ORIGINAL ARTICLE

Use of Longitudinal Dose–Response Modeling to Support the Efficacy and Tolerability of Alitretinoin in Severe Refractory Chronic Hand Eczema (CHE)

GD Schmith[1,2]*, R Singh[1], R Gomeni[3], O Graff[4], AG Hamedani[1], JS Troughton[5] and SM Learned[6]

Longitudinal dose–response analyses of alitretinoin (an investigational agent in the US) were conducted to supplement results from phase III studies in severe, refractory chronic hand eczema, with objectives to address several outstanding development issues (e.g., optimal dose, possible factors affecting efficacy and/or tolerability). Models were fitted to the physicians' global assessment score and triglycerides over time. Five hundred trials were simulated to evaluate the relevance of findings. Analyses clarified that the optimal dose of alitretinoin was 30 mg once daily, where response rates were ~10% over placebo at 12 weeks and increased by 5–7% over placebo for every 4 weeks thereafter, for up to 24 weeks. Elderly subjects had higher magnitudes of efficacy and an increased probability of high triglycerides. Results from analyses sufficiently addressed the development issues, thereby adding to the weight of evidence supporting the efficacy and safety of alitretinoin in the treatment of severe, refractory chronic hand eczema.

Alitretinoin (BAL4079, 9-*cis* retinoic acid, Toctin), a physiological metabolite of vitamin A, is an investigational product in the US for the treatment of severe chronic hand eczema (CHE) refractory to treatment with potent topical corticosteroids. The product is already approved in 31 countries based on a phase II study (BAP00003[1]) and a phase III study (BAP00089[2]). GlaxoSmithKline (GSK, Research Triangle Park, NC) acquired alitretinoin after a second phase III study (BAP01346[3]) was conducted to provide additional independent substantiation of the phase III study results for the US Food and Drug Administration (FDA). In order to supplement the information provided by BAP01346 with regard to several outstanding development issues (**Supporting Table S1**), longitudinal dose–response (LDR) analyses were planned and conducted.

There are no currently approved treatments for severe refractory CHE in the US. Severe CHE is characterized by thick scaly skin with painful fissures, vesicles, and excoriation, erythema, and edema resulting in pain, itching, and bleeding that can make manual work (e.g., buttoning a shirt) difficult to perform and may prevent participation in social/work employment situations.[4]

Phase II/III studies of alitretinoin demonstrated a clinically meaningful benefit using a 5-point physician global assessment (PGA) scale (**Table S2**) with a response defined as a PGA score of 1 (clear) or 2 (almost clear) at end of treatment (EOT). Response rates were higher after 30 mg (~48%) than 10 mg (~27%) and placebo (~17%) once daily, with secondary endpoints (including the modified total lesion severity score [mTLSS], **Table S1**, among others) also supporting efficacy.[2,3] Adverse events (AEs) were con-

sistent with oral retinoids, which also appeared to be dose-related.[1–3,5]

The overall goals of the LDR analyses were to:

- Characterize efficacy and triglycerides over time following alitretinoin administration to assess the most appropriate dose;
- Evaluate factors affecting efficacy and triglycerides; and
- Simulate clinical trials to assess the clinical relevance of any findings and potential labeling implications.

METHODS

Efficacy and tolerability dose–response analyses were conducted based on double-blind, placebo-controlled phase II and/or phase III studies including BAP00089, BAP00091 (Part A double-blind retreatment only), BAP01346, and BAP00003 (**Figure 1**). All studies were conducted in accordance with the principles of Good Clinical Practice and were approved by Ethics Committees. BAP00089, BAP00091, and BAP01346 were posted to clinicaltrials.gov (NCT00124475, NCT00124436, NCT00817063, respectively), while BAP00003 was conducted between December 2001 and May 2002, prior to the ICMJE trial registration requirement. Informed consent was obtained for all subjects prior to participation and the studies were performed in accordance with the version of the Declaration of Helsinki that applied at the time the studies were conducted.

Prior to analyses, data were randomly divided by study and treatment into: the model development (MD) dataset (70% of data used in the development of the model) and

[1]Quantitative Sciences, GlaxoSmithKline (GSK), Research Triangle Park, North Carolina and Upper Merion, Pennsylvania, USA; [2]Currently at Nuventra Pharma Sciences, Research Triangle Park, North Carolina and Upper Merion, Pennsylvania, USA; [3]Pharmacometrica, Longcol, France; [4]Clinical Development, Stiefel, a GSK Company, Research Triangle Park, North Carolina, USA; [5]Regulatory Affairs, GSK, Research Triangle Park, North Carolina, USA; [6]Medicines Development Leader, Stiefel, a GSK Company, Research Triangle Park, North Carolina, USA. *Correspondence: G Schmith (gschmith@nuventra.com)
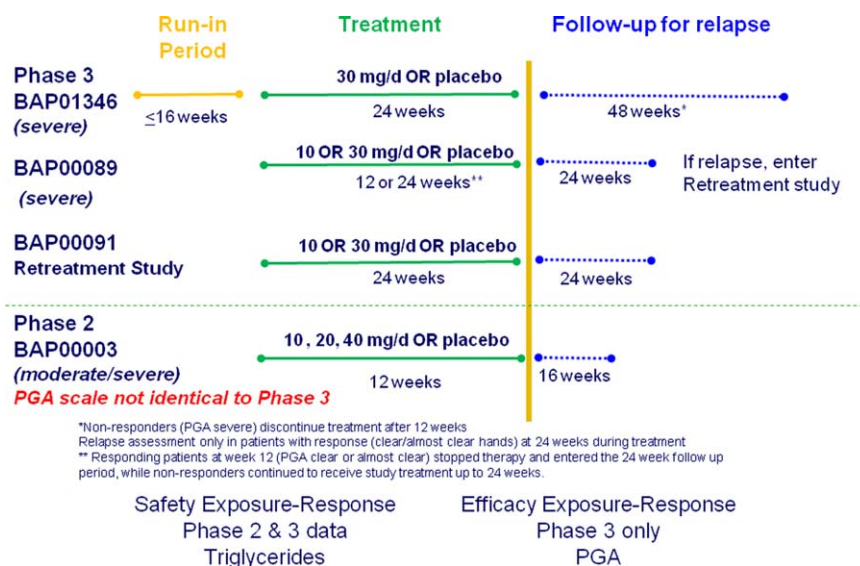
Figure 1 Important design features of the studies included in the dose–response analyses.

the model validation (MV) dataset (remaining 30% retained for external validation).

Longitudinal efficacy dose response analysis

Efficacy dose–response analysis was conducted using the PGA (primary endpoint), a 5-point scale (**Table S1**); PGA was collected at screening; baseline; every 4 weeks during treatment in all subjects; and every 4 weeks posttreatment in responders only for BAP00089, BAP00091, and BAP01346.

A longitudinal logistic regression model (**Figure S3**) was fitted to observed PGA over time using NONMEM. Inter-subject variability (IIV) was modeled as an additive variability on cumulative probability of PGA.

Covariate model building was a stepwise process consisting of forward addition (using decreased objective function value [OFV] ≥ 6.64, $\chi^2 < 0.01$ with 1 degree of freedom [*df*] as criteria) and backward elimination (using increased OFV ≥ 10.83, $\chi^2 < 0.001$ for 1 *df* as criteria). In situations where there was colinearity between covariates (age/creatinine clearance), the covariate was selected based on the change in OFV, effect size, physiology, and precision of the estimates. Including more than one colinear covariate on a parameter was avoided, unless goodness of fit (GoF) criteria suggested it was necessary.

Model performance/validation and stability were examined by:

○ Comparing NONMEM results to nonparametric bootstrapping ($n = 500$) and comparing observed/predicted using visual predictive checks (VPCs, $n = 1,000$) (internal approach).
○ Applying the parameter estimates from the MD dataset to an external MV dataset and assessing VPCs and mirror plots (external approach).

Triglycerides dose response analyses

Triglycerides were chosen as the safety/tolerability endpoint for the safety dose–response analyses with the

understanding that the analysis could inform dose selection, but not in isolation of other safety/tolerability information.

Observed triglycerides at baseline and during treatment were modeled using two approaches: a triglycerides LDR analysis (modeling the change from baseline in triglycerides as a continuous variable) and a time to event approach (modeling the time to reach triglycerides >200 mg/dL). The triglycerides LDR model was developed and validated using MD and MV datasets, respectively, using NONMEM with postprocessing within *R*. The time-to-event model was developed with the entire dataset (MD+MV datasets) using SAS (Cary, NC).

The triglycerides LDR model was fit to all triglycerides during treatment using the following equation:

$$TRI = BAS + AL1 * (1 - e^{(-AL2*Time)})$$

where BAS = baseline triglycerides, AL1 = maximal increase from baseline, and AL2 = rate constant defining the median time to reach the maximal change from baseline. The data supported IIV parameters on BAS and AL1, using proportional error models and residual error using a proportional error model (**Figure S6**).

Covariate analyses were conducted using forward addition and backward elimination as described for efficacy, assuming that the selected covariates could have a potential impact on the BAS and/or AL1. Because food is an important covariate known to affect the baseline triglycerides; fasted/fed status was not collected in BAP00003, and triglycerides from the 40 mg dose in this study could help with dose selection, a mixture model was used to describe the fed status for subjects in this study (**Figure S6**). The mixture model was possible because other studies included many more subjects than the phase II study and included a reasonable distribution of fasted triglycerides (2/3rd) and unfasted triglycerides (1/3rd).

Model performance was evaluated using similar internal and external approaches. In addition, using the final model developed by using the MD dataset, individual empirical Bayes estimates of triglycerides for the MV dataset were estimated; the distribution of the difference was estimated and compared to zero using a *t* statistic.

For the time-to-event model, the triglycerides for each individual at each measured time were classified as 0 (≤200 mg/dL) or 1 (>200 mg/dL), with those who did not experience the event during the study duration classified as censored. Data were analyzed using a Kaplan–Meier approach to identify the shape of the survival function and whether or not the survivals in the subpopulations are proportional.

The formal time-to-event analysis was conducted using the Cox proportional hazards model using SAS where the model was semiparametric (baseline hazard can take any form, but covariates enter the model linearly). Covariates were added using a stepwise process using the same criteria as for the LDR model. Fed/fasted status was assigned based on either the known status or the assigned status from the mixture model within the LDR model for those with unknown fed/fasted status.

The GoF for the time-to-event model was performed using the analysis of the Martingale residuals distribution,[6] which should be linear against the individual estimate of predictors (covariates) if the model is appropriate.

Clinical trial simulations (CTS)

CTS were conducted, assuming 100 subjects per arm (placebo and alitretinoin 10 mg, 20 mg, 30 mg, and 40 mg once daily for 24 weeks) to address the clinical relevance of each statistically significant finding for PGA and triglycerides. Simulations were conducted using NONMEM and *R* for postprocessing for the LDR analyses and within SAS for the time-to-event approach. The endpoints selected for CTS included:

○ Response at EOT: PGA score of 1 or 2 at the EOT.
○ Time to onset of effect, defined as the time from the initial study dose to a 2-point reduction in PGA in ≥30% of subjects, a variable that was not consistent with time to response, given that this was a population-based (not subject-based) analysis.
○ Proportion of responders at EOT who did not relapse to severe disease by 24 weeks posttreatment (and would not be expected to require retreatment).
○ The median changes in triglycerides, relative to placebo.
○ The probability of reaching triglycerides >200 mg/dL.

No comparisons of posttreatment PGA scores were made between the placebo/active groups for CTS because:

○ protocols stated that PGA scores should only be collected in responders posttreatment;
○ more responders received active than placebo treatment;
○ topical corticosteroids were allowed posttreatment when subjects had a PGA ≥ 3 in BAP01346 or a mTLSS > 75% of baseline mTLSS in BAP00089.

RESULTS
Efficacy LDR analysis

In all, 12,196 observations from 1,442 subjects in phase III studies (**Figure 1**) were included in the analysis. Subjects were 17–81 years of age, including 126 subjects ≥65 years; male (56%) or female (44%) with body weights of 42.8–169 kg and body mass indices (BMI) of 14.8–58.4 kg/m^2; and had normal renal function or mild or moderate renal impairment by estimated creatinine clearance (CrCL) and estimated glomerular filtration rate (eGFR):

• 523 subjects with mild and 108 with moderate renal impairment by CrCL; or
• 925 subjects with mild and 81 subjects with moderate renal impairment by eGFR.

Approximately 66% of subjects had severe pruritus/pain at baseline based on the mTLSS, while 1.5%, 7%, and 26% had no, mild, or moderate pruritus/pain at baseline, respectively. There were wide ranges of duration of condition, duration of present condition, and duration of treatment.

PGA scores during treatment showed (**Figure S1**):

• The proportion of subjects with PGA = 5 (severe disease) decreased at 4 weeks and continued to decrease for placebo and active treatment. Simultaneously, the proportion of responders (subjects with PGA = 1 or 2) increased every 4 weeks, with more substantial changes for alitretinoin 30 mg once daily than placebo or alitretinoin 10 mg.
• The proportion of responders was higher with the 30 mg dose, as early as 4 weeks.

PGA scores posttreatment showed (**Figure S2**):

• The proportion of responders increased for placebo, but remained relatively constant for alitretinoin groups.
• The large placebo response posttreatment may be related to:
  • Fewer responders in the placebo group than in active treatment groups and the fact that PGA was only collected from responders posttreatment (see Methods).
  • Topical corticosteroids were allowed posttreatment when subjects had a PGA ≥ 3 (BAP01346) or mTLSS > 75% (BAP00089).

A longitudinal logistic regression model was fitted to the observed PGA scores over time and covariates were evaluated using a forward addition and backward elimination process. All parameters for the final model were estimated with good precision (**Table S3**). Statistically significant covariates are given in **Figure S3**.

Model performance showed excellent agreement between predicted/observed probabilities and demonstrates that the efficacy LDR model adequately characterizes the efficacy of alitretinoin over time and is appropriately robust for CTS.

• Parameter estimates from NONMEM were similar to bootstrap estimates.
• VPCs showed good agreement for the MD dataset for alitretinoin and placebo during treatment (**Figure S4**); agreement posttreatment was good for alitretinoin and less so, but still adequate, for placebo.

Table 1 Summary of clinical trial simulations evaluating the effect of dose on the time to onset of effect, proportion of responders at end of treatment (EOT), and proportion of nonrelapsers at 24 weeks posttreatment

Dose	Time to onset of effect (a drop of 2 or more points in PGA score in 30% of subjects) median (5th & 95th percentile) (days)	Median number of responders with PGA score = "clear" or "almost clear" at EOT *n* (median % [5th percentile, 95th percentile])	Median number of responders at EOT who did not relapse (PGA score ≠ severe) 24 weeks posttreatment *n* (median % [5th percentile, 95th percentile])
Placebo (*n* = 100)	62 (49, 77)	16 (16.1 [10, 23])	12 (77.5 [60, 92])
10 mg (*n* = 100)	56 (42, 70)	23 (23.3 [16, 30])	16 (69.9 [54, 85])
20 mg (*n* = 100)	51 (42, 63)	32 (31.8 [25, 39])	25 (77.6 [65, 89])
30 mg (*n* = 100)	49 (42, 56)	40 (40.4 [33, 48])	34 (83.1 [73, 93])

External validation using an independent MV dataset showed good/excellent agreement between observed/predicted proportions using VPCs during treatment (**Figure S5**) and mirror plots. Posttreatment PGA scores were underpredicted for placebo (given the small *n*), but were well predicted for active treatment. Therefore, CTS were not intended to show comparisons between placebo and active posttreatment; data posttreatment were used descriptively to estimate the proportion of subjects who were responders at the EOT who did not return to severe disease 24 weeks posttreatment after alitretinoin administration.

CTS provided information about the clinical relevance of each statistical finding, as described below.

Dose. The effect of daily dose during the treatment phase was best described as a linear model. While there were no dose-related effects posttreatment, there was a statistically significant effect of active vs. placebo on the posttreatment probabilities.

CTS showed that the time to onset of effect, the proportion of responders at the EOT, and the proportion of subjects who did not relapse (PGA ≠ 5) 24 weeks after treatment were dose-dependent (**Table 1**). The proportion of subjects who were responders at EOT receiving alitretinoin 30 mg was substantially higher than those receiving alitretinoin 10 mg (30 mg = 17%↑ over 10 mg) or placebo (30 mg = 24%↑ over placebo). Of those who responded to alitretinoin 30 mg, >83% did not return to severe disease within 24 weeks posttreatment.

Duration of treatment. CTS, assuming durations of 4, 8, 12, 16, 20, or 24 weeks of treatment with alitretinoin 30 mg or placebo once daily, showed that:

• Relative to placebo, alitretinoin 30 mg treatment resulted in ∼5% to 7% new responders with each additional 4 weeks of treatment after 8 weeks, which is consistent with clinical data.[2,3]
• In subjects who reached a PGA = 1 or 2, there was no relationship between duration of treatment and relapse status at 24 weeks posttreatment.

Age. CTS showed that advanced age was associated with faster response onset, a higher magnitude of a treatment effect at EOT (28%, 29%, or 22% in a 65-year-old, 75-year-old, or 30-year-old, respectively); and a higher probability of

not relapsing 24 weeks posttreatment (87%, 89%, and 79%, respectively) (**Table 2**).

Run-in period of potent topical corticosteroids. While the effect of a run-in period did not significantly affect the probabilities of each PGA when evaluated as a yes/no or linear parameter, a categorical approach (0, <4 weeks, 4–8 weeks, 8–12 weeks, or >12 weeks run-in period) suggested some differences:

○ When the run-in period was categorized as no run-in period (*n* = 737) or as 2–4 weeks (*n* = 42), 4–8 weeks (*n* = 130), 8–12 weeks (*n* = 65), and ≥12 weeks (*n* = 43) run-in period, individual parameters for each group could not be statistically justified (i.e., ΔOFV, parameter estimates similar and/or large %RSE). The best model combined those subjects with no run-in period and those subjects with a >8 weeks run-in period as one group.
○ Separate parameters were statistically justified for subjects with a 2–4 weeks run-in period and for those with a 4–8 weeks run-in period. CTS showed that subjects with a 2–4 weeks run-in period had a much slower (by 3–4 weeks) time to onset of efficacy and lower response rates in active and placebo compared to the main group or to those with a run-in period of 4–8 weeks (**Figure 3**) (active-placebo of 19%, 26%, and 24%, respectively).

Disease severity. All subjects in BAP00089 and BAP01346 started with a PGA score of 5, while those subjects in study BAP00091 had baseline PGA scores between 3 and 5. Baseline PGA scores and baseline mTLSS (excluding pruritus/pain) were statistically significant covariates for the probability of each PGA score during treatment, while the PGA score at the EOT influenced the probability of each PGA score posttreatment. CTS showed that subjects with more severe disease (at 95th percentile for mTLSS) had a slower onset and were less likely to respond (**Table S4**).

Duration of present condition. CTS of duration of present condition showed that subjects with a longer duration of present condition were also less likely to respond and had a slower onset of effect (**Table S5**).

Other covariates. There were no statistically significant effects of baseline pruritus/pain subscore, CrCL or eGFR, body weight or BMI, retreatment, disease subtype, allergens or avoiding allergens, or region (North America vs. Europe).

Table 2 Summary of clinical trial simulations evaluating the effect of age on the time to onset of effect, proportion of responders at end of treatment (EOT), and proportion of nonrelapsers at 24 weeks posttreatment

Age	Treatment	Time to onset of effect (a drop of 2 or more points in PGA score in 30% of subjects) median (5th & 95th percentile) (days)	Median number of responders with PGA score = "clear" or "almost clear") at EOT *n* (median % [5th percentile, 95th percentile])	Median number of responders at EOT who did not relapse (PGA score ≠ severe) 24 weeks posttreatment *n* (median % [5th percentile, 95th percentile])
30 y	Placebo (*n* = 100)	88 (63, 140)	12 [11.8 (7–18]]	8 [71.5 (50, 90)]
	30 mg (*n* = 100)	58 (49, 70)	34 [33.9 (26–42]]	27 [78.7 (67, 90)]
50 y	Placebo (*n* = 100)	63 (49, 84)	16 [16.0 (10–22]]	12 [77.0 (60, 93)]
	30 mg (*n* = 100)	49 (42, 56)	41 [41.1 (33–49]]	34 [83.2 (73, 92)]
65 y	Placebo (*n* = 100)	51 (42, 63)	20 [20.3 (14–27]]	17 [81.4 (67, 94)]
	30 mg (*n* = 100)	43 (35, 49)	48 [48.0 (40–56]]	42 [86.6 (78, 94)]
75 y	Placebo (*n* = 100)	46 (35, 56)	24 [24.0 (17–31]]	20 [84.1 (72, 96)]
	30 mg (*n* = 100)	39 (35, 42)	53 [53.0 (45–62]]	47 [88.7 (81, 95)]

Triglycerides dose–response analyses

In all, 9,373 observations from 1,697 subjects were included in the triglycerides analysis including subjects in phase III studies (**Figure 1**) receiving placebo or alitretinoin 10 mg or 30 mg and from 291 subjects in a phase II study (BAP00003) receiving placebo or alitretinoin 10, 20, or 40 mg. The population was diverse, with a wide range of ages, BMI, and renal function as for the efficacy dataset. Approximately 8–9% of subjects received statins and 5–6% of subjects were diabetic. Triglycerides were collected in the fasted state (65%) or fed state (18%), with 17% having an unknown fed status.

Triglycerides LDR model

There was a subtle increase in triglycerides with increasing dose, with high inter/intrasubject variability. A model was fit to triglycerides over time, with the statistically significant covariates, resulting from forward addition/backward elimination, illustrated in **Figure S6**.

Most parameters were estimated precisely, while relative precision on AL1 (maximum increase in triglycerides) and AL2 (rate constant describing change over time) was less (**Table S6**). Lower precision of estimates was related to the need for an additional parameter to handle those with unknown food status. Since relative changes from placebo by dose and covariate were more important than the actual triglycerides value, the higher precision of covariate effects (RSE ≤38%) were of higher importance than that for AL1 or AL2.

GoF plots (**Figure S7**) and the following showed good model performance:

- Covariate parameter estimates from NONMEM (**Table S6**) were nearly identical to results from bootstrap analysis.
- VPCs showed reasonable agreement between observed and predicted triglycerides from the MD dataset (**Figure S8**).
- External validation showed good to excellent agreement between the observed triglycerides in an independent MV dataset (30% randomly selected) and the predicted triglycerides:

  ○ Although the t statistics results (t = 2.74, df = 2748) for the mean difference (Diff) between observed and predicted triglycer-

ides (Diff = observed-predicted values) was statistically different from zero, the amount was very small at 3.1 mg/dL (95% confidence interval = 1.7–6.3 mg/dL; **Figure S9**) and not clinically relevant.

  ○ VPCs of the MV dataset showed good/excellent agreement between the observed and predicted triglycerides.

Thus, the triglycerides LDR model adequately characterizes changes in triglycerides and is robust to conduct CTS to evaluate the clinical relevance of increases in fasted triglycerides due to dose, age, and BMI. The median increase in triglycerides, from placebo, with each dose (as a difference from placebo), depends on age and BMI (**Table 3**) with:

- Manageable (<50 mg/dL) increases in triglycerides (over placebo) in younger subjects receiving alitretinoin 30 mg and more pronounced (>60–80 mg/dL) increases in subjects 75 years old regardless of BMI.
- Median alitretinoin-induced increase in triglycerides 9–18 mg/dL higher in those with a BMI = 25 kg/m^2 than in those with a BMI = 30 kg/m^2.

Time-to-event model

Kaplan–Meier survival analysis showed that the time to triglycerides >200 mg/dL is dependent on dose (**Figure 4**), fasted/fed status, and age (**Figure 5**). The shape of the survival functions was parallel, supporting the subsequent use of the Cox proportional hazards model and confirming assumptions of the proportionality of the hazard functions.

Table 3 Median increase from placebo in triglycerides (mg/dL) by dose, BMI, and age

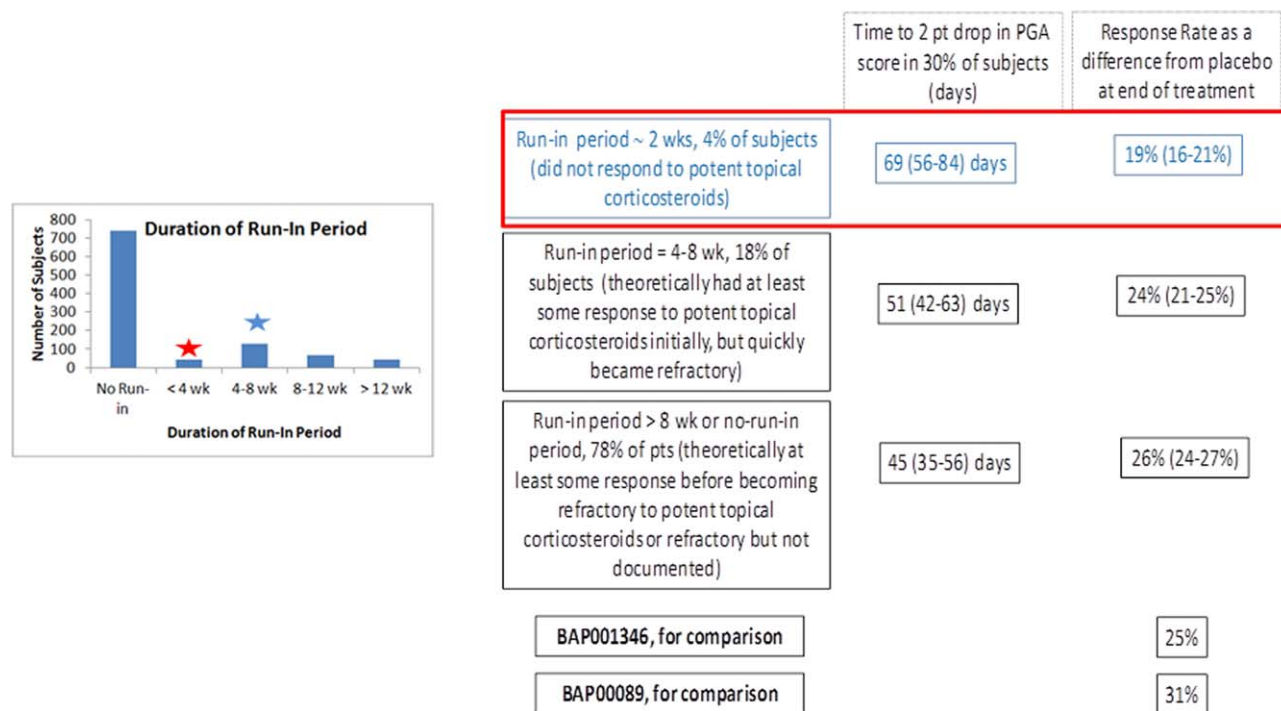|	Median increase in triglyceride levels (mg/dL)					
	BMI = 25 Age (yr)			BMI = 30 Age (yr)		
Dose (mg)	30	50	75	30	50	75
10	8.9	8.9	17.8	8.9	8.9	17.8
20	17.8	26.7	35.6	17.8	26.7	44.5
30	26.7	35.6	62.3	35.6	44.5	80.1
40	35.6	53.4	89	44.5	62.3	116

Figure 2 Results from clinical trial simulations evaluating the effect of run-in period with potent topical corticosteroids on the efficacy of alitretinoin 30 mg compared to results from phase III clinical trials BAP00089[2] and BAP01346.[3]

Using the Cox proportional hazards model, five covariates (baseline triglycerides, fed/fasted status, dose, BMI, and age) were retained in the model based on the stepwise procedure (**Figure 2**, **Table S7**), with hazard ratios for food and baseline triglycerides being much larger than other covariates. Gender, statin use, diabetes, CrCL, eGFR, BSA, and body weight did not affect the time to triglycerides >200 mg/dL. CTS showed that:

- The largest probability of triglycerides >200 mg/dL occurred after 16 weeks of treatment in the elderly.
- The time to an 80% probability of achieving triglycerides >200 mg/dL during alitretinoin 30 mg treatment was about 24 weeks for a 50-year-old with a baseline triglyceride level of 150 mg/dL and a BMI of 30 kg/m^{2} and 16 weeks in a similar subject with a BMI of 40 kg/m^{2}.
- Increased risk for higher triglycerides in obese subjects was more dependent on higher baseline triglycerides than on alitretinoin-induced increases in triglycerides.

DISCUSSION

The present article describes the longitudinal efficacy and triglycerides dose–response analyses of alitretinoin in severe, refractory chronic hand eczema. These analysis supplement phase III study results and provide insight to address development issues raised upon acquiring alitretinoin regarding dose selection, duration of treatment, design features (e.g., run-in period, baseline pruritus/pain), and subgroups. Phase II/III studies of alitretinoin showed dose-related clinically meaningful benefits at EOT and safety/tolerability consistent with oral retinoids.[1–5] The dose–response analyses corroborated the findings from BAP00089 and showed that the optimal dose of alitretinoin for treatment of severe, refractory CHE was 30 mg once daily. The LDR model also showed that there was no relationship between the duration of treatment and relapse status at 24 weeks in responders at EOT. Thus, there was no added benefit to continuing treatment once patients had responded and the optimal duration of treatment is 12 to 24 weeks, with discontinuation upon "clear" or "almost clear" hands.

The triglycerides analyses showed a dose-related increase in triglycerides and the time to triglycerides >200 mg/dL, supporting the 30 mg dose as the optimal dose. This information should be taken in context with other safety/tolerability issues, which were consistent with the 30 mg dose as the optimal dose.[1–3]

The efficacy analysis confirmed that design features did not bias the results from phase III studies.

○ Pruritus/pain (which are considered medically important in the assessment of disease severity and efficacy[7]) at baseline did not influence the probability of a specific PGA score.
○ Those with a short run-in period with potent topical corticosteroids were more difficult to treat, but still maintained a clinically meaningful benefit of alitretinoin 30 mg at EOT (19% over placebo). Thus, the analysis supports that this run-in period was not responsible for differences in efficacy seen between two phase III studies[2,3] (where subjects in BAP00089 had a history of being refractory to potent topical corticosteroids, while those in BAP01346 had refractory status confirmed as part of the clinical study).
○ Subjects with more severe disease or those with a longer duration of present condition were less likely to respond and had slower
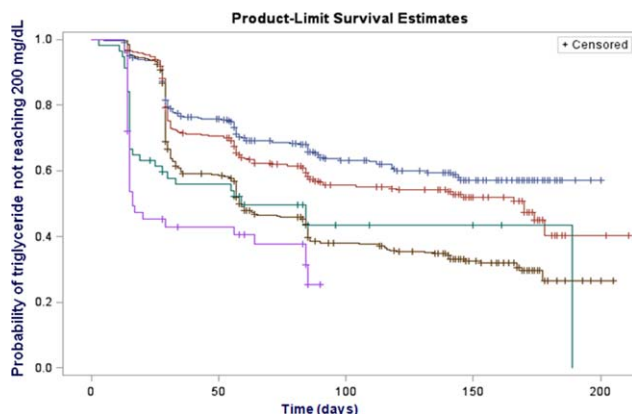
Figure 3 Kaplan–Meier survival plot of time (days) to reach triglyceride levels of greater than 200 mg/dL for placebo (blue), alitretinoin 10 mg (red), 20 mg (green), 30 mg (brown), or 40 mg (purple).

onsets of effect. Importantly, each subgroup still experienced clinically meaningful benefit.

Age was the most clinically relevant covariate, where elderly subjects responded to treatment faster, with a higher response rate at EOT, and less relapsers 24 weeks posttreatment. As expected, baseline triglycerides were higher in elderly patients. Alitretinoin-induced increases in triglycerides were also higher in elderly subjects (62–80 mg/dL↑ in a 75-year-old subject relative to placebo), which was reduced to 36–45 mg/dL with 20 mg. The time to reach triglycerides >200 mg/dL was faster in elderly subjects and more commonly occurred between 12–24 weeks. The efficacy and tolerability differences observed in the elderly population did not appear to be related to pharmacokinetic differences. Thus, since elderly patients responded earlier and had more pronounced efficacy, they may require shorter treatment durations, thus avoiding reaching the triglycerides >200 mg/dL, even if receiving alitretinoin 30 mg. Triglycerides can be monitored with a dose reduction if required.

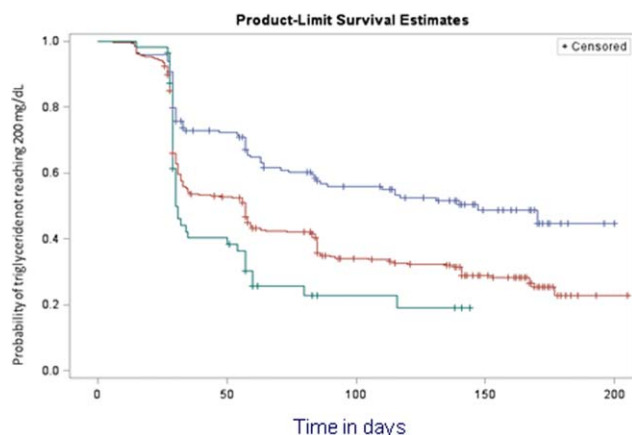There were higher median triglycerides observed during alitretinoin treatment in obese subjects which were driven by higher baseline triglycerides, and not a clinically significant increase (<10 mg/dL) in the alitretinoin-induced increase in triglycerides, except in elderly obese subjects.

Mild to moderate renal impairment did not affect efficacy or triglycerides during alitretinoin treatment. Because a pharmacokinetic study was not conducted on renal impairment, insight into the effect of mild or moderate renal impairment was gained from the analyses. These analyses included data from a substantial number of subjects in both categories: ≥523 and ≥81 subjects with mild or moderate renal impairment, respectively, and can be used to support the recommendation that no initial dosage adjustments are needed in subjects with mild to moderate renal impairment.

Protocol design posttreatment (e.g., collection of PGA in responders only, potential use of topical corticosteroids) and the fact that there were fewer responders receiving placebo than active treatment limited conclusions from the analysis. The VPCs posttreatment showed good agreement between observed and predicted data for alitretinoin, where there were more data. Therefore, data posttreatment were only used descriptively to estimate how many subjects receiving alitretinoin 30 mg who were responders at the EOT would be expected to develop severe disease 24 weeks posttreatment and potentially be eligible for retreatment, if refractory.

The triglycerides analysis was limited by the unknown fed/fasting in the phase II study, where higher doses were studied. While the unavailability of fed/fasted status is not ideal, a mixture model was able to match subjects' data to the most likely situation, as indicated by the precision of the estimates and the reasonable GoF of the model (**Table S3**). Therefore, the lack of information on fed/fasted state in the phase II study did not bias the conclusions around the optimal dose or the effects of various covariates on triglycerides.

In summary, this LDR analyses provided insight about the optimal dose and duration of treatment, addressed questions around study design features and subpopulations, and added to the weight of evidence for efficacy and safety/tolerability of alitretinoin in severe, refractory CHE.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✔ Phase II/III studies of alitretinoin demonstrated a clinically meaningful benefit at end of treatment in severe chronic hand eczema refractory to potent topical corticosteroids. Response rates were higher after 30 mg and 10 mg than placebo, with secondary endpoints also supporting efficacy. Adverse events were consistent with oral retinoids, which also appeared to be dose-related.

WHAT QUESTION DID THIS STUDY ADDRESS?

✔ What is the optimal dose and duration of therapy? Did study design features bias the outcome of phase III studies? Are there patient-related factors that affect efficacy and tolerability?

Figure 4 Kaplan-Meier survival plot of time (days) to reach triglyceride levels of greater than 200 mg/dL for <40 years of age (blue), 40 to 65 years of age (red), and >65 years of age (green) for a 30 mg dose.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

✓ These analyses provided insight into the key development concerns raised by regulatory agencies regarding dose selection, duration of treatment, design features (e.g., run-in period, baseline pruritus/pain), and subgroups.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY AND THERAPEUTICS?

✓ The longitudinal dose response analyses added weight to the evidence of efficacy and safety; provided appropriate dosing in the overall population and subpopulations for labeling of alitretinoin; and addressed pertinent safety and efficacy questions that stand-alone clinical trials cannot.

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Supplementary information accompanies this paper on the *CPT: Pharmacometrics & Systems Pharmacology* website (http://www.wileyonlinelibrary.com/psp4)