.64 (38.77, 52.51)	-8.08 (-15.21, -0.95)	44.29 (36.76, 51.82)	-4.75 (-13.58, 4.09)
11	45.69 (38.69, 52.69)	-8.03 (-15.81, -0.26)	44.34 (36.37, 52.31)	-3.98 (-13.37, 5.40)
12	46.56 (38.97, 54.15)	-7.16 (-15.17, 0.84)	43.59 (35.86, 51.32)	-4.73 (-14.43, 4.88)
13	41.41 (33.84, 48.98)	-12.31 (-20.21, -4.42)	45.80 (37.99, 53.62)	-2.52 (-11.56, 6.53)
14	41.84 (34.03, 49.64)	-11.89 (-20.07, -3.70)	41.11 (32.97, 49.25)	-7.44 (-16.75, 1.88)
15	40.67 (32.82, 48.51)	-12.84 (-20.83, -4.85)	36.51 (28.56, 44.46)	-13.55 (-22.84, -4.26)
16	42.28 (34.99, 49.57)	-11.44 (-18.82, -4.07)	37.14 (29.74, 44.55)	-11.18 (-19.73, -2.63)
17	41.21 (33.65, 48.78)	-12.51 (-20.05, -4.97)	36.59 (29.36, 43.82)	-11.73 (-20.39, -3.07)
18	42.93 (35.19, 50.68)	-10.79 (-18.44, -3.13)	39.64 (32.41, 46.88)	-8.68 (-18.04, 0.68)
19	42.56 (34.95, 50.17)	-11.16 (-18.77, -3.56)	39.71 (32.74, 46.68)	-8.61 (-17.25, 0.04)
20	41.56 (34.24, 48.88)	-12.16 (-20.04, -4.29)	35.82 (28.74, 42.90)	-12.50 (-21.18, -3.82)
21	40.85 (33.77, 47.94)	-12.87 (-20.69, -2.73)	35.73 (28.55, 42.90)	-12.04 (-21.08, -2.99
22	41.13 (33.19, 49.08)	-11.71 (-20.69, -2.73)	36.86 (28.75, 44.97)	-9.16 (-19.45, 1.12)

Source Data: Table 17 and Table 18
VAS = visual analogue scale

Index Lesion severity

Reductions from baseline in lesion severity scores of increasing magnitude were observed from Day 1 to Day 22 in the GW842470X group and for placebo. A summary of lesion severity score and change from baseline by treatment and visit is presented in Table 14.

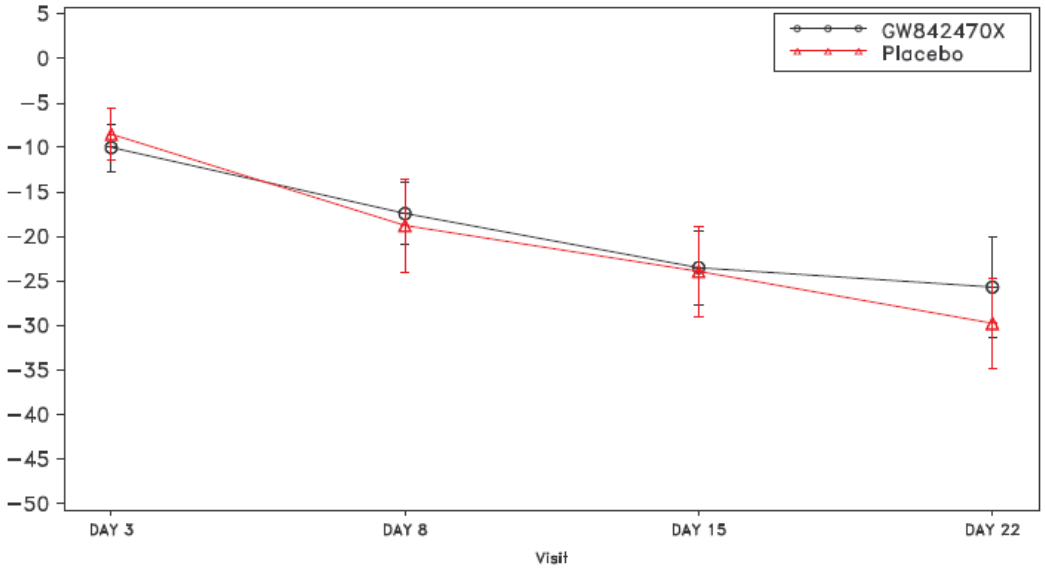
Table 14 Summary of mean summed index lesion severity scores (95% confidence intervals)

	Mean (95% Confidence Intervals)			
	GW842470X (3% w/w) (N =72)		Placebo (N = 71)	
Day	Lesion severity score	Change from Baseline	Lesion severity score	Change from Baseline
1	4.97 (4.76, 5.17)		4.75 (4.46, 5.04)	
3	4.43 (4.14, 4.72)	-0.53 (-0.80, -0.26)	4.45 (4.10, 4.79)	-0.30 (-0.61, 0.00)
8	4.03 (3.71, 4.36)	-0.93 (-1.28, -0.59)	3.98 (3.44, 4.52)	-0.77 (-1.27, -0.26)
15	3.75 (3.34, 4.16)	-1.21 (-1.64, -0.79)	3.75 (3.20, 4.30)	-1.00 (-1.51, -0.49)
22	3.59 (3.07, 4.11)	-1.38 (-1.92, -0.83)	3.45 (2.91, 3.98)	-1.30 (-1.80, -0.80)

Source Data: Table 27 and Table 28

The mean percentage change from baseline of lesion severity scores is presented in Figure 7.

Figure 7 Mean percentage change from baseline in lesion severity score



Source Data: Figure 32

Investigator's Global Assessment – total scores

There were no statistically significant differences in IGA scores between GW842470X and placebo on days 3, 8, 15 or 22. A summary of point estimates and associated 95% CIs for the comparison of interest in IGA score is presented in Table 15.

Table 15 Summary of point estimates and associated 95% confidence intervals for investigator's global assessment scores

Parameter	Day	Comparison	PE	95% C.I.	SDb
IGA	Day 3	GW842470X – Placebo	-0.16	(-0.38, 0.07)	0.59
	Day 8	GW842470X – Placebo	0.02	(-0.20, 0.24)	
	Day 15	GW842470X – Placebo	-0.16	(-0.39, 0.06)	
	Day 22	GW842470X – Placebo	0.02	(-0.20, 0.24)	

Source Data: Table 5
IGA = investigator's global assessment, PE = point estimate, CI = confidence interval, SDb = standard deviation.

15.4. Safety

15.4.1. Extent of Exposure

A total of 140 subjects received study medication. Seventy-one received GW842470X (3% w/w) BID and 69 received placebo BID. A summary of extent of exposure (mean cumulative dose) is presented in Table 16.

Table 16 Extent of exposure

	GW842470X (N = 72)	Placebo (N = 71)
	n = 71	N = 69
Mean cumulative dose (FTU) (sd)	401.9 (307.47)	338.4 (230.72)
Duration (Days) (sd)	19.4 (4.20)	19.5 (4.25)

Source Data: Table 10.1
FTU = finger tip unit, sd = standard deviation

15.4.2. Adverse Events

15.4.2.1. Adverse events irrespective of causality

Eighty-two (57%) subjects experienced AEs during the study. Seven (5%) subjects experienced AEs pre-treatment. The most frequently reported post-treatment AE was headache (34 subjects) followed by nasopharyngitis (10 subjects). Most of the AEs were mild or moderate in intensity. Six subjects experienced AEs of severe intensity. The most frequently reported AEs in more than one subject in any group are summarised in Table 17.

Table 17 Summary of adverse events irrespective of causality: more than one subject in any group

Adverse Event (Preferred Term)	Pre-treatment N = 143	GW842470X N = 72	Placebo N = 71
	n (%)	n (%)	n (%)
Headache	0	23 (32)	11(15)
Nasopharyngitis	1 (<1)	7 (10)	3 (4)
Back pain	0	3 (4)	3 (4)
Pharyngolaryngeal pain	0	4 (6)	2 (3)
Nausea	0	3 (4)	2 (3)
Pruritus	0	4 (6)	1 (1)
Application site irritation	0	3 (4)	1 (1)
Abdominal pain	0	2 (3)	1 (1)
Dermatitis atopic	0	1 (1)	2 (3)
Eczema	0	0	3 (4)
Fatigue	0	2 (3)	1 (1)
Lymphadenopathy	0	2 (3)	1 (1)
Bacteria urine identified	0	2 (3)	0
Conjunctivitis	2 (1)	0	0
Diarrhoea	0	2 (3)	0
Dry skin	0	2 (3)	0
Ear pain	0	2 (3)	0
Neuromuscular blockade	0	0	2 (3)
Seasonal allergy	0	2 (3)	0
Skin burning sensation	0	0	2 (3)
Toothache	0	2 (3)	0

Source Data: Table 10.03

Six (4%) subjects experienced severe AEs as follows:

- [redacted] Fatigue was not considered by the investigator to be related to the investigational drug; however, nausea was judged to be drug related.
- [redacted] The AE resolved after 31 days; the investigator did not consider this to be related to the investigational drug.
- [redacted] The AE resolved after 2 days; the investigator did not consider this to be related to the investigational drug.
- [redacted] The AE resolved after 2 days; the investigator did not consider this to be related to the investigational drug.
- [redacted] The AE resolved after 10 days; the investigator did not consider this to be related to the investigational drug.

- [redacted] The AE resolved after 10 days; however, this subject was withdrawn from the study. The investigator considered this AE to be related to the investigational drug.

15.4.2.2. Adverse events judged related to the investigational product by the Investigator

Seventeen (12%) subjects, eight of whom had received (GW842470X (3% w/w) and nine who had received placebo, experienced 26 AE episodes considered to be related to the investigational product (Table 18). All but one of the AE episodes were of mild or moderate intensity. [redacted]

Table 18 Adverse events related to investigational product

[redacted]

Source Data: Table 10.25

a. [redacted]
b. [redacted]
c. [redacted] /Four episodes resolved in 1 day; however, the fifth episode resolved after 12 days.
d. [redacted]

15.4.3. Serious Adverse Events

One subject experienced a serious AE (SAE) as follows:

- [redacted] This SAE was not considered to be related to the investigational product.

15.5. Adverse Events Leading to Premature Discontinuation of Investigational Product and/or Study

Six (4%) subjects experienced AEs which led to premature withdrawal from the study. [redacted] Four of the AEs were of mild or moderate intensity and one was assessed as severe.

Table 19 Summary of adverse events leading to withdrawal

[redacted]

Source Data: Table 10.25

15.5.1. Pregnancies

No female subjects became pregnant during this study.

15.5.2. Clinical Laboratory Evaluations

15.5.2.1. Abnormalities of potential clinical concern

Haematology

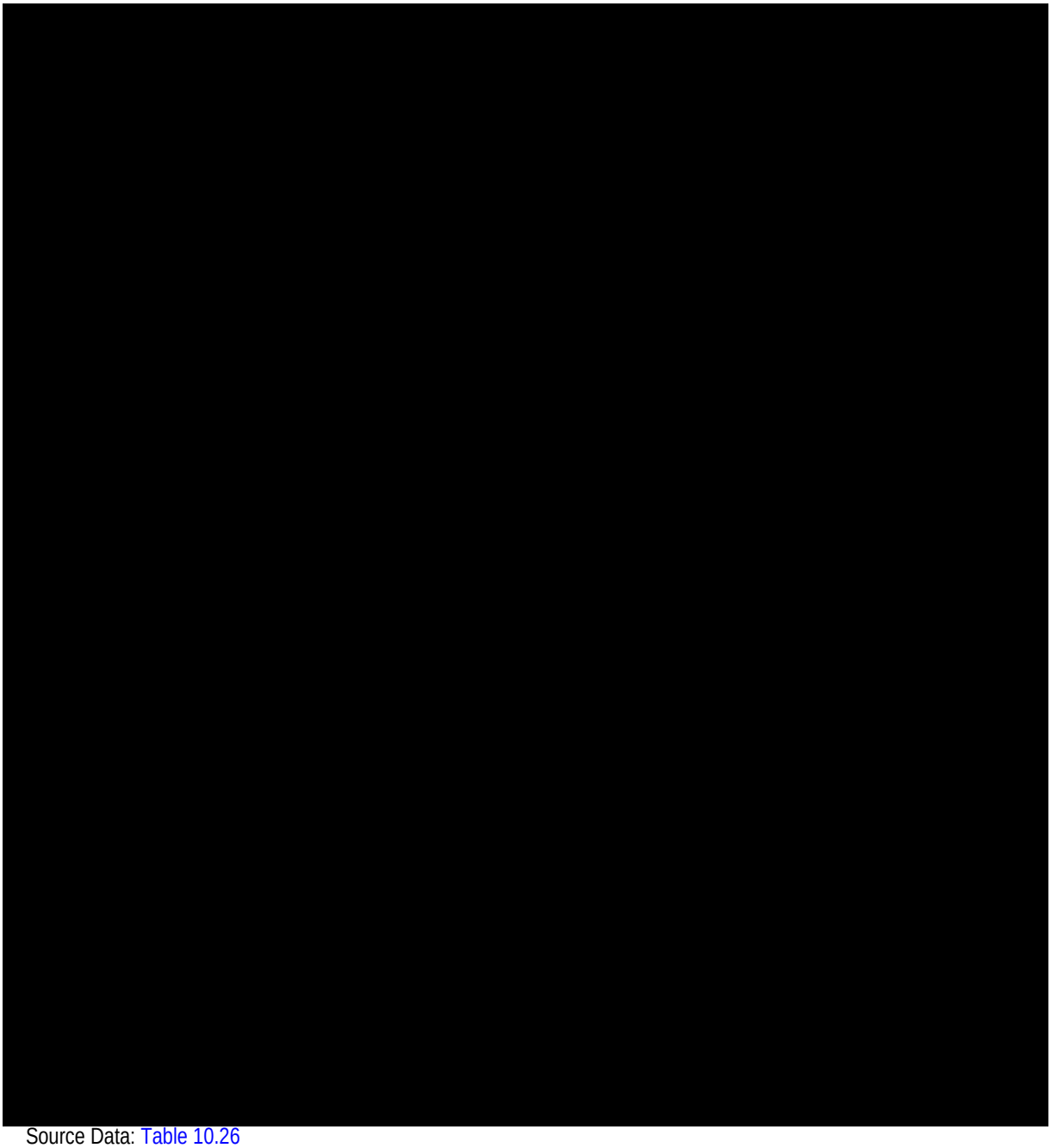
Three subjects had haematology values reported as AEs as follows:

- [redacted] This event was not considered to be related to investigational product.
- [redacted] This value returned to normal within 8 days and the condition was of moderate intensity and not considered to be related to the investigational product.
- [redacted] These values did not return to normal during the time period of the study. Both

conditions were of moderate intensity and not considered to be related to the investigational product.

Sixteen subjects had haematology values considered to be of potential clinical concern, summarised in Table 20. None of these was reported as an AE.

Table 20 Summary of haematology values of potential clinical concern



Source Data: Table 10.26

Clinical Chemistry

Eleven subjects had clinical chemistry values considered to be of potential clinical concern, as summarised in Table 21. None of these was reported as an AE.

Table 21 Summary of clinical chemistry values of potential clinical concern

Source Data: Table 10.26
a = Except Day 8
b = Except Day 15

Urinalysis

Five subjects had urinalysis results recorded as AEs as follows:

- This AE did not resolve during the course of the study, however it was not considered to be related to the investigational product.
- The AE was not considered to be related to the investigational product. These AEs also recovered after 29 days and were not considered to be related to the investigational product.
- The AE was of moderate intensity and not considered to be related to the investigational product.
- Both AEs were of moderate intensity and not considered to be related to the investigational product.
- The AE was of mild intensity and not considered to be related to the investigational product. This subject also experienced leukocyturia of mild intensity, which

resolved in 8 days and was not considered to be related to the investigational product.

A summary of the urine dipstick results is presented in Source Data Table 10.10.

15.5.3. Vital Signs

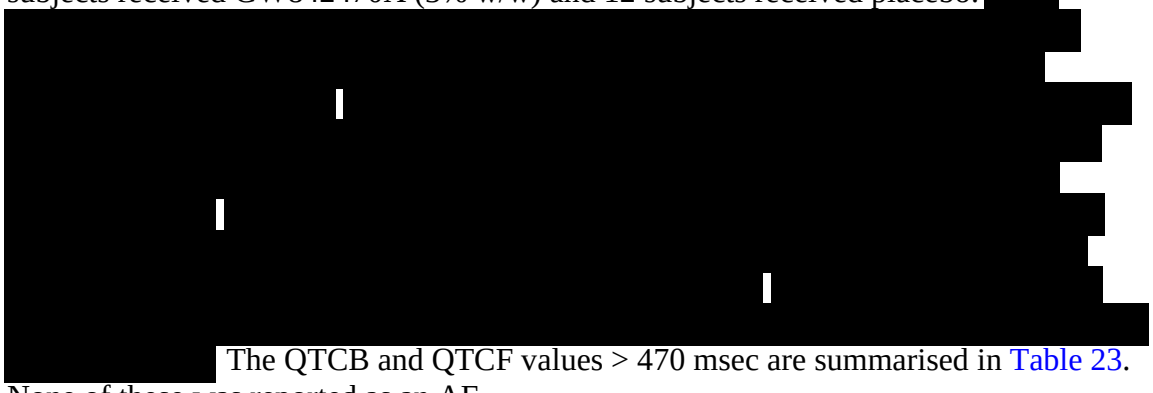
Thirteen subjects had blood pressure values of potential clinical concern; eight subjects receiving GW842470X and five subjects receiving placebo as summarised in Table 22.

Table 22 Summary of blood pressure values (mmHg) of potential clinical concern

Source Data: Table 10.27
PCC = potential clinical concern

15.5.4. Electrocardiography

Thirty-one subjects had ECG values of potential clinical concern, of these nineteen subjects received GW842470X (3% w/w) and 12 subjects received placebo.



The QTCB and QTCF values > 470 msec are summarised in Table 23. None of these was reported as an AE.

Table 23 Summary of electrocardiography: QTCF (msec) and QTCB (msec) values of potential clinical concern >470 (msec)

[redacted]

Source Data: Table 10.28

15.6. Pharmacokinetics

15.6.1. Pharmacokinetic Analyses

[redacted]

These two subjects were excluded from pharmacokinetic analyses.

[redacted] The two consecutive NQ concentrations were then followed by more quantifiable concentrations. The aforementioned concentrations were excluded from pharmacokinetic analyses, the two consecutive NQ concentrations were treated as leading

NQs (zeroes), and pharmacokinetic analyses were run on the remaining concentrations in the respective profiles.

[redacted]
No pharmacokinetic parameters were calculated for these subjects.

[redacted] Only Cmax was calculated for these subjects on Day 1 and only Cmax, Cmin, and Cτ were calculated for these subjects on Day 22.

[redacted]

15.6.2. GW842470X Plasma Pharmacokinetics

Summaries of the pharmacokinetic parameters are presented in Source Data Table 12.1, Table 12.2, Table 12.3 and Table 12.4. GW842470X pharmacokinetic parameters are summarised in Table 24. A summary of AUC(0–τ) and Cmax values by %BSA affected by AD is presented in Table 25.

Table 24 Summary of GW842470X Pharmacokinetic Parameters

	AUC(0–τ) (ng·h/mL)	Cmax (ng/mL)	Cτ (ng/mL)	Cave (ng/mL)	Cmin (ng/mL)	Df[1]	Ro[1]
Day 1	1.74 (75.7) [0.496–14.3] n = 40	0.237 (105) [0.0518–2.37] n = 58	NA	NA	NA	NA	NA
Day 8	NA	NA	0.221 (123) [0–11.3] n = 69	NA	NA	NA	NA
Day 15	NA	NA	0.186 (84.0) [0–1.47] n = 65	NA	NA	NA	NA
Day 22	2.44 (108) [0.406–33.5] n = 60	0.361 (141) [0.0520–6.18] n = 63	0.223 (112) [0–5.23] n = 61	0.204 (108) [0.0338–2.79] n = 60	0.116 (85.2) [0.0501–1.35] n = 63	1.53 (109) [0.377–11.7] n = 60	2.47 (85.3) [0.188–9.91] n = 35

Source Data: Table 12.1 and Table 12.2
Data are geometric mean (CVb%) and [range].
1. Arithmetic mean (CV%).
NA = Not applicable.

Repeat BID topical administration of 3% GW842470X cream resulted in increased mean GW842470X AUC(0–τ) and Cmax values on Day 22 compared with Day 1. Mean Cmax

values increased approximately 1.5-fold and Ro values showed a nearly 2.5-fold increase in AUC(0–τ) values for Day 22 compared with Day 1. These results indicate accumulation of GW842470X after repeated administration. Mean Cτ values were approximately equivalent across days 8, 15, and 22 indicating that steady-state was generally achieved by Day 8.

Table 25 Geometric Mean (CVb%) GW842470X AUC(0–τ) and Cmax by %BSA Affected by Atopic Dermatitis

	% BSA Affected	AUC(0–τ) (ng·h/mL)	Cmax (ng/mL)
Day 1	5–10%	1.23 (50.8) n = 5	0.169 (84.8) n = 11
	10–20%	1.38 (47.6) n = 19	0.203 (82.8) n = 28
	20–30%	2.09 (81.5) n = 9	0.318 (130) n = 11
	>30%	3.39 (96.4) n = 7	0.426 (140) n = 8
	All Subjects	1.74 (75.7) n = 40	0.237 (105) n = 58
Day 22	0–5%	1.23 (63.7) n = 16	0.192 (89.7) n = 18
	5–10%	2.64 (114) n = 14	0.518 (214) n = 14
	10–20%	2.46 (79.9) n = 18	0.337 (90.7) n = 18
	20–30%	4.19 (47.0) n = 5	0.420 (171) n = 6
	>30%	6.71 (97.4) n = 7	0.933 (77.8) n = 7
	All Subjects	2.44 (108) n = 60	0.361 (141) n = 63

Source Data: Table 12.1, Table 12.3 and Table 12.4
NA = Not applicable.

Average systemic exposure, Cmax and AUC(0–τ) generally increased with increases in % BSA affected by AD (Table 12.3 and Table 12.4). Within days 1 and 22, a greater than 2-fold increase in mean AUC(0–τ) and Cmax values was observed in subjects with >30% BSA affected compared with subjects with 5–10% BSA affected with the exception of Cmax on Day 22 where the increase was approximately 1.8-fold.

15.7. Skin Tissue Biomarker Investigation

Skin tissue biopsy specimens were collected from a subset of randomized patients to investigate the expression of a range of genes known to be impacted by PDE4 inhibitors and/or by the pathological process of AD. The primary objective of this exploratory sub –study was to confirm pharmacologic activity of GW842470X in relevant tissues of

the skin (i.e., epidermis and dermis). To fulfill a total of 15 subjects per treatment group, 30 subjects were planned for inclusion in the biopsy sub-study. The number of samples planned for this sub-study was entirely derived from an assessment of feasibility and the subsequent analysis is deemed exploratory.

15.7.1. Biopsy Acquisition

At screening a second index lesion was identified for biopsy sampling of skin tissue to be used in the exploratory biomarker sub-study. The index lesion was selected from the subject's neck, hands or flexural sites of the elbow or knees and represented common lesions i.e., not the most or least severe lesions. Baseline (pre-dose on Day 1) and post-treatment (pre-dose on Day 22) 3 mm punch biopsies were collected from the middle of biopsy index lesions in a sub-set of randomised subjects. Both pre-dose and post-treatment punch biopsy specimens were taken from the same index lesion. Following acquisition, biopsy samples were immediately placed into RNALater solution and stored in sterile containers at –20°C. Samples were then shipped to analysis laboratories at GlaxoSmithKline in the UK for isolation of RNA and analysis of gene expression.

15.7.2. Gene Expression Analysis

A total of 48, 3 mm skin biopsy samples were collected from 24 subjects (i.e., Day 1 and Day 22 paired skin samples). Unforeseen sample handling and processing issues (related to acquisition of high quality RNA) resulted in successful analysis of a range of PDE4-related genes in only nine subjects (five who received placebo versus four who received GW842470X). An analysis of gene expression data for these nine subjects' paired biopsy samples identified a number of genes, which were differentially expressed between active and placebo groups. The most significant change in expression was noted with the PDE4C isoform, exhibiting a 3.2 fold reduction in expression in GW842470X treated skin compared to placebo at Day 22. This magnitude of change is unlikely to have occurred due to chance (ANOVA p=0.004, corrected for multiplicity) and is relevant to the pharmacology of GW842470X.

16. CONCLUSIONS

- There were no statistically significant differences in EASI scores between GW842470X and placebo on days 3, 8, 15 or 22. Therefore, 35% difference in EASI change from baseline between GW842470X and placebo was not observed.
- There were no statistically significant differences in SCORAD and IGA scores between GW842470X and placebo on days 3, 8, 15 or 22.
- Generally, GW842470X was well tolerated. There was no difference between GW842470X and placebo in overall frequency of AEs and AEs judged to be drug related.
- The most frequently reported AE was headache, which appeared to be more frequently reported in subjects who received GW842470X compared with placebo

(32% versus 15%). There were no notable differences between groups for other AEs. No drug related SAEs were reported.

- Three subjects had haematology values recorded as AEs and five subjects had urinalysis results recorded as AEs, however, in all cases these were not considered to be related to the investigational product. No clinical chemistry, vital signs or ECG values were recorded as AEs.
- GW842470X Cmax and AUC(0–τ) values generally increased as the %BSA affected with AD increased after both single and repeat BID topical administration of 3% GW842470X cream.
- Accumulation was apparent after repeated BID topical administration of 3% GW842470X cream on Day 22 where GW842470X Cmax and AUC(0–τ) values were approximately 2-fold greater than those after a single treatment for subjects with 5–10%, 20–30%, and >30% BSA affected.
- GW842470X trough (Cτ) values were relatively constant indicating that steady-state was achieved by Day 8 of dosing.
- An exploratory biomarker study in a sub-population of subjects suggests that GW842470X was pharmacologically active in skin tissue following 22 days of topical application.

17. REFERENCES

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NDA-21-32 Protopic information available on www.fda/gov/cder/approval/index.htm under Clinical Pharmacology Biopharmaceutics Review: Study Study ASMW 204 (NDA 21-302).

18. DATE OF REPORT

June 2007.