CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

050803Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA #:	50-803 (Originally submitted under (b) (4))
Submission Date:	October 15, 2009
Brand Name:	Veltin Gel™ (Proposed by the Sponsor)
Generic Name:	Clindamycin Phosphate and Tretinoin
Dosage Form:	Topical Gel
Dosage Strength:	Clindamycin 1%, Tretinoin 0.025%
Reviewer:	Chinmay Shukla, Ph.D.
Team Leader:	Capt. E. Dennis Bashaw, Pharm.D.
OCP Division:	DCP-3
OND Division:	Division of Dermal and Dental Products
Sponsor:	Stiefel
Relevant IND(s):	065369
Submission Type:	Resubmission
Indication:	Treatment of Acne Vulgaris

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1. Executive Summary

The original NDA for Velac Gel (clindamycin 1% and tretinoin 0.025%) for the treatment of acne vulgaris was submitted on August 23, 2004 by Connetics Corporation under NDA (b) (4) The application was subsequently reassigned to NDA number 50-803. Stiefel, a GSK company acquired Connetics Corporation in December 2006.

A "Not Approvable" action letter was issued by the Agency on June 10, 2005 due to a positive carcinogenicity signal observed in a Tg.AC mouse model after dermal exposure in both the vehicle and clindamycin phosphate arms.

The Sponsor reformulated Velac Gel to contain only excipients found in the US FDA's Inactive Ingredients Guide (IIG). Specifically, (b) (4) polyoxyethylene 4 monolauryl ether (POE 4) was (b) (4) in the vehicle. This represents the only change to the formulation and was treated as comparable to a SUPAC-SS Level 3 change. The proposed proprietary name for the new formulation is Veltin™ Gel and is referred to as "CT Gel" throughout the submission.

Following discussions with the Agency at post-special protocol assessment guidance meeting on December 18, 2007; in order to establish a clinical bridge between CT Gel and Velac Gel, the sponsor was asked to perform 6 clinical studies using the reformulated combination study product. Specifically, studies conducted with CT Gel include a phase 1 cutaneous irritation study (CTG.103), a phase 1 phototoxicity study (W0265-103), a phase 1 photoallergy study (W0265-104), a phase 2 bioavailability study (W0265-02), a phase 3b tolerability study with benzoyl peroxide (W0265-306), and a phase 3 safety and efficacy study (W0265-03).

The bioavailability study (W0265-02) was designed to evaluate the systemic exposure of clindamycin, clindamycin sulfoxide (active metabolite of clindamycin) and tretinoin, individually, following multiple topical applications of either CT Gel or Velac Gel. The results show that with CT Gel the exposure of clindamycin and clindamycin sulfoxide increased about two times while the exposure of tretinoin was comparable with Velac Gel. Further, following a consult with Pharm Tox, it was found that the non-clinical studies were dosed at sufficient access to cover this increase in bioavailability of clindamycin and clindamycin sulfoxide. Also no events suggestive of systemic toxicity were reported by any subjects in this study and in the Phase 3 (W0265-03) safety and efficacy study. Hence, this suggests that an increase in clindamycin and clindamycin sulfoxide exposure with CT Gel might not result into a clinically meaningful safety concerns above the reference treatment.

1.1 Recommendation

From a Clinical Pharmacology Standpoint, the Sponsor has met the requirements under 21 CFR 320 and the application is acceptable provided the labeling comments are adequately addressed by the Sponsor.

1.2 Post-Marketing Requirements/ Commitments

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

One of the studies conducted in order to establish a clinical bridge between CT Gel and Velac Gel was an additional bioavailability study (W0265-02). Specifically, this was a single-center, randomized, open-label, comparative study in male and female subjects 12

years of age or older who presented with moderate-to-severe acne. The study was designed to evaluate the systemic exposure of clindamycin, clindamycin sulfoxide (active metabolite of clindamycin) and tretinoin, individually, following multiple topical applications of either CT Gel or Velac Gel.

The study consisted of a 5-day treatment period during which subjects with acne were instructed to apply 3 grams of the study product (CT Gel or Velac Gel) once daily (every morning) to the face, neck, upper chest and upper back. The specific aim of this study was to show that the levels of absorption of CT Gel were similar to those with Velac Gel. A previous study with Velac Gel (Study VLC.C.201) showed that the mean plasma clindamycin and tretinoin levels measured on day 5, did not exceed those measured on day 28. Hence the Sponsor determined that a 5-day application period would to be adequate for the evaluation of the bioavailability of the individual components of CT Gel.

In this study, 34 subjects were randomized (1:1) to either CT Gel or Velac Gel and 32 subjects (17 CT Gel and 15 Velac Gel) were included in the PK analysis. In the Velac Gel arm, one subject was excluded from the study as a result of missed product applications and the second subject was lost to follow up. Following the baseline visit (day 1), subjects returned to the study center at day 5 and day 6 for the collection of blood samples and assessment of safety. The absorption of clindamycin and tretinoin, were evaluated individually from blood samples collected at baseline; day 5 (prior to study product application, and at 1, 2, 4, 8 and 12 hours post application; and day 6 (24 hours post-day 5 study product application).

Overall, the results of the study showed the following:

(1) After daily topical application of CT Gel or Velac Gel, clindamycin concentrations were measured in almost all plasma samples collected from pre-dose to 24 hours post-dose on day 5, with peak concentrations occurring between 4 and 8 hours after product application. Plasma concentrations of clindamycin sulfoxide were either not measurable or much lower than those of clindamycin; however, the trends in concentration distribution for clindamycin sulfoxide between the 2 study product groups were similar to those described for the parent compound, clindamycin.
(2) The over all systemic exposure to clindamycin and clindamycin sulfoxide is about two times higher with CT Gel compared to Velac gel and this is evident from the values of 90% CI for C_{max} and AUC_{tau} as shown in Table 1 below.
(3) The exposure of tretinoin was comparable between the two formulations and the values of the confidence interval for C_{max} and AUC_{tau} were within the acceptable limit of 80% - 125%.

Table 1: Summary of statistical analysis of the pharmacokinetic parameters between study products

			Geometric LS Mean					90% CI	
Analyte	**PK Parameter**	**n**	**CT Gel**	**n**	**Velac Gel**	**Comparison**	**Ratio**	**Lower**	**Upper**
Clindamycin	AUC_{tau} (hr*ng/mL)	17	21.01	15	13.54	CT Gel vs Velac Gel	1.55	92	261
	C_{max} (ng/mL)	17	1.53	15	0.92		1.67	95	294
Clindamycin Sulfoxide	AUC_{tau} (hr*ng/mL)	13	3.45	10	2.51	CT Gel vs Velac Gel	1.37	90	209
	C_{max} (ng/mL)	15	0.19	11	0.13		1.42	92	220
Tretinoin	AUC_{tau} (hr*ng/mL)	17	29.14	15	27.76	CT Gel vs Velac Gel	1.05	96	1.14
	C_{max} (ng/mL)	17	1.53	15	1.54		1.00	89	1.11
	Avg Day 5 Conc (ng/mL)	17	1.22	15	1.18		1.03	95	1.13
	AUC_{0-24} (hr*ng/mL)	17	29.24	15	28.31		1.03	95	1.13

(4) After 5 daily applications, in the CT Gel group all plasma clindamycin concentrations were $\leq$ 5.56 ng/mL, except for one subject who had a maximum clindamycin concentration of 8.73 ng/mL at 4 hours post-dose. On the other hand with Velac Gel group all plasma clindamycin concentrations were $\leq$ 4.93 ng/mL.

(5) Systemic exposure to tretinoin, as determined by the mean C_{day5}, C_{max} and AUC_{tau} values, was not significantly different between the 2 study products. After daily topical application of CT Gel and Velac Gel for 5 days, there was no appreciable increase in the systemic exposure to tretinoin as compared to the baseline*. The mean tretinoin concentration across all sampling times on day 5 was 1.232 ng/mL and 1.190 ng/mL for the CT Gel and Velac Gel groups, respectively, compared to the corresponding baseline mean tretinoin concentrations of 1.304 ng/mL and 1.160 ng/mL, respectively.

(6) Due to potential safety concern with higher clindamycin and clindamycin sulfoxide exposure with CT Gel, a consult was sent to pharmacology/toxicology to comment on the adequacy of the Sponsor's nonclinical testing as to whether or not it covers the greater exposure of clindamycin and clindamycin sulfoxide using the same clindamycin concentration (1%), but in CT Gel compared to Velac Gel. Following response was obtained from the Pharm Tox reviewer Dr. Jill Merrill:

"Although Veltin Gel provides 1.5 to 2 times higher exposure to clindamycin and clindamycin sulfoxide, the nonclinical studies were dose at sufficient excess to cover this increase in bioavailability."

In general the product was well tolerated. One subject in the CT Gel group reported two mild events during the study. These events include excoriation and erythema, both of which were deemed not related to the study product. No subject in the Velac Gel group experienced any adverse events. Dr. Gary Chiang (reviewing medical officer) reported *"Seven serious AEs: abdominal pain, bronchitis, concussion, infectious mononucleosis, ovarian cyst, suicide attempt, and depression. None of the serious AEs were felt related to the study product by the sponsor or this reviewer".* In addition to this Dr. Chiang

summarized that *"No new safety concerns were evident in the phase 3 clinical trial conducted with the combination Veltin Gel (clindamycin 1% - tretinoin 0.025%)"*. This shows that an increase in clindamycin and clindamycin sulfoxide exposure might not result into any clinically meaningful safety concern for CT Gel.

** Tretinoin is an endogenous substance.*

2. Question Based Review

2.1 General Attributes of the Drug

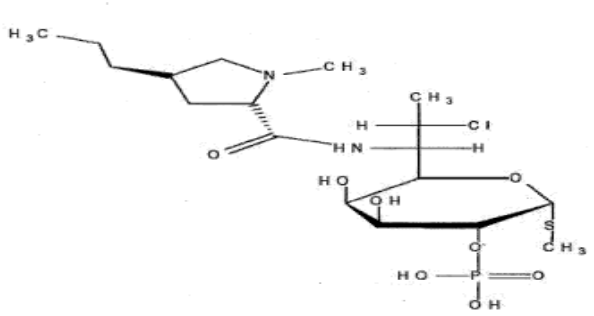
2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation?

Drug substance and Formulation

CT Gel is a fixed combination of drug product that contains 1% clindamycin (as clindamycin phosphate 1.2%) and 0.025% tretinoin in an aqueous gel base.

Clindamycin is a broad-spectrum antibacterial belonging to the class of lincoasmides. It is synthetically derived from the antibiotic lincomycin. The chemical structure of clindamycin phosphate is shown in Figure 1.

Figure 1: Structure of clindamycin phosphate



Tretinoin (all-trans retinoic acid) is the acid form of vitamin A and belongs to the class of retinoids. The chemical structure of tretinoin is shown in Figure 2 below.

Figure 2: Structure of tretinoin

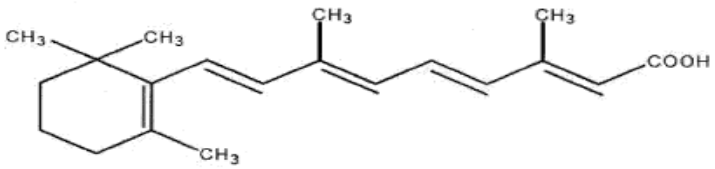


Table 2 below, compares the formulation of Velac Gel with CT Gel and shows that the only difference between the two formulations is the (b) (4) POE 4 (b) (4) CT Gel.

Table 2: Composition of Velac Gel and CT Gel

Ingredients[#]	Functions	Velac Gel (% w/w)	CT Gel (% w/w)
Clindamycin phosphate (USP)	Active ingredient	1.00 (expressed as clindamycin)	1.00 (expressed as clindamycin)
Tretinoin (USP)	Active ingredient	0.025	0.025
Propylene glycol (USP)	(b) (4)		
Laureth 4, Polyoxyethylene 4 monolauryl ether (POE 4)[+]			
(b) (4)			
Carbomer 940 (b) (4) (NF)			
Tromethamine (USP)			
Methylparaben (NF)			
Citric acid, anhydrous (USP)			
Edetate disodium (USP)			
Butylated hydroxytoluene (NF)			
Purified water (USP)			

[#] (b) (4)

[+] *Non-compendial manufacturer's specifications.*

2.1.2 What are the proposed mechanism of action and the therapeutic indications?

Acne is a disease with complex pathogenesis that is caused by multiple etiologic factors. It presents as non-inflammatory (presence of open and closed comedones) and inflammatory (presence of papules, pustules and nodules) lesions in different grades of severity.

Inflammatory acne is mainly attributed to the overgrowth of *Propionibacterium acn*es on the skin and can be treated with a number of therapeutic agents including antimicrobials. Clindamycin is an antimicrobial agent that inhibits bacterial protein synthesis by irreversibly binding to 50S subunit of the bacterial ribosome. Clindamycin phosphate is biologically inactive and is rapidly hydrolyzed to active clindamycin sulfoxide in-vivo.

Non-inflammatory acne is treated with comedolytic or keratolytic agents, such as topical retinoids. Tretinoin is a retinoid, and is expected to decrease the cohesiveness of follicular epithelial cells and to decrease microcomedone formation. It is also expected to influence the skin permeability and thus enhance the penetration of topical antibiotics when used as a combination therapy.

2.1.3 What are the proposed dosage and route of administration?

The proposed route of administration is topical for the treatment of acne vulgaris in patients 12 years or older. This product should be applied once daily in the evening after washing the face with mild soap and warm water and patting the skin dry, and using enough to lightly cover the entire affected area. Intended duration of application is 12 weeks.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and the clinical studies used to support dosing or claims?

In order to establish a clinical bridge between CT Gel and Velac Gel, the sponsor has performed 6 clinical studies using the reformulated combination study product. Specifically, studies conducted with CT Gel include a phase 1 cutaneous irritation study (CTG.103), a phase 1 phototoxicity study (W0265-103), a phase 1 photoallergy study (W0265-104), a phase 2 bioavailability study (W0265-02), a phase 3b tolerability study with benzoyl peroxide (W0265-306), and a phase 3 safety and efficacy study (W0265-03).

2.2.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to access pharmacokinetic parameters and exposure response relationship?

Yes; clindamycin, clindamycin sulfoxide (active metabolite) and tretinoin were adequately identified in plasma using well validated analytical methods.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

2.3.1.2 Effect of Gender

The effect of gender on the pharmacokinetic parameters was not determined by the sponsor in this submission.

2.3.2.1 Pediatric patients

The sponsor is seeking a partial waiver for pediatric studies with CT Gel in subjects 11 years of age and younger since acne prevalence and severity correlates with advancing pubertal maturation.

2.3.2.2 Renal impairment

No clinical studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics. Low levels of absorption when compared to the systemic exposure obtained following administration of clindamycin hydrochloride capsules (150 mg dose) and tretinoin (0.05% topical gel*) does not justify the study requirement.

* *Approved for topical treatment of acne vulgaris.*

2.3.2.3 Hepatic impairment

No clinical studies have been conducted to evaluate the effect of hepatic impairment on the PK of clindamycin, clindamycin sulfoxide and tretinoin, nor are they required given the low level of absorption when compared to clindamycin hydrochloride capsules (150 mg dose) and tretinoin (0.05% topical gel*).

* *Approved for topical treatment of acne vulgaris.*

2.3.2.4 What pregnancy and lactation use information is there in the application?

No information is provided. However, the currently marketed Clindamycin phosphate 1.2% and tretinoin 0.025% Gel (Ziana® Gel) is labeled as Pregnancy Category C. Its use in pregnant and lactating women should be done only if potential benefit justifies the potential risk to the fetus.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or response and what is the impact of any differences in exposure or response?

The extrinsic factor influence on dose-exposure and/or response was not explored.

2.4.2 Drug-drug interactions

Drug-drug interactions are not normally evaluated for topically applied products because of low plasma exposure and they were not studied in this case.

2.5 General Biopharmaceutics

2.5.1 Based on biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

Not Applicable

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The proposed-to-be-marketed formulation is the same as the formulation used in the pivotal phase 3 trial (W0265-03).

2.5.2.1 What data support or do not support a waiver of in vivo BE data?

Not applicable

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Not applicable.

2.6 Analytical Section

2.6.1 How are the active moieties identified, and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Clindamycin, Clindamycin Sulfoxide and Tretinoin – Reverse phase HPLC with MS/MS detection using Waters Acquity HPLC connected with Micromass Quattro Premier triple quadrupole mass spectrometer.

2.6.2 Which metabolites have been selected for analysis and why?

Clindamycin sulfoxide has been selected for analysis because it is a major bioactive metabolite of clindamycin.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Total concentrations (unbound and bound) were measured for clindamycin, clindamycin sulfoxide and tretinoin.

2.6.4 What is the range of the standard curve? How does it relate to the requirements for clinical studies?

- Clindamycin and clindamycin sulfoxide: 0.05 ng/mL – 20.0 ng/mL

- Tretinoin: 0.4 ng/mL – 10.0 ng/mL

The above range is sufficient for clinical studies because, the mean tretinoin concentrations following 14 daily applications of another combination product ranged from 1.0 to 1.6 ng/mL and clindamycin concentrations generally did not exceed 3.5 ng/mL, with the exception of one subject whose plasma concentration reached 13.1 ng/mL (clindamycin phosphate 1.2% and tretinoin 0.025% gel [Ziana Gel, Package insert, 2006]).

2.6.5 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

- Clindamycin and clindamycin sulfoxide
  LLOQ: 0.05 ng/mL
  ULOQ: 20.0 ng/mL

- Tretinoin
  LLOQ: 0.4 ng/mL
  ULOQ: 10.0 ng/mL

2.6.6 What are the accuracy, precision, and selectivity at these limits?

- Clindamycin
  LLOQ: 0.05 ng/mL
  Accuracy: %DEV = - 1.4
  Precision: %CV = 3.2

- Clindamycin sulfoxide
  LLOQ: 0.05 ng/mL
  Accuracy: %DEV = - 4.2
  Precision: %CV = 8.7

- Tretinoin
  LLOQ: 0.4 ng/mL
  Accuracy: %DEV = 1.5
  Precision: %CV = 3.8

2.6.7 What us the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

The analytical report contained sufficient information to support that clindamycin, clindamycin sulfoxide and tretinoin samples were stable at room temperature for > 24 hrs and the samples were also stable for a minimum of 3 freeze thaw cycles.

3. <u>Detailed Labeling Recommendations</u>

The following changes are recommended in the 12.3 Pharmacokinetics Section under Clinical Pharmacology Section of the Sponsor's proposed labeling (Appendix 7 shows the Clinical Pharmacology section of Sponsor submitted package insert). The BLUE text indicates insertion suggested by the reviewer and the RED strikethroughs indicate deletion in the Sponsor's proposed text.

12.3 Pharmacokinetics

(b) (4)

4. Detailed Biopharmaceutics Findings

Clinical Study W0265-02 - A Randomized Open-Label Study to Evaluate the Bioavailability (Absorption) of Clindamycin Phosphate and Tretinoin in Subjects with Acne Vulgaris Using CT Gel or Velac Gel

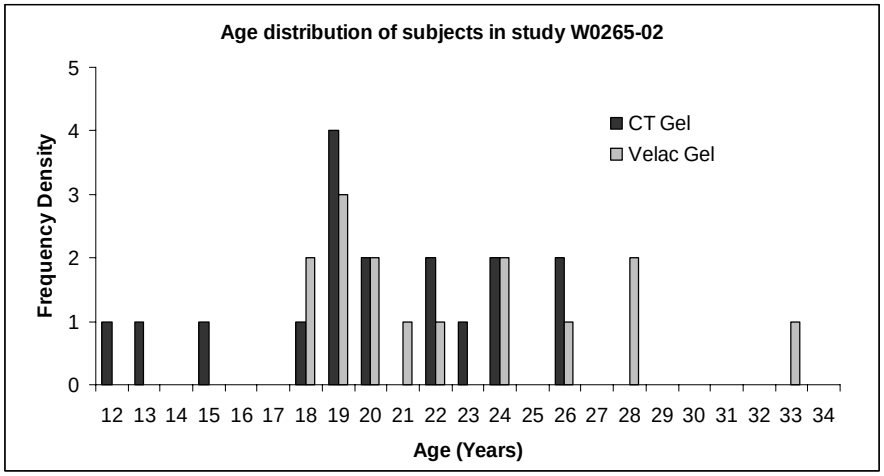
Objective: The objective of this study was to evaluate the systemic bioavailability (absorption) of clindamycin and tretinoin, individually, in subjects with acne vulgaris following multiple applications of CT Gel or Velac Gel under maximal use conditions.

Methods: This was a single-center, randomized, open-label, comparative bioavailability study in male and female subjects 12 years of age or older with acne vulgaris. 34 subjects were enrolled and randomized 1:1 (CT Gel: Velac Gel). The study consisted of a 5 day treatment period during which subjects were instructed to apply all 3 grams of study product once daily (every morning) to the face, neck, upper chest, and upper back. Following the baseline visit (day 1), subjects returned to the study center at day 5 and day 6 for collection of blood samples for evaluation of absorption and for safety assessments. Absorption of clindamycin phosphate and tretinoin were evaluated individually from

blood samples collected at baseline, day 5 (prior to treatment application, and at 1, 2, 4, 8, and 12 hours post treatment application) and day 6 (24 hours post day 5 application).

Number of Subjects: In this study, 34 subjects were randomized (1:1) to either CT Gel or Velac Gel and 32 subjects (17 CT Gel and 15 Velac Gel) were included in the PK analysis. In the Velac Gel group, one subject was excluded from the study as a result of missed product applications and the second subject was lost to follow up (subject 001-0003 and 001-0007 did not complete the study and were not included in the PK analysis). Further, in the CT Gel group, there were 3 subjects below 18 years of age while Velac Gel group did not contain any subjects in this age group. Figure 3 below shows the age distribution of subjects in this study. A detailed demographics table is in Appendix 1.

Figure 3: Age distribution of subjects



Test Product: CT Gel (clindamycin 1% as clindamycin phosphate and tretinoin 0.025%), Batch number WMA-C. CT Gel is a reformulation of Velac Gel made by (b) (4) excipient (polyoxyethylene 4 glycerol monolauryl ether [POE 4]).

Reference Product: Velac Gel (clindamycin 1% as clindamycin phosphate and tretinoin 0.025%), Batch number WMC-C.

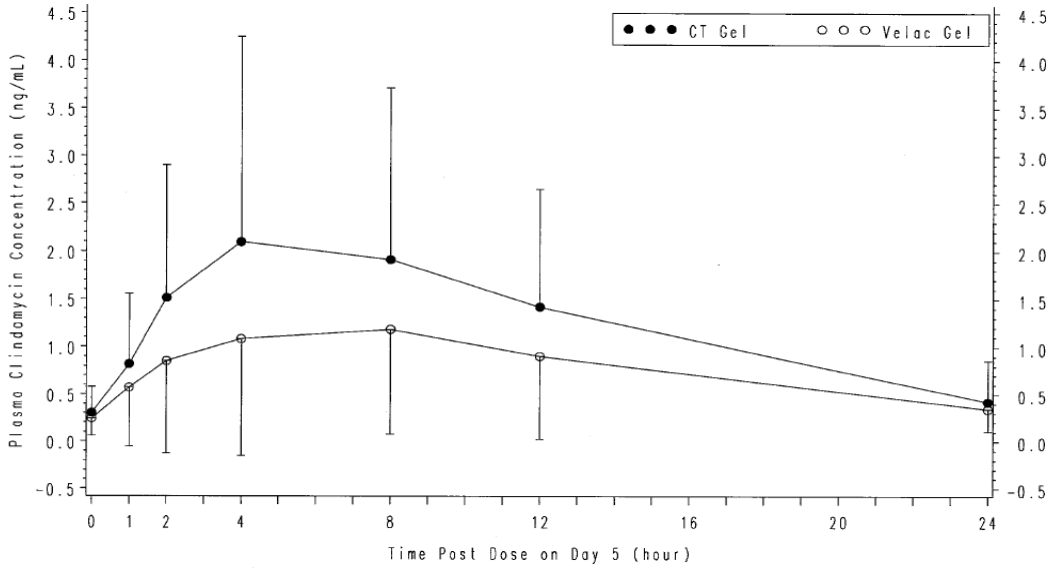
Statistical Methods: Plasma concentration versus time data were analyzed for each analyte on day 5 by noncompartmental pharmacokinetic method and the following parameters were obtained: C_{max} (maximum measured plasma concentration), t_{max} (time of the C_{max}), AUC_{0-t} (area under the plasma concentration-time curve from time zero to the last time point with measurable analyte concentration), and AUC_{tau} (AUC over a steady state dosing interval). For tretinoin, the average C_{day5} (the average concentration across all sampling times on day 5) and AUC_{0-24} (AUC from time zero to 24 hours post dose, calculated as average $C_{day5 \times 24}$) were also determined.

Pharmacokinetic Results:

Plasma Concentrations of Clindamycin: The pre-dose samples on day 1 in either study product groups did not have any measurable clindamycin concentrations. Prior to application of the study product on day 5, 3 out of 17 subjects in the CT Gel group and 2 out of 15 subjects in the Velac Gel group did not have measurable clindamycin concentrations. Following topical application of study products on day 5, clindamycin concentrations were measurable in all plasma samples collected from 1 to 24 hours post dose in both groups (Appendix 2).

Plasma clindamycin concentrations generally peaked around 4 to 8 hours post dose. The mean plasma clindamycin exposure on day 5 was approximately two times higher in the CT Gel group compared to the exposure in the Velac Gel group. The mean trough concentrations of clindamycin on day 5 (i.e., at pre-dose and 24 hours post dose) were quite comparable between the 2 study product groups as shown in Figure 4 below.

Figure 4: Plasma clindamycin concentration (Mean ± SD) vs. time pre-dose and post-dose on day 5

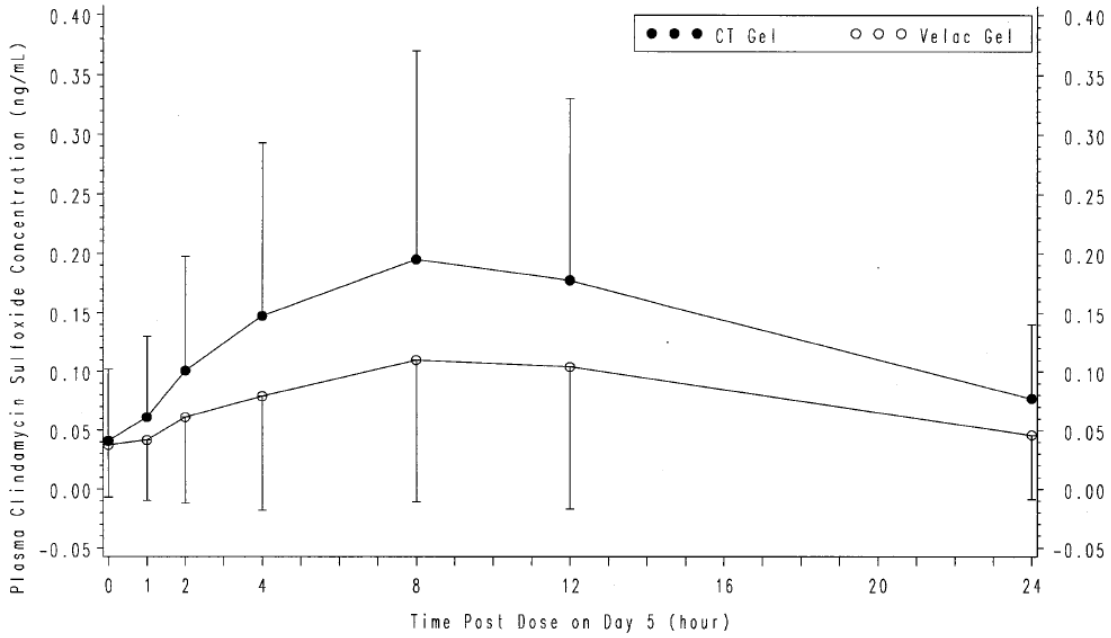


After 5 daily applications, in the CT Gel group all plasma clindamycin concentrations were ≤ 5.56 ng/mL, except for one subject who had a maximum clindamycin concentration of 8.73 ng/mL at 4 hours post-dose. On the other hand with Velac Gel group all plasma clindamycin concentrations were ≤ 4.93 ng/mL. Appendix 2 shows the summary of pharmacokinetic parameters of clindamycin and clindamycin sulfoxide for CT Gel and Velac Gel and Appendix 5 shows plasma clindamycin concentration vs. time curves in individual subjects following administration of CT Gel or Velac Gel.

Plasma Concentrations of Clindamycin Sulfoxide: The plasma clindamycin sulfoxide concentrations were much lower than plasma clindamycin concentrations. There were 2 subjects in the CT Gel group and 4 subjects in the Velac Gel group that did not have

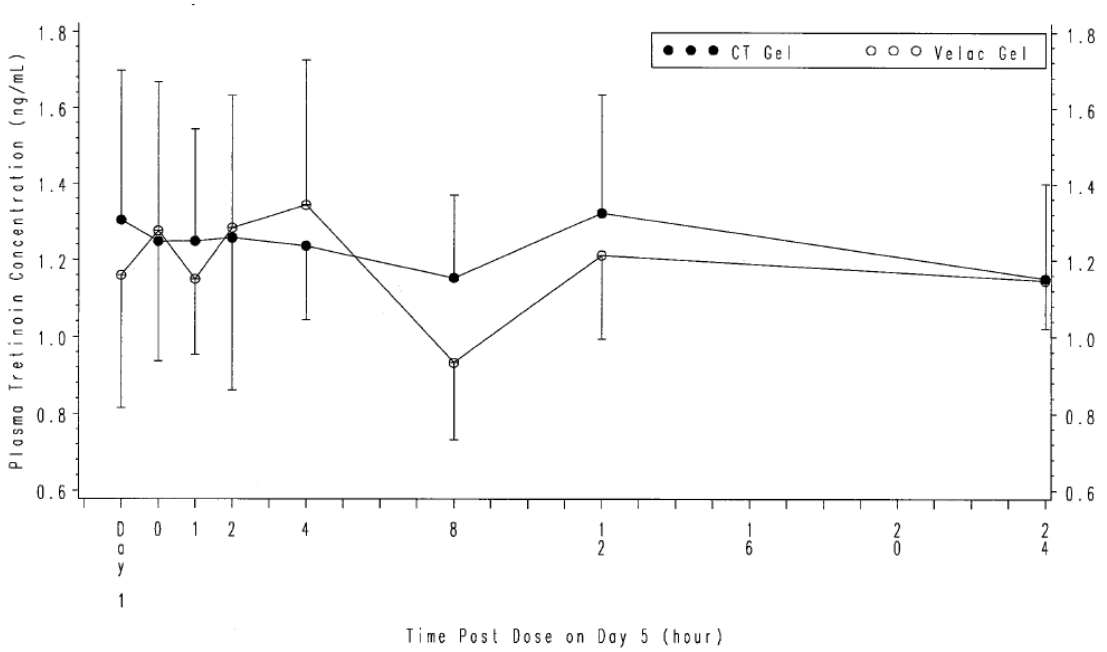
quantifiable clindamycin sulfoxide concentrations throughout the entire sampling period on day 5. In addition, several subjects in both study product groups did not have quantifiable clindamycin sulfoxide concentrations at pre dose and 1 hour post dose on day 5 (Appendix 3). Plasma concentrations peaked around 8 to 12 hours post dose. The average clindamycin sulfoxide exposure with CT Gel was also about two times higher than the one obtained following Velac gel. Figure 5 below shows the average clindamycin sulfoxide concentrations pre and post dose on day 5. The pharmacokinetic parameters of clindamycin sulfoxide are shown in Appendix 2. Individual subject plasma clindamycin sulfoxide concentration vs. time curves is shown in Appendix 5.

Figure 5: Plasma clindamycin sulfoxide concentration (Mean ± SD) vs. time pre-dose and post-dose on day 5



Plasma Concentrations of Tretinoin: The plasma concentrations of tretinoin, an endogenous substance were measurable in all samples collected throughout the study except in one subject (subject 001-0017) in Velac Gel group where tretinoin was not quantifiable in the sample obtained 1 hour post dose on day 5 (Appendix 4). Figure 6 below shows that the mean tretinoin concentrations were comparable between the two products across time points and also there was no substantially measurable increase in the mean tretinoin concentration from baseline after 5 once daily applications.

Figure 6: Plasma Tretinoin concentration (Mean ± SD) vs. time on day 1 and pre-dose and post-dose on day 5



The pharmacokinetic parameter estimates for tretinoin are shown in Appendix 4. Individual subject plasma tretinoin concentration vs. time curves following application of CT Gel or Velac Gel are shown in Appendix 6.

Statistical Analysis of Pharmacokinetic Parameters: The specific aim of this analysis was to show that the levels of clindamycin, clindamycin sulfoxide and tretinoin are not different between CT Gel and Velac Gel.

However, the results showed that the over all systemic exposure to clindamycin and clindamycin sulfoxide is about two times higher with CT Gel compared to Velac gel and this is evident from the values of 90% CI for C_{max} and AUC_{tau} as shown in the table below. On the other hand, the exposure of tretinoin was comparable between the two formulations and the values of the confidence interval for C_{max} and AUC_{tau} were within the acceptable limit of 80% - 125%.

Due to potential safety concern with higher clindamycin and clindamycin sulfoxide exposure with CT Gel, a consult was sent to pharmacology/toxicology to comment on the adequacy of the Sponsor's nonclinical testing as to whether or not it covers the greater exposure of clindamycin and clindamycin sulfoxide using the same clindamycin concentration (1%) but in CT Gel compared to Velac Gel and the following response was obtained from the Pharm Tox reviewer Dr. Jill Merrill:

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	C_{max} (ng/mL)	15	0.19	11	0.13		1.42	92	220
Tretinoin	AUC_{tau} (hr*ng/mL)	17	29.14	15	27.76	CT Gel vs Velac Gel	1.05	96	1.14
	C_{max} (ng/mL)	17	1.53	15	1.54		1.00	89	1.11
	Avg Day 5 Conc (ng/mL)	17	1.22	15	1.18		1.03	95	1.13
	AUC_{0-24} (hr*ng/mL)	17	29.24	15	28.31		1.03	95	1.13

Summary of statistical analysis of the pharmacokinetic parameters between study products

Further, in this study (Study W0265-02), 1 subject in the CT Gel group reported 2 mild events during the study. These events include excoriation and erythema, both of which were deemed not related to the study product. No subject in the Velac Gel group experienced any adverse events. Additionally, the systemic exposure to tretinoin was not different between the two study product groups and there was no appreciable increase in its systemic exposure when compared to baseline. Further, in his Mid Cycle Review; Dr. Gary Chiang from Clinical reported *"Seven serious AEs: abdominal pain, bronchitis, concussion, infectious mononucleosis, ovarian cyst, suicide attempt, and depression. None of the serious AEs were felt related to the study product by the sponsor or this reviewer"*. In addition to this Dr. Chiang summarized that *"No new safety concerns were evident in the phase 3 clinical trial conducted with the combination Veltin Gel (clindamycin 1% - tretinoin 0.025%)"*. This shows that an increase in clindamycin and clindamycin sulfoxide exposure might not result into any clinically meaningful safety concern for CT Gel.

Hence, this study shows that a change in formulation (b) (4) (b) (4) in (b) (4) POE 4 (b) (4) is likely to cause the two times higher exposure of clindamycin and clindamycin sulfoxide with CT Gel (new formulation) when compared to Velac Gel (Old formulation) under maximal use conditions.

Conclusions: The studies conducted for the development of Veltin Gel (CT Gel) were considered appropriate from a Clinical Pharmacology perspective.

Appendix

LIST OF TABLES

Appendix 1: <u>Demographics</u>

	CT Gel n=17	Velac Gel n=17
Age		
n	17	17
mean (sd)	20.1 (4.1)	22.8 (4.3)
median	20	22
min, max	12, 26	18, 33
Age Category		
< 18 years	3 (18%)	0
>= 18 years	14 (82%)	17 (100%)
Sex		
Male	9 (53%)	7 (41%)
Female	8 (47%)	10 (59%)
Race		
American Indian or Alaska Native	0	0
Asian	0	3 (18%)
Black	1 (6%)	1 (6%)
Multiracial	1 (6%)	0
Native Hawaiian or Other Pacific Islander	0	0
White	15 (88%)	13 (76%)
Ethnicity		
Hispanic or Latino	1 (6%)	1 (6%)
Not Hispanic or Latino	16 (94%)	16 (94%)

Appendix 2: Individual Subject Plasma Concentrations of Clindamycin and Summary of Pharmacokinetic Parameters of Clindamycin and Clindamycin Sulfoxide

Individual Subject Plasma Concentrations of Clindamycin (ng/mL) Following CT Gel Application

Treatment	Subject	Day 1 Predose	Day 5 Predose	Day 5 Time Post Dose (hour) 1.0	2.0	4.0	8.0	12.0	24.0
CT Gel	001-0001								(b) (4)
	001-0002								
	001-0005								
	001-0006								
	001-0009								
	001-0012								
	001-0013								
	001-0016								
	001-0019								
	001-0020								
	001-0022								
	001-0023								
	001-0026								
	001-0028								
	001-0029								
	001-0032								
	001-0033								
	N	17	17	17	17	17	17	17	17
	Mean	BQL	0.300	0.820	1.510	2.096	1.914	1.419	0.421
	SD		0.278	0.733	1.390	2.148	1.797	1.228	0.439
	Min	BQL	0.000	0.059	0.081	0.099	0.208	0.122	0.065
	Median	BQL	0.227	0.622	1.200	1.280	1.290	1.110	0.301
	Max	BQL	1.070	3.020	5.560	8.730	6.370	4.880	1.600
	CV%		93	89	92	102	94	87	104
	Lower 95% CI		0.157	0.443	0.795	0.991	0.990	0.787	0.195
	Upper 95% CI		0.443	1.197	2.224	3.200	2.838	2.050	0.647

Individual Subject Plasma Concentrations of Clindamycin (ng/mL) Following Velac Gel Application

Treatment	Subject	Day 1 Predose	Day 5 Predose	Day 5 Time Post Dose (hour) 1.0	2.0	4.0	8.0	12.0	24.0
Velac Gel	001-0003								(b) (4)
	001-0004								
	001-0007								
	001-0008								
	001-0010								
	001-0011								
	001-0014								
	001-0015								
	001-0017								
	001-0018								
	001-0021								
	001-0024								
	001-0025								
	001-0027								
	001-0030								
	001-0031								
	001-0034								
	N	17	15	15	15	15	15	15	15
	Mean	BQL	0.240	0.572	0.852	1.082	1.181	0.905	0.343
	SD		0.181	0.624	0.980	1.236	1.106	0.884	0.235
	Min	BQL	0.000	0.056	0.084	0.130	0.136	0.106	0.061
	Median	BQL	0.233	0.464	0.557	0.665	0.849	0.673	0.252
	Max	BQL	0.661	2.480	3.910	4.930	4.540	3.730	0.820
	CV%		75	109	115	114	94	98	69
	Lower 95% CI		0.140	0.227	0.309	0.397	0.569	0.415	0.213
	Upper 95% CI		0.340	0.918	1.395	1.766	1.794	1.394	0.473

Summary of Pharmacokinetic Parameters of Clindamycin and Clindamycin Sulfoxide for CT Gel and Velac Gel

Parameter	Statistic	Clindamycin		Clindamycin Sulfoxide	
		CT Gel N = 17	Velac Gel N = 15	CT Gel N = 17	Velac Gel N = 15
AUC_{tau} (hr*ng/mL)	n	17	15	15	14
	Mean (%CV)	29.41 (83)	18.63 (93)	3.51 (75)	2.08 (103)
	95% CI	16.83 – 42.00	8.99 – 28.27	2.05 – 4.97	0.84 – 3.31
	Median	21.62	12.23	3.57	1.87
	Minimum, Maximum	2.62, 84.14	2.30, 71.56	0, 10.14	0, 8.02
	Geometric Mean (%CV_b)	21.01 (112)	13.54 (99)	3.45 (67)	2.51 (58)
C_{max} (ng/mL)	n	17	15	17	15
	Mean (%CV)	2.329 (95)	1.285 (92)	0.206 (86)	0.113 (106)
	95% CI	1.193 – 3.464	0.628 – 1.942	0.115 – 0.296	0.047 – 0.180
	Median	1.620	0.963	0.153	0.091
	Minimum, Maximum	0.208, 8.730	0.136, 4.930	0, 0.698	0, 0.474
	Geometric Mean (%CV_b)	1.534 (130)	0.918 (108)	0.186 (80)	0.131 (60)
t_{max} (hours)	n	17	15	15	11
	Mean (%CV)	5.47 (54)	7.07 (35)	8.80 (35)	7.45 (54)
	Median	4	8	8	8
	Minimum, Maximum	1, 12	2, 12	4, 12	0, 12

Abbreviations: AUC_{tau} = area under the plasma concentration-time curve over a steady-state dosing interval, %CV = coefficient of variation; %CV_b = between-subject variability; CI = confidence interval; C_{max} = maximum measured plasma concentration; t_{max} = time of the maximum measured plasma concentration

Note: Subject 001-0003 and 001-0007 in the Velac Gel group did not complete the study.

Appendix 3: <u>Individual Subject Plasma Concentrations of Clindamycin Sulfoxide</u>

<u>Individual Subject Plasma Concentrations of Clindamycin Sulfoxide (ng/mL) Following CT Gel Application</u>

Treatment	Subject	Day 1 Predose	Day 5 Predose	Day 5 Time Post Dose (hour) 1.0	2.0	4.0	8.0	12.0	24.0
CT Gel	001-0001	(b) (4)							
	001-0002								
	001-0005								
	001-0006								
	001-0009								
	001-0012								
	001-0013								
	001-0016								
	001-0019								
	001-0020								
	001-0022								
	001-0023								
	001-0026								
	001-0028								
	001-0029								
	001-0032								
	001-0033								
	N	17	17	17	17	17	17	17	17
	Mean	BQL	0.041	0.061	0.101	0.148	0.195	0.178	0.077
	SD		0.061	0.069	0.097	0.145	0.175	0.153	0.063
	Min	BQL	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	Median	BQL	0.000	0.059	0.081	0.127	0.143	0.153	0.074
	Max	BQL	0.170	0.232	0.348	0.547	0.698	0.613	0.227
	CV%		150	112	96	98	90	86	82
	Lower 95% CI		0.009	0.026	0.051	0.073	0.105	0.099	0.045
	Upper 95% CI		0.072	0.096	0.150	0.222	0.285	0.256	0.110

<u>Individual Subject Plasma Concentrations of Clindamycin Sulfoxide (ng/mL) Following Velac Gel Application</u>

Treatment	Subject	Day 1 Predose	Day 5 Predose	Day 5 Time Post Dose (hour) 1.0	2.0	4.0	8.0	12.0	24.0
Velac Gel	001-0003	(b) (4)							
	001-0004								
	001-0007								
	001-0008								
	001-0010								
	001-0011								
	001-0014								
	001-0015								
	001-0017								
	001-0018								
	001-0021								
	001-0024								
	001-0025								
	001-0027								
	001-0030								
	001-0031								
	001-0034								
	N	17	15	15	15	15	15	15	15
	Mean	BQL	0.037	0.042	0.061	0.079	0.110	0.104	0.046
	SD		0.045	0.051	0.073	0.097	0.121	0.121	0.055
	Min	BQL	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	Median	BQL	0.000	0.000	0.056	0.071	0.091	0.079	0.000
	Max	BQL	0.122	0.156	0.269	0.364	0.474	0.465	0.160
	CV%		119	124	119	123	110	116	119
	Lower 95% CI		0.013	0.013	0.021	0.025	0.043	0.037	0.016
	Upper 95% CI		0.062	0.070	0.102	0.133	0.177	0.171	0.076

Note: Subject 001-0003 and 001-0007 in the Velac Gel group did not complete the study and the summary of pharmacokinetic parameters of clindamycin sulfoxide are included in Appendix – 2.

Appendix 4: Individual Subject Plasma Concentrations of Tretinoin and Summary of Pharmacokinetic Parameters

Individual Subject Plasma Concentrations of Tretinoin (ng/mL) Following CT Gel Application

Treatment	Subject	Day 1 Predose	Day 5 Predose	Day 5 Time Post Dose (hour) 1.0	2.0	4.0	8.0	12.0	24.0
CT Gel	001-0001								(b) (4)
	001-0002								
	001-0005								
	001-0006								
	001-0009								
	001-0012								
	001-0013								
	001-0016								
	001-0019								
	001-0020								
	001-0022								
	001-0023								
	001-0026								
	001-0028								
	001-0029								
	001-0032								
	001-0033								
	N	17	17	17	17	17	17	17	17
	Mean	1.304	1.248	1.248	1.257	1.236	1.153	1.323	1.152
	SD	0.392	0.312	0.295	0.396	0.192	0.216	0.313	0.249
	Min	0.672	0.864	0.958	0.775	0.955	0.811	0.822	0.676
	Median	1.200	1.170	1.160	1.170	1.230	1.120	1.370	1.110
	Max	2.470	1.990	2.110	2.340	1.590	1.540	1.990	1.610
	CV%	30	25	24	32	16	19	24	22
	Lower 95% CI	1.102	1.088	1.097	1.054	1.138	1.042	1.162	1.023
	Upper 95% CI	1.506	1.409	1.400	1.461	1.335	1.264	1.484	1.280

Individual Subject Plasma Concentrations of Tretinoin (ng/mL) Following Velac Gel Application

Treatment	Subject	Day 1 Predose	Day 5 Predose	Day 5 Time Post Dose (hour) 1.0	2.0	4.0	8.0	12.0	24.0
Velac Gel	001-0003								(b) (4)
	001-0004								
	001-0007								
	001-0008								
	001-0010								
	001-0011								
	001-0014								
	001-0015								
	001-0017								
	001-0018								
	001-0021								
	001-0024								
	001-0025								
	001-0027								
	001-0030								
	001-0031								
	001-0034								
	N	17	15	14	15	15	15	15	15
	Mean	1.160	1.276	1.150	1.283	1.343	0.933	1.213	1.146
	SD	0.345	0.392	0.197	0.349	0.382	0.201	0.220	0.125
	Min	0.487	0.796	0.860	0.576	0.784	0.726	0.841	0.964
	Median	1.150	1.140	1.180	1.340	1.340	0.914	1.150	1.120
	Max	1.690	2.150	1.550	2.020	2.090	1.450	1.700	1.350
	CV%	30	31	17	27	28	22	18	11
	Lower 95% CI	0.983	1.059	1.036	1.090	1.132	0.822	1.091	1.077
	Upper 95% CI	1.337	1.493	1.264	1.477	1.555	1.044	1.334	1.216

Summary of Pharmacokinetic parameter estimates of Tretinoin for CT Gel and Velac Gel

Pharmacokinetic Parameter	Statistics	CT Gel N = 17	Velac Gel N = 15
AUC_{tau} (hr*ng/mL)	Mean (%CV)	29.47 (15)	27.95 (12)
	95% CI	27.14 – 31.80	26.07 – 29.82
	Median	28.91	27.36
	Minimum, Maximum	21.49, 37.46	21.61, 35.47
	Geometric Mean ($\%CV_b$)	29.14 (16)	27.76 (12)
C_{max} (ng/mL)	Mean (%CV)	1.559 (20)	1.566 (20)
	95% CI	1.401 – 1.717	1.395 – 1.737
	Median	1.560	1.390
	Minimum, Maximum	1.160, 2.340	1.200, 2.150
	Geometric Mean ($\%CV_b$)	1.533 (19)	1.540 (19)
t_{max} (hours)	Mean (%CV)	5.00 (97)	6.27 (130)
	Median	4	4
	Minimum, Maximum	0, 12	0, 24
average C_{day5} (ng/mL)	Mean (%CV)	1.232 (15)	1.190 (14)
	95% CI	1.136 – 1.327	1.097 – 1.284
	Median	1.160	1.160
	Minimum, Maximum	0.962, 1.640	0.972, 1.510
	Geometric Mean ($\%CV_b$)	1.219 (15)	1.179 (14)
Baseline concentration (ng/mL) (day 1 predose)	N	17	17
	Mean (%CV)	1.304 (30)	1.160 (30)
	95% CI	1.102 – 1.506	0.983 – 1.337
	Median	1.200	1.150
	Minimum, Maximum	0.672, 2.470	0.487, 1.690

Abbreviations: AUC_{tau} = area under the plasma concentration-time curve over a steady-state dosing interval, %CV = coefficient of variation; $\%CV_b$ = between-subject variability; CI = confidence interval; C_{max} = maximum measured plasma concentration; t_{max} = time of the maximum measured plasma concentration; average C_{day5} (the average concentration across all sampling times on day 5)

Note: Subject 001-0003 and 001-0007 in the Velac Gel group did not complete the study.

LIST OF FIGURES

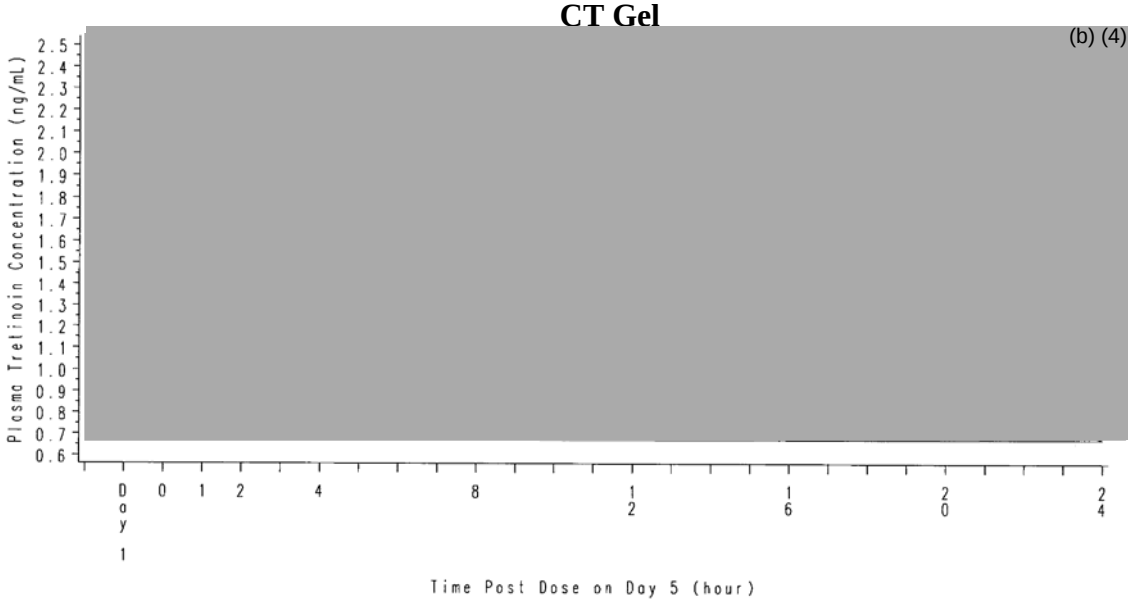
Appendix 5: Plasma Clindamycin and Clindamycin Sulfoxide Concentration vs. Time Curves in Individual Subjects Following Administration of CT Gel or Velac Gel

Clindamycin Concentrations

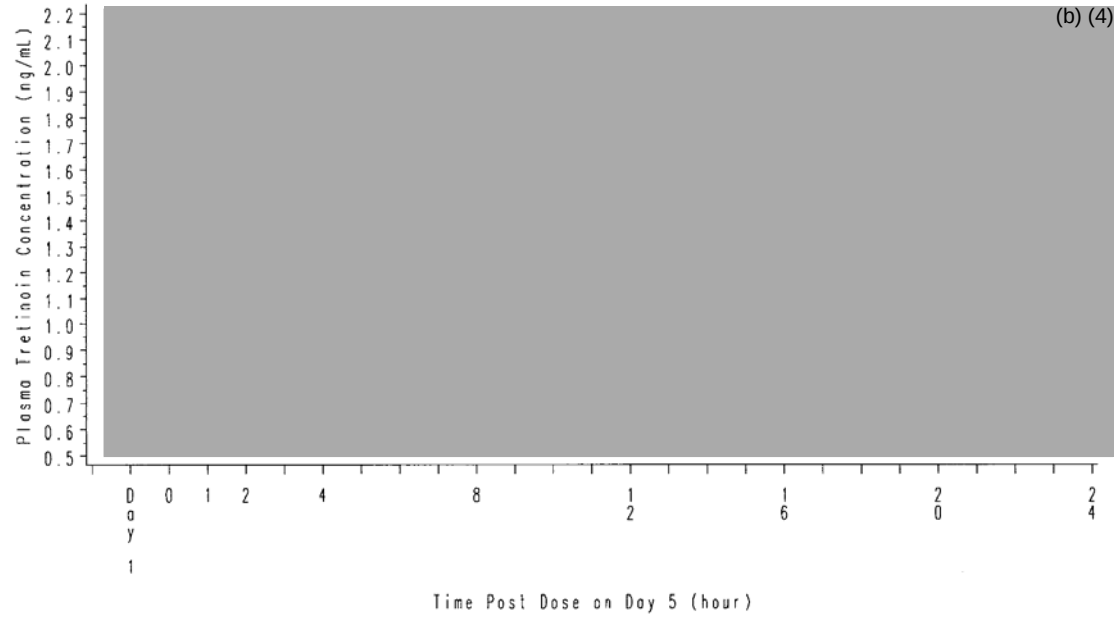
Clindamycin Sulfoxide Concentrations

Appendix 6: <u>Plasma Tretinoin Concentration vs. Time Curves in Individual Subjects Following Administration of CT Gel or Velac Gel</u>

CT Gel



Velac Gel



Appendix 7: <u>Sponsor Submitted Package Insert – Clinical Pharmacology Section</u>

VELTIN - clindamycin phosphate and tretinoin gel
STIEFEL LABORATORIES INC

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Clindamycin

[See Microbiology (12.4).]

Tretinoin

Although the exact mode of action of tretinoin is unknown, current evidence suggests that topical tretinoin decreases cohesiveness of follicular epithelial cells with decreased microcomedo formation. Additionally, tretinoin stimulates mitotic activity and increased turnover of follicular epithelial cells causing extrusion of the comedones.

(b) (4)


(b) (4)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-50803	ORIG-1	STIEFEL A GSK CO	Veltin

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/s/

CHINMAY SHUKLA
04/28/2010

EDWARD D BASHAW
04/28/2010

ONDQA (Biopharmaceutics) Review

NDA: 50-803 (SN 030)
Submission Date: 10/15/09
Product: Clindamycin 1% - tretinoin 0.025% Gel
Type of Submission: Resubmission
Sponsor: Stifel
Reviewer: Tapash K. Ghosh, Ph.D.

Background: The sponsor, Stifel, submitted a complete response to the Agency's non-approvable action letter issued for NDA 50-803 on 10 June 2005. Pursuant to previous correspondences, Stifel reformulated the vehicle of the drug product and conducted nonclinical and clinical studies to address the non-approvability issues and to support approval of NDA 50-803 for the topical treatment of acne vulgaris. The following main studies were conducted with the reformulated products: a 2-year dermal carcinogenicity study in mice, a bioavailability study, a pivotal phase 3 safety and efficacy study, two phase 1 safety studies and one phase 1 tolerability study. In addition, the sponsor also submitted *in-vitro* release study report (Report ASI-176-05) entitled "*Comparison of the Release of Tretinoin and Clindamycin Phosphate from Six Connectics' formulations*".

This review will comment only on the *in-vitro* release study report (Report ASI-176-05) mentioned above. The other CMC aspects of the submission will be addressed by the Chemistry reviewer.

Recommendation: Review of *in-vitro* release study report (ASI-176-05) is deemed unnecessary as the reported results do not have any Regulatory utility.

Tapash K. Ghosh, Ph. D.
Primary Reviewer

FT by Patrick Marroum, Ph. D. _____

Description and composition of the drug product [clindamycin 1% - tretinoin 0.025% gel]:

Stiefel has reformulated Velac Gel, now referred to as CT Gel, (b) (4) the polyoxylethylene 4 monolauryl ether (also referred to as Laureth 4 or POE 4), (b) (4) to maintain desired and acceptable formulation characteristics. (b) (4) POE 4 (b) (4) (b) (4) were included in the original formulation (b) (4) in the gel while maintaining acceptable physical characteristics. There are no other changes in the CT Gel formulation to that of the original Velac Gel. A comparison of the quantitative compositions of the two formulations is presented below:

Table 1 Velac Gel and CT Gel Formulations

Ingredients[a]	Velac Gel Formulation Concentration (% w/w)	CT Gel Formulation Concentration (% w/w)
Clindamycin Phosphate	1.00 (expressed as clindamycin)	1.00 (expressed as clindamycin)
Tretinoin	0.025	0.025
Propylene Glycol		(b) (4)
Laureth 4, Polyoxyethylene 4 Monolauryl Ether (POE 4)		
(b) (4)		
Carbomer 940 (b) (4)		
Tromethamine		
Methylparaben		
Citric Acid, Anhydrous		
Edetate Disodium		
Butylated Hydroxytoluene (BHT)		
Purified Water		
(b) (4)		

Specifications [clindamycin 1% - tretinoin 0.025% gel]: The proposed drug product specifications for CT Gel are provided in the table below.

Table 1 CT Gel Drug Product Specifications

(b) (4)

Discussion: In the *in-vitro* release study report ASI-176-05, the sponsor compared *in-vitro* release profiles of 6 different Connectics' formulations with varying amounts of clindamycin phosphate, tretinoin and POE4. The study appears to be an initial formulation development study. The sponsor did not attempt to set any *in-vitro* release specification based on the study results. According to SUPAC-SS guidance, "The development and validation of an *in vitro* release test are not required for approval of an NDA, ANDA or AADA nor is the *in vitro* release test required as a routine batch-to-batch quality control test" and "*In vitro* release testing, alone, is not a surrogate test for *in vivo* bioavailability or bioequivalence."

As mentioned earlier, the sponsor conducted several non-clinical and clinical studies including the Phase 2 study (W0265-02) entitled "*A randomized, open label study to evaluate the Bioavailability (Absorption) of Clindamycin Phosphate and Tretinoin in subjects with acne vulgaris using CT gel or Velac gel*". The review of this study by the Office of Clinical Pharmacology will address the systemic exposure of both clindamycin phosphate and tretinoin. The *in-vitro* release study report (ASI-176-05), therefore, will not be reviewed as the reported results do not have any Regulatory utility.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-50803	ORIG-1	STIEFEL A GSK CO	Veltin

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TAPASH K GHOSH
01/20/2010

PATRICK J MARROUM
01/21/2010

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 50-803/N000	**(originally submitted under NDA** (b) (4)
Brand Name:	Velac Gel™ *(Proposed by the Sponsor)*
Generic Name:	Clindamycin Phosphate/Tretinoin
Dosage Form:	Topical Gel
Dosage Strength:	Clindamycin1%, Tretinoin 0.025%
Indication:	Treatment of Acne Vulgaris
NDA Type:	Original NDA 505 (b)(2)
Relevant IND	IND 65,369
Submission Date(s):	08/23/2004
Sponsor:	Connetics Corporation, Palo Alto, CA
Reviewer:	Chandra S. Chaurasia, Ph.D.
Team Leader:	Raman K Baweja, Ph.D.
OCPB Division:	DPE III (HFD-880)
OND Division:	DDDDP (HFD-540)

EXECUTIVE SUMMARY

The Sponsor, Connetics is seeking approval of the new combination product Velac Gel, containing clindamycin phosphate equivalent to 1% clindamycin and 0.025% tretinoin under a 505(b)(2) application for the treatment of acne vulgaris. Currently, there is no US approved combination product containing both clindamycin and tretinoin moieties. However, clindamycin phosphate (equivalent to 1% clindamycin) as a single ingredient product is approved as topical gel (Cleocin T, NDA 50-615, Pharmacia, Jan 7, 1987), lotion (Cleocin T, NDA 50-600, Pharmacia, May 31, 1989), and solution (Cleocin T, NDA 50-537, Pharmacia, prior to Jan 1, 1982) for the treatment of acne vulgaris. Similarly, products containing tretinoin are approved as topical gel in 0.01% and 0.025% strengths (Retin-A, NDA 17-955 and 17-579, Johnson and Johnson, prior to Jan 1, 1982), and in 0.04% and 0.1% strengths as micro-gel (Retin-A Micro, NDA 20-475, J &J, May 10, 2002 and Feb 7, 1997, respectively) for the treatment of acne vulgaris. In addition, tretinoin is also available as topical cream (0.025%-0.1%) and solution 0.05% strengths for the treatment of acne, and as tretinoin 0.02% and 0.05% emollient creams (Renova, NDA) for use in the mitigation of fine wrinkles and mottled hyperpigmentation.

To characterize the percutaneous absorption of clindamycin phosphate and tretinoin following daily application of Velac Gel (Clindamycin 1%/Tretinoin 0.025%) , the Sponsor conducted a pivotal, Phase 1, multiple dose study under maximal exposure conditions in 15 evaluable male and female patients with acne vulgaris, ages 12 to 20 years. Plasma levels for clindamycin, tretinoin, and the principal retinoid metabolite 4-oxo-tretinoin were analyzed at screening, on Day 1 (baseline), Day 5 - hours 0 through 24, and on Day 28 at the end of treatment. The limit of quantitation (LOQ) was 0.5 ng/mL for clindamycin, 0.2 ng/mL for tretinoin, and 1 ng/mL for 4-oxo-tretinoin.

On Day 5 of topical administration, low clindamycin levels were detected in plasma of all 15 subjects, with 4 subjects having only one or two concentration values above the LOQ of 0.5 ng/mL. The maximum clindamycin concentrations ranged from 0.597 to 6.52 ng/mL and occurred between 4 to 12 hours postdose, with mean Cmax of 2.5 ng/mL. On Day 28, 3 of 15 subjects had detectable

clindamycin levels, however, these levels did not exceed the mean Cmax demonstrated on Day 5. Additionally, less than 0.1% of daily clindamycin dose of 3g was excreted in urine supporting minimal systemic absorption of clindamycin following Velac Gel topical application.

Both tretinoin and 4-oxo-tretinoin were present in only trace concentrations in plasma of patients with acne dosed with topical Velac Gel (Clindamycin 1%/Tretinoin 0.025%) for 5 days, and these concentrations were not different from those reported at Screening, or predose of Day 1 or on day 28. Additionally, tretinoin is a naturally occurring compound in humans, with endogenous plasma concentrations of approximately 1 to 4 ng/mL. The plasma concentrations of tretinoin and 4-oxo-tretinoin on Day 28 (post treatment) were within this range indicating no significant systemic absorption of tretinoin following topical administration of the test product.

Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the information submitted in support of NDA 50-803 for clindamycin phosphate 1%//tretinoin 0.025% gel, and found it to be acceptable for meeting the requirements of 21CFR320.

OCBP LABELING RECOMMENDATIONS:

The following changes in the Clinical Pharmacology section of the Sponsor's proposed labeling are recommended. The BLUE texts indicate insertion suggested by the reviewer and the RED Strikethroughs indicate deletion in the Sponsor's proposed text.

CLINICAL PHARMACOLOGY

(b) (4)

SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

The transdermal absorption of tretinoin and clindamycin are both well characterized and numerous studies have been published describing the safe and effective use of clindamycin and tretinoin in humans.

Background of Product Development:
With respect to this NDA 50-803, initial formulation of the combination product was originally developed by Brocades Pharma BV, Netherlands, which was acquired by Yamanouchi Pharmaceuticals. Yamanouchi formulation included (b) (4) methylparaben (b) (4). In 2002 Connetics purchased the rights to Velac Gel from Yamanouchi. The Connetics formulation which is the subject of this NDA was modified to (b) (4) of methylparaben (b) (4) It is noted that the pivotal Clinical and Clinical Pharmacology studies were conducted with the test product (Lot no. SIAC-C) containing (b) (4) methylparaben.

Clinical Program:
The clinical study program included two pivotal Phase 3, randomized, double-blind, multicenter, four-armed, active-and vehicle-controlled studies (VLC.C.304 and VLC.C.305) to evaluate the safety and efficacy of Velac Gel compared with Clindamycin Gel, Tretinoin 0.025% Gel and Vehicle in the treatment of acne vulgaris**.** Primary measurements of efficacy in these studies were facial lesion counts (total, inflammatory, non-inflammatory) and the ISGA (Investigator's Static Global Assessment) as recommended by the FDA at the End of Phase 2 meeting. The primary efficacy endpoints of the studies were the percent reduction from Baseline to Week 12 (end of treatment) for two of three lesion counts and the proportions of subjects who had an ISGA score of 0 or 1 at Week 12 (end or treatment). The secondary efficacy endpoints were the absolute reduction in lesion counts from Baseline to Week 12, the proportion of subjects who had a SGA score of 0 or 1 at Week 12, and the time to a 50% reduction in total lesion counts.

Clinical Pharmacology Program:

The Sponsor conducted a single-center, open-label, multiple dose evaluation to assess the absorption and safety of Velac Gel under maximal exposure conditions. The site enrolled 15 patients (9 males and 6 females, all Caucasians) with acne vulgaris with an Investigator's Static Global Assessment of 2 or greater at screening (i.e., some non-inflammatory lesions present, with few inflammatory lesions [papules/pustules only, no nodulo-cystic lesions]). Other inclusion/exclusion criteria were similar to standard guidelines for evaluating anti-acne drugs. Subject ages ranged from 12 to 20 years, with a mean of 15 years. All patients completed the study.

The test product Velac Gel 3 gm was applied topically once every morning to the face, neck, upper chest and upper back areas for 28 consecutive days. Blood samples were collected at screening, on Day 1 prior to first treatment, on Day 5 (prior to application on Day 5 and 1,2,4,8,12, and 24 hours following treatment), and Day 28 post-dosing. Urine was collected on Day 5 and Day 6 for a 24-hour collection.

Clinical Pharmacology Results:

Clindamycin

Table 1 summarizes plasma concentrations for clindamycin at Screening, Day 1 (Predose) and Day 28, providing the mean, standard deviation, and range for the respective sampling. Tables 2 and 3 summarize individual plasma clindamycin concentrations (ng/mL) and pharmacokinetic parameters of clindamycin, respectively over 24 hr on Day 5 of once daily dosing with Velac Gel.

On Day 5 of topical administration, low clindamycin levels were detected in plasma of all 15 subjects, with 4 subjects having only one or two concentration values above the LOQ of 0.5 ng/mL (Table 2). Peak concentrations ranged from 0.60 to 6.52 ng/mL, and occurred between 4 to 12 hours postdose. On Day 28, 3 of 15 subjects (#7,11 and 15, Table 1) had detectable clindamycin levels, however, these levels did not exceed the mean Cmax value of 2.5 ng/mL (Table 3) demonstrated on Day 5.

Data from the pooled urine samples collected over 24 hour post-dose on Day 5, indicate a less than 0.1% of the daily clindamycin dose being excreted in urine (Table 3).

Table 1. Plasma Clindamycin, Concentrations (ng/ml) at Screening, Day 1 (Predose) and Day 28 of Daily Dosing with Velac Gel (N=15). Study Protocol VLC.C.201

Sub#	Clindamycin ng/mL)		
	Screening	Day 1	Day 28
1	(b) (4)		
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
Mean	0.00	0.00	0.36
SD	-	-	0.82
Range	-	-	0.0-2.41

Table 2. Plasma Clindamycin Concentrations (ng/mL) Over 24 hr
on Day 5 of Once Daily Dosing with Velac Gel. Study Protocol VLC.C.201

Best Available Copy

Subject Number	Sample Times (hr) 0 *	1	2	4	8	12	24
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
Mean	0.045	0.723	1.108	2.115	1.835	1.290	0.122
Median	0.000	0.541	0.792	1.770	1.600	1.350	0.000
SD	0.176	0.871	1.097	1.903	1.114	0.705	0.253
N	15.000	15.000	15.000	15.000	15.000	15.000	15.000
Minimum	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Maximum	0.681	2.730	3.240	6.520	3.850	2.290	0.648

Samples below the lower limit of quantification (0.500 ng/mL) are reported as 0.000.
* = indicates that the 0 sample time was collected 5 minutes prior to dosing.

Table 3. Summary of Pharmacokinetic Parameters of Plasma and Urine Clindamycin Over
24 Hours on Day 5 of Once Daily Dosing with Velac Gel (N=15). Study Protocol VLC.C.201

Pharmacokinet Parameters	Arithmetic Mean	SD
Clindamycin: Plasma		
Cmax (ng/mL)	2.486	1.717
AUC0-24 (ng*hr/mL)	27.11	17.24
Tmax (hr)	6.40	2.53
Clindamycin: Urine		
Conc. (Urine) (ng/mL)	24.96	20.90
Vol. (Urine) (mL)	1133	513.5
Xu (ng)	23700	13820
% Dose	0.079%	-

Tretinoin and 4-Oxo-Tretinoin

Table 4 summarizes plasma concentrations for tretinoin and 4-oxo-tretinoin at Screening, Day 1 (Predose) and Day 28, providing the mean, standard deviation, and range for the respective sampling. Tables 5 and 6 summarize individual base-line adjusted plasma tretinoin and 4-oxo-tretinoin concentrations (ng/mL) over 24-hour on Day 5 of once daily dosing with Velac Gel. The pharmacokinetic parameters of tretinoin and 4-oxo-tretinoin over 24 hr on Day 5 of once daily dosing with Velac Gel is summarized in Table 7.

Table 4. Plasma Tretinoin, and 4-Oxo-Tretinoin Concentrations (ng/ml) at Screening, Day 1 (Predose) and Day 28 of Daily Dosing with Velac Gel (N=15). Study Protocol VLC.C.201

Sub#	Tretinoin (ng/mL)			4-Oxo-Tretinoin (ng/mL)		
	Screening	Day 1	Day28	Screening	Day 1	Day28
1	(b) (4)					
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
Mean	0.40	0.36	0.15	0.34	0.14	0.39
SD	0.15	0.18	0.20	0.76	0.37	0.65
Range	0.0-0.59	0.0-0.61	0.0-0.55	0.0-2.41	0.0-1.09	0.0-1.69

Table 5. Baseline-Adjusted Plasma Tretinoin Concentrations (ng/mL) Over 24 hr on Day 5 of Once Daily Dosing with Velac Gel. Study Protocol VLC.C.201

Best Available Copy

Subject Number	Sample Times (hr) 0 *	1	2	4	8	12	24
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
Mean	0.082	0.064	0.098	0.130	0.010	0.035	0.071
Median	0.000	0.000	0.000	0.074	0.000	0.000	0.000
SD	0.145	0.133	0.141	0.182	0.023	0.080	0.135
N	15.000	15.000	15.000	15.000	15.000	15.000	15.000
Minimum	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Maximum	0.477	0.357	0.370	0.656	0.081	0.265	0.392

Baseline concentration was calculated by subtracting the average of the concentration values at Screening and Day 1 from the concentration values at each time point. Any resultant negative concentration was set to 0.000.
* = indicates that the 0 sample time was collected 5 minutes prior to dosing.

Table 6. Baseline-Adjusted Plasma 4-Oxo-Tretinoin Concentrations (ng/mL) Over 24 hr on Day 5 of Once Daily Dosing with Velac Gel. Study Protocol VLC.C.201

Best Available Copy

Subject Number	Sample Times (hr) 0 *	1	2	4	8	12	24
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
Mean	0.22	0.27	0.16	0.09	0.15	0.01	0.00
Median	0.00	0.00	0.00	0.00	0.00	0.00	0.00
SD	0.44	0.74	0.45	0.34	0.56	0.03	0.00
N	15.00	14.00	15.00	15.00	15.00	14.00	14.00
Minimum	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Maximum	1.27	2.64	1.63	1.30	2.18	0.10	0.00

Baseline concentration was calculated by subtracting the average of the concentration values at Screening and Day 1 from the concentration values at each time point. Any resultant negative concentration was set to 0.000.
* = indicates that the 0 sample time was collected 5 minutes prior to dosing.
. = Insufficient sample as discussed in Section 6.2 of the analytical report.

Table 7. Summary of Pharmacokinetic Parameters of Plasma Tretinoin and 4-Oxo-tretinoin Over 24 Hours on Day 5 of Once Daily Dosing with Velac Gel (N=15). Study Protocol VLC.C.201

Pharmacokinet Parameters	Arithmetic Mean	SD
Tretinoin: Plasma		
Cmax (ng/mL)	0.166	0.195
AUC0-24 (ng*hr/mL)	1.389	2.251
Tmax	5.07	5.96
4-OxoTretinoin: Plasma		
Cmax (ng/mL)	0.502	0.814
AUC0-24 (ng*hr/mL)	2.475	6.556
Tmax	2.67	4.65

The percutaneous absorption of tretinoin on Day 5- and Day 28- of consecutive daily applications of Velac Gel (clindamycin 1%/ tretinoin 0.025%) was minimal. These concentrations were consistent with those reported at Screening and predose on Day 1. Additionally, the concentrations of tretinoin and 4-oxo-tretinoin on Day 28 (post treatment) were within endogenous plasma concentrations of approximately 1 to 4 ng/mL.

No events suggestive of systemic toxicity (i.e. intestinal/abdominal discomfort, diarrhea) associated with Velac Gel or clindamycin were reported by any subjects.

Chandra S. Chaurasia, Ph.D._____ Date: _____
Clinical Pharmacology and Biopharm Reviewer
Division of Pharmaceutical Evaluation III

RD/FT Initialed by Raman K. Baweja, Ph.D. _____ Date: _____
Team Leader
Division of Pharmaceutical Evaluation III

CC: NDA 50-803, HFD-850 (P. Lee), HFD-540 (M. Owens), HFD-880 (J. Lazor, A. Selen, R. Baweja, C. Chaurasia)

APPENDICES

Appendix 1. Proposed Package Insert (Original and Annotated)

Proposed by the Sponsor in the original NDA 50-803, submitted through EDR dated Aug 24, 2004.

7 Pages Draft Labeling have been Withheld in Full Immediately Following this Page as B4 (CCI/ TS)

Appendix 1. Individual Study Review

Pivotal Pharmacokinetic Study

Title of Study: Protocol No. VLC.C-201: An open-label study to evaluate the bioavailability of clindamycin and tretinoin in subjects with acne vulgaris.

Investigator: James C. Kisicki, MD
Study Centers: MDS Pharma Services, 621 Rose Street, Lincoln, Nebraska 68502.
Studied period: March 24, 2003 to April 20, 2003
Study Design: Single center, open label, multiple dose.

Objectives: The purpose of this study was to evaluate the bioavailability of clindamycin and tretinoin, in subjects with acne vulgaris following multiple applications of Velac Gel.

Number of subjects (planned and analyzed): A total of 15 healthy subjects (9 males and 6 females, all Caucasians), 12 years of age or older with acne vulgaris were enrolled in the study. All subjects completed the study. The patients' demography was as follows:
Age (Years): Mean 15, Range 12-20
Gender: Male 9 (60%) Female 6 (40%)
Height (in): Mean 68.7, Range 62-69
Weight (lb): Mean 171.7, Range 121-276

Diagnosis and main criteria for inclusion and exclusion
Inclusion Criteria: Male or female subjects, 12 years of age and older, with an Investigator's Static Global Assessment of 2 or greater at screening.
Exclusion Criteria: Pregnant or breastfeeding.
Complete inclusion and exclusion criteria are given in section 5.3.1.1.1 page 28 Volume 1.5.

Test product, **batch number, dose and mode of administration:** Velac Gel (Lot No. SIAC-C, **containing** (b) (4) **methylparaben**), three grams, applied topically once every morning to the face, neck, chest, upper chest and upper back areas for 28 consecutive days.

Duration of Treatment: Once daily for 28 days

Criteria for evaluation:
Blood samples were collected at screening, on Day 1 prior to first treatment, Day 5 (prior to application), and 1, 2, 4, 8, 12, and 24 hours following treatment, and on Day 28 post-dosing.

Urine was collected at Day 5 and Day 6 (a 24-hour collection beginning post-application on Day 5 and ending prior to application of study medication on Day 6).

Analytical Method:
Plasma samples for clindamycin, tretinoin and the retinoid metabolite 4-oxo-tretinoin, and urine samples for clindamycin were analyzed using HPLC/MS/MS method (b) (4) The method validation reports for each of these analytes are described in details in Module 5.3.1.1.1 Vol. 1.6.

Method Validation for Clindamycin in Plasma:
The assay for clindamycin in human plasma was validated for a range of 0.50 to 65.0 ng/mL with a limit of quantitation of 0.5 ng/mL. The assay procedure was found to be linear (r^2 0.9987). The precision (%CV) for QC samples for clindamycin in human plasma ranged from 2.8% to 5.0%. The between-batch accuracy (% nominal) ranged from 95.4% to 97.2% for low, medium and high QC samples. The long term stability samples at -20 ºC for 6 weeks were within 4% of their theoretical concentrations.

Method Validation for Clindamycin in Urine:
The assay for clindamycin in human urine was validated for a range of 0.50 to 65.0 ng/mL with a limit of quantitation of 0.5 ng/mL. The assay procedure was found to be linear (r^2 0.9997). The between-batch precision (%CV) for low, medium and high QC samples for clindamycin in human urine ranged from 6.1% to 12.7%. The between-batch accuracy (% nominal) ranged from 96.9% to 101.5% for low, medium and high QC samples. The long term stability samples at -22 ºC for 117 days were within 4.6% of their theoretical concentrations.

Method Validation for Tretinoin and 4-Oxo-Tretinoin in Plasma:
The assay for tretinoin and 4-Oxo-Tretinoin (OXT) was validated for a range of 0.20 to 100 ng/mL and 1.0 to 500 ng/mL with respective r^2 values of 0.9988 and 0.9993, respectively. The limits of quantitation were 0.2 ng/mL and 1.0 ng/mL, respectively. The between-batch coefficient of variations (%CV) for low, medium and high QC samples for tretinoin and OXT were 3.6% to 8.5% and 5.2% to 17.5%, respectively. The between-batch accuracy (% nominal) ranged from 94.5% to 105.0% and 90.2% to 115.8%, respectively for tretinoin and OXT. Tretinoin and OXT exhibit a reported long term stability at -80 ºC for 165 and 26 days, respectively.

Reviewer's Comments on Analytical Method Validation:
The analytical method was found acceptable.

Safety:
Vital signs, clinical laboratory tests (chemistry, hematology, and urinalysis), physical exam findings, and occurrence of adverse events were collected at pre-specified intervals throughout the study.

Pharmacokinetics:
The pharmacokinetic parameters AUC0-24, Cmax, Tmax, and CL/F were calculated for clindamycin, and baseline (average of screening and Day 1 predose) corrected tretinoin and 4-oxo-tretinoin from the Day 5 data. Additionally, cumulative 24-hours urine was collected on Day 5 for clindamycin analysis. The amount of clindamycin excreted in urine (Xu), renal clearance (CLr) and percent of clindamycin dose excreted (% Dose) were computed.

Results:
The PK results are summarized in Tables 1-10, and graphically represented in Figures 1-3 below. Table 1 summarizes plasma concentrations for clindamycin, tretinoin, and its metabolite 4-oxo-tretinoin at Screening, Day 1 (Predose) and Day 28, providing the mean, standard deviation, and range for the respective sampling. Table 2 summarizes the plasma clindamycin concentrations corresponding to the individual sampling time points on Day 5 of once daily dosing. Table 3 summarizes pharmacokinetic parameters of clindamycin (in plasma and urine) and those of plasma tretinoin and 4-oxo-tretinoin over 24 Hours on Day 5 of once daily dosing with Velac Gel. The

individual plasma and urine clindamycin PK profile for Day 5 are summarized in Table 4. Individual plasma tretinoin, 4-oxo-tretinoin and the respective PK profiles are summarized in Tables 5-10.

On Day 5 of topical administration, low clindamycin levels were detected in plasma of all 15 subjects, with 4 subjects (#3, 10, 12 and 15, Table 2) having only one or two concentration values above the LOQ of 0.5 ng/mL. Peak concentrations ranged from 0.597 to 6.52 ng/mL, and occurred between 4 to 12 hours postdose. On Day 28, 3 of 15 subjects (#7, 11 and 15, Table 1) had detectable clindamycin levels, however, these levels did not exceed the mean Cmax value of 2.5 ng/mL (Table 3) demonstrated on Day 5.

Data from the pooled urine samples collected over 24 hour post-dose on Day 5, indicate a less than 0.1% of the daily clindamycin dose being excreted in urine.

For tretinoin, 5 subjects in all had missing data points due to insufficient sample volume -Sub #5 at Screening, and Sub # 2,8,12, and 13 on Day 28. Thirteen subjects had detectable tretinoin concentrations at Screening and on Day 1 at predose. Mean baseline-adjusted plasma concentrations on Day 5 (0.01 to 0.13 ng/mL) of dosing were generally lower than those at Screening (0.40 ng/mL) or at predose on Day 1 (0.36 ng/mL) (Table 1 and Table 6).

Plasma 4-oxo-tretinoin was detectable in 3 of the 15 subjects (#4,8, and 12, Table1) at screening and in 2 of the 15 subjects (#4 and 8, Table 1) at predose of Day 1, and in only 4 of the 15 subjects (#4,8,9 and 11, Table 8) at predose of Day 5. For Day 5 post dose sampling, only 5 subjects (#2,4,8,11, and 14) had at least one time point where the plasma 4-oxo-tretinoin concentration was above the baseline (Table 8). At the end of treatment on Day 28, only four of the 14 evaluable subjects (#4,7,11 and 14, Table 1) had 4-oxo-tretinoin levels above the LOQ value (1 ng/mL).

Table 1. Plasma Clindamycin, Tretinoin, and 4-Oxo-Tretinoin Concentrations (ng/ml) at Screening, Day 1 (Predose) and Day 28 of Daily Dosing with Velac Gel (N=15). Study Protocol VLC.C.201

	Analyte								
Sub#	Clindamycin ng/mL)			Tretinoin (ng/mL)			4-Oxo-Tretinoin (ng/mL)		
	Screening	Day 1	Day28	Screening	Day 1	Day28	Screening	Day 1	Day28
1	(b) (4)								
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
13									
14									
15									
Mean	0.00	0.00	0.36	0.40	0.36	0.15	0.34	0.14	0.39
SD	-	-	0.82	0.15	0.18	0.20	0.76	0.37	0.65
Range	-	-	0.0-2.41	0.0-0.59	0.0-0.61	0.0-0.55	0.0-2.41	0.0-1.09	0.0-1.69

Table 2. Plasma Clindamycin Concentrations (ng/mL) Over 24 hr on Day 5 of Once Daily Dosing with Velac Gel. Study Protocol VLC.C.201

Subject Number	Sample Times (hr) 0 *	1	2	4	8	12	24
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
Mean	0.045	0.723	1.108	2.115	1.835	1.290	0.122
Median	0.000	0.541	0.792	1.770	1.600	1.350	0.000
SD	0.176	0.871	1.097	1.903	1.114	0.705	0.253
N	15.000	15.000	15.000	15.000	15.000	15.000	15.000
Minimum	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Maximum	0.681	2.730	3.240	6.520	3.850	2.290	0.648

Samples below the lower limit of quantification (0.500 ng/mL) are reported as 0.000.
* = indicates that the 0 sample time was collected 5 minutes prior to dosing.

Table 3. Summary of Pharmacokinetic Parameters of Plasma and Urine Clindamycin, and Plasma Tretinoin and 4-Oxo-Tretinoin Over 24 Hours on Day 5 of Once Daily Dosing with Velac Gel (N=15). Study Protocol VLC.C.201

Pharmacokinet Parameters	Arithmetic Mean	SD
Clindamycin: Plasma		
Cmax (ng/mL)	2.486	1.717
AUC0-24 (ng*hr/mL)	27.11	17.24
Tmax (hr)	6.40	2.53
Clindamycin: Urine		
Conc. (Urine) (ng/mL)	24.96	20.90
Vol. (Urine) (mL)	1133	513.5
Xu (ng)	23700	13820
% Dose	0.079%	0.046%
Tretinoin: Plasma		
Cmax (ng/mL)	0.166	0.195
AUC0-24 (ng*hr/mL)	1.389	2.251
Tmax	5.07	5.96
4-OxoTretinoin: Plasma		
Cmax (ng/mL)	0.502	0.814
AUC0-24 (ng*hr/mL)	2.475	6.556
Tmax	2.67	4.65

Table 4. Plasma and Urine Clindamycin PK Parameters Over 24 Hours on Day 5 of Once Daily Dosing with Velac Gel. Study Protocol VLC.C.201

	Parameters								
Subject Number	Cmax ng/mL	Tmax hr	AUC(0-24) ng*hr/mL	CL/F L/hr	Conc(Urine) ng/mL	Vol.(Urine) mL	Xu ng	CLr mL/hr	% Dose
1	4.680	4.00	50.40	595.22	36.00	850.0	30600	607.12	0.10
2	1.770	4.00	28.53	1051.4	16.50	1400	23100	809.56	0.077
3	0.634	8.00	4.213	7120.6	5.140	1825	9380.5	2226.5	0.031
4	2.100	4.00	26.07	1150.6	18.70	1375	25713	986.14	0.086
5	1.430	8.00	15.63	1919.7	22.30	875.0	19513	1248.6	0.065
6	6.520	4.00	61.07	491.27	88.40	650.0	57460	940.95	0.19
7	1.600	8.00	23.38	1283.2	9.100	2400	21840	934.15	0.073
8	3.850	8.00	40.29	744.56	25.50	850.0	21675	537.94	0.072
9	4.320	4.00	46.95	638.91	44.60	975.0	43485	926.10	0.14
10	0.958	8.00	9.337	3213.1	12.50	1400	17500	1874.3	0.058
11	1.360	8.00	19.62	1529.0	26.90	1350	36315	1850.8	0.12
12	1.710	12.0	13.65	2198.4	10.70	1250	13375	980.14	0.045
13	3.550	4.01	36.97	811.53	30.50	575.0	17538	474.41	0.058
14	2.210	4.00	27.32	1097.9	23.10	675.0	15593	570.64	0.052
15	0.597	8.00	3.152	9517.3	4.400	550.0	2420.0	767.73	0.0081
Mean	2.486	6.40	27.11	2224.2	24.96	1133	23700	1049.0	0.079
Median	1.770	8.00	26.07	1150.6	22.30	975.0	21675	934.15	0.072
SD	1.717	2.53	17.24	2615.3	20.90	513.5	13820	531.23	0.046
N	15.000	15.0	15.00	15.000	15.00	15.00	15.000	15.000	15
Minimum	0.597	4.00	3.152	491.27	4.400	550.0	2420.0	474.41	0.0081
Maximum	6.520	12.0	61.07	9517.3	88.40	2400	57460	2226.5	0.19

Table 5. Plasma Tretinoin Concentrations (ng/mL) Over 24 hr on Day 5 of Once Daily Dosing with Velac Gel. Study Protocol VLC.C.201

Subject Number	Sample Times (hr) 0 *	1	2	4	8	12	24
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
Mean	0.324	0.287	0.393	0.462	0.219	0.164	0.314
Median	0.369	0.306	0.348	0.488	0.261	0.000	0.392
SD	0.230	0.183	0.164	0.120	0.158	0.197	0.197
N	15.000	15.000	15.000	15.000	15.000	15.000	15.000
Minimum	0.000	0.000	0.246	0.228	0.000	0.000	0.000
Maximum	0.750	0.632	0.758	0.656	0.530	0.552	0.537

Samples below the lower limit of quantification (0.200 ng/mL) are reported as 0.000.
* = indicates that the 0 sample time was collected 5 minutes prior to dosing.

Table 6. Baseline-Adjusted Plasma Tretinoin Concentrations (ng/mL) Over 24 hr on Day 5 of Once Daily Dosing with Velac Gel. Study Protocol VLC.C.201

Subject Number	Sample Times (hr) 0 *	1	2	4	8	12	24
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
Mean	0.082	0.064	0.098	0.130	0.010	0.035	0.071
Median	0.000	0.000	0.000	0.074	0.000	0.000	0.000
SD	0.145	0.133	0.141	0.182	0.023	0.080	0.135
N	15.000	15.000	15.000	15.000	15.000	15.000	15.000
Minimum	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Maximum	0.477	0.357	0.370	0.656	0.081	0.265	0.392

Baseline concentration was calculated by subtracting the average of the concentration values at Screening and Day 1 from the concentration values at each time point. Any resultant negative concentration was set to 0.000.
* = indicates that the 0 sample time was collected 5 minutes prior to dosing.

Table 7. Baseline-Adjusted Plasma Tretinoin PK Parameters Over 24 Hours on Day 5 Of Once Daily Dosing with Velac Gel. Study Protocol VLC.C.201

Subject Number	Parameters Cmax ng/mL	Tmax hr	AUC(0-24) ng*hr/mL	CL/F L/hr
1	0.339	4.00	1.573	476.8
2	0.000	.	0.00	.
3	0.390	23.9	5.098	147.1
4	0.370	2.00	3.561	210.6
5	0.656	4.00	7.526	99.66
6	0.012	4.00	0.03600	20830
7	0.007	8.00	0.02610	28740
8	0.051	4.00	0.1515	4950
9	0.007	4.00	0.02100	35710
10	0.147	0.00	0.8947	838.3
11	0.074	4.01	0.4912	1527
12	0.066	2.00	0.1163	6449
13	0.000	.	0.00	.
14	0.118	4.00	0.4541	1652
15	0.261	2.00	0.8931	839.8
Mean	0.166	5.07	1.389	7883
Median	0.074	4.00	0.4541	1527
SD	0.195	5.96	2.251	12250
N	15.000	13.0	15.00	13.00
Minimum	0.000	0.00	0.00	99.66
Maximum	0.656	23.9	7.526	35710

. = T_{max} is not reportable and CL/F is not calculable

Table 8. Plasma 4-Oxo-Tretinoin Concentrations (ng/mL) Over 24 hr on Day 5 of Once Daily Dosing with Velac Gel. Study Protocol VLC.C.201

Subject Number	Sample Times (hr) 0 *	1	2	4	8	12	24
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
Mean	0.38	0.36	0.32	0.09	0.15	0.10	0.00
Median	0.00	0.00	0.00	0.00	0.00	0.00	0.00
SD	0.67	0.80	0.67	0.34	0.56	0.39	0.00
N	15.00	14.00	15.00	15.00	15.00	14.00	14.00
Minimum	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Maximum	1.92	2.64	1.81	1.30	2.18	1.46	0.00

Samples below the lower limit of quantification (1.01 ng/mL) are reported as 0.00.
* = indicates that the 0 sample time was collected 5 minutes prior to dosing.
. = Insufficient sample as discussed in Section 6.2 of the analytical report.

Table 9. Baseline-Adjusted Plasma 4-Oxo-Tretinoin Concentrations (ng/mL) Over 24 hr on Day 5 of Once Daily Dosing with Velac Gel. Study Protocol VLC.C.201

Subject Number	Sample Times (hr) 0 *	1	2	4	8	12	24
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
Mean	0.22	0.27	0.16	0.09	0.15	0.01	0.00
Median	0.00	0.00	0.00	0.00	0.00	0.00	0.00
SD	0.44	0.74	0.45	0.34	0.56	0.03	0.00
N	15.00	14.00	15.00	15.00	15.00	14.00	14.00
Minimum	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Maximum	1.27	2.64	1.63	1.30	2.18	0.10	0.00

Baseline concentration was calculated by subtracting the average of the concentration values at Screening and Day 1 from the concentration values at each time point. Any resultant negative concentration was set to 0.000.
* = indicates that the 0 sample time was collected 5 minutes prior to dosing.
. = Insufficient sample as discussed in Section 6.2 of the analytical report.

Table 10. Baseline-Adjusted Plasma 4-Oxo-Tretinoin PK Parameters Over 24 Hours on Day 5 Of Once Daily Dosing with Velac Gel. Study Protocol VLC.C.201

Subject Number	Parameters Cmax ng/mL	Tmax hr	AUC(0-24) ng*hr/mL	CL/F L/hr
1	0.000	.	0.00	.
2	1.050	1.00	1.051	713.4
3	0.000	.	0.00	.
4	0.095	12.0	0.8443	888.3
5	0.000	.	0.00	.
6	0.000	.	0.00	.
7	0.000	.	0.00	.
8	0.840	0.00	1.515	495.1
9	1.270	0.00	.	.
10	0.000	.	0.00	.
11	1.630	2.00	6.885	108.9
12	0.000	.	0.00	.
13	0.000	.	0.00	.
14	2.640	0.981	24.35	30.80
15	0.000	.	0.00	.
Mean	0.502	2.67	2.475	447.3
Median	0.000	0.991	0.00	495.1
SD	0.814	4.65	6.556	372.7
N	15.000	6.00	14.00	5.000
Minimum	0.000	0.00	0.00	30.80
Maximum	2.640	12.0	24.35	888.3

. = T_{max} is not reportable, and AUC_{0-24} and CL/F are not calculable.

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Figure 1: Mean (+/-SD) Plasma Clindamycin Concentrations Versus Time - Linear Scale

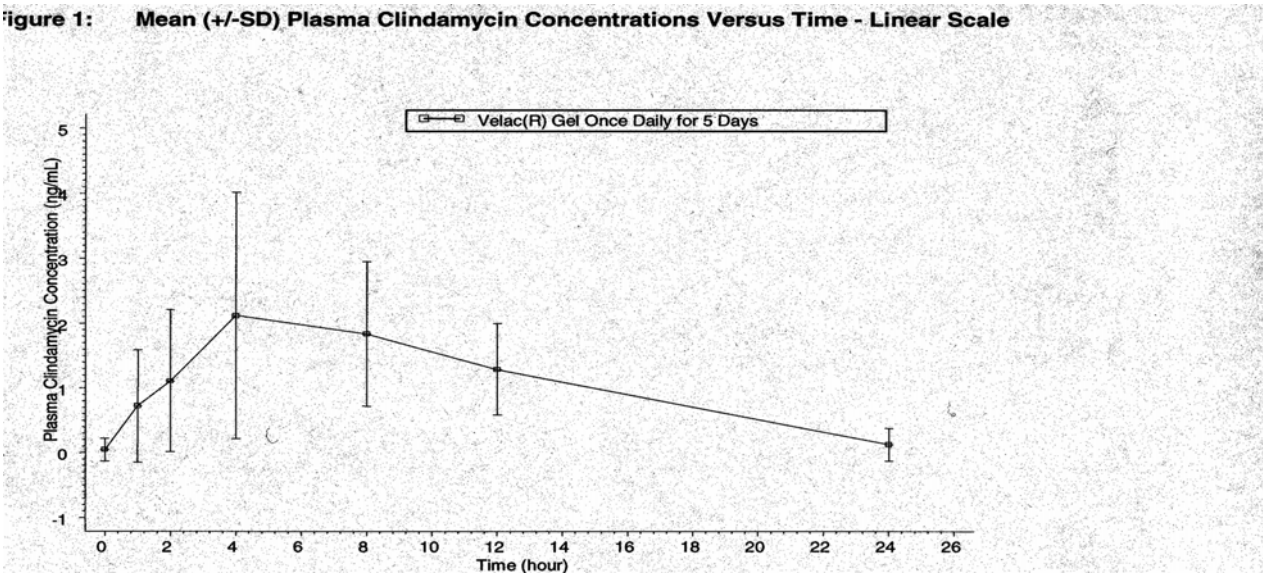

Figure 2: Mean (+/- SD) Baseline-Adjusted Plasma Tretinoin Concentrations Versus Time-Linear Scale

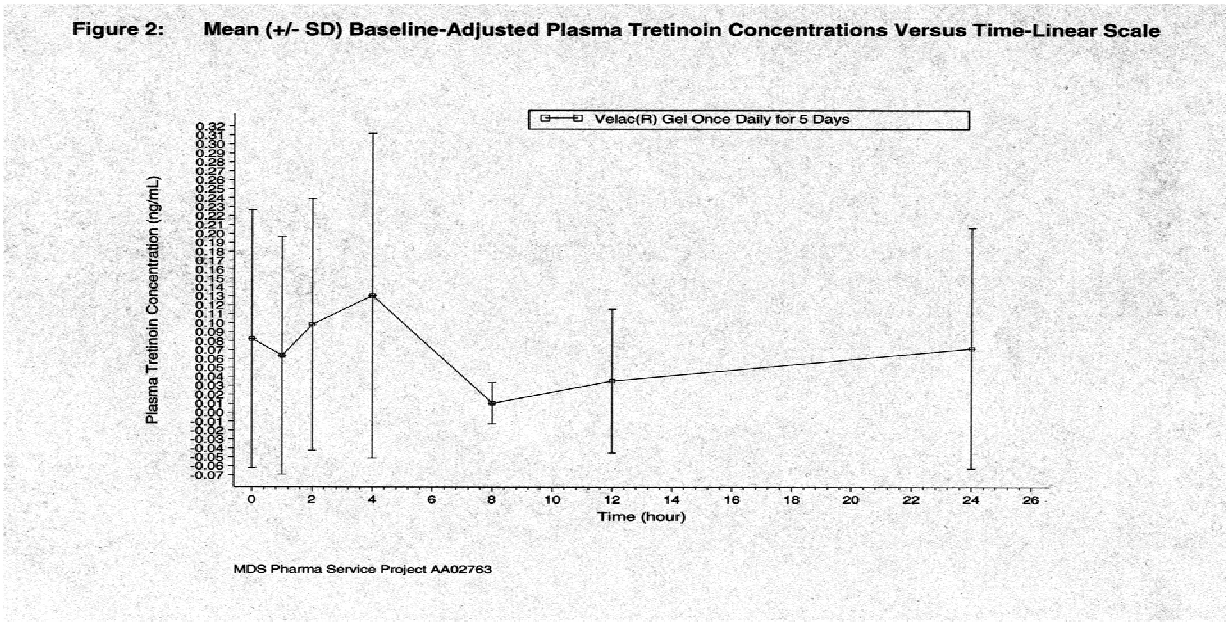

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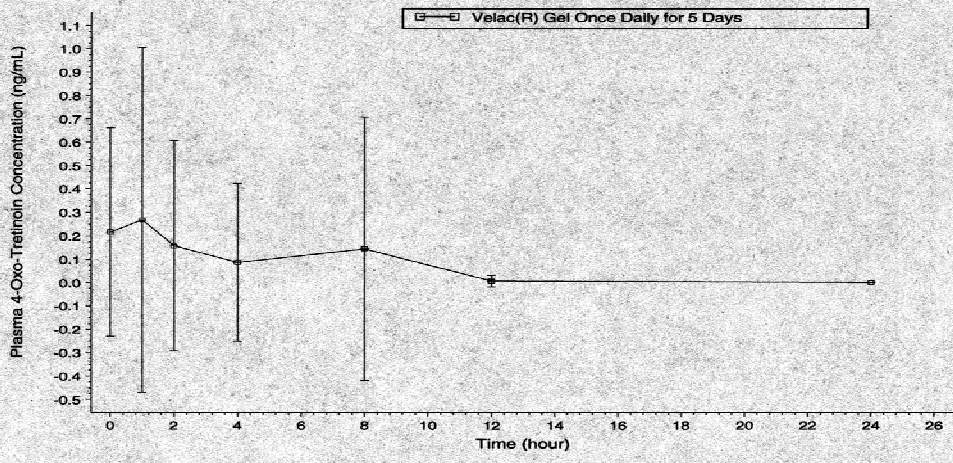
Figure 3: Mean (+/- SD) Baseline-Adjusted Plasma 4-Oxo-Tretinoin Concentrations Versus Time-Linear Scale



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Brief Summary of Adverse Events
Nine of the 15 subjects (60%) reported a total of 27 adverse events. All 27 events were mild or moderate in intensity. Nineteen of the 27 events were associated with the study drug application site, and were considered to be definitely or probably related to Velac Gel. These AEs included dryness, erythema, burning, pruritus, rash, pustules and reactions not otherwise specified (cheek peeling). All systemic reactions (headache and sore throats) were considered probably not related to study medication. All AEs were resolved. There were no severe adverse events reported and no subject discontinued the study due to an adverse event.

FORMULATION

Velac Gel Formulation Commercial Batch*

Ingredients	Concentration (%w/w)
Clindamycin Phosphate	1.0% (expressed as clindamycin)
Tretinoin	0.025
Butylated Hydroxytoluene	(b) (4)
Carbomer 940	
Citric Acid, Anhydrous	
Edetate Disodium	
Methylparaben	
Polyoxyethylene 4 Monolauryl Ether	
(b) (4)	
Propylene Glycol	
Tromethamine	
Purified Water	

*Also used for the pivotal clinical and clinical pharmacology studies: Lot no. SIAC-C.

Pharmacokinetic Conclusions from the Pivotal Study VLC.C-201:

1. Low levels of clindamycin were detected (LOQ 0.5 ng/mL) in plasma of all subjects on Day 5 of dosing with topical Velac Gel. Peak concentrations ranged from 0.60 to 6.52 ng/mL. The mean Cmax, AUC0-24 and Tmax were 2.49 (±1.72) ng/mL, 27.11 (±17.24) ng*hr/mL, and 6.40 (±2.53) hours, respectively.

2. On Day 28 (end of treatment), detectable levels of clindamycin were observed in 3 of 15 evaluable subjects. However, these levels (0.67, 2.27, and 2.41 ng/mL) did not exceed the mean Cmax (2.49 ng/mL) demonstrated on Day 5.

3. Less than 0.1% of daily clindamycin dose was excreted in the urine.

4. Tretinoin was present in only trace concentrations in plasma of subjects treated with Velac Gel for 5 days. Generally, these concentrations were not different from those reported at Screening and predose of Day 1. For tretinoin, the mean baseline adjusted Cmax, and AUC0-24 values were 0.17 (± 0.19) ng/mL, 1.39 (± 2.25) ng*hr/mL, respectively. The mean Tmax

value was 5.05 (± 5.96) hr. On Day 28, detectable levels of tretinoin were observed in 5 out of 11, evaluable subjects. Again, these levels (0.2 to 0.55 ng/mL) were consistent with endogenous levels for tretinoin detected at the baseline visits.

5. For the principal 4-oxo-tretinoin metabolite, the mean baseline adjusted Cmax and AUC0-24 values on Day 5 were 0.50 (± 0.81) ng/mL, 2.48 (± 6.56) ng*hr/mL, respectively. The mean Tmax value was 2.67(± 4.65) hr. The plasma 4-oxo-tretinoin levels on Day 5 were not different from those reported at Screening and predose of Day 1. On Day 28, detectable levels of 4-oxo-tretinoin were observed in 4 out of 14 evaluable subjects. Again, these levels (1.08 to1.69 ng/mL) were consistent with endogenous levels of 4-oxo-tretinoin detected at the baseline visits.

6. Neither tretinoin nor its metabolite showed any increase in plasma concentration levels post treatment when compared to their respective plasma concentration levels measured at baseline.

7. Although application site reactions were commonly reported, Velac Gel was well tolerated by the subjects who participated in the study.

PILOT Study No. 91-CTC-06: A crossover comparison of the absorption of clindamycin from three topically applied formulations in healthy volunteers.

Study Objectives: To compare the percutaneous absorption of clindamycin from clindamycin hydrochloride 1% plus tretinoin 0.025%, clindamycin phosphate 1% plus tretinoin 0.025% and from a commercially available clindamycin phosphate lotion.

Study Site: Brocades Pharma Research, Biopharmaceutical Research Department/Clinical Pharmacology Unit, Fleminglaan 1, Delft, The Netherlands

Investigator: I.J. Terpstra, M.D.

Study Design: Open, Crossover, Healthy male subjects, N=12, Age 20-24 yrs, Weight: 67-72 kg.

Dosing/Treatment: One mL applied to skin of chin, cheeks and forehead, once daily for 5 days, washout period of two-and half-weeks.

Duration of Study: 7 weeks

Clinical study period: From April 1992 to June 1992

Formulations tested:
Clindamycin phosphate 1% plus tretinoin 0.025% (Velac gel): Lot No. FP-001-F **(containing** (b) (4) (b) (4) **methyl paraben)**.
Clindamycin hydrochloride 1% plus tretinoin 0.025%,
Clindamycin phosphate 1% lotion. N=12, 1 mL once daily for 5 days.

Analytical Site: Brocades Pharma Research, The Netherlands.
Samples collection: On the 5th Day of each treatment, blood (10 mL) samples were collected predose, and at 15, 30 60 min and 1.5, 2, 3, 5, 7, 9 and 12 hr post-dose. In addition, urine samples were collected over a 12 h period following the last application on the 5th Day. Clindamycin was assayed in plasma and urine using HPLC with a LOQ of 5 ng/mL.

Results: Plasma pharmacokinetic data indicated clindamycin levels undetected at the LOQ of 5 ng/mL for each of the three formulations, except in one subject (#6) the clindamycin hydrochloride/tretinoin gave a detectable level 8 ng/mL.

Urinary excretion data of clindamycin indicated a comparable extent of percutaneous drug absorption from the clindamycin phosphate/tretinoin gel and the clindamycin phosphate lotion (mean urinary excretion 11 ± 4 mcg/12 hr and vs. 10 ± 6 mcg/12 hr, respectively). However, relative to these two formulations, repeated application of clindamycin hydrochloride/tretinoin gel exhibited higher excretion of clindamycin ($p<0.05$; mean urinary excretion 23 ± 22 mcg/12 hr).

In addition, the clindamycin hydrochloride/tretinoin formulation was relatively more irritant compared to that of the clindamycin phosphate/tretinoin formulation. It is noted that formulation selection was the purpose of this study.

PILOT Study 92-CTC-01: Transdermal tretinoin uptake after once daily clindamycin 1%/ tretinoin 0.025% gel in patients with moderate to severe acne vulgaris.

This pilot study was conducted by Brocades Pharma Research in Europe using clindamycin 1%/tretinoin 0.025%, **Lot No. FP-009L-92D (contains (b) (4) methylparaben).** The objective of the study was to find out the significance of transdermal uptake of tretinoin from the combination clindamycin 1%/ tretinoin 0.025% gel formulation. Forty patients with moderate to severe acne, entered the double blind, randomized multi-center study. Twenty patients were included in each treatment arm, viz. clindamycin 1%/tretinoin 0.025% gel or tretinoin 0.025% gel. Gels were applied once daily at night for a period of 12 weeks. Plasma collected at 12 weeks was used for the assessment of tretinoin levels using HPLC method with a validated analytical method. The limit of detection was 2 ng/mL and the limit of quantification was 5 ng/mL. None of the plasma samples contained measurable tretinoin levels. In 9 of the 19 evaluable samples tretinoin levels were below the limit of detection 2 ng/mL.

Conclusion from the Pilot Study 92-CTC-01: There were no indications for a notable increase of systemic tretinoin levels during daily application of clindamycin 1%/tretinoin 0.025% gel in patients with moderate to severe acne for 12 weeks at a LOQ value 2 ng/mL.

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA Number	(b) (4)	Brand Name	Velac Gel
OCPB Division	DPE III, HFD 880	Generic Name	Clindamycin* 1% Tretinoin 0.025% *active form is clindamycin base from Clindamycin Phosphate as the active pharmaceutical ingredient
Medical Division	ODE V, HFD 540	Drug Class	Acne Treatment
OCPB Reviewer	Chandra S. Chaurasia, Ph. D.	Indication(s)	Topical treatment of acne vulgaris
OCPB Team Leader	Raman K. Baweja	Dosage Form	Topical Gel
Type of Submission	Original Submission 505(b)(2) application	Strength	1%/0.025%
Related NDAs/ANDAs/INDs	IND 65,369	Route of Administration	Topical
Date of Submission	Aug 23, 2004	Dosing Regimen	Once daily in the evening
Estimated Due Date of OCPB Review	March 25, 2005	Sponsor	Connetics Corporation Palo Alto, CA
PDUFA Due Date	June 25, 2005	Priority Classification	1S
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	***X***			
Labeling	**X**			

Reference Bioanalytical and Analytical Methods	**X**			HPLC/MS for Pivotal Study VLC.C.01. LOQ for clindamycin 0.5 ng/mL in plasma and urine matrices; LOQ for tretinoin and 4-oxo-tretinoin 0.2 ng/mL and 1 ng/mL, respectively in plasma. Analytical Site for Clindamycin: (b) (4) Analytical Site for tretinoin and 4-oxo-tretinoin: (b) (4) . HPLC/UV for Study 92-CTC-01 LOQ for tretinoin 5 ng/mL Analytical Site (b) (4)
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose in **pediatric population**:				
multiple dose:	**X**	**1**		**Study No. 91-CTC-06**: • A crossover comparison of the absorption of clindamycin from three topically applied formulations in **healthy volunteers:** • Formulations tested: Clindamycin phosphate 1% plus tretinoin 0.025% (Velac gel), clindamycin hydrochloride 1% plus tretinoin 0.025%, and clindamycin phosphate 1% lotion. N=12, 1 mL once daily for 5 days. • Single center European study • Lot No. FP-001-F
Patients-				
single dose:				

multiple dose:	**X**	**2**		**Pivotal Study VLC.C.201**: • Open-label study to evaluate the bioavailability of clindamycin and tretinoin in subjects with acne vulgaris. • Single site, N=15 (6 females and 9 males, Caucasian, **12-20-years** old, mean age 15 yrs), 3 g qd for 28 days. • Study with to-be-marketed formulation **containing** (b) (4) **methyl paraben (Lot No. SIAC-1C)**. • Clindamycin levels measured in plasma and urine PK measures (Cmax, AUC, Tmax, CL/F) reported. T1/2 not reported. • Tretinoin and 4-oxo-tretinoin levels measured in plasma and Cmax, AUC, Tmax, CL/F values reported for each. • **Supportive Study 92-CTC-01:** European Study conducted by Yamanouchi • Transdermal tretinoin uptake after once daily clindamycin 1% tretinoin 0.025% gel in patients with moderate to severe acne vulgaris., N=40, Once daily at night application of Velac gel (N=20) or tretinoin (N=20) for 12 weeks. • Objective: To evaluate the plasma levels of tretinoin during treatment with Velac gel. • **Lot No. FP-009L-92D (contains** (b) (4) **methyl paraben)**
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:	***X***			Pooled Data

pediatrics:	**X**			
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution: In Vitro				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	**X**			Module 5: 16.1.12
Total Number of Studies		**3**		

Filability and QBR comments

	"X" if yes	Comments
Application filable?	***YES***	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm		Comments have been sent to firm (or attachment included). FDA letter date if applicable.

QBR questions (key issues to be considered)	• **Is there systemic absorption of Clindamycin and Tretinoin from the topical administration of the gel based on conditions of use as described in the labeling?**
Other comments or information not included above	
Primary reviewer Signature and Date	**Chandra S. Chaurasia, Ph. D.**
Secondary reviewer Signature and Date	**Raman K. Baweja, Ph. D.**

Chandra S. Chaurasia, Ph.D. _____ Date: _____
Clinical Pharmacology and Biopharm Reviewer
Division of Pharmaceutical Evaluation III

RD/FT Initialed by Raman K. Baweja, Ph.D. _____ Date: _____
Team Leader
Division of Pharmaceutical Evaluation III

CC: NDA (b) (4) HFD-540 (M. Owens), HFD-880 (J. Lazor, A. Selen, R. Baweja, C. Chaurasia)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Chandra S. Chaurasia
4/26/05 09:18:19 AM
BIOPHARMACEUTICS

Raman Baweja
4/26/05 02:26:09 PM
BIOPHARMACEUTICS